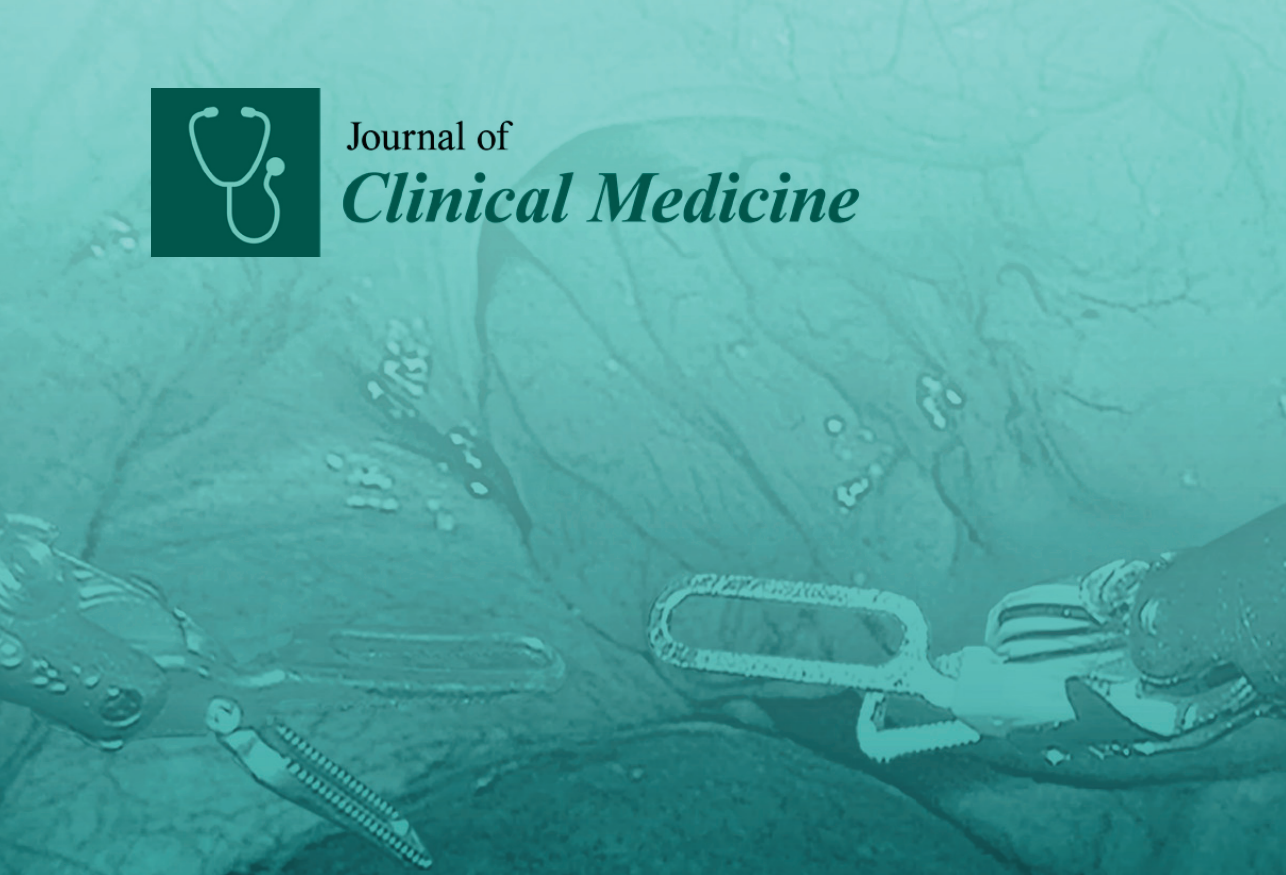

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Recent Advances in Minimally Invasive Surgery

Edited by
Ibrahim Alkatout and Matthias Biebl

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Editors

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Cover image courtesy of Ibrahim Alkatout.

Contents

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Editorial

Recent Advances in Laparoscopy

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At the end of 2019, we received reports of abnormally high rates of severe pneumonia and mortality in a city named Wuhan in the province of Hubei in China. The reports reached Europe and Germany, and the rising number of infections became an impending threat to public health on a worldwide basis. More than 400,000 cases of the disease and more than 18,000 deaths were reported in March 2020. A novel form of the coronavirus known as "severe acute respiratory syndrome coronoavirus-2 (SARS-CoV-2)" was responsible for a disease complex referred to as the coronavirus disease 2019 (COVID-19). The virus reached Germany as early as 27 January 2020. Despite initial hopes of being able to curtail the problem, private and professional lives were severely locked down due to COVID-19, which evolved into a worldwide pandemic and a most serious threat to global health within a few months [1].

The pandemic had far-reaching effects on personal and economic lives in Europe and throughout the world. One of the first consequences in surgery was the postponement of elective procedures. The numbers of patients admitted for surgery in hospitals were reduced to a minimum, and the resources of emergency care units were maximized to provide sufficient care for patients with the new disease.

An invitation from the Journal of Clinical Medicine to release a special issue on Recent Advances in Laparoscopy was received exactly during this time period. To quote the erstwhile British Prime Minister Sir Winston Churchill: "Never let a good crisis go to waste." The unprecedented crisis of a pandemic became the nascent hour of this special issue. Although many researchers were preoccupied with several matters other than academic paperwork, we pursued the formidable task of wrapping up and presenting the last decade of surgical progress in appropriate form.

The name coined for the special issue was Recent Advances in Minimally Invasive Surgery. Both editors of the special issue are aware of the fact that minimally invasive surgery encompasses the entire field of surgery. Since we serve a gynecological surgeon as well as a visceral surgeon in Europe, this issue is focused on the story of minimally invasive surgery in these two fields. A great deal has happened in both sectors. The aim of the minimally invasive surgeons is, and always has been, to reduce the trauma of surgical access for the patient. In patients with thoracic or abdominal pathologies, the surgical access should provide vision, access to the field of surgery, sufficient working space for safe dissection, and—in cases of resection—the ability to remove the specimen through the access route. Given the skills of several generations of surgeons in open surgery, it became clear that the reduction of surgical access trauma could only be achieved by consistent improvement of surgical instruments, paired with profound knowledge of anatomy and standardized procedures. Another fundamental prerequisite would be a transformed mindset towards surgery as such, and the ability "to think outside the box." We are faced with the challenge of finding new solutions to old problems.

Since ancient times, medical practitioners wished to inspect the insides of the human body in order to understand its complexity and treat diseases effectively. Easily accessible

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body cavities, such as the mouth, rectum, or vagina were inspected in ancient times with the aid of speculums. The origin of endoscopy can be traced back to a reference in the Babylonian Talmud. The treatise describes a lead funnel with a curved mouth, furnished with a wooden outlet (Mechul). The origin of minimally invasive surgery is largely associated with Philipp Bozini, who died in 1809 at the young age of 36 years. His innovative approach resulted in the gift of light conductors to the medical community, which permitted the investigator to view the body through an endoscope. The journey that followed was a challenging one. Georg Kelling performed the first endoscopic procedure. He viewed the stomach of a dog using Nitze's cystoscope and an air insufflation apparatus at the Natural Scientists' Meeting in Hamburg, Germany, in 1901. The history of laparoscopy and its introduction in surgical practice is a story of many researchers and pioneers who, for many years, battled against prevailing opinion and confronted rejection of their brainchild: their vision of performing "gentle operations". Many of these pioneers were ignored, shunned as dreamers, or even considered insane [2].

An interesting characteristic of minimally invasive surgery is that its evolution was never linear. It was by no means similar to oncologic surgery, which followed the familiar academic path of introducing new treatments through formal evaluation in a prospective study environment. Almost every breakthrough or innovation in minimally invasive surgery was initiated by a few innovators, picked up enthusiastically by a select group, and then disseminated to others. Subsequently, the innovations were evaluated carefully in a formal setting and incorporated definitively into the medical armamentarium. This problematic evolution *per se* was further aggravated by the medical technology industry, which developed new devices but promoted their dissemination in the interests of profit rather than patient benefit [3,4].

Over the past decades, this evolution was accompanied by profound changes in oncologic principles during the last few decades. It led to a refinement of surgical techniques as well as the extent of resection. Through a meticulous scientific approach and suitably designed trials, the medical community worked diligently to establish reasonable standards. Simultaneously, ongoing specialization in the field of surgery has demonstrably improved the quality of patient care. In addition to organ-oriented specialists, we now even have disease-oriented specialists. Both of these have clearly replaced the traditional distinction between a medical doctor and a surgeon, as we knew them fifty years ago. However, innovative surgeons who tried to introduce new ideas were bitterly opposed by an academic community focused on creating their own standards based on proven and established principles of long duration. Until recently, the section of minimally invasive surgery at many surgical departments in Europe was an ill-defined mixture of whatever the hospital had to offer by way of appendectomy, hernia surgery, bariatric and reflux surgery, and selected procedures in colon surgery.

Fortunately, the situation changed very profoundly for the better over the last decade. All of the above mentioned subspecialities have—albeit reluctantly in some cases—adopted the existing minimally invasive techniques in their respective fields. These procedures have fully arrived in several major academic centers worldwide. It was a much desired and urgently needed step forward. The academic force of a well-connected international medical community is a prerequisite for the timely development, evaluation, and dissemination of new techniques. Based on the notion of reducing access trauma, the innovators had to (a) balance the new techniques against evolving oncologic standards, and (b) realize that no subsequent measure to reduce access trauma could be as impressive as the initial departure from open surgery in favor of the minimally invasive approach.

Consequently, not all techniques stood the test of time and not all promises could be fulfilled. Single-port surgery created a stir in the medical community more than a decade ago [5], but has long descended into the assortment of several existing but meagerly utilized techniques. The purpose of NOTES (natural orifice transluminal endoscopic surgery) [6] is to perform surgery without leaving any visible scars, but the procedure has almost disappeared after more than ten years of eager innovation. However—and this seems

to be another unique aspect of the evolution of minimally invasive surgery—virtually every technique, invention, and new approach left its footprint in the evolution of surgery even after the initial concept had been abandoned [7]. Both, single-port surgery and NOTES paved the way for a novel type of pelvic floor surgery [8–10]. Transanal access routes were also subject to the rise and fall of new and thrilling techniques. The role of these access routes in specialized surgery for low rectal cancers is yet to be defined. Robotic surgery—designed as a means of remote access to medical care on a worldwide basis—has evolved through several generations of technical advancement. Robotic surgery has demonstrably revolutionized the precision of surgery, and also promises to achieve a hitherto unprecedented improvement in the outcome of treatment for patients [11]. Randomized controlled trials will be needed to prove this fact in the clinical setting.

Revolutionary perioperative treatment algorithms such as fast track and enhanced recovery after surgery (ERAS) have shown how much needs to be done around the operating room in order to optimize patient care. This gave rise to the rather puzzling situation of fewer complications and more favorable recovery in patients undergoing open surgery with optimized perioperative treatment compared to those who underwent minimally invasive surgery without an appropriate environment. Besides, it hindered the translation of reduced operative trauma into measurable patient outcome parameters such as the length of hospital stay or postoperative recovery in patients undergoing extensive cancer surgery, including esophageal resection. Again, it became clear that surgery is one instrument in the "concert" of patient care. No expert can play alone. This became even more evident after the advent of complex and highly successful medical cancer treatments with staged, perioperative, and truly multimodal treatment algorithms. The current task of oncologic surgery is no longer a "once in a lifetime" chance to "get rid" of the tumor. Rather, it is a module in modern cancer care that can be used repeatedly and also must be integrated into the mosaic of ongoing multidisciplinary treatment. This—together with the optimization of perioperative care—will be the true challenge of minimally invasive surgery in the coming decade [12].

Therefore, this issue of the Journal is not only focused on the winners of widespread medical attention such as robotic surgery, but also provides a platform for some of the lesser known advances, techniques, and sophisticated surgical solutions in gynecologic and visceral surgery [13,14]. Furthermore, we have tried to shed light on questions concerning the implementation and appropriate teaching of new techniques [15], in addition to flanking solutions aimed at improving perioperative patient care.

The common goal of this collection of medical studies is to present the various elements of a rather difficult symbiosis of technical progress, industrial participation in healthcare, medical knowledge, and global data exchange.

With this approach, the authors express the hope that every medical obstacle between China and Germany will be overcome, and will prove surmountable in current times as well as in the future.

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Article

Embryological Development and Topographic Anatomy of Pelvic Compartments—Surgical Relevance for Pelvic Lymphonodectomy

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Abstract: Background: The oncological outcome of surgery for the treatment of pelvic malignancies can be improved by performing pelvic lymphonodectomy. However, the extent and regions of lymph node harvest are debated and require profound knowledge of anatomy in order to avoid collateral damage. Methods: The embryological development and topographic anatomy of pelvic compartments in relation to pelvic lymphonodectomy for rectal, uterine, and prostate cancer are reviewed. Based on pre-dissected anatomical specimens, lymph node regions and drainage routes of the posterior and urogenital pelvic compartments are described in both genders. Anatomical landmarks are highlighted to identify structures at risk of injury during pelvic lymphonodectomy. Results: The ontogenesis of urogenital and anorectal compartments and their lymphatic supply are key factors for adequate lymphonodectomy, and have led to compartment-based surgical resection strategies. However, pelvic lymphonodectomy bears the risk of injury to somatic and autonomic nerves, vessels, and organs, depending on the regions and extent of surgery. Conclusion: Embryologically defined, compartment-based resection of pelvic malignancies and their lymphatic drainage routes are based on clearly delineated anatomical landmarks, which permit template-oriented pelvic lymphonodectomy. Comprehensive knowledge of pelvic anatomy, the exchange of surgical concepts between specialties, and minimally invasive techniques will optimize pelvic lymphonodectomy and reduce complications.

Keywords: pelvic compartments; embryologic development; oncologic surgery; pelvic lymphonodectomy; topographic anatomy; autonomic pelvic nerves; rectal cancer; uterine cancer; prostate cancer

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1. Introduction

1.1. Lymphonodectomy

Surgery for the treatment of malignant disease is not limited to the affected organ alone. According to clinical guidelines across surgical specialties, surgery performed with a curative intention consistently involves the removal of lymph nodes along lymphatic drainage routes. Different types of lymphonodectomy (e.g., systematic, therapeutic, sentinel, sampling, debulking) have been described [1]. These are viewed as an integral part of the surgical procedure and the overall therapeutic concept for the underlying malignant disease. In radical surgery, the purpose of removing locoregional lymph node metastases

is to improve the prognosis of disease. Moreover, lymphonodectomy allows exact post-operative staging of the underlying malignant disease and provides a basis for adjuvant therapy [2,3].

Lymphatic drainage of a given organ mainly occurs in centripetal direction and follows its blood supply which, in turn, is determined by the embryological development of the organ. Therefore, the extent and regions of lymphonodectomy must be based on the ontogenesis of the affected organ as well as the corresponding anatomical compartment. This concept is especially true of intrapelvic malignancies because pelvic organs have different embryological origins and are arranged in predefined compartments. Figure 1 provides a summary of major pelvic lymph node regions in the female and male pelvis.

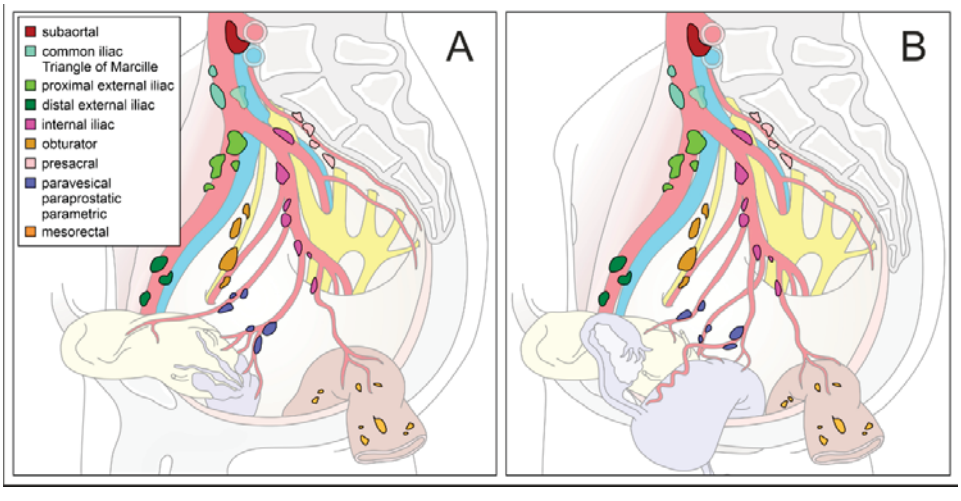

Figure 1. Schematic diagram of pelvic lymph node compartments. Mediolateral view of a right-sided male (**A**) and female (**B**) hemipelvis with pelvic organs and supplying arteries. Regional lymph nodes are colored differently (inserted legend in (**A**). Modified according to the Committee on Classification of Regional Lymph Nodes of the Japan Society of Clinical Oncology [4].

1.2. Pelvic Compartments

The pelvic cavity is subdivided into two (male) or three (female) compartments. While the posterior compartment corresponds to the anorectum, the anterior compartment comprises the bladder and the prostate/seminal vesicles in males. In females, the additional middle compartment consists of the uterovaginal complex and the adnexa. Based on ontogenetic development, each of these compartments is marked by organ-specific lymphatic drainage routes, which have led to specific surgical approaches for lymphonodectomy.

Despite the diverse concepts and extent of pelvic lymphonodectomy propagated in colorectal, gynecologic, and urologic cancer surgery, similar technical challenges are faced in all of these surgical specialties. On the one hand, the removal of lymph nodes should be as radical as necessary. On the other hand, functional and structural damage should be as minimal as possible. A prerequisite for the achievement of these aims is profound knowledge of both, the ontogenetic and topographic anatomy of pelvic organs. These aspects will be addressed in the present work by briefly recapitulating embryologic origins, describing the anatomical features of each pelvic compartment, and surgical concepts derived from these. Anatomical landmarks that must be preserved during pelvic lymphonodectomy are given special attention. Although the anatomical features apply to all types of surgery (open, laparoscopic, robot-assisted approaches), they are particularly important for minimally invasive techniques because the surgeon's topographic orientation must be aligned to the limited and optically magnified surgical fields.

2. Methods

2.1. Selection of Pelvic Malignancies

The most common malignancies in each pelvic compartment were selected to illustrate radical surgical approaches and the respective concepts of lymphonodectomy. Rectal cancer was chosen for the posterior compartment, cervical/uterine cancer for the middle compartment, and prostate cancer for the anterior compartment. Although the surgical regimen for these cancers is organ specific, pelvic lymphonodectomy is performed within anatomical regions of overlapping interdisciplinary interest. A comprehensive description of pelvic topographic anatomy appears to be mandatory for all involved surgical specialties (colorectal, gynecological, urological surgery).

2.2. Dissection of Anatomical Specimens

Body donors were recruited from the body donation program at the Institute of Anatomy, Christian-Albrechts University of Kiel, after previous written consent had been obtained for educational and research purposes. After formalin (3%) perfusion fixation via femoral arteries and subsequent fixation in ethanol (70%), pelvic specimens were removed and sectioned either transversely or sagittally for macroscopic dissection. Pelvic lymph node regions, pelvic organs with their respective blood vessels, and anatomical structures at risk during lymphonodectomy were exposed for each pelvic compartment. In selected cases, regional lymph nodes were first identified and then removed in a stepwise manner to simulate an extended pelvic lymphonodectomy and demonstrate the anatomical topography before and after lymph node dissection. Two female (67 and 70 years old) and three male (65, 75, and 81 years old) pelvic specimens with no evidence of pelvic disease or previous surgery were used for photographic illustration. Photographs were taken with a digital camera (Sony Alpha 7.III, 35 mm full frame with Sony FE 90 mm F2.8 Macro GOSS lens, Sony Corporation, Tokyo, Japan) and processed with compatible software (Sony Remote Version 1.4.00.01241, Sony Corporation, Tokyo, Japan; Adobe Photoshop CS6 2012, San Jose, California, USA. Structures of interest were highlighted with different semitransparent colors using the CorelDRAW software (Version 2019, Ottawa, ON, Canada).

3. Posterior Pelvic Compartment

3.1. Embryology

The primitive gut is an endoderm-derived organ system subdivided into the foregut, midgut and hindgut, supplied by the celiac trunk, the superior and the inferior mesenteric arteries, respectively. Derivatives of the hindgut comprise the left colic flexure, the descending and sigmoid colon, the rectum, and the upper anal canal. During early embryologic development, the anorectal tube is still connected to the urogenital system via the endodermal cloaca, resembling a common pouch closed in the caudal aspect by the cloacal membrane. An emerging urorectal septum subdivides the cloacal cavity into a ventrally located urogenital sinus and a dorsally located anorectal canal. Once the cloacal membrane vanishes, the anal canal is temporarily closed by the anal membrane. At embryonic week 9, the anal canal reopens at the level of the dentate line, connecting the upper endoderm-derived anal canal with the lower ectoderm-derived one [5]. Given the endodermal origin of the rectum, this last segment of the hindgut is mainly supplied by the superior rectal artery, which is a branch of the inferior mesenteric artery. Thus, blood supply as well as lymphatic routes of the rectum are located in perirectal tissue, also referred to as the mesorectum.

3.2. Surgery

Translation of these embryological considerations into surgical concepts for rectal cancer was achieved by the introduction of total mesorectal excision (TME) [6], which was implemented and promoted by Richard Heald [7]. The concept of TME takes the embryological origin of the rectum into account by completely removing the mesorectal

tissue as an intact package harboring the lymphatic drainage of this organ. Dissection is performed along an embryologically defined avascular plane ("holy plane") between the mesorectal and parietal pelvic fascia, thus allowing complete harvest of mesorectal lymph nodes as well as preservation of pelvic autonomic nerves. TME can be performed either transabdominally by laparotomy, laparoscopy, robot-assisted surgery [8–10], or by transanal approach [11].

While TME addresses the main lymphatic route of the rectum, the distal anorectal segment is additionally drained by the internal iliac route via the middle rectal and pudendal vessels. The frequency of the middle rectal artery is reported to range from 12% to 97%. Therefore, its relevance for lymphatic drainage is not fully understood [12]. Progression of advanced rectal cancer along the lateral rectal pedicles may lead to so-called lateral spread of the disease, affecting lymph nodes of the pelvic sidewall. However, the need for extended lateral pelvic lymphonodectomy in addition to TME for curative treatment of primary rectal cancer is still under debate. Currently it is agreed that pre-existing enlarged lymph nodes must be addressed, either by radiotherapy or surgery [13]. Recent data indicate that acceptable rates of disease-free and overall survival can be achieved by neoadjuvant chemoradiotherapy with selective lateral pelvic lymph node dissection [14].

3.3. Anatomy

The mesenteries are responsible for blood supply and lymphatic drainage of the entire gastrointestinal tract. The mesorectum corresponds to the most caudal part and is composed of perirectal adipose tissue, harboring branches of the superior rectal artery and the mesorectal lymph nodes (see Figure 2A). Mesorectal tissue is most developed at its dorsolateral aspect (so-called mesorectal cheeks), becomes thinner along the ventral rectal wall, and is circumferentially enveloped by the visceral pelvic fascia (mesorectal fascia). While the mesorectal fascia is contiguous in its dorsal and ventral aspect, it is pierced bilaterally by rectal nerves originating from the inferior hypogastric plexus and small branches of middle rectal arteries (if present). These connections between the mesorectum and the pelvic sidewall correspond to the paraproctium, frequently referred to as the lateral rectal ligaments, rectal pedicles, or T-junctions. Subsequently, complete surgical mobilization of the mesorectum requires sharp dissection laterally, while posterior and anterior mesorectal dissection can be achieved by using "self-opening" surgical planes. The correct surgical plane for TME corresponds to an avascular interface between the mesorectum and the parietal pelvic fascia, characterized by loose areolar connective tissue (also known as angel's hair) (see Figure 2B). Dissection in this embryologically determined retrorectal space [15], resembling the "innermost dissectable perirectal layer" (personal communication from Richard Heald), provides the basis for complete removal of an intact lymphovascular mesorectal package.

The parietal pelvic fascia covers the inner surface of the pelvic wall. Due to its bilaminar structure, the fascia envelopes the pelvic autonomic nerve plexus and the ureters (see Figure 2C). Dorsally, the parietal pelvic fascia is adjacent to the presacral fascia, which covers the medial and lateral sacral arteries and the presacral venous plexus running along the sacral concavity. The presacral space is located between the parietal pelvic fascia and the presacral fascia. This interface has similar morphological features as the retrorectal space (self-opening plane with loosely arranged connective tissue), and may therefore be easily mistaken for the proper dissection plane for TME. However, following this plane would result in the excision of pelvic autonomic nerves coursing within the parietal pelvic fascia and lead to autonomic denervation of pelvic organs. Approximately at the fourth sacral vertebra, all fascial layers fuse in the midline and are densely connected to the posterior rectal wall via the rectosacral ligament [16] (see Figure 2B).

Preservation of the autonomic pelvic nerves which govern anorectal and urogenital functions is best achieved by respecting the parietal pelvic fascia. In fact, the superior hypogastric plexus, the hypogastric nerves, and the inferior hypogastric plexus are all ensheathed in this bilaminar pelvic fascia (see Figure 2D). The elaborate network of the

inferior hypogastric plexus is fed by sympathetic input from the hypogastric nerves, and by parasympathetic input from pelvic splanchnic nerves originating from the second, third, and fourth ventral sacral nerves (see Figure 3B). At the level of the rectal pedicles, rectal branches diverge from the main nerve plexus and enter the mesorectum. The inferior hypogastric plexus continues ventrally to supply the seminal vesicles, distal ureters, bladder, and vasa deferentia. More caudally, nerve fibers extend towards the prostatic apex and supply the internal urinary sphincter and the cavernous bodies (the neurovascular bundle of Walsh). Nerve fibers also approach the anterolateral aspect of the anorectal junction and supply the internal anal sphincter [17]. The ventral margin of the posterior compartment is delineated by the rectoprostatic septum in males and the rectovaginal septum in females (see Figure 3A). Anterolaterally, the neurovascular bundles are closely related to the rectogenital septum. However, as most autonomic nerves responsible for the mediation of urogenital functions extend in front of the rectogenital septum, dissection behind this septum is the preferred approach for nerve-preserving anterior mobilization of the rectum.

In advanced low rectal carcinoma, lateral lymphatic spread towards the pelvic sidewall via the lateral rectal pedicles along the middle rectal arteries must be taken into account. In these cases, lymphonodectomy will address those regions of the lateral pelvic wall that harbor suspicious lymph nodes. These regions include lymphatic tissue surrounding the common and internal iliac vessels and the obturator fossa. During lymphonodectomy, the parietal pelvic fascia ensheathing the inferior hypogastric plexus should be respected as the medial border of the dissection plane, unless the tumor has spread into these structures. While the obturator nerve must be preserved, the obturator vessels may be removed [13].

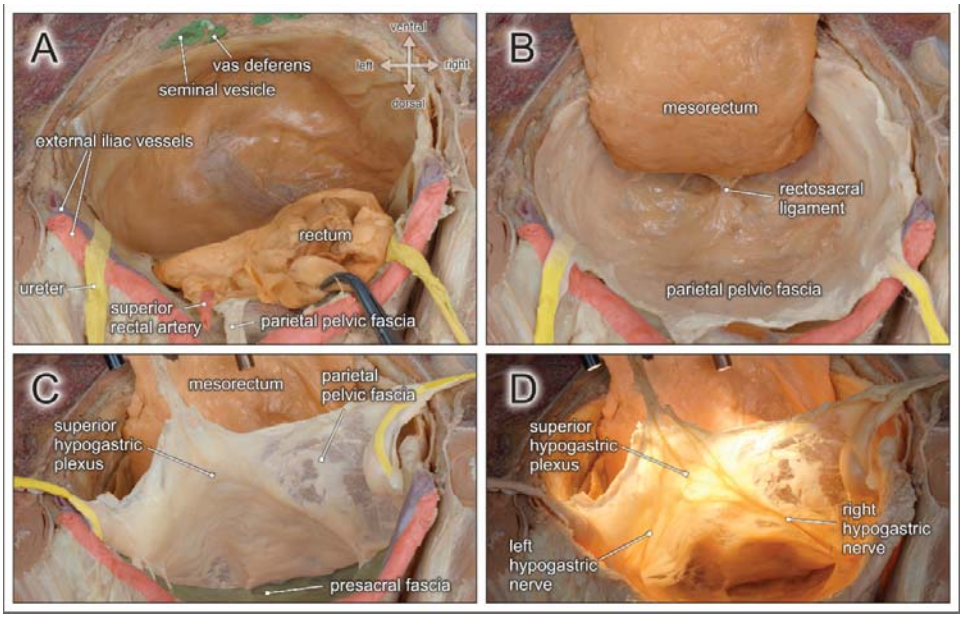

Figure 2. Topographic anatomy of the posterior pelvic compartment. Dorsocranial view of a male pelvis. (**A**) The rectum and the mesorectum with the superior rectal artery are transected at the rectosigmoid junction (clamp). (**B**) Dorsolateral mobilization of the mesorectum in a TME-like manner between the parietal pelvic fascia and the mesorectal fascia along the retrorectal space. Both fasciae are fused by the rectosacral ligament. (**C**) The parietal pelvic fascia and both ureters are lifted to expose the presacral space behind the presacral fascia. (**D**) Diaphanoscopy of the parietal pelvic fascia reveals the embedded superior hypogastric plexus and both hypogastric nerves.

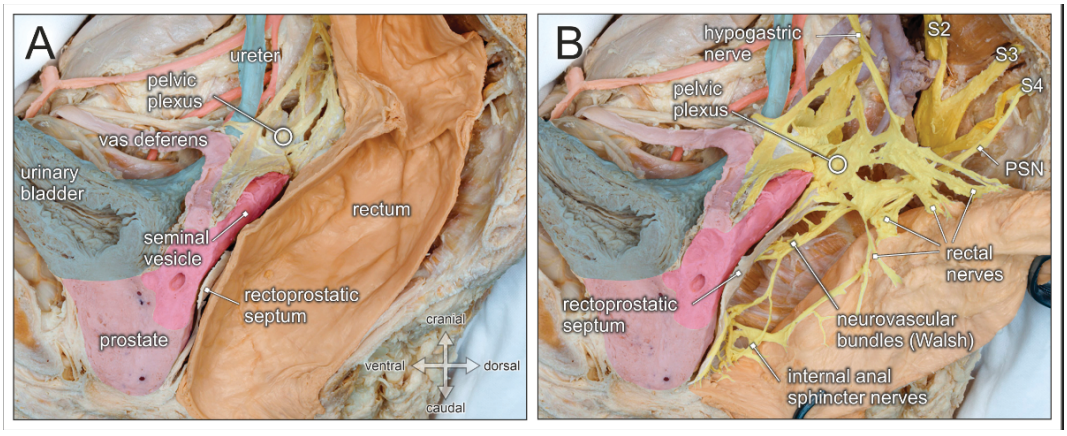

Figure 3. Topographic anatomy of the posterior pelvic compartment. Medial view of a right-sided male hemipelvis. The parietal pelvic fascia is removed to visualize the embedded autonomic pelvic nerves. (**A**) The posterior pelvic compartment is delimited from the urogenital compartment by the rectoprostatic septum (Denonvilliers fascia). (**B**) The rectum is pulled aside to reveal the inferior hypogastric/pelvic plexus, the hypogastric nerve, and the pelvic splanchnic nerves (PSN, from sacral nerve S4). The inferior hypogastric nerve gives rise to rectal nerves and more caudally to internal anal sphincter nerves, as well as the neurovascular bundle of Walsh.

4. Middle (Female) Pelvic Compartment

4.1. Embryology

The female reproductive tract is derived from three different primordial tissue complexes: cranially from the Müllerian tubercle complex, in the middle from the deep urogenital sinus and the vaginal plate complex, and caudally from the superficial urogenital sinus genital folds and the tubercle complex [18]. The Müllerian tubercle complex is the origin of the uterine tubes, the uterus, and the upper part of the vagina. During early embryologic development, the Müllerian ducts develop bilaterally along the urogenital crests from the mesoderm, as elongated indentations of the coelomic epithelium. The Müllerian ducts run parallel to the urinary tract, opening distally into the upper urogenital sinus. During male embryological development, the Müllerian ducts regress due to the anti-Müllerian hormone produced in Sertoli cells of the fetal testicles. As female fetuses lack Sertoli cells and are unable to produce anti-Müllerian hormone, the Müllerian ducts further differentiate under the influence of estrogens to give rise to the major components of internal female genital organs. In fact, the bilaterally located Müllerian ducts develop into the uterine tubes on both sides. Along the midline both Müllerian ducts fuse to give rise to the uterus. If the fusion of the Müllerian ducts is incomplete, a bicornuate uterus may develop. Moreover, the entire uterine cervix (supravaginal and vaginal portion) as well as the upper third of the vagina originate from the Müllerian ducts. Thus, the uterine tubes, uterus/cervix and upper vagina are all derivates of the paramesonephric ducts and resemble the so-called Müllerian compartment. The Müllerian compartment is mainly supplied by uterine and vaginal blood vessels originating from internal iliac vessels and drained by lymphatic vessels extending via the mesometrium towards the pelvic side wall.

4.2. Surgery

As the uterine cervix belongs to the Müllerian compartment, which is primarily connected to mesometrial lymph nodes and their corresponding drainage routes along the iliac vessels, total mesometrial resection (TMMR) has been proposed as the surgical approach for curative resection of cervical cancer [19]. As this concept adheres to, and fits best, the embryological considerations outlined above, it is the main focus of this anatomy-based report. Radical hysterectomy in accordance with the principles of TMMR

involves excision of the derivatives of the Müllerian ducts, including the vascular and ligamentous mesometrium, followed by therapeutic lymphonodectomy. TMMR can be performed by open, laparoscopic, or robot-assisted techniques [20,21]. However, long-term data on oncologic survival are available so far only for the open approach, while data confirming non-inferiority for minimally invasive approaches are still lacking.

Analogous to the concept of TME introduced for rectal cancer surgery, TMMR is based on an ontogenetic, compartment-based resection template corresponding to the Müllerian morphogenetic unit, which is permissive for malignant propagation and progression [22]. The results of a prospective observational single-center cohort study revealed good local tumor control and good survival outcomes in patients with cervical cancer treated with TMMR guided by stage-associated ontogenetic cancer fields and removal of associated lymph nodes without adjuvant radiotherapy [23]. On the one hand, TMMR is aimed at radical removal of the complete Müllerian compartment. On the other hand, extra-compartmental organs of different embryonic origins (e.g., ureters, urinary bladder, rectum, autonomic pelvic nerves) can be fully preserved despite their close vicinity to the tumor because compartment margins remain intact and undisrupted.

Therapeutic lymphonodectomy during TMMR includes removal of mesometrial, paravisceral, external iliac, common iliac, and presacral lymph nodes, defined as first-line lymph nodes, depending on the pattern of lymphatic spread [24]. In case of diseased first-line lymph nodes, those further downstream are resected additionally. The latter are referred to as second- and third-line lymph nodes. Depending on the stage of cervical cancer and the pattern of regional metastases, the regions include inframesenteric, infra- and suprarenal, periaortic, and pericaval lymph nodes [23]. The relevance of these surgical fields holds true for cervical as well as endometrial cancer.

4.3. Anatomy

Given the several intrapelvic regions to be addressed during lymphonodectomy when performing radical hysterectomy for cervical cancer, detailed knowledge of the corresponding topographic anatomy is mandatory. Figure 4 illustrates stepwise removal of the relevant lymph node compartments and highlights the anatomical structures at potential risk of injury.

External iliac lymph nodes in the distal aspect are located next to the deep inguinal ring, in close proximity to the branches of the genitofemoral nerve, and are crossed by the deep circumflex iliac vessels (see Figures 4A and 5). Neural structures, and especially the deep circumflex iliac vein, are endangered during removal of these lymph nodes. External iliac lymph nodes in the proximal aspect are located along, or intercalated between, the external iliac artery and vein. These lymph nodes are flanked laterally by the genitofemoral nerve which passes upon the psoas muscle. At the level of the iliac bifurcation, the ureter crosses the external iliac vessels and can be easily injured because of its superficial course. Common iliac lymph nodes extend on both sides of the common iliac vessels to the aortic bifurcation. Endangered nerves during lymph node removal include the obturator nerve running laterally along the border of the psoas muscle and the lumbosacral trunk (L4–L5), in the medial aspect, adjacent to the presacral region.

Lymph nodes within the obturator fossa extend mediocaudally to the external iliac vein, covering the internal obturator muscle and the tendinous arch of the levator ani muscle (see Figures 4B and 5). The main structures at risk are the obturator nerve and, more caudally, the obturator vessels passing towards the inner opening of the obturator canal below the superior pubic ramus. Lymphatic tissue can be found in the superior and inferior aspect of the obturator nerve. Therefore, complete removal requires clear identification and preservation of this nerve. Particular attention must be given to anastomotic branches between the obturator vessels and the external iliac/inferior epigastric vessels, also known as corona mortis. The frequencies of arterial and venous corona mortis are reported to be 8–65% and 17–60%, respectively, depending on the pattern of branching and anastomosis [25].

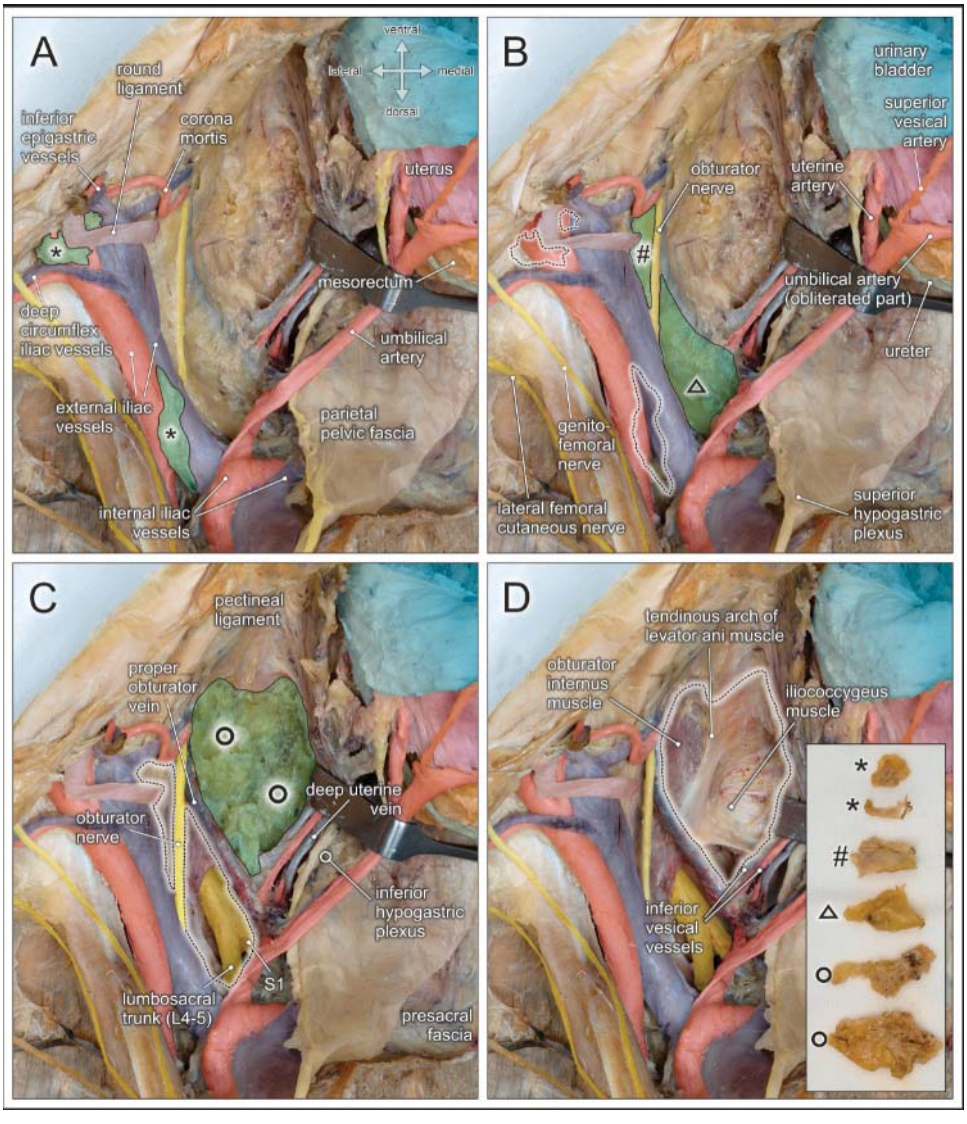

Figure 4. Topographic anatomy and stepwise pelvic lymphonodectomy. Dorsocranial view of a left female pelvis. Pelvic organs (urinary bladder, uterus, rectum, ureter) and their blood vessels are shifted to the right side (hook), and the round uterine ligament is transected. Regional lymph nodes are highlighted in green and dotted black lines after removal. (**A**) Distal and proximal external iliac lymph nodes (asterisks) are located in the vicinity of the deep circumflex iliac vessels, the corona mortis, and the genitofemoral nerve. (**B**) Lymph nodes of the obturator fossa (hashtag) are closely related to the obturator nerve and vessels, and the corona mortis. Presacral lymph nodes (triangle) extend along the sacral concavity and cover the sacral spinal nerves and the lumbosacral trunk (depicted in C after removal). (**C**) Paravisceral/paravesical lymph nodes (circles) are located between the pelvic sidewall and the urinary bladder, extending along the surface of the levator ani muscle. (**D**) Complete removal of pelvic lymph node regions with exposure of relevant anatomical structures at risk of potential injury during pelvic lymphonodectomy. Insert shows the lymphatic tissue harvested from the regions indicated in (**A**–**C**).

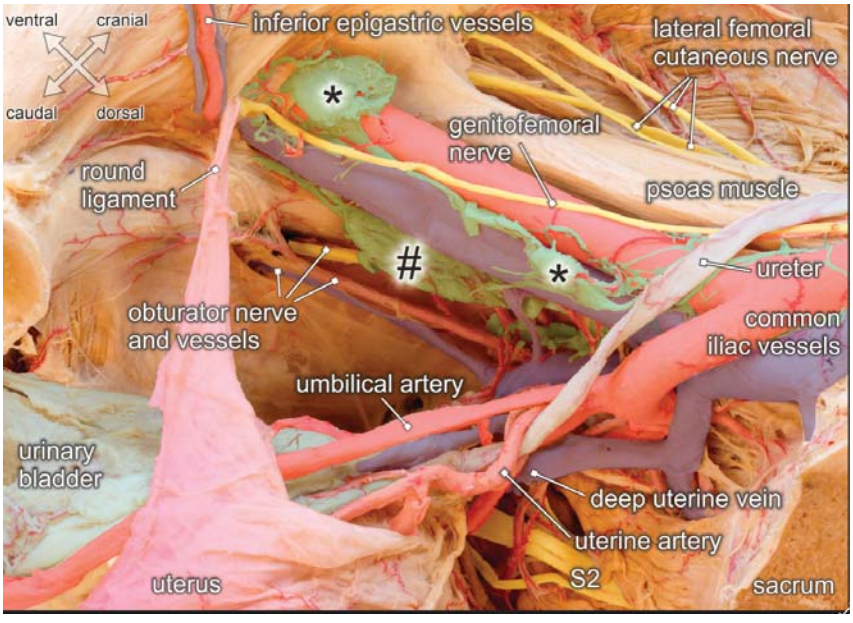

Figure 5. Topographic anatomy of the pelvic sidewall. Medial view of a right female hemipelvis. The bladder and uterus are shifted to the left side; fascia and parametric tissue are removed. Distal and proximal external iliac lymph nodes (asterisks), obturatory lymph nodes (hashtag) and interconnecting lymphatic vessels are exposed. Structures at risk during lymphonodectomy are the genitofemoral nerve running across the external iliac vessels, the obturator nerve and vessels extending throughout the obturator fossa, and the ureter crossing the proximal external iliac vessels. While both, the umbilical and uterine artery are undercrossed by the ureter, the deep uterine vein runs beneath the ureter.

The paravisceral lymph node compartment in women corresponds to the paravesical tissue extending between the pelvic sidewall and the urinary bladder (see Figure 4C). Complete removal of lymphatic tissue exposes the surface of the levator ani muscle and its tendinous arch originating from a condensation of the obturator fascia (See Figure 4D). Inferior vesical vessels branching from the internal iliac artery and reaching the bladder neck must be preserved.

Presacral lymph nodes extend along the sacral concavity, and are located in the vicinity of branches from the posterior division of the internal iliac vessels, such as the superior gluteal and lateral sacral vessels. During removal of these lymph nodes, ventral spinal nerves (mainly S1–S2) departing from the sacral foramina and the lumbosacral nerve trunk (L4–L5), and descending over the pelvic brim to join the first sacral nerve are endangered.

According to Cibula et al. [1], these pelvic lymph node regions are interconnected and drained by two major lymphatic trunks coursing along the pelvic sidewalls. While a superficial trunk passes ventrally to the external and common iliac vessels and continues to the precaval/preaortic regions, a deep trunk courses more medially, crosses the obturator fossa, and divides into two segments which flank the common iliac vessels on either side. After collecting lymph nodes from the presacral and internal iliac regions, the deep trunk enters the pre/paraaortic lymph node basin.

Despite its radical nature, lymphonodectomy should not compromise the autonomic pelvic nerves because the latter are essential for the preservation of anorectal and urogenital functions. In the TME procedure for the posterior pelvic compartment as well as in radical hysterectomy involving the middle pelvic compartment, care should be taken to ensure that the inferior hypogastric plexus embedded within the parietal pelvic fascia and the pelvic splanchnic nerves are preserved. Thus, nerve-sparing radical hysterectomy is aimed

at the transection of only those nerves that branch off from the inferior hypogastric plexus via the vascular mesometrial/paracervical tissue into the uterus, while nerves supplying the rectum, and especially the bladder, are preserved [26].

5. Ventral (Male) Pelvic Compartment

5.1. Embryology

Differentiation of the Müllerian ducts (paramesonephric ducts) is further promoted by the absence of the anti-Müllerian hormone in female embryos. In male embryonic development, the paramesonephric components degenerate and the Wolffian ducts (or mesonephric ducts) give rise to the male urogenital organs. The Wolffian ducts are connected to the urogenital sinus and form the epididymis, the vas deferens, seminal vesicles, and the trigone of the urinary bladder. The remaining bladder components, the prostate and the urethra develop from the urogenital sinus. Initially, both pelvic compartments—the posterior rectal and the anterior urogenital compartment—are connected by opening together into the primitive urogenital sinus (common cloaca). However, the two organ systems are subsequently separated by an ingrowing urorectal septum subdividing the urogenital sinus into a ventral portion connected to the Wolffian duct and a dorsal portion giving rise to the anorectal canal. Thus, at the end of embryologic development, the distal connection between the two pelvic compartments is completely detached and separated by the rectoprostatic septum (Denonvilliers fascia).

5.2. Surgery

Surgical treatment of both localized and locally advanced prostate cancer with curative intention consists of radical prostatectomy and lymphonodectomy. While the organ-related technical procedures of radical prostatectomy are well defined and standardized, the extent of pelvic lymphonodectomy is still a debated issue [27,28]. Standard lymphonodectomy is limited to the removal of lymph nodes in the obturator fossa and along the external iliac vessels, and has been recommended for locally limited prostate cancer in patients with a low risk profile. However, patients with locally advanced prostate cancer and/or a high risk profile may undergo extended pelvic lymphonodectomy combined with radical prostatectomy [29]. Extended template-based pelvic lymphonodectomy includes the removal of lymph nodes lining the internal and common iliac vessels, as well as presacral lymph nodes. A sufficient number of lymph nodes must be harvested for an optimal clinical outcome [27]. In cases of recurrent prostate cancer, some authors recommend a salvage extended pelvic lymph node dissection, which includes the additional removal of interiliac/subaortic and paraaortic lymph nodes [30]. Marcille's triangle or fossa has been given special attention in the creation of adequate anatomical templates for lymph node dissection. Lymph nodes located in this region are covered by the iliac vessels and therefore less obvious, but are considered relevant for achieving optimal lymph node clearance [31–33].

5.3. Anatomy

The functional outcome of radical prostatectomy must include the preservation of pelvic autonomic nerves because they govern urinary and fecal continence as well as sexual functions. Accordingly, nerve-sparing radical prostatectomy introduced by Patrick C. Walsh and based on anatomical dissection studies performed together with Pieter J. Donker (1981) has become the standardized surgical procedure for prostate cancer [34]. Similar to the TME procedure for rectal cancer in the posterior pelvic compartment and radical hysterectomy in the middle pelvic compartment, nerve-sparing techniques in the anterior pelvic compartment are aimed at removal of the affected organs while ensuring the integrity of the autonomic pelvic nerves. This is particularly true of the neurovascular bundles (also known as the bundle of Walsh) which originate from the caudal portion of the inferior hypogastric plexus, descend along the rectoprostatic septum, extend towards the prostatic apex and the urethral sphincter complex, and finally enter the penile cavernous bodies (see Figure 3).

In lymphonodectomy for prostate cancer, the crucial anatomical landmarks are quite similar to those described for lymphonodectomy in cervical cancer. In both procedures, the lymphatic drainage routes along the laterodorsal pelvic sidewall must be addressed. Thus, structures at risk include the deep circumflex iliac vein crossing the distal external iliac artery, the genitofemoral nerve running along the medial border of the psoas muscle, the obturator nerve and vessels within the obturator fossa, and the ureter crossing the iliac bifurcation(see Figure 6A). In extended lymphonodectomy, which additionally includes lymph nodes lining the common iliac vessels and the presacral region, attention should be given to the ureter at the pelvic brim and, more medially, to the superior hypogastric plexus and hypogastric nerves embedded within the parietal pelvic fascia (Figure 6).

A rather neglected lymph node region extends behind the proximal iliac vessels and corresponds to the triangle or fossa of Marcille, which is explored surgically by some surgeons during extended or salvage lymphonodectomy [31–33]. Marcille's triangle is limited by the anterolateral aspect of the fifth lumbar vertebra, the medial border of the psoas muscle, and the ala of the sacrum (see Figure 6B). The base of the triangle projects onto the transverse process of the fifth lumbar vertebra and the lumbosacral and iliolumbar ligaments, which extend across the ala of the sacrum to the sacroiliac joint [35]. Access to Marcille's triangle can only be achieved by full exposure, mobilization, and medial retraction of the external iliac vessels together with the ureter (Figure 6). The obturator nerve crosses this region laterocranially, followed by the lumbosacral trunk (L4–L5) more mediocaudally. Moreover, branches from the posterior division of the internal iliac vessels are exposed. These include iliolumbar vessels running in cranial direction, lateral sacral vessels extending towards the sacral concavity, and superior gluteal vessels descending into the suprapiriform foramen.

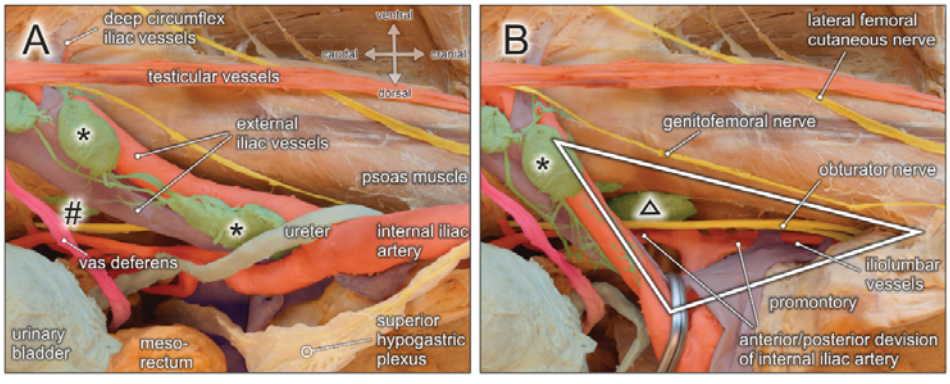

Figure 6. Topographic anatomy of the pelvic sidewall. Medial view of a right male hemipelvis. The urinary bladder and the mesorectum/rectum are shifted to the left side. (**A**) External iliac lymph nodes (asterisks), obturatory lymph nodes (hashtag), and interconnecting lymphatic vessels are exposed. Structures at risk during lymphonodectomy are the genitofemoral nerve running lateral along the external iliac artery, testicular vessels and the vas deferens, the obturator nerve and vessels extending throughout the obturator fossa, the ureter crossing the proximal external iliac vessels, and the hypogastric nerve. (**B**) External iliac vessels (clamp) and the ureter are shifted medially to the contralateral/left side to expose the triangle of Marcille (white triangle) limited by the fifth lumbar vertebra/promontory, the medial border of the psoas muscle, and the lateral aspect of the sacral concavity. Structures at risk during removal of lymph nodes (black triangle) within the triangle of Marcille are the proximal segment of the obturator nerve, the lumbosacral trunk (L4–L5), and the anterior and posterior division of the internal iliac vessels, in particular the iliolumbar vessels.

6. Lymph Nodes and Lymphatic Vessels

The commonly used terms *lymphonodectomy*, *lymphadenectomy* or *lymph node dissection* suggest that only lymph nodes are dissected and removed. However, surgical clearance of lymphatic drainage routes includes concomitant harvesting of lymphatic vessels/trunks

that connect the different lymph node regions. Lymphatic fluid enters into a lymph node via several afferent lymphatic vessels, passes through the cortex and medulla, and is drained into efferent lymphatic vessels at the lymph node hilum to reach the next collecting lymph node station. Thus, lymphatic drainage routes resemble a finely meshed network of lymphatic vessels with intercalated lymph nodes. These morphological features become particularly obvious when the surrounding fatty tissue is meticulously removed to expose the lymphatic vascular network (Figures 5–7).

Whereas lymph nodes possess a rather robust fibrous capsule, lymphatic vessels have thin walls and an inner endothelial lining only surrounded by a thin muscular and adventitial layer. Moreover, lymphatic tissue is embedded within fatty and connective tissue, has a pale appearance, and is therefore not easily discernible. Given these peculiarities, lymphatic vessels are easily prone to injury due to mechanical or thermal factors during surgical lymphonodectomy. Rupture of afferent as well as efferent lymphatic vessels is more likely to occur when lymph nodes are harvested by blunt dissection or gross plucking (Figure 7). Complications resulting from surgically induced injury of lymphatic vessels during pelvic lymphonodectomy include lymphatic fistula, lymphocele, chylopelvic fistula, chylous ascites, and subsequent wound infection [36,37]. These complications can be reduced by skilled and careful manipulation of lymphatic tissue, en bloc harvesting, and adequate sealing of lymphatic vessels.

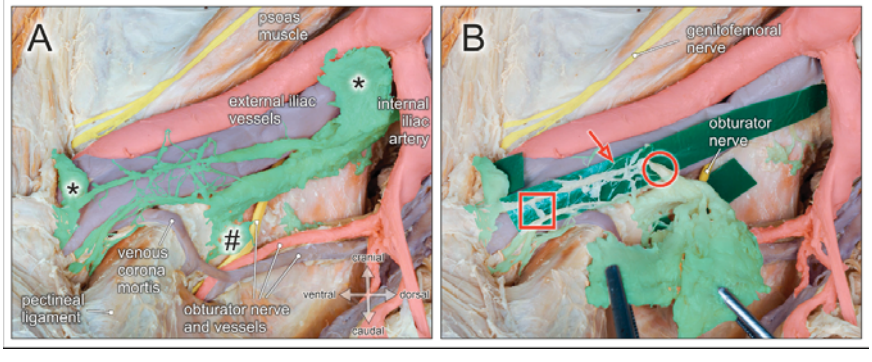

Figure 7. Lymph nodes and lymphatic vessels of the pelvic sidewall. Medial view of a right male hemipelvis. Pelvic organs, their blood vessels and autonomic nerves are shifted to the contralateral side; fatty tissue is removed. (**A**) External iliac lymph nodes (asterisks), obturator lymph nodes (hashtag), and interconnecting lymphatic vessels are highlighted (green). The obturator nerve is partly concealed by lymphatic tissue in the obturator fossa. Venous corona mortis is discernible. (**B**) The lymphatic tissue is partly pulled out of the obturator fossa en bloc (forceps). Green plastic strips are inserted to expose the morphological features of lymphatic vessels arranged in finely meshed networks extending between lymph nodes. Lymphatic vessels are of small (red arrow) and large (red circle) diameters, with rope ladder-like ramifications (red square), and susceptible to mechanical damage due to their thin walls.

7. Discussion

The removal of malignant tumors with large safety margins has been the traditional approach in surgical oncology. This has been replaced by embryologically defined compartment-based surgery for several cancer entities. According to this concept, malignant tumors and their lymphatic drainage routes are resected in the anatomical compartments derived from their embryological differentiation [38]. This approach is supported by insights into the early embryologic development of the lymphatic system consisting of lymphatic primordia which give rise to several lymphatic sacs/basins (e.g., bilateral iliac lymphatic plexus) [39]. These lymphatic regions and therein developing lymph nodes are specific for each region and allow selective surgical removal. Therefore, structures and/or organs, although anatomically located in close proximity to the tumor, may be left in situ without worsening the prognosis of disease, because they are derived from a

different embryological compartment, drained by different lymph node basins, and thus not primarily involved in the progression of malignancy. In fact, surgical procedures following this concept could not only improve oncological outcomes, but should also reduce operation-related morbidity by preserving functionally relevant structures outside the affected compartment [19].

As for pelvic malignancies, the above-mentioned concept was first applied to rectal carcinoma by introducing TME [7]. TME involves the removal of the rectal tumor with its main lymphovascular tissue enclosed by the mesorectum, while preserving pelvic autonomic nerves for the maintenance of urogenital functions. This surgical technique has considerably improved the prognosis of disease and been adopted worldwide as the standard surgical approach for rectal cancer [6]. In contrast, the benefit of additional "prophylactic or indicated" lateral lymph node dissection is still a debated issue [13]. This procedure is mainly performed in the eastern hemisphere, while neoadjuvant treatment regimens followed by TME are favored elsewhere. Recent studies show that a combination of these approaches could further improve the prognosis of disease, especially in patients with advanced disease [40]. In view of longer operating times and the risk of complications, lateral lymph node dissection could be omitted in patients with low-stage tumors [41]. If a lymphonodectomy is performed at the pelvic sidewall in patients with rectal cancer, colorectal surgery will face the same technical challenges and should adhere to the same anatomical landmarks as those encountered in pelvic lymphonodectomy for urogenital malignancies.

Analogous to the TME procedure in rectal cancer surgery, total mesometrial excision (TMMR) was introduced in surgery for cervical cancer by Michael Höckel [19,42]. TMMR is based on the fact that the uterine tubes, the uterus, and the cranial vagina develop from the Müllerian ducts. TMMR for cervical cancer includes the removal of paravisceral, external and common iliac, and presacral lymph nodes [43] and is based on the pioneering work of Günther Reiffenstuhl, who described the lymphatic system of the female genital organs and its surgical relevance for cervical/uterine cancer [44]. Given the prognostic importance of lymph node status [45], additional resection of the inframesenteric, infrarenal and suprarenal periaortic/pericaval lymph nodes may also be indicated, depending on the tumor stage [43]. In line with the improved prognosis of rectal cancer by the use of TME, this embryologically defined compartment-based surgical procedure has improved local tumor control and the overall oncologic prognosis in cervical cancer [19,22,23]. Although not widely accepted or generally performed, extended mesometrial resection based on the ontogenetic concept can also be used in locally advanced or relapsed cervical cancer [46,47].

A variety of pelvic lymphonodectomy procedures have been proposed for cervical cancer, depending on the extent of lymph node dissection [1]. Whereas type I dissection is limited to the superficial external and common iliac lymph nodes and obturator lymph nodes above the obturator nerve, type II and type III dissection involves the extension of lymphonodectomy to the deep external, internal, common iliac, caudal obturator lymph nodes and the presacral region, including exposure of the lumbosacral trunk.

In radical prostatectomy for prostate cancer, the standard approach of lymphonodectomy has traditionally been limited to the area of the obturator fossa and the external iliac vessels. Although still controversially discussed [48,49], many centers recommend extended lymphonodectomy in accordance with the embryologic origins and lymphatic drainage routes of the ventral pelvic compartment when performing primary curative resection [29]. This involves the removal of lymph nodes along the common and internal iliac vessels as well as in the presacral region and the triangle of Marcille [31]. Extensive pelvic lymphonodectomy has been shown to improve the prognosis of disease, especially in patients with intermediate- or high-risk prostate cancer [50]. Moreover, the additional removal of interiliac and paraaortic lymph nodes has been advised in patients with local recurrence [30].

Despite the proven prognostic relevance of lymphonodectomy for pelvic malignancies in all three pelvic compartments, the anatomical terminology and topographic delineation

of pelvic lymph node basins are not uniformly defined across surgical disciplines. For example, the terms *interiliac*, *subaortic*, *paravisceral*, *presacral* or *internal iliac* lymph node regions are interpreted differently by surgeons of various specialties, such as urology, gynecology, or surgery. These diversities may give rise to biased data concerning the description, extent, and potential benefits of lymphonodectomy in patients with pelvic malignancies. To overcome this drawback, pelvic lymph node regions should be defined as precisely as possible by clear delineation of their topographic boundaries. This will provide reliable anatomical landmarks for orientation during dissection. A standardized classification and terminology of lymph node regions will optimize interdisciplinary and international research related to lymphonodectomy procedures. The Committee on Classification of Regional Lymph Nodes of the Japan Society of Clinical Oncology has published guidelines which have addressed these requirements and should be used in future studies [4].

Current surgical approaches are rapidly shifting from open to laparoscopic and robot-assisted procedures. On the one hand, these minimally invasive approaches are technically more demanding because of the limited operating field, unfamiliar surgical access routes, and hampered anatomical orientation. On the other hand, minimally invasive techniques and especially robot-assisted interventions offer optimal degrees of freedom for surgical instruments, three-dimensional and magnified visualization, and tremor-free manipulation of anatomical structures. These advantages permit the surgeon to overcome the challenges of pelvic lymphonodectomy, which include precise removal of lymphatic tissue and meticulous preservation of adjoining susceptible anatomical structures [10,21,51,52]. The increasing acceptance of minimally invasive robot-assisted techniques for pelvic lymphonodectomy will further improve oncological outcomes as well as the functional integrity of pelvic organs. However, regardless of the surgical approach, profound knowledge of the anatomy of pelvic compartments will remain an essential prerequisite for successful radical surgery in patients with pelvic malignancies.

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Review

Challenges Posed by Embryonic and Anatomical Factors in Systematic Lymphadenectomy for Endometrial Cancer

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Abstract: Lymph node involvement has been shown to be one of the most relevant prognostic factors in a variety of malignancies; this is also true of endometrial cancer. The determination of the lymph node status is crucial in order to establish the tumor stage, and to consider adjuvant treatment. A wide range of surgical staging practices are currently used for the treatment of endometrial cancer. The necessity and extent of lymph node dissection is an ongoing controversial issue in gynecological oncology. Lymph node surgery in endometrial cancer is technically challenging, and can be time consuming because of the topographic complexity of lymphatic drainage as such, and the fact that the lymph nodes are directly adjacent to both blood vessels and nerves. Therefore, profound and exact knowledge of the anatomy is essential. Sentinel lymph node mapping was recently introduced in surgical staging with the aim of reducing morbidity, whilst also obtaining useful prognostic information from a patient's lymph node status. The present review summarizes the current evidence on the role of lymph node surgery in endometrial cancer, focusing on the embryological, anatomical, and technical aspects.

Keywords: endometrial cancer; lymphadenectomy; embryology; sentinel lymph node mapping; indocyanine green; PMMR; technical aspects

1. Introduction

Endometrial cancer is the most common gynecological cancer in developed countries; more than 380,000 new cases are reported each year worldwide [1]. In accordance with the growing age of the

population and the increasing prevalence of metabolic syndromes and obesity, data from the U.S. suggest a consistent increase in the prevalence of this disease [2]. As the symptoms usually occur quite early, the majority of patients (71%) present with early-stage malignancies [3]. The overall survival (OS) rates are high for stage I of the disease: more than 90% of patients are free of disease at five years after surgery [3,4]. The mainstay of treatment for this cancer is surgery [5–8]. Total hysterectomy with or without bilateral salpingo-oophorectomy and lymphadenectomy permits the removal of the cancer, as well as its classification on the basis of its histological subtype, grading, myometrial invasion, and lymph node status. Traditionally, surgery is performed via open laparotomy. Since the introduction of laparoscopy in the 1990s, a number of studies have shown that laparoscopic treatment is a safe and feasible option for the management of endometrial cancer. Laparoscopy is associated with a lower rate of postoperative complications than open laparotomy [9]. The largest randomized trial comparing laparoscopy with laparotomy was the LAP2study in 2009, which consisted of patients with clinical stage I-IIA uterine cancer who underwent hysterectomy, salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and pelvic cytology. The LAP2 study showed that laparoscopic surgical staging is safe and feasible in terms of short-term outcomes, and is associated with shorter hospital stays and fewer complications [10]. The long-term results of this trial were published in 2012 [11]. In the laparoscopy group, the authors observed a small increase in cancer recurrence. However, the overall survival was identical in both groups [11].

According to the ESMO–ESGO–ESTRO guidelines, minimally-invasive surgery is recommended for the surgical management of low- (stage I endometrioid, grade 1–2, <50% myometrial invasion, no lymphovascular space invasion) and intermediate-risk endometrial cancer (stage I endometrioid, grade 1–2, ≥50% myometrial invasion, no lymphovascular space invasion) [12].

Histologically, endometrioid adenocarcinomas are the most common type of endometrial cancer. Other subtypes, including adenosquamous, clear-cell, and serous carcinomas are associated with a poorer prognosis. They are typically more aggressive, and in a more advanced FIGO stage. Endometrial cancer grows into the surrounding tissue, most frequently the myometrium and the cervix. Lymphatic spread also occurs, mainly to the pelvic lymph nodes and then to the para–aortic nodes. The probability of lymph node metastasis across all of the FIGO stages is 15% [12].

Lymph node involvement has been shown to be one of the most relevant prognostic factors in a variety of malignancies. The determination of the lymph node status is crucial in order to establish the tumor stage, and to consider adjuvant treatment [13]. In two randomized trials published in 2008 and 2009, patients who received systematic pelvic lymphadenectomy were compared to those who did not undergo node dissection; the studies demonstrated no benefit in terms of recurrence-free survival (RFS) or overall survival (OS). Since this time, the necessity of lymph node dissection is an ongoing controversial issue in gynecological oncology [14–18]. The extent of para-aortic lymphadenectomy is also a debated issue. Sentinel lymph node mapping is gaining increasing importance in recent times.

The introduction of minimally-invasive surgery in routine gynecology and oncology has minimized the invasive nature of many operations in the female pelvis and retroperitoneum. As mentioned earlier, minimally-invasive surgery benefits patients in many ways. Robotically-assisted surgery is the most dynamic advancement of minimally-invasive surgery, and a significant step in terms of technical evolution. The better visualization of the field of surgery by means of 3D technology and the extension of surgical instruments to 7 degrees of freedom permit the use of minimally-invasive surgery even in complex situations such as obesity or severe adhesions.

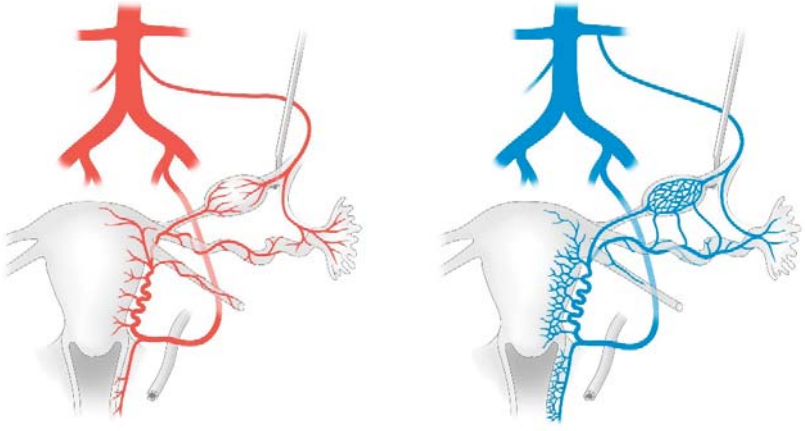
A wide range of surgical staging practices are currently used for the treatment of endometrial cancer. The spectrum of lymph node surgery includes sentinel lymph node mapping and systematic pelvic or pelvic and para-aortic lymph node dissection. Peritoneal mesometrial resection (PMMR, initiated by M. Höckel) involves therapeutic pelvic and para-aortic lymphadenectomy (tLNE).

The aim of the present review is to summarize the current evidence on the role of lymph node surgery in endometrial cancer, focusing on the anatomical, embryological, surgical, and technical aspects. The technical challenge of MIS (conventional laparoscopy and robotic surgery) is compared with conventional laparotomy.

2. Anatomy

2.1. Lymphatic Drainage and Blood Supply to the Uterus and Uterine Adnexa

Lymphatic drainage follows the blood supply of the respective organs. As the arterial supply to the uterus and uterine appendages is derived from two different sources, lymphatic drainage is provided by the pelvic as well as the para-aortic pathways. Due to the peculiar ontogenetic anatomy of the female genital tract, the lymphatic drainage is multidirectional and complex, and has a direct impact on the surgical strategy for endometrial cancer [19]. Lymph node dissection in this area can be time consuming because of the topographic complexity of lymphatic drainage as such, and the fact that the lymph nodes are directly adjacent to both blood vessels and nerves [19]. As such, profound and exact knowledge of the anatomy of the corresponding areas is essential. The following section is focused on anatomy (this is summarized in schematic form in Figures 1–3).



(**a**) (**b**)

Figure 1. Blood supply: the (**a**) arterial and (**b**) venous blood supply to the female genital organs. The figure schematically shows that the ureter crosses underneath the uterine artery 1–2 cm lateral to the cervix and lateral vaginal fornix. In the majority of cases, only one single uterine artery exists on each side. Additionally, multiple uterine veins of different sizes drain the uterine venous plexus. These veins frequently do not directly follow the course of the uterine artery, but often pass underneath the ureter [19].

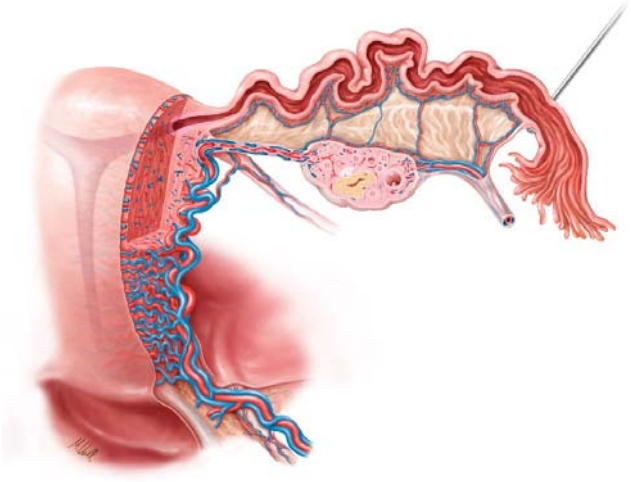


Figure 2. Schematic illustration of the blood flow in the inner female genital organs.

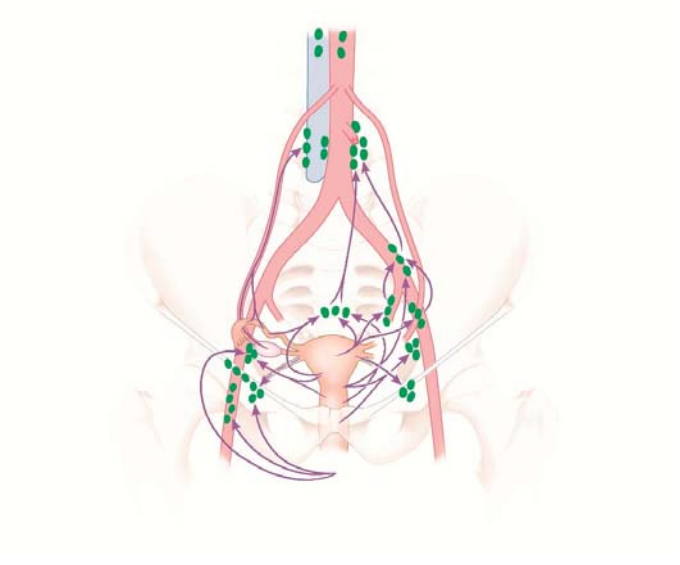


Figure 3. Lymphatic drainage and regional lymph nodes of the female genital organs. The individual lymph node groups are marked green; violet arrows indicate the lymphatic flow from the respective anatomical region.

2.2. Blood Supply

As shown in Figure 1a, the arterial blood to the ovaries is provided by the respective uterine and ovarian arteries. The ovarian artery arises from the aorta, below the renal artery, and courses in the suspensory ligament of the ovary in order to reach the ovarian hilum. Before entering the medulla, it divides into a tubal branch. In the mesosalpinx, this branch forms an anastomosis with the eponymous branch of the uterine artery. The uterine artery arises from the internal iliac artery and

courses in the connective tissue from the lateral pelvic wall to the lateral part of the cervix. It crosses the ureter before entering the bladder and then branches off in a T-shaped manner. In the caudal aspect, it forms a vaginal branch lying in the paracolpos, and in the cranial aspect, it forms the markedly convoluted helicine branch which goes on to the mesometrium. Concentric 'rings' of blood vessels, or so-called arcuate branches, arise from both branches and supply the uterus and vagina [19,20].

2.3. Venous Blood Flow

As shown in Figure 1b, the ovarian vein arises at the ovarian hilum from a markedly-tortuous venous plexus known as the ovarian venous plexus. This drains on the right side into the inferior vena cava. On the left side, the ovarian vein flows into the left renal vein. The venous blood flow from the uterus and the vagina starts at the pairwise uterovaginal plexus, which lies in the lateral aspect of the uterus and vagina in the parametrium and the paracolpos. This plexus drains into the internal iliac vein through the uterine vein [19,20]. Figure 2 illustrates the blood supply to the female genital organs.

2.4. Lymphatic Drainage

The lymphatic drainage in the lower part of the vagina and the external genital organs is achieved through the superficial inguinal lymph nodes flowing into the external iliac lymph nodes. The lymphatic drainage from the upper part of the vagina is achieved mainly through the internal iliac lymph nodes. From the uterine cervix, lymphatic pathways reach the lymph nodes in the region of the large pelvic vessels and their branches: the external and internal iliac lymph nodes, the obturator lymph nodes, and the sacral lymph nodes. The subsequent lymph node chain, namely the common iliac lymph nodes and the lumbar lymph nodes, is located around the common iliac artery and the abdominal aorta. Lymphatic pathways from the uterine fundus, the fallopian tubes, and the ovaries course in the suspensory ligament of the ovary (also known as the infundibulopelvic ligament) along the ovarian vessels to the lumbar lymph nodes. The lymphatic pathways from the tube and the uterine corpus extend from the round ligament of the uterus through the deep inguinal ring to the lymph nodes in the groin, namely the superficial inguinal lymph nodes, and further on to the external iliac lymph nodes [19,20]. Figure 3 shows the lymphatic drainage pathways and the regional lymph nodes of the female genital organs [20].

2.5. Embryologic Assessment of the Lymphatic Drainage in the Median Compartment

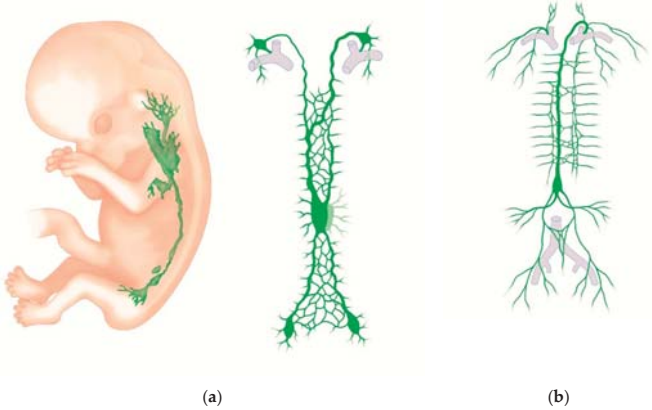
Embryonic Origins of Lymphatic Vessels

Malignancies of the uterus metastasize, as described earlier, by the lymphatic or hematogenic route, or by the direct invasion of neighboring structures. Since metastasis is mainly caused by lymphogenic tumor spread, and since the lymph drainage of the female genital tract (such as the uterus) is highly complex compared to other organs, the embryology of the lymphatic system will be considered in the following figure (Figure 4a,b). Embryologically, the female genital tract, the uterus, the fallopian tubes, and the upper part of the vagina arise from the paramesonephric ducts (Müllerian ducts). The distal fusion of the two ducts induces the development of the uterovaginal canal, the formation of the mesometrial tissue, and the broad ligaments. The fallopian tubes develop from the unfused cranial parts of the Müllerian ducts [19].

Historically, the investigation of the lymphatic vessels started in the 17th century. The anatomy of the large part of the lymphatic system had been described by the beginning of the 19th century. In 2010, Ribatti et al. presented an historical review of the embryonic origins of lymphatic vessels [21].

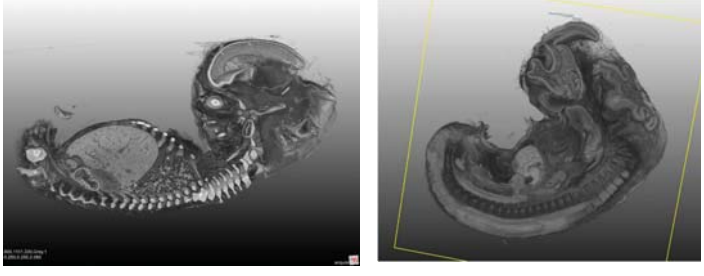
The lymphatic system develops in close association with the venous system from the fifth week of gestation (Figure 4a) [22]. Endothelial cells grow from the cardinal veins into the surrounding mesenchyme. This occurs mainly at the origin of the internal iliac vein and the jugular vein. The newly-formed lymphatic vessels develop into bag-like structures, also known as lymph sacs. The left and right jugular lymph sacs, and the left and right posterior lymph sacs (iliac sacs) develop

at this time. Between the sacs, a plexus of lymph vessels is formed along the dorsal thoracic wall. At the root of the mesentery, this plexus turns into an unpaired retroperitoneal sac. The chyle cistern is formed in front of the previously-mentioned retroperitoneal sac, in the region of the celiac trunk. The right lymphatic duct and the thoracic duct arise from the plexus of lymph vessels. The lymph system of the head, neck, and extremities develops from the posterior (iliac) lymphatic sacs and the jugular lymphatic sacs. Whether lymphatic vessels also arise directly from the mesenchyme due to vasculogenesis is a debated issue. Growth factor VEGF-C and the lymphoendothelial VEGF receptor 3 are essential for lymphangiogenesis. The lymph node colonization of mesenchymal bridges within the lymphatic sacs and larger lymphatic vessels gives rise to lymph nodes. Figure 4a,b provides a graphic overview of embryological development and the adult lymphatic system [22]. Figure 5a,b shows lateral views of a human embryo in various stages of development.



(**a**) (**b**)

Figure 4. (**a**) Embryological development of the lymphatic system. Extreme left: schematic lateral view of an embryo in the eighth week of gestation, with three primitive lymph sacs. Middle: the lymphatic vessel system from the ventral aspect in a nine-week-old fetus, showing the pairwise thoracic duct. (**b**) Schematic illustration of the adult lymphatic system. The final thoracic duct and the right-sided lymphatic duct are also seen from the ventral aspect.



(**a**) (**b**)

Figure 5. Lateral views of a human embryo obtained through computed tomography and magnetic resonance imaging. (a) Lateral view of an approximately-eight-week-old embryo. The human embro already has a visible human shape. However, the head is still disproportionately large, and accounts for nearly a half of the total length. The axial skeleton is formed. The protrusion of the abdomen is mainly caused by the large liver. The rudiments of the kidneys are seen in the caudal aspect. (**b**) A lateral view in an earlier stage of development. The embryo already has a characteristic C-shaped curvature.

2.6. Anatomy-Based Methodology of Surgical Lymphadenectomy

Lymphatic drainage is achieved in endometrial carcinoma, as shown in the anatomical overview: on the one hand, through the pelvic lymph nodes, and on the other hand, through lymphatic pathways which can drain directly into the para-aortic regions through the adnexa. For this reason, para-aortic lymph nodes may be positive even in the presence of unaffected pelvic lymph nodes [19,20,22].

The pelvic lymph node groups include those of the obturator fossa, the lymph nodes in the region of the internal iliac artery and vein, the lateral and medial lymph nodes in the region of the external iliac artery and vein, and in the region of the common iliac artery and vein. In addition to the previously-mentioned vessels, the area of surgery encompasses other structures which must be visualized and protected. These include the ureter, the obturator nerve, the genitofemoral nerve with its femoral and genital branches, the lumbosacral trunk, and the superior hypogastric plexus in the region of the presacral lymph nodes [20,22]. In the obturator fossa runs the neurovascular obturator pedicle, which consists of the obturator nerve and the obturator vein and artery, which join the nerve coming from below. According to the location related to the obturator pedicle, lymph nodes in this area may be subdivided into supraobturator and infraobturator nodes [19].

The para-aortic lymph node groups include the cranial portions of the common iliac artery, the region of the caudal vena cava, including the aorta and the inferior mesenteric artery, and further cranially, the interaortocaval tissue extending to the renal pedicle, which becomes visible through the renal vein [20,22]. During para-aortic lymphadenectomy, the sympathetic trunk must be preserved also.

The challenge of cancer surgery is twofold: to strive for a maximum radical operation on the one hand, in order to ensure curative therapy, and to strive for the least loss of function on the other hand, in order to preserve the quality of life after surgery [19]. In the following, we highlight a specific anatomical area because of its topographical complexity (Figure 6). In front of the left side of the fourth lumbar vertebra, the common iliac arteries originate at the aortic bifurcation. They pass along the medial borders of the psoas major muscle, and divide into the internal and external iliac arteries. The common, internal, and external veins are located medial or dorsomedial to their arterial equivalents. The ureter is crossed posteriorly by the genitofemoral nerves, and anteriorly by the ovarian vessels. In addition, on the left side, the ureter crosses under the root of the sigmoid mesocolon and the inferior mesenteric pedicle. In the majority of cases, the ureter enters the pelvic cavity on the right side anterior to the external iliac artery, and on the left side anterior to the common artery [19]. Numerous sympathetic and parasympathetic autonomic nerves also contribute to the complexity of this region. These autonomic nerves must be preserved because they mediate anorectal and urogenital functions [19].

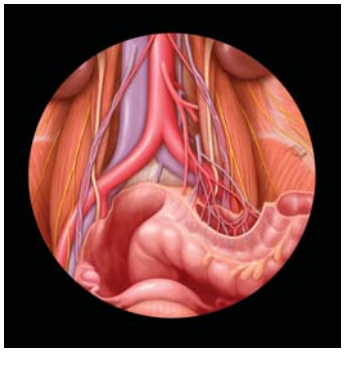


Figure 6. Schematic illustration of the anatomical area. This view is from the caudal–ventral aspect. The parietal peritoneum and the organs of the gastrointestinal tract to the sigmoid colon have been removed. The especially-complex anatomical area is on the left side, specifically the left common iliac artery and vein.

But why exactly this area? The lymph nodes that can be accessed with the least collateral damage are removed. Examples of these are the lymph nodes to the obturator nerve, but not further dorsally. Another example is the resection to the cross-over point of the renal vein, but not further cranially.

We only operate within accessible anatomical areas, and not in the corresponding compartments derived from anatomical or embryological studies.

2.7. Strategy of Lymphadenectomy

Lymphadenectomy has been referred to by various names in the published literature. As listed in Table 1, these include radical/complete or systematic lymphadenectomy, sentinel lymph node biopsy, therapeutic lymphadenectomy, lymph node debulking, and lymph node sampling.

Table 1. Terms associated with lymphadenectomy.

Radical/Complete or Systematic Lymphadenectomy	Excision of All Lymph Nodes with Surrounding Fatty Tissue along the Vascular Pathways Corresponding to Lymphatic Flow in the Targeted Anatomical Region
Sentinel lymph node biopsy	Excision of preoperatively marked sentinel lymph nodes as the primary filtering point of lymphatic flow to the organ and the tumor
Therapeutic lymphadenectomy	Radical lymphadenectomy within the limits of embryonic anatomical development (as established by Michael Höckel)
Lymph node debulking	Reduction of tumor burden by the excision of enlarged lymph nodes in an advanced stage of cancer
Lymph node sampling	Unsystematic excision of separate, clinically unusual lymph nodes

The individual aspects are addressed here in detail.

3. Surgical Staging in Endometrial Cancer

The surgical management of endometrial cancer has undergone significant changes in the last few decades, including a change from open to minimally-invasive surgery. When the findings of the GOG#33 trial were published in 1998, the International Federation of Gynecology and Obstetrics (FIGO) introduced a shift from clinical to surgical staging, including lymphadenectomy [23,24]. Since this time, the question as to whether all patients need a lymphadenectomy, and the extent of the lymph node dissection have been the most controversial issues in gynecological oncology. In two randomized controlled trials published in 2008 and 2009, patients who received systematic pelvic lymphadenectomy were compared to those who did not undergo node dissection, and revealed no survival benefit in either group [14,15]. Both trials included patients with early-stage endometrial cancer. The data were evaluated critically because para-aortic lymph node dissection was not performed, and a rather small number of lymph nodes were excised [16]. A variety of surgical staging strategies were then used in gynecological oncology, ranging from complete bilateral pelvic +/− aortic lymph node dissection, random node sampling, and selected node dissection based on intraoperative frozen-section findings, to no lymph node dissection at all [17,18]. Sentinel lymph node mapping has gained increasing importance in recent times as an alternative concept to complete lymph node dissection.

3.1. Systematic or Complete Pelvic and Para-Aortic Lymph Node Dissection

Preoperative imaging studies to identify positive lymph nodes with techniques including magnetic resonance imaging, positron emission tomography or computed tomography have been unsatisfactory because of their poor sensitivity [25]. Surgical staging remains the gold standard for the assessment of lymph node involvement, and is performed by systematic pelvic and para-aortic lymph node dissection [26,27].

The revised FIGO staging system in 2009 divided stage IIIC endometrial cancer into IIIC1 (positive pelvic nodes) and IIIC2 (positive para-aortic nodes with or without positive pelvic nodes), reflecting the fact that the prognosis is worse when para-aortic lymph nodes are involved [24].

We still lack a standardized definition of adequate complete lymphadenectomy [12]. The current approaches include pelvic lymphadenectomy, para-aortic lymphadenectomy to the inferior mesenteric artery, and para-aortic lymphadenectomy to the renal vein [12].

The outcome of an international survey about the surgical management and adjuvant treatment of endometrial carcinoma throughout the world was published in 2015 [17]. Six-hundred and eighteen institutions around the world participated in this study. The indication for lymphadenectomy, anatomic limits, and extension were the main surgical issues. Of those centers at which lymphadenectomy was performed, 66% of the respondents conducted a systematic excision of lymph nodes, and 4% performed the sampling of the nodes. Both pelvic and para-aortic dissection were used (73.17%). Pelvic nodes alone were dissected by 15% of the respondents. The upper limit of the para-aortic dissection differed between the institutions: 7.9% of the respondents performed para-aortic dissection at the level of the inferior mesenteric artery, and 75.5% performed para-aortic dissection at the level of the renal vessels. In total, 2.9% of the respondents stated that they routinely resected lymph nodes in the suprarenal area. In Central Europe, lymphadenectomy was performed to the renal vessels in 86.8%, in USA/UK in 51.2%, in Asia in 80.8%, and in Southern Europe in 45.1% ($p < 0.001$) of cases [17].

The probability of lymph node metastasis across all FIGO stages is 15%.

A longer period of overall survival and fewer deaths were noted in patients with endometrial cancer who received pelvic lymphadenectomy combined with para-aortic lymph node dissection compared to those who received pelvic lymphadenectomy alone [28,29].

Three percent of the patients had isolated positive para-aortic lymph nodes and no positive pelvic lymph nodes. Of the 3%, 67–100% had lymph node metastases in a high para-aortic location, i.e., between the renal vein and the inferior mesenteric artery [30].

In a study performed by Mariani et al., 281 patients with endometrial cancer received lymphadenectomy. Twenty-two percent of patients with high-risk endometrial cancer had positive lymph nodes. Of the 22%, 51% had positive pelvic and para-aortic nodes, 33% only had positive pelvic lymph nodes, and 16% had isolated para-aortic nodes. Seventy-seven percent of patients with para-aortic nodes had metastases above the inferior mesenteric artery. These findings indicate that para-aortic lymphadenectomy up to the renal vein is advisable [31].

In terms of surgical boundaries for pelvic lymph node dissection, the published literature recommends the removal of lymphatic tissue from the deep circumflex iliac vein to the midpoint of the common iliac artery [30]. Complete para-aortic lymphadenectomy includes the removal of all nodal tissues and fat surrounding the aorta, inferior vena cava, and renal vessels, from the midpoint of the common iliac vessels caudally to the left renal vein cranially [32]. The left renal vein runs between the aorta and the origin of the superior mesenteric artery. The superior mesenteric artery needs to be preserved, because this artery provides the blood flow to the proximal of the transverse colon, the ascending colon, the cecum, the jejunum, the ileum, and the third portion of the duodenum [19].

In a multitude of solid malignancies, the lymph node count has become a marker of the adequacy of lymph node dissection. The results of two retrospective studies showed that patients with endometrial cancer had improved survival when 10–12 lymph nodes were removed [33,34]. The sampling of lymph nodes has a low sensitivity in endometrial cancer [12].

Systematic pelvic and para-aortic lymph node dissection enables the clinician to provide tailored adjuvant therapy and reduce adjuvant therapy-related morbidity [30].

According to the ESMO–ESGO–ESTRO guidelines, lymphadenectomy is not recommended in patients with low-risk endometrioid cancer. A systematic lymphadenectomy should be recommended to patients with major risk factors (grade 3 with deep myometrial invasion >50%) because of the higher prevalence of nodal metastasis in this population. In cases of intermediate-risk patients (deep

myometrial invasion >50% or grade 3 superficial myometrial invasion >50%), the data have shown no survival benefit; a lymphadenectomy may be considered in this group for staging purposes [12].

3.2. What Is the Role of Sentinel Lymph Nodes in Endometrial Cancer?

Complete pelvic and para-aortic lymph node dissection is associated with major comorbidities, including lymphedema, lymphocysts, cellulitis, and damage to adjacent nerves. Furthermore, complete lymph node dissection is technically difficult in obese women, and the latter constitute a large part of patients with endometrial cancer [35].

Historically, the first successful instance of SLN mapping was reported in 1977; the procedure was a lymphangiography of the penis [36]. Since then, SLN mapping techniques have been investigated and developed for several other solid malignancies, including breast cancer and melanoma [37,38]. In gynecology, SLN mapping was first performed and accepted for patients with vulvar cancer. It is also promising in patients with endometrial and cervical cancer [35,39,40]. Although the concepts are similar, the approaches towards the standardization of the procedure differ because of differences in the incidence of the respective cancer, rates of lymph node metastasis, and the treatment or prognostic impact of the lymph node status for each disease [36].

As shown in Table 2, a number of tracers (indocyanine green, technetium, and blue) and various injection sites (cervical, subserosal myometrial, hysteroscopic peri-tumoral) have been described after SLN mapping was introduced for endometrial cancer [16,40,41]. ICG injected into the cervix emerged as the most consistently effective detection technique for endometrial cancer because of its high success rates and reproducibility [40].

Table 2. Characteristics of tracers for sentinel mapping in endometrial cancer [16,41].

Tracer Characteristics	ICG	Blue Dyes	Tc-99m
Injection	intraoperative	intraoperative	preoperative, including lymphoscintigraphy/SPECT
Signal duration	persistent	30 min	24 h
Costs	Low	Low	high
Allergic reactions	0.05%	2%	1–6/100,000
Other toxicity	None	color change of skin and urine, skin necrosis	radioactivity

SLN mapping must possess a high sensitivity and negative predictive value in order to be an acceptable staging method [36]. The FIRES trial, published in 2017, was a prospective multicenter cohort study in which sentinel lymph node mapping was followed by complete pelvic +/− para-aortic lymphadenectomy. Sentinel lymph node mapping with complete pelvic lymphadenectomy was performed in 340 patients, and para-aortic lymphadenectomy was performed in 196 patients (58%). Forty-one patients (12%) had positive nodes. SLN mapping had a sensitivity of 97.2% for the detection of node-positive disease, and a negative predictive value of 99.6%. The authors confirmed the high accuracy of sentinel lymph node mapping with the aid of indocyanine green for the detection of metastases, and conclude that SLN mapping might safely replace lymphadenectomy in the staging of endometrial cancer [35].

Pelvic sentinel lymph nodes follow two consistent lymphatic pathways: the upper paracervical pathway drains the medial external and/or obturator lymph nodes, and the lower paracervical pathway drains the internal iliac and/or presacral nodes. Furthermore, a non-pelvic pathway courses along the infundibulopelvic ligament to the para-aortic lymph nodes. SLN mapping for endometrial cancer revealed metastases in areas not usually included in a standard lymph node dissection. Sentinel lymph nodes are usually seen as ‘colored nodes’ or ‘radioactive nodes’ without regard to lymphatic anatomy [40]. In a prospective trial, How et al. examined the anatomical location of sentinel

lymph nodes after the intraoperative cervical injection of tracers: the external iliac and obturator areas were the most frequent locations for SLN detection. Interestingly, positive SLNs were seen in the pre-sacral and parametrial regions, and around the internal iliac vein [40]. Metastatic lymph nodes in atypical regions were also reported by Geppert et al. [42]. Compared to standard lymph node dissection, SLN mapping increases the detection of overall metastases [43].

An increasing body of evidence suggests the non-inferiority of sentinel lymph node mapping compared to systematic lymphadenectomy in endometrial cancer [44]. In 2014, the National Comprehensive Cancer Network (NCCN) guidelines accepted SLN mapping as an alternative to complete lymphadenectomy in selected cases of endometrial cancer. In 2018, the NCCN extended the application of sentinel lymph node mapping to high-grade carcinomas [41]. Last updated in 2015, the ESMO–ESGO–ESTRO guidelines recommend the use of sentinel lymph node mapping only in controlled trials [12].

Recent data suggest that, in endometrial cancer, sentinel lymph node mapping does not influence the oncologic outcome of disease. Based on six studies comprising a total of 3536 patients, the authors of this meta-analysis concluded that, in terms of recurrence rates (any site and nodal recurrence) and the detection of positive para-aortic lymph nodes, sentinel node mapping is not inferior to standard lymphadenectomy. The overall recurrence rates revealed no significant difference (4.3% after sentinel node mapping and 7.3% after lymphadenectomy; $p = 0.63$). With regard to the detection of positive pelvic lymph nodes, the authors concluded that sentinel node biopsy may be considered superior to lymphadenectomy [44].

Sentinel nodes are processed according to an ultrastaging protocol. Pathologic ultrastaging (including immunohistochemical (ICH) staining and deeper serial sections) enhances the detection of malignant cells. The clinical significance of the increased detection of isolated tumor cells and micrometastasis is currently uncertain. Furthermore, the strategies used for the pathological investigation of SLNs vary among institutions and within the published data [36].

Future trials will have to address these questions and determine oncologic outcomes after the use of sentinel node mapping for endometrial cancer.

3.3. Therapeutic Pelvic and Para-Aortic Lymphadenectomy (tLNE)

Our extended knowledge of the embryological development of organ compartments, tissue boundary control, and their association with tumor spread and tumor progression has resulted in a new approach in cancer surgery: compartmental surgery in cancer, as established by M. Höckel in gynecological oncology [45].

According to this concept, tumor spread is initially restricted to permissive ontogenetic compartments and their corresponding lymph node basins. The complete surgical removal of these embryologically-defined areas by whole compartment resection with intact margins following ontogenetic planes will result in optimal tumor control [19]. Embryologically, the female genital tract, the uterus, the fallopian tubes, and the upper part of the vagina arise from the paramesonephric ducts (Müllerian ducts). The distal fusion of the two ducts induces the development of the uterovaginal canal, the mesometrial tissue, and the broad ligaments. The fallopian tubes develop from the unfused cranial portions of the Müllerian ducts. The lymphatic network of the Müllerian system derives from embryonal veins [19,46].

The transfer of this concept to endometrial cancer led to peritoneal mesometrial resection (PMMR) combined with pelvic and para-aortic therapeutic lymphadenectomy (tLNE) [45]. The lymphatic system plays a major role in tumor spread and progression. The first part of this review summarized the anatomy and embryonic origins of lymphatic vessels. Via lymph drainage, malignant cells are able to reach the blood circulation through the jugular veins, and cause hematogenic metastases. These mechanisms might be highly relevant in endometrial cancer, because the metastatic spread in this malignancy occurs predominantly through the lymphatic system [45]. There is convincing evidence that

compartment resection, including the regional lymph compartment, reduces loco-regional recurrence even without adjuvant radiation [45,47–50].

Following TMMR and therapeutic lymphadenectomy without adjuvant radiation, Höckel et al. conducted a prospective single-center study comprising 305 cervical cancer patients with FIGO stage Ib to IIB disease, of whom 71 had positive lymph nodes; the authors noted recurrence-free and overall 5-year survival rates of 94% and 96%, respectively [51]. The preliminary evidence indicates that this concept yields comparable results even when it is used for endometrial cancer [52]. In cases of endometrial cancer, the compartmental concept could be equated with the Müllerian compartment, including the lymph compartments that drain regionally, and the so-called intercalating lymph nodes [52]. Kimmig et al. showed that PMMR with tLNE, performed by robotic-assisted laparoscopy, is a safe and feasible approach with low recurrence rates in patients with intermediate- and high-risk endometrial cancer [52]. The authors used indocyanine green (ICG)-enhanced fluorescence for the visualization of the Müllerian compartment and the subsequent lymphatic compartment. They injected ICG into the mid-corporal and fundal myometrium, and demonstrated two pathways for the transport of fluorescent lymphatic fluid. The first pathway was along the uterine vessels, passing the vascular mesometrium and reaching the pelvic lymph nodes along the internal and external vessels. The second was the ovarian mesonephric pathway to the para-aortic nodes. No drainage was observed along the ligamentous mesometrium (uterosacral ligament). The authors concluded that the number of patients (68) was too low to draw final conclusions about oncological outcomes, and that further multicenter trials will be needed in order to evaluate the value of compartmental surgery in endometrial cancer. A trial addressing this question is currently under way.

As described earlier, the lymphatic network of the uterus can be visualized by the injection of indocyanine green (ICG) as a guide in compartmental surgery. This is conceptually different from its use in sentinel lymph node detection. In a trial published in 2016, Kimmig et al. [45] investigated the intraoperative visualization of embryologically-defined organ compartments and their drainage after the injection of indocyanine green (ICG). Thirty-six patients with uterine cancer and no suspicious lymph nodes on macroscopic investigation participated in the study: 20 cervical cancer patients with FIGO stages Ib to IIB, and 16 endometrial cancer patients with FIGO stage I-III. Patients with endometrial cancer received PMMR (peritoneal mesometrial resection) with or without pelvic/para-aortic lymphadenectomy, and those with cervical cancer received TMMR (total mesometrial resection) and therapeutic pelvic lymphadenectomy. Prior to surgery, ICG was injected into the body of the uterus or the cervix. The authors showed that the lymphatic drainage differs according to whether ICG is injected into the cervix, the mid-corpus, or the fundus. The cervix drained along the caudal portion of the vascular mesometria, and along the ligaments. Fundal and mid-corporal drainage occurred by the mesonephric pathway along the ovarian vessels and the upper part of vascular mesometria [45]. The authors concluded that the visualization of the compartment and the lymphatic drainage system may assist the surgeon's orientation intraoperatively, and may enhance the surgeon's comprehension of the compartmental arrangement of the Müllerian system, as well as its borders to adjacent compartments. This may help to adapt surgery to individual circumstances. Furthermore, morbidity in the adjacent compartments of the bowel, bladder, ureter and nerves may be reduced [45].

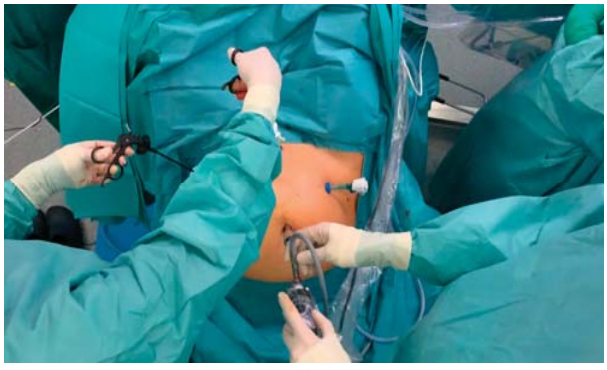
4. Practical Aspects of Lymph Node Surgery

Technical Challenges in Endoscopic Surgery

Several trials over the last few years have shown that minimally-invasive surgery is equivalent to open surgery with regard to the adequacy of the surgical resection and lymph node counts [53]. The additional positive effects of the minimally-invasive approach include a lower risk of intraoperative and postoperative complications (fewer wound-related complications, faster recovery, and earlier return to the activities of daily living) [53–55].

Within the spectrum of surgical laparoscopy, pelvic and paraaortic lymphadenectomy remain difficult high-end procedures. As described earlier, lymph node surgery in endometrial cancer is technically challenging, and can be time consuming because of the topographic complexity of lymphatic drainage as such, and the fact that the lymph nodes are directly adjacent to both blood vessels and nerves. Therefore, profound and exact knowledge of the anatomy is essential.

Figure 7 provides a detailed overview of the demanding requirements of endoscopic surgery, as well as the anatomical complexity of this area. As patients with endometrial cancer are often morbidly obese, performing a pelvic and paraaortic lymphadenectomy can be very challenging.



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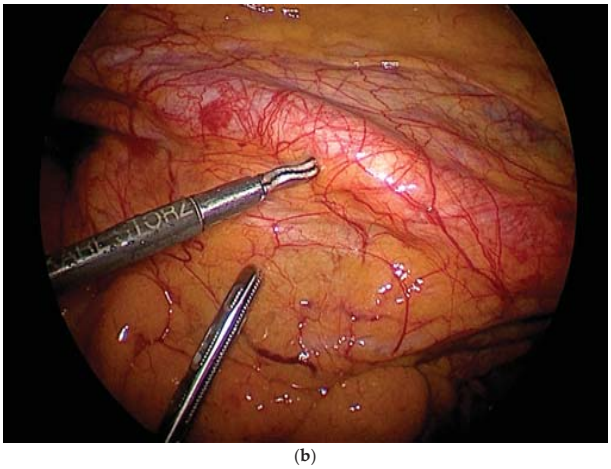

(**b**)

Figure 7. Trocar placement, the positioning of the surgical team, and operative findings. (**a**) The surgeon is to the patient's left, and the first assistant to the patient's right. The central trocar is inserted through the umbilicus. The working trocars are placed in the pelvis laterally and in the suprasymphysiary position. The first assistant holds the camera and uses the central trocar. The first assistant uses the right lateral trocar to provide assistance. The surgeon uses the left lateral and middle trocar. The middle working trocar should not be placed in the usual suprasymphysiary position, as this will inevitably cause the surgeon to work in his own direction. The middle trocar should be placed midway between the symphysis and the umbilicus. In order to avoid intraabdominal interference, the middle trocar should not be placed too close to the optical trocar. (**b**) Laparoscopic cranial view. Iliac vessels at the entrance to the right-sided pelvis. The ureter crosses the artery.

The following questions are yet to be answered conclusively:

- What is the most appropriate time to switch from the umbilical optical trocar to the suprasymphysiary trocar (perspective from above/below versus below/above)?
- What is the most suitable position for the working trocars with reference to the steps of surgery (perspective from above/below as well as below/above) so that the mutual angle of the instruments, as well as the mechanical actions of the surgeon, can be achieved smoothly and conventionally (i.e. not towards the surgeon but away from the surgeon)?

Conclusion: the course of the operation should not be oriented to the technical access and its limitations. Rather, it should be oriented towards the underlying anatomy and the embryological–oncological aspects.

5. Conclusions

Minimally-invasive surgery (conventional laparoscopy and robotic surgery) has rapidly replaced the open approach in endometrial cancer staging. Within the spectrum of surgical laparoscopy, pelvic and paraaortic lymphadenectomy remain difficult high-end procedures. Profound and exact knowledge of anatomy, including uterine lymphatic drainage, is essential for every surgeon. Lymph node assessment has also undergone significant changes after the introduction of SLN mapping. As in other diseases, the concept of 'less is more' has pervaded the treatment of endometrial cancer.

However, a number of significant questions remain unanswered, regarding the following: oncologic outcomes when sentinel lymph node mapping is used, the clinical management and impact of low-volume metastases in SLNs, and a consensus concerning the technique. These issues will have to be investigated in further large prospective trials.

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Review

Do Small Incisions Need Only Minimal Anesthesia?—Anesthetic Management in Laparoscopic and Robotic Surgery

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Abstract: Laparoscopic techniques have established themselves as a major part of modern surgery. Their implementation in every surgical discipline has played a vital part in the reduction of perioperative morbidity and mortality. Precise robotic surgery, as an evolution of this, is shaping the present and future operating theatre that an anesthetist is facing. While incisions get smaller and the impact on the organism seems to dwindle, challenges for anesthetists do not lessen and could even become more demanding than in open procedures. This review focuses on the pathophysiological effects of contemporary laparoscopic and robotic procedures and summarizes anesthetic challenges and strategies for perioperative management.

Keywords: general anesthesia; anesthetics; perioperative care; minimally invasive surgery; laparoscopic surgery; robotic surgery

1. Background

Since its introduction to the operating theatre, laparoscopic surgery has become a mainstay of surgical management. The evolution of minimally invasive techniques enabled laparoscopic surgery and has come a long way until today. This evolution ranges from Bozzini, who in 1805 tried to observe the urethra with a simple tube and candlelight [1], to the first use of pneumoperitoneum by Kelling in 1901, the first clinical implementations in diagnostics and treatment by gynecologists to the first laparoscopic cholecystectomy performed by the surgeon Phillipe Mouret in 1988 [1,2]. Remarkable advances in laparoscopic surgery have led to multiple benefits such as reduced blood loss, tissue trauma, postoperative morbidity and pain [3,4]. Many procedures now require a shorter hospital stay or can be performed on an ambulatory basis [5,6]. Furthermore, robotic surgery as the technical pinnacle of laparoscopic technique has rapidly evolved to be used in different surgical procedures and is a vital option for otherwise inoperable obese patients [7,8]. As the clinical implications for laparoscopic and robotic surgery broaden and the procedures get more complex, different challenges arise for the anesthesiologist. Here, we give an overview about the operative conditions, the physiological and pathophysiological changes and possible complications which have to be considered by the anesthetist. Additionally, we review the evidence for the anesthetic management of patients undergoing laparoscopic and robotic surgery.

2. Technique of Laparoscopic and Robotic Surgery

To successfully master potential challenges of laparoscopic and robotic surgery it is vital to understand the basic principles of their technique. The laparoscopic and robotic site is defined by the use of smaller and more precise incisions compared to their counterparts in open surgery, which leads to a reduction of tissue trauma [3]. To make room for optimal visualization of the targeted abdominal region pneumoperitoneum usually needs to be established, although other techniques, such as the "Abdominal lift" have been studied and applied to ensure visualization and accessibility [9]. Pneumoperitoneum is achieved by the insufflation of the abdominal cavity with gas [10]. Many different gases have been studied for induction of pneumoperitoneum, including room air, oxygen (O_2), nitrous oxide (NO) and carbon dioxide (CO_2). CO_2 has been found to be the safest option, as its risk for gas embolism is lower than for O_2 and room air due to higher resorption rate. There is increased risk for intra-abdominal combustion if NO is mixed with methane produced by the intestines [11,12]. Usually, laparoscopic access is done via a trocar or a needle through which the gas can be insufflated [13]. After pneumoperitoneum has been established, the surgeon is able to advance instruments via different trocar locations into the abdominal cavity. View of the operating site is generated via a camera trocar. To establish good sight of the targeted abdominal region, specific positioning of the patient is established. While many procedures can be done in supine position, different unphysiological positions like Trendelenburg, anti-Trendelenburg or lithotomy position are sometimes needed. As for standard laparoscopy, the surgeon and the operating team stand next to the patient. In modern robotic laparoscopy the surgeon can use telesurgery to control his instruments from a different location other than the operating table (e.g., DaVinci®). The advantages and disadvantages of laparoscopic and robotic surgery for the patient are summarized in Table 1.

Table 1. Surgical advantages and disadvantages of laparoscopic and robotic surgery [3–8].

Advantages	Disadvantages
Intraoperative:	**Intraoperative:**
- reduced tissue trauma - reduced blood loss with lower need for transfusion of blood and coagulation factors [14] - visualization of the whole abdominal cavity	- higher cost - prolonged operating time - higher difficulty of technique, lack of haptic feedback - surgical control of bleeding complications might be delayed - certain surgical instruments not usable (e.g., automated cell salvage)
Robotic surgery specific:	**Robotic surgery specific:**
- articulation beyond normal manipulation - three-dimensional magnification and steadier camera position - filtering of tremor	- prolonged learning curve - needs careful positioning and more space
Postoperative:	**Postoperative:**
- better cosmetic results - reduced pain with lower need of analgesia - preserved lung function with shorter recovery time - reduced rate of wound infections - shortened in-hospital stay	- tissue damage and nerve injury due to positioning and prolonged operating time

3. Anesthetic Challenges

3.1. Hemodynamics

Many different factors of laparoscopic surgery influence the hemodynamic situation of the patient. Most notably, this is seen in the increase of intraabdominal pressure (IAP) due to the inflation with CO_2 and positioning of the patient. With the initiation of pneumoperitoneum the IAP slowly rises and therefore pressure on the splanchnic veins is higher. This leads to an increase of preload followed by a higher blood pressure in the early phase of the laparoscopic procedure. Pain and neuro-humoral response to peritoneal stretching might also release catecholamines, which can lead to critical rises in blood pressure and tachyarrhythmia [15]. If IAP exceeds intravenous pressure in the splanchnic veins (≥15 mmHg), venous collapse is possible; this effect is reversed up to enhance inferior V. cava compression. Surgical manipulation and vasodilatation induced by anesthetic agents, release of prostaglandins (eventeration syndrome) and co-morbidities might add to hemodynamic instability. Changes in the patient's position play an important role as well. Surgery in the upper abdominal quadrants like cholecystectomy needs anti-Trendelenburg positioning, which might lower Cardiac Index (CI) due to reduced venous return from the lower body parts. Procedures in the lower abdominal quadrants often need Trendelenburg positioning. In consequence of the elevated lower body, venous return increases, which raises CI, central venous pressure (CVP) and intracranial pressure (ICP) [15,16]. Depending on the phase and the technique of the procedure, the anesthetist should therefore be prepared for either critical hypertension or hypotension. Close monitoring of IAP is warranted with a target of ≤15 mmHg [17].

3.2. Respiratory Function

General anesthesia with progressive muscle relaxation already reduces residual capacity of the lung by up to 20% [18]. This effect is based on paralyzation of the diaphragm, which limits ventilation of basal lung segments and facilitates development of atelectasis. If pneumoperitoneum is applied and IAP increases in laparoscopic surgery, lung ventilation is increasingly compromised due to cranial movement of intraabdominal organs and rising pressure on the diaphragm. Trendelenburg position of the patient adds to this even further. Compliance of the lung and thorax is therefore impaired in the patient undergoing laparoscopic surgery and lung protective ventilation might be a challenge for the anesthetist, especially when iatrogenic hypercapnia must be compensated for by increased minute ventilation. Intraoperative impairment of lung ventilation and formation of atelectasis also have an impact on postoperative lung function [19]. Vital capacity and forced expiratory volume are found to be reduced in patients after laparoscopic surgery [20].

3.3. Renal and Hepatic Function

Abdominal blood flow inversely correlates to IAP. As IAP rises and exceeds arterial pressure of the abdominal arteries, perfusion of abdominal organs like kidney and liver will be impaired and venous drainage reduced. The reduction of renal blood flow causes a reduction of glomerular filtration with a decrease of urine secretion and retention of creatinine. Optimization of intravascular volume can help to mitigate this effect [21]. The anesthetist should therefore closely monitor the intravascular volume state, as well as perioperative diuresis and kidney function of the patient. If blood flow to the liver or venous drainage is reduced, hepatic dysfunction and a rise of liver enzymes can be seen [22]. In patients with normal liver function these effects are mostly self-limited and are not associated with any morbidity [23]. If there is preexisting impairment of liver function or the rise of IAP is severely prolonged, liver function should be of concern for the anesthetist.

3.4. CO_2 Resorption

CO_2 in the abdominal cavity as in pneumoperitoneum will be resorbed into the blood stream over time. Abdominal CO_2 resorption depends on IAP, location of CO_2 application and phase of the procedure [18]. There is evidence that extra-peritoneal insufflated CO_2 as used in laparoscopic prostatectomy will be resorbed much faster than intraperitoneal CO_2 [24]. At the start of the procedure CO_2 resorption will rise with the induction of pneumoperitoneum, reach a steady state and might shortly rise again during the release of pneumoperitoneum at the end of the procedure due to the increase of venous return with falling IAP. Resorbed CO_2 is then transported to the lungs and will be exhaled along with CO_2 produced by the normal metabolism. As CO_2 partial pressure is a determining factor of acid base homeostasis, adjustment of ventilation is required to prevent hypercapnia and acidosis. Minute ventilation has to be increased by up to 15% to match the respiratory demand generated by increased CO_2 resorption in pneumoperitoneum [25]. The use of a valve-less trocar by the surgeons has been shown to improve respiratory mechanics in robot-assisted radical cystectomy and could help to ease ventilatory demands if prolonged pneumoperitoneum is required [26]. If ventilatory adjustment is not possible, the surgeons should be asked to reduce IAP or stop the CO_2 flow for a few minutes. Otherwise, hypoventilation leads to hypercapnia and acidosis. Increased pCO_2 and acidosis lead to vasodilatation of cerebral vessels, followed by an increase of cerebral blood flow and ICP. This can be fatal in patients with already elevated ICP. Acidosis leads to pulmonary vasoconstriction, which results in a higher pulmonary vascular resistance, with increased right-left shunt, which can lead to cardiac decompensation in patients with right heart failure. It is therefore vital to always monitor gas exchange, acid base homeostasis and end-tidal pCO_2 ($p_{et}CO_2$) of the patient.

3.5. Positioning

As already described, laparoscopic and, even more, robotic surgery demand particular positioning to access the targeted abdominal region. Besides the impact on hemodynamics and lung function, patient positioning can be tremendously detrimental for the accessibility of the patient. Covering of the head and extremities by surgical drape and positioning of the patient with possible intraoperative changes might inhibit control of the airway, vascular access and monitoring devices of the patient. Close attention should also be paid to pressure-free positioning to prevent damage to skin, nerves and especially to the eyes. Anesthetists should plan patient positioning together with the surgeons and evaluate monitoring as well as options for airway and vascular access to anticipate potential intraoperative problems.

3.6. Intra- and Postoperative Complications

Many different complications can arise during anaesthesia of patients undergoing laparoscopic and robotic procedures. In Tables 2 and 3 we provide an overview about incidence, pathophysiology, diagnosis and management of important intra- and postoperative complications.

Table 2. Intraoperative complications of laparoscopic and robotic surgery.

Complications	Vascular Injury	Gas Embolism	Secondary One-Sided Intubation	Volume Overload	Pneumothorax/ Pneumo-Pericardium/ Pneumo-Mediastinum	Carboxyhemo-Globinemia
Incidence	7–13.8% [27]	significant: 0.001–0.59% [28] subclinical: ~30% [29,30]	0.2% [31]	depending on the procedure [18]	0.01–0.4% [32]	0.03% [33]
Pathophysiology	Advancement of trocars and needles in major abdominal vessels.	Insufflation of CO_2 into an injured vessel. Danger for embolism rises after *IAP* ≥ 10 mmHg. Portal veins are prone to embolism.	Cranial displacement of diaphragm and carina due to higher *IAP* from pneumoperitoneum and patient positioning.	Resorption of fluids through peritoneum potentially leading to hyponatremia, heart failure and lung edema.	CO_2 spreading through the diaphragm along anatomical openings or surgical lesions.	Intraabdominal smoke formation and resorption over peritoneum [18].
Diagnosis	RR [1] ↓, HF [2] ↑, Hb [3] ~ (↓ later), lactate ↑ Communication with surgeons	RR ↓, HF~, arrhythmia SpO_2 [4] ↓, p_{AW} [5] ~, $etCO_2$ [6] ↑ (↓ later) auscultation ("machinery murmur"), transesophageal echocardiography (TEE)	RR~, HF~ SpO_2 ↓, p_{AW} ↑, $etCO_2$ ↓, Compliance ↓ auscultation	RR~, HF~, electrolyte disorder SpO_2 ↓ auscultation, Point-of-care ultrasound (POCUS)	RR ↓, *HF* ↑ (↓ later) SpO_2 ↓, p_{AW} ↑, $etCO_2$ ↑ (↓), Compliance ↓ auscultation, POCUS	*RR*~, HF~ SpO_2~, lactate ↑ COHb [13] ↑
Prophylaxis and Treatment	large bore i.v. access, close monitoring of hemodynamics and sufficient relaxation	immediate termination of pneumoperitoneum, hyperventilation, F_iO_2 [7] 1,0, (ECMO [8])	Endotracheal tube placement close to vocal cords, cautious monitoring of ventilation	cautious monitoring of hemodynamics, electrolytes and volume state (*CVP* [9], *PPV* [10])	cautious monitoring of ventilation and hemodynamics PEEP [11] > IAP [12]	suctioning of developing smoke

Abbreviations: ↑—increase of, ↓—decrease of; [1] Blood pressure, [2] Heart rate, [3] Hemoglobin, [4] Peripheral capillary oxygen saturation, [5] Mean Airway Pressure, [6] Partial pressure of end-tidal CO2, [7] Fraction of inspiratory O2, [8] Extracorporeal membrane oxygenation, [9] Central venous pressure, [10] Pulse pressure variation, [11] Positive end-expiratory pressure, [12] Intraabdominal pressure, [13] Carboxyhemoglobin.

Table 3. Postoperative complications of laparoscopic and robotic surgery.

Complications	Cerebral Edema	Laryngeal Edema	Shoulder Tip Pain	Ocular Injury
Incidence	case reports [34,35]	2–22% [36]	up to 60% [37]	0.05–3% [38]
Pathophysiology	High *ICP* and capillary leak in consequence of increased *CVP* in Trendelenburg position with pneumoperitoneum. [34,35,38].	Increased *CVP* due to positioning and pneumoperitoneum [39].	Abdominal irritation of the diaphragm and phrenic nerve caused by high *IAP* and CO_2-induced intraperitoneal acidosis [37].	Corneal abrasions and higher incidence of ischemic optic neuropathy due to incomplete eye closure, increased *ICP* and prolonged operating time [40].
Diagnosis	altered/depressed mental state	post-extubation stridor respiratory failure	shoulder pain 24 h up to 4 days after surgery, frequently on the same side of procedure	visual loss and ocular pain
Prophylaxis and Treatment	check for conjunctival edema, restrict angle of Trendelenburg position to 30°, restrictive fluid management [35]	check for conjunctival edema, cuff leak test [39], intraoperative corticosteroids, posture with head up position prior to extubation, prolonged observation and careful extubation	sufficient analgesia, brief Trendelenburg-positioning and repeated lung recruitment-maneuvers at the end of the procedure [37]	Protective eye coverings, limited time in steep Trendelenburg position, restrictive fluid management [40]

4. Anesthetic Management

4.1. Patient Selection

After laparoscopic surgery was met with skepticism in its early days, it is now seen as a safe and viable surgical option to treat a broad array of indications. If feasible, it can be advantageous in patients with underlying cardiac and pulmonary diseases and can be safely performed on frail patients [10,41]. Reduced blood loss and tissue trauma, less pain and shorter hospital stays can make laparoscopy better in the longer term for the less fit patient [42]. However, intraoperative stress on the cardiopulmonary system, extreme positioning and occasionally prolonged operating times demand careful patient selection. For relative contraindications like significant cardiovascular and cerebrovascular disease, thorough preoperative evaluation and judgement in a team with the surgeon are key to enabling surgery with a good outcome. Clear contraindications have been narrowed down to only a few in adult patients. In patients with increased ICP, laparoscopic surgery should be avoided. Absorbed CO_2 and increased IAP due to pneumoperitoneum and extreme positioning pose the risk for further increase of ICP. In children, the detrimental effects of pneumoperitoneum and positioning on hemodynamics and pulmonary function might be even more pronounced [18]. Therefore, more caution is warranted for young patients with underlying cardiovascular and pulmonary diseases.

4.2. Preoperative Considerations

Preoperative evaluation of the patient is the basis for successful anesthesia. It is composed of risk stratification based on the patient's medical history and physical examination, including functional assessment and preoperative testing [42]. The anesthetist should check for cardiovascular, pulmonary and metabolic issues in the patient as these pose the highest risk to be aggravated by laparoscopic surgery. Treatment of underlying cardiopulmonary and metabolic diseases, as well as optimization of medication should then be carried out if possible. Careful planning of airway management is warranted, as limited accessibility, CO_2 resorption, extreme positioning with increased IAP are challenges to overcome. Potential occurrence of facial or laryngeal edema might require a delay of extubation or the use of advanced techniques for airway management [43]. As intraoperative bleeding happens less often during laparoscopic procedures, it can be highly difficult for the surgeon to contain [44]. Adequate patient blood management is crucial in perioperative management of patients undergoing laparoscopic procedures [45]. It is important to avoid preoperative coagulopathy and anemia, which is an important predictor of perioperative morbidity and mortality itself [46–49]. Therefore, it is always worthwhile to screen for and treat anemia, but most important in laparoscopic procedures predicted to have a higher risk of blood loss of ≥500 mL or likelihood of transfusion of ≥10%. Laparoscopic tumor resection and vascular surgery typically belong in this category.

4.3. Choice of Technique

To induce and maintain anesthesia in laparoscopic surgery, total intravenous anesthesia (TIVA) with propofol or balanced anesthesia with use of inhalational agents present the options for general anesthesia. Each technique has different advantages and disadvantages. Use of propofol in TIVA lowers the risk of postoperative nausea and vomiting (PONV) and reduces pollution of the operating theatre and environment with anesthesia gas [50]. Propofol could also prevent an increase in intraocular pressure (IOP) after pneumoperitoneum and Trendelenburg positioning compared with sevoflurane [7,50]. Whereas balanced anesthesia has the benefits of easier monitoring and potentially safer supply of anesthesia if venous access is not in sight, e.g., if arms are attached to the body during the procedure, and, although controversially discussed even in cardiac surgery, the proposed cardio-protective effects of inhalational anesthesia [7,51]. Suppression of spinal reflexes is also more pronounced through volatile anesthetics such as sevoflurane compared to propofol [52,53]. As instruments in laparoscopic and especially robotic surgery cannot be retracted fast enough in response to sudden unpredictable movement of the patient, spinal reflexes should be sufficiently

suppressed. General anesthesia with continuous analgesia through remifentanil might help to reduce the occurrence of these to a minimum. However, no superiority has been shown for either of these techniques in laparoscopic and robotic surgery and the final choice needs to be made by the anesthetist, depending on experience and setting. Neuraxial anesthesia could be another option, but is usually limited to lower abdominal and pelvic procedures. However, evidence shows an association with intraoperative pain referred to the shoulder, required anesthetic conversion in 3.4% of the cases and no respiratory benefits for patients with normal pulmonary function [54]. General anesthesia can be combined with epidural analgesia in extensive laparoscopic surgery with the benefit of lowered postoperative pain intensity through patient-controlled epidural anesthesia (PCEA). There is evidence that thoracic epidural analgesia provides additional benefits to patients with pulmonary risk factors undergoing laparoscopic surgery of the upper abdomen [55]. However, it is still unclear if the benefits of epidural anesthesia outweigh the risks for every patient. Therefore, careful individual benefit-to-risk consideration is needed. Airway management is of high importance to facilitate adequate ventilation under increased IAP in pneumoperitoneum with CO_2 and extreme positioning. Here, higher ventilation pressures and prevention of aspiration are possible. While intubation represents the standard, the use of second generation supraglottic airway devices can also be considered in selected cases, e.g., in lower abdominal and pelvic procedures. Such devices offer optimized fit and the option to insert a stomach tube and might therefore be able to accomplish safe ventilation in laparoscopic procedures even in obese patients [56]. There is evidence from randomized double blind prospective studies for a reduction in PONV and postoperative throat pain and avoidance of hemodynamic changes occurring during endotracheal intubation, when laryngeal masks are used in comparison to endotracheal intubation [57,58]. Pressure-controlled ventilation and neuromuscular blockade have been proven to be optimal for lung-protective ventilation and sufficient oxygenation [10]. So far, there is some evidence that deep neuromuscular blockade can improve surgical conditions when compared to moderate degree of neuromuscular block, which might allow for lower IAP to be used [59]. However, there is still controversy as to whether this intervention is generally advisable or should only be limited to selected procedures or even be dedicated to difficult surgical situations [60,61]. Development of atelectasis should be controlled and treated by careful lung recruitment maneuvers and titration to adequate positive end-expiratory pressure (PEEP) [62]. Hemodynamic changes, especially intraoperative spikes in blood pressure cause the release of catecholamines and represent a big challenge to the anesthetist. To prepare for this event, continuous analgesia with remifentanil can be helpful. In addition, intravenous magnesium sulphate given before pneumoperitoneum can attenuate increases in arterial pressure during laparoscopic cholecystectomy [16].

4.4. Monitoring

As a standard in laparoscopic procedures, ECG, pulse oximetry and oscillometric blood pressure measurement should always be monitored. Due to induction of pneumoperitoneum, it is also of high importance to monitor capnography and neuromuscular blockade, ideally through the procedure, e.g., by using train-of-four (TOF) monitoring. Capnography allows timely adaption of ventilation to expiratory CO_2. As the differences between p_aCO_2 and $p_{et}CO_2$ (normal range 2–5 mmHg) can vary depending on patient age, regular adjustment through arterial blood gas analysis is warranted [63]. Close monitoring of $p_{et}CO_2$, as well as p_aCO_2 helps to detect development of atelectasis and complications caused by laparoscopic procedures like gas embolus, pneumothorax and secondary one-sided intubation. Adequate muscular relaxation could be performed to optimize surgical conditions and allow for lower IAP in pneumoperitoneum. The anesthetist should therefore manage relaxation steered by TOF response along with intraabdominal manipulation. For deep neuromuscular blockade (NMB), post-tetanic count (PTC) needs to be monitored and evaluated. Deep NMB is typically considered to be present if the PTC is ~2, although the definitions vary to a great extent. If TIVA is chosen for anesthesia, its depth should be monitored through electroencephalogram (EEG) devices. Continuous assessment of anesthesia depth helps to avoid insufficient stages of anesthesia, which is

especially dangerous in robotic surgery. Extended hemodynamic monitoring should be chosen for patients with cardiovascular risk factors as indications are the same as for patients undergoing open procedures. However, the anesthetist should anticipate limited accessibility after the start of the procedure and should implement adequate vascular access and monitoring beforehand, since any establishment of advanced hemodynamic monitoring or vascular access may only be realized with delay.

4.5. Perioperative Pain Management

Adequate perioperative pain management is one of the most important ways in which the anesthesiologist can improve patient comfort, which then allows earlier recovery and mobility and improved postoperative respiratory function. Laparoscopic surgery eases this task through smaller incisions and reduced tissue trauma. Therefore, analgesic requirements including opioids are lower compared to open surgery [10]. However, small incisions do not mean no pain because severe pain might not be expected. It has been shown that minor procedures, including laparoscopic approaches quite commonly result in unexpectedly high levels of postoperative pain [64]. It has been hypothesized that surgeries in which higher pain scores are anticipated, better adherence to evidence-based pain treatment recommendations and improved quality of care is provided [64]. As optimal pain management is still a controversially discussed topic, evidence-based recommendations are available in national guidelines by the European Society of Regional Anesthesia and Pain Management in the form of PROSPECT (PROcedure-SPECific postoperative pain managemenT) [65]. Looking at the local situation and performing a proper needs assessment may help to find adequate analgesic protocols. To secure basic analgesia for the postoperative period, pre- or intraoperative paracetamol and NSAID (e.g., ibuprofen) or COX-2 (e.g., parecoxib) selective inhibitors should be used. Preoperative dexamethasone is recommended for its analgesic and anti-emetic effects. Opioids are rescue medication if basic analgesia is not sufficient [65]. However, many laparoscopic procedures may not be well-tolerated without opioid analgesia even in the immediate postoperative period. Regional anesthesia with transversus abdominis plane (TAP) block may become a further option to reduce intraoperative opioid requirements [66]. Ultrasound guided transversus abdominis plane block has been shown to reduce morphine consumption and somatic pain after robotic partial nephrectomy [67]. However, beneficial effects still remain controversial as only limited evidence for TAP block in laparoscopic surgery is available [68]. Therefore, PROSPECT guidelines do not recommend TAP block for laparoscopic cholecystectomy, hysterectomy and sleeve gastrectomy so far [65]. Perioperative lidocaine infusion could also help to ease postoperative pain and enhance recovery but more evidence is needed [69]. As even the small port site incisions can be quite painful, infiltration with long-acting local anesthetics by the surgeon is recommended [66]. Shoulder tip pain is a common pain management challenge after laparoscopic procedures due to irritation of the diaphragm and the phrenic nerve through the pneumoperitoneum. This can be eased by thorough expulsion of the intraabdominal gas at the end of the surgery through aspiration and repeated lung recruitment maneuvers [37].

5. Special Patient Subgroups

5.1. Pregnant Women

It is not uncommon for pregnant women to need abdominal surgery that is not related to obstetrics. Mostly, these procedures are appendectomy or cholecystectomy, which are usually managed in laparoscopic technique [70]. There is sufficient evidence for the advantages of laparoscopic technique over open procedures in non-pregnant women [71]. Occasionally, laparoscopic appendectomy is still associated with an increased risk of miscarriage [48]. However, after adjusting for possible confounders laparoscopy shows no elevated fetal risk compared to an open procedure [72]. Thus, the decision for or against one method is therefore more dependent on the circumstances of the individual case and experience and should not be dependent on the technology itself. Importantly, the preference for one regional anesthesia as part of an appendectomy typically implies an open

approach. Laparoscopic cholecystectomy should be the technique of choice in pregnant women [73]. Careful evaluation of the fetal and uterine state should be carried out pre- and postoperatively. To avoid aortocaval compression syndrome the patient might be positioned with lateral tilt, although the resulting benefit of this action is far from being clear and *IAP* should not surpass 15 mmHg [74]. The anesthetist should also be aware of potential harmful drug effects.

5.2. Children

Modern laparoscopic surgery and its advantages are also implemented in pediatric surgery. An anesthetist has to be careful as the physiological conditions in children differ significantly compared to adults. Because of the smaller abdominal cavity, increased IAP due to pneumoperitoneum and positioning has a much stronger impact on the cardiovascular system and the lungs. Vagal reflexes in response to mesenterial traction and abdominal distension occur more frequently and pose the biggest threat to pediatric hemodynamics [75]. Therefore, a lower IAP under 8 mmHg should be targeted and parasympatholytic medication should be prepared to be accessed fast. If Trendelenburg or anti-Trendelenburg positioning is needed, a tilt of 15° should not be exceeded [18]. Volume state should be monitored closely and adapted to tolerate the effects of pneumoperitoneum. Diuresis should not be used to monitor the volume state as infants and children can be anuric or oliguric in the first 45 min of the procedure. This is recompensated through increased diuresis up to 6 h after the procedure [75]. A correct and safe tube fixation should be implemented and consistent control is warranted as tube dislocation is more frequent in children due to abdominal distension after induction of pneumoperitoneum.

5.3. Obese Patients

In obese patients, special attention must be drawn to adjustment of ventilation since chest and lung compliance is known to be reduced per se [76]. The induction of a pneumoperitoneum as well as extreme patient positioning (Trendelenburg) can further deteriorate ventilation and contribute to atelectasis formation. Therefore, application of adequate PEEP and pulmonary recruitment maneuvers are especially vital in obese patients [77].

6. Conclusions

Laparoscopic and robotic surgery have become essential techniques in the modern operating theatre and offer various benefits for the patient. Smaller incisions with less tissue trauma through minimally invasive techniques are one of the main advantages. However, specific requirements, like extreme positioning and pneumoperitoneum are needed. These pose impactful risks on the physiology of the patient; various complications that will not be seen in open procedures might arise and could be difficult to manage. The anesthetist must carefully select which patients can undergo such procedures and must always be prepared for intraoperative difficulties, although absolute contraindications are rare. Small incisions also do not necessarily mean lower pain levels, as pain in patients undergoing laparoscopic procedures, like appendectomy is likely to be underestimated. Based on the aforementioned findings and statements the famous sayings, “Small incisions do not equal minimal anesthesia,” or “There may be minor surgery, but typically this is not associated with minor anesthesia,” are perfectly true.

Key Points:

- ➢ Laparoscopic surgery offers impactful benefits through reduced tissue trauma and has become a mainstay of surgical technique.
- ➢ Robotic surgery has matured into a safe surgical option that may sometimes enable precise procedures on otherwise inoperable patients.

- ➢ Surgical requirements for laparoscopic and robotic technique, like pneumoperitoneum and extreme positioning induce undesirable pathophysiological changes on hemodynamics and pulmonary function and obstruct access to and visual control of the patient for the anesthetist.
    - Adequate airway management, hemodynamic monitoring, vascular access and careful patient positioning should be established preoperatively, as intraoperative adjustment might not be possible and procedures might take longer than open surgery.
    - High vigilance for hemodynamic and pulmonary changes, especially at the induction and release of pneumoperitoneum is warranted.
- ➢ Anesthesiologist and surgeon should approach the procedure as a team and communicate closely.
- ➢ Cautious patient selection and preoperative optimization of cardiovascular and pulmonary problems is key.
- ➢ Preoperative optimization of anemia and coagulation through Patient Blood Management is crucial, as intraoperative bleeding might be rare, but can be disastrous due to reduced accessibility.
- ➢ Adequate and evidence-based pain management is required for every laparoscopic surgery, as postoperative pain is often underestimated in procedures with less tissue trauma

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Review

Radiotherapy and Its Intersections with Surgery in the Management of Localized Gynecological Malignancies: A Comprehensive Overview for Clinicians

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Abstract: Surgery, including minimally invasive surgery, and radiotherapy are key modalities in the treatment of gynecological malignancies. The aim of this review is to offer the multidisciplinary care team a comprehensive summary of the intersections of surgery and radiotherapy in the local treatment of gynecological malignancies. Recent advances in radiotherapy are highlighted. Relevant publications were identified through a review of the published literature. Ovarian, endometrial, cervical, vaginal, and vulvar cancer were included in the search. Current guidelines are summarized. The role of radiotherapy in adjuvant as well as definitive treatment of these entities is synthesized and put into context with surgery, focusing on survival and quality of life. Although these outcomes have improved recently, further research must be focused on the number of life years lost, and the potential morbidity encountered by patients.

Keywords: minimally invasive surgical procedures; surgery; radiotherapy; ovarian neoplasms; endometrial neoplasms; uterine cervical neoplasms; vaginal neoplasms; vulvar neoplasms; survival analysis; quality of life

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1. Introduction

The last decades have witnessed significant advancements in surgical techniques for the treatment of gynecological cancers. The results are shorter hospital stays, less blood loss, and lower morbidity levels due to the minimally invasive approach [1–4]. Simultaneously, major innovations have transformed the field of radiation oncology (Figure 1) [5]. These innovations have led to more precise and more effective treatment by radiation therapy.

The precision of treatment delivery was greatly enhanced by the introduction of three-dimensional conformal radiotherapy based on CT scans. This permitted computer-based delineation and the definition of target volumes as well as organs to be spared from external beam radiation ("organs at risk"). The next step in technical innovation was the introduction of intensity-modulated radiotherapy in the late 1990s, and volumetric-modulated arc radiotherapy by the 2000s. Both techniques employ multiple precise collimators ("multi-leaf collimator") of linear accelerators to shape the radiation beam to the target volume and limit the dose to surrounding tissue. Using advanced treatment planning algorithms, the intensity of the dose is modulated to the treatment volume. This enhances the conformality of the prescription dose to the target volume. Organs at risk in close proximity to the target volume can be spared more effectively (Figure 2). Randomized controlled trials have shown that these techniques result in significantly lower toxicity levels and better health-related quality of life compared to older radiation therapy techniques for several anatomic sites. This is also true of gynecological cancers, as evidenced by lower gastrointestinal and urinary toxicity levels [6]. More precisely, grade 3 or higher acute

gastrointestinal toxicity in cervical cancer patients was significantly reduced from 20–27.3% to 4.5–5% by intensity-modulated radiotherapy [7,8]. Similarly, grade 3 or higher acute genitourinary toxicity was significantly reduced from 15% to 5% [8]. Late toxicity is also significantly lower after intensity-modulated radiotherapy compared to older radiotherapy techniques [9]. However, as many as 11% of patients with cervical cancer may experience grade 3 or higher late gastrointestinal/urinary toxicity [9].

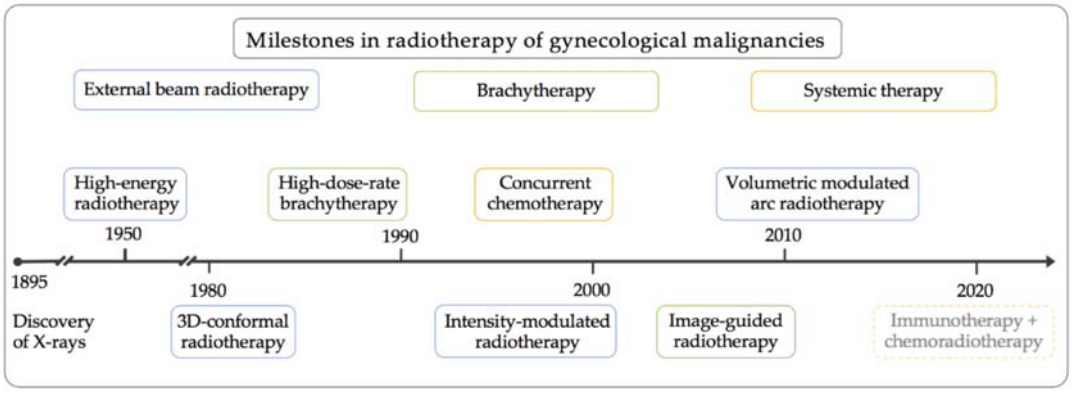

Figure 1. Milestones in radiotherapy for gynecological malignancies. A schematic timeline showing innovations in radiotherapy, including external beam radiotherapy, brachytherapy, and systemic therapy.

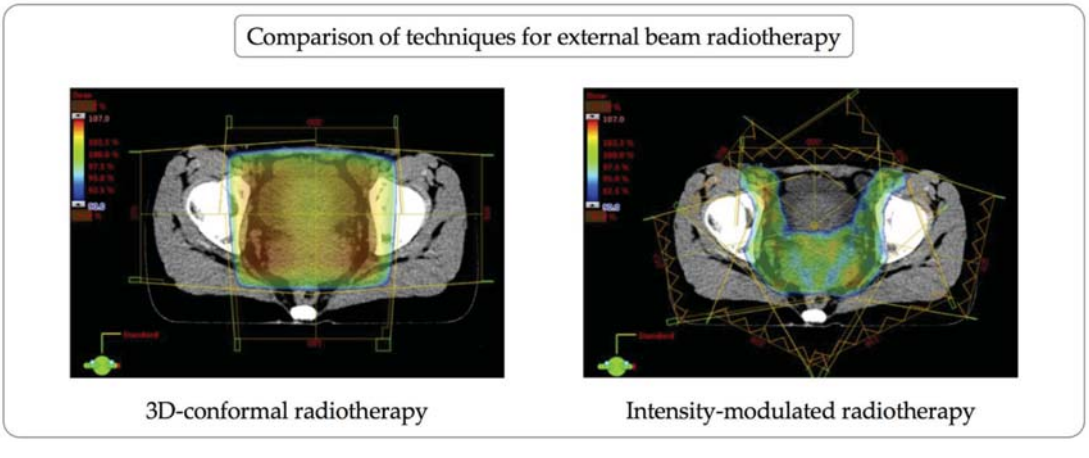

Figure 2. Comparison of techniques for external beam radiotherapy. FIGO stage IIIC cervical cancer in a 30-year-old woman treated with definitive radiotherapy including external beam radiotherapy, high-dose-rate brachytherapy, and concurrent cisplatin. She had laparoscopic nodal staging and ovarian transposition prior to radiotherapy. The actual intensity-modulated treatment plan (**right**), allowing for superior conformality, is juxtaposed to an alternative 3D-conformal plan (**left**). Inguinal nodes are included in the radiation field due to distal vaginal extension of the primary cancer.

Modern radiotherapy techniques have been suspected to increase the incidence of radiation-induced secondary malignancies because of larger quantities of tissue receiving relatively low doses. Although this concern does not appear to hold true, the 15-year probability of a radiation-induced malignancy is estimated to be approximately 2% across treatment sites and entities [10,11]. In irradiated cervical cancer survivors, a large database study reported a standardized incidence ratio (observed vs. expected incidence) of 1.3

(95% CI, 1.28–1.33) for secondary malignancies [12]. This moderate risk of radiation-induced malignancies must be addressed when counseling patients before treatment.

In parallel with the advent of intensity-modulated radiotherapy and volumetric modulated arc radiotherapy, image-guided radiotherapy was introduced in the clinical setting [13]. Patients used to be positioned exclusively with skin marks, but modern linear accelerators have a built-in capacity to produce three-dimensional images with the treatment beam (megavoltage CT) or separate X-ray tubes and detectors (kilovoltage CT). Recently, two hybrid machines integrating a linear accelerator and magnetic resonance imaging were approved for clinical use [14]. While the results of magnetic resonance-guided external beam radiotherapy for gynecological malignancies are not available yet, the technique offers exciting prospects for daily adaptive radiotherapy and live imaging during treatment delivery without additional exposure to ionizing radiation.

Not only external beam radiotherapy but also brachytherapy has evolved and is now a field of active research. Brachytherapy is a key element in the treatment of gynecological cancers. Image-guided or magnetic resonance imaging-guided three-dimensional brachytherapy effectively reduces radiation doses to organs at risk and may also reduce toxicity [15–17].

The addition of chemotherapy enhanced the effectiveness in terms of overall survival and local control of radiotherapy-based approaches in multiple entities [18]. Typically, chemotherapeutic agents such as cisplatin are administered concomitantly during the course of radiotherapy. In fact, gynecological entities such as cervical cancer rank among those entities that benefit most from the addition of chemotherapy in terms of overall survival [18]. The purpose of combining radiotherapy and chemotherapy is to achieve "supra-additive" efficacy [19]. In other words, the combination is more effective in terms of tumor control than one would expect by the mere addition of each individual modality. Mechanistically speaking, tumor cells are more prone to radiation-induced DNA damage when exposed to chemotherapeutic agents that also interfere with DNA or its repair. Although normal tissue also experiences a higher level of acute toxicity, late toxicity is usually not, or just mildly increased after chemoradiotherapy compared to radiotherapy alone [20].

More recently, the combination of radiotherapy and immunotherapy has emerged as an attempt to further improve survival [21]. As radiotherapy harbors immunomodulatory effects that could enhance the effectiveness of immunotherapy, clinical trials have investigated their combination in multiple entities [22]. As shown in a phase-III trial, the immune checkpoint inhibitor durvalumab is associated with a significant survival benefit in patients with stage III non-small cell lung cancer who have undergone definitive chemoradiotherapy [23]. Several phase-I/II trials are currently investigating a similar approach in gynecological malignancies such as cervical cancer [24].

Taken together, innovations in the planning and delivery of radiotherapy as well as the delivery of concomitant chemotherapy have improved the therapeutic index of radiotherapy-based approaches by increasing efficacy and reducing toxicity. Radiotherapy continues therefore to be indicated as an adjuvant or alternative treatment to surgery in some gynecological cancers and clinical scenarios, whereas it may be obsolete in others. However, the various indications for radiotherapy and their relation to surgery may not be well known to all members of the multidisciplinary care team. Furthermore, a specialist in one field may find it difficult to consider all aspects that require attention in the interdisciplinary setting. Therefore, interdisciplinary tumor boards and the sharing of knowledge play an increasing role in the treatment of gynecological cancers. This comprehensive review summarizes the role of radiotherapy and its intersections with surgery for gynecological cancers. The review is intended to provide an overview for physicians outside the field of radiation oncology.

2. Methods

A narrative literature review was performed. This review focusses on newly diagnosed gynecological malignancies without distant metastases. The primary aim was to assess the

current evidence and developments concerning radiotherapy and to put them into context with surgery in order to offer an overview for clinicians. The context of surgery was chosen, as both are local modalities that may complement each other. The most recent US-American National Comprehensive Cancer Network guidelines and European guidelines (ESMO, ESTRO, ESGO) were reviewed. In addition, PubMed/MEDLINE was searched for relevant studies in the English language with no time restriction (see Table S1). The search strategy included ovarian, endometrial, cervical, vaginal, and vulvar cancer. The intervention was radiotherapy, and outcomes were survival and quality of life. Studies were chosen by judgment of the authors and relevance to the multidisciplinary care team without preset eligibility criteria. Additional relevant studies were included from the personal reference databases of the authors. The search was conducted in July 2020.

3. The Role of Radiotherapy in Newly Diagnosed Localized Disease

3.1. Epithelial Ovarian Cancer

Ovarian cancer is the seventh most common type of cancer in women; the global 5-year survival rate for this entity is low at 30–40%. The highest incidence rates are 11.6/100,000 women in Central and Eastern Europe [25]. Most cases are of epithelial histology, and various subtypes exist [26]. Cytoreductive surgery and adjuvant systemic therapy are the mainstays of treatment for newly diagnosed cases, and have led to better survival rates [27]. Notwithstanding diverse opinions on the subject, the primary and most widely used surgical access is laparotomy. As shown in a meta-analysis of retrospective studies, minimally invasive surgery might yield similar survival outcomes compared to laparotomy. However, this thesis will have to be confirmed in prospective studies [28].

Neither US-American nor European guidelines recommend radiotherapy for epithelial ovarian cancer in the primary or adjuvant setting [29,30]. Historically, adjuvant whole abdominal radiotherapy has been used with the intention of reducing relapse rates and prolonging survival. Retrospective data suggest an absolute increase of 20% in 5-year disease-free survival for patients with FIGO stage IC and II by the addition of radiotherapy to surgery and chemotherapy [31]. However, the large majority of randomized controlled trials performed in the 1990s yielded no robust benefit from radiotherapy when compared to chemotherapy [32,33]. Although one randomized controlled study reported a significantly improved 5-year progression-free survival after adjuvant radiotherapy (56%) compared to chemotherapy (36%) in FIGO stage III patients, it also reported higher toxicity in the radiotherapy arm [34]. In these earlier trials, the authors employed radiotherapy techniques considered outdated in current times, because the procedures hardly permitted sparing of organs at risk. Recently, a prospective phase-II-trial reported favorable toxicity results for adjuvant whole abdominal radiotherapy using intensity-modulated radiotherapy in FIGO stage III ovarian cancer [35]. Yet, we still lack robust efficacy data for this approach. Therefore, adjuvant whole abdominal radiotherapy should not be used for the treatment of epithelial ovarian cancer.

3.2. Endometrial Cancer

Endometrial cancer of the uterine body is the fifth most common cancer in women and the most common gynecological cancer in high-income countries. Its incidence is highest in the USA at 19.1/100,000 women. Endometrial cancer usually occurs in postmenopausal women; obesity is a major risk factor [36]. As most patients are diagnosed in early stages by the presence of atypical vaginal bleeding, 5-year overall survival rates exceed 80% in high-income countries [37]. However, in patients with FIGO stage III or IV disease, the 5-year overall survival rate drops to approximately 57% or 20%, respectively [36]. Traditionally, endometrial cancer was classified as type I (endometrioid carcinoma) or type II disease (serous or clear-cell carcinoma) with distinct clinical and molecular features, although this may be regarded as a simplistic distinction [38]. Using advanced methods with genomic, transcriptomic, and proteomic characterization, molecular classification of endometrial cancer yielded four distinct molecular subtypes [39]. Recent data from the PORTEC-3 trial

(see below) suggest that molecular subtypes may influence the choice of adjuvant therapy. This aspect will be addressed prospectively in the PORTEC 4a-trial for adjuvant vaginal brachytherapy [40–42].

Laparoscopic surgical staging is generally recommended, and includes hysterectomy with bilateral salpingo-oophorectomy with or without bilateral pelvic and para-aortic lymph node dissection [43,44]. The resulting tumor stage may be confined to the uterus (FIGO I), extend to the cervix (FIGO II), beyond the uterus (FIGO III), or invade adjacent organs with or without distant metastases (FIGO IV) [45]. Early-stage disease (FIGO stage I) is further subdivided into a low, intermediate, or high-risk subgroup based on the depth of invasion, histology, and grading [46]. Brachytherapy as well as external beam radiotherapy, each with or without chemotherapy, have been investigated extensively in different clinical scenarios of endometrial cancer.

In the adjuvant setting, vaginal brachytherapy is not indicated for FIGO stage I low-risk disease, but is usually recommended for intermediate-risk cases, especially in the presence of further risk factors ("high-intermediate risk") [43,44]. This rationale was elaborated among others by the PORTEC-1 and PORTEC-2 trials. The PORTEC-1 trial studied adjuvant external beam radiotherapy versus observation in intermediate-risk cases [47]. No benefit was registered in overall survival, but intermediate-risk cases with additional risk factors had fewer local vaginal recurrences after external beam radiotherapy at the expense of higher toxicity. These results were confirmed by two other randomized controlled trials on external beam radiotherapy vs. observation [48,49]. Therefore, the PORTEC-2 trial studied external beam radiotherapy versus vaginal brachytherapy in high-intermediate risk patients. Although more pelvic recurrences were noted in the brachytherapy group, the vaginal control rate and overall survival rate were comparable [50]. However, brachytherapy was associated with significantly less toxicity and better health-related quality of life [51,52]. Concerning "real-world" data, vaginal brachytherapy was also associated with fewer recurrences as well as reduced mortality rates in a large US-American population-based analysis of FIGO stage I disease [53]. Brachytherapy was potentially underused compared to guideline recommendations.

Concerning high-risk patients, which include those with FIGO stage I (high risk subgroup) and FIGO II-IV disease, most guidelines recommend adjuvant external beam radiotherapy to the pelvis [43,44]. Important evidence has recently been added to the adjuvant management of these high-risk cases, as the role of systemic therapy with or without radiotherapy was unclear until then. The randomized phase-III-trial PORTEC-3 reported the results of adjuvant external beam radiotherapy with or without chemotherapy [54]. The study included FIGO stage I (high risk), stage II, and stage III cases. Overall 5-year survival rates were significantly improved with chemoradiotherapy (81.4% vs. 76.1%, $p = 0.034$), after two cycles of cisplatin during radiotherapy and four cycles of carboplatin/paclitaxel after radiotherapy compared to radiotherapy alone. Although grade 3 toxicity was similar, grade 2 toxicity was higher after chemoradiotherapy mainly due to peripheral neuropathy. This is reflected in health-related quality of life data at 12 and 24 months after treatment; most scales were similar between groups except for neurological symptoms [55].

The role of external beam radiotherapy was further refined by the randomized phase-III-trial GOG 258, in which adjuvant chemoradiotherapy was compared with adjuvant chemotherapy alone [56]. The large majority of patients included in the investigation had locally advanced FIGO stage III disease. The primary endpoint of the study, namely relapse-free survival, did not differ significantly between the two arms. Overall survival data were not available in the primary publication. At 5 years, vaginal recurrences (2% vs. 7%; HR 0.36) and pelvic or para-aortic nodal recurrences (11% vs. 20%; HR 0.43) were lower in the chemoradiotherapy group. However, distant recurrences (27% vs. 21%; HR 1.36) were more common after chemoradiotherapy compared to chemotherapy alone. Overall toxicity rates were comparable, but toxicity profiles differed. Health-related quality of life parameters were worse after chemoradiotherapy, but did not achieve the preset clinically meaningful difference. The essence of these data is that both modalities, radiotherapy and

chemotherapy, are important for local and distant control, respectively. Their combination may prolong overall survival in high-risk patients. In fact, a registry-based study on FIGO stage III patients reported the increased use of chemoradiotherapy over time, which was accompanied by higher overall survival rates [57]. Further trials could elucidate whether a sequential or "sandwich" combination of radiotherapy and chemotherapy would reduce toxicity without compromising the prognosis [58]. Until then, shared decision-making remains the key factor in determining the appropriate adjuvant treatment modality for the individual patient.

The extent of external beam radiotherapy is strongly dependent on prior surgical evaluation of lymph nodes. Extension of the field of treatment to the para-aortic lymph nodes is associated with greater toxicity. The approach towards lymph node assessment varies considerably among institutions. There is a paucity of randomized trials comparing different approaches such as pelvic lymph node dissection with or without para-aortic lymph node dissection, sentinel lymph node biopsy, or no surgical nodal staging in different clinical scenarios. Each of these approaches may be associated with benefits, depending on the clinical scenario and the patient's preference [59,60]. In accordance with recent clinical trials, para-aortic lymph nodes should be included in the radiation field only in patients with evidence of nodal spread to this site on imaging studies or pathological investigation [56].

Upfront primary radiotherapy is not recommended as a substitute for surgery because of the absence of appropriate evidence and the potentiality of a compromised prognosis. Radiotherapy, however, is used and recommended as primary treatment in patients who are medically unfit for surgery or when primary surgery is technically not feasible [43,44]. The treatment is usually based on brachytherapy with or without external beam radiotherapy, depending on the extent of the tumor. Although the majority of published reports in this regard are either retrospective or small prospective single-center studies, a systematic review of 2694 patients yielded promising results [61]. Grade 3 or poorer late toxicity rates were below 4%, and the disease-specific 5-year survival rate approached 80%, though highly dependent on the extent of disease. The rather favorable disease-specific survival is reflected in studies reporting as much as a 3.4-fold higher risk of dying due to intercurrent disease than due to endometrial cancer after primary radiotherapy [62,63].

The efficacy of a primary radiotherapy-based approach may be enhanced by the addition of chemotherapy, although the patient's tolerance of an intensified treatment regimen could be limited in this medically unfit population. Larger prospective multicenter trials will be needed to validate the efficacy and elucidate the impact of this approach on health-related quality of life in patients who receive primary radiotherapy for endometrial cancer.

To sum up, adjuvant brachytherapy should be considered in intermediate risk FIGO stage I disease with additional risk factors to reduce vaginal recurrences (Table 1). External beam radiotherapy combined with chemotherapy is indicated in many high-risk patients in order to improve local control and overall survival. Primary radiotherapy is an option in patients who are not eligible for surgery (Table 2).

Table 1. Schematic overview of common indications for adjuvant radiotherapy in newly diagnosed localized gynecological malignancies. Adjuvant radiotherapy is not used for ovarian cancer. The approach to vaginal cancer is similar to that for cervical cancer. Ovarian and vaginal cancer are therefore not listed here.

Entity	Endometrial Cancer		Cervical Cancer	Vulvar Cancer	
Postoperative clinical scenario	High-interm. risk in early stage	High risk in early stage or advanced stage	Risk factors (e.g., tumor > 4 cm, deep stromal invasion, positive resection margins)	Primary tumor with persistent positive resection margins	Lymphadenectomy with ≥2 positive LN or ECE
Radiotherapy	BT	EBRT +/− Chemo	EBRT +/− Chemo +/− BT	EBRT	EBRT
Most relevant available efficacy outcome	Vaginal recurrence	Pelvic/Vaginal recurrence, overall survival	Local recurrence, progression-free survival	Overall survival	Overall survival
Corresponding Publications	Prospective, randomized [46,49]	Prospective, randomized [53,55]	Prospective, randomized [64]	Retrospective [65]	Prospective,randomized [66]

Abbreviations: +/−, with or without; BT, brachytherapy; EBRT, external beam radiotherapy; LN, lymph node; ECE, extracapsular extension.

Table 2. Schematic overview of common indications for primary radiotherapy in newly diagnosed localized gynecological malignancies. Primary radiotherapy is generally not used for ovarian cancer. The approach towards vaginal cancer is similar to that for cervical cancer. Ovarian and vaginal cancer are therefore not listed here.

Entity	Endometrial Cancer	Cervical Cancer	Vulvar Cancer	
Clinical scenario	Medically or surgically inoperable	FIGO stage > IB2 or >II	Singular micrometastasis (≤2 mm) in SLN-biopsy	Medically or surgically inoperable
Radiotherapy	BT +/− EBRT +/− Chemo	EBRT + BT + Chemo	EBRT to the groin	EBRT + Chemo
Most relevant available efficacy outcome	Disease-specific survival	Overall survival	Local recurrence	Complete response rate
Corresponding Publications	Retrospective [60]	Prospective, randomized [67,68]	Prospective, non-randomized [69]	Prospective, non-randomized [70]

Abbreviations: +/−, with or without; BT, brachytherapy; EBRT, external beam radiotherapy; SLN, sentinel lymph node.

3.3. Cervical Cancer

Cervical cancer is the fourth most common cancer in women. While the global incidence is 13.1/100,000 women, low- and middle-income countries have markedly higher rates of 75/100,000 women [71]. As the incidence has already dropped in countries with effective screening programs, a further decrease is expected with the implementation of HPV vaccination [72,73]. The most common histological subtype is squamous cell carcinoma. Adenocarcinoma may be associated with a poorer prognosis [74]. The FIGO staging system was revised in 2018 [75]. The tumor may be confined to the uterine cervix (FIGO I), extend beyond the uterus (FIGO II), extend further into the true pelvis and/or with lymph node involvement (FIGO III), or invade the bladder or rectum with or without distant metastases (FIGO IV). Depending on the presence of risk factors, each of these stages is divided into further subgroups.

Generally, most patients with FIGO stage I disease are treated with surgery [76–78]. Surgical approaches include conization, trachelectomy, and (radical) hysterectomy with or without lymph node dissection. The surgical approach in the individual patient depends on risk factors and the resulting substage, the patient's desire to preserve her fertility, and local expertise. Guidelines suggested minimally invasive surgery or laparotomy for radical hysterectomy in early stages [78]. Minimally invasive surgery was routinely used before the availability of randomized data compared to open surgery [79]. Surprisingly, however, minimally invasive surgery is associated with significantly poorer survival outcomes, as reported recently in a randomized trial and a large cohort study [80,81]. The former trial randomized 613 women with cervical cancer of FIGO IA1 (and lymphovascular invasion) to FIGO IB1 either to minimally invasive surgery or open surgery. At a median follow up of 2.5 years, the 3-year overall survival was worse after minimally invasive surgery compared to open surgery (93.8% vs. 99%; HR 6.00; CI, 1.77–20.30). Of 34 recurrences, all women except one had stage IB1 disease of grade 2 or higher. Therefore, the role of minimally invasive surgery for early stages may be debated. However, only about 8% of the patients in both groups had early stages of IA1 or IA2. In addition, the survival benefit after open surgery was still present even after adjusting for stage of disease [80]. Therefore, the minimally invasive access was more or less abandoned in the surgical treatment of cervical cancer. One of its disadvantages is that, despite its widespread popularity, many surgeons may lack the experience to perform these challenging and financially attractive operations. Recently, retrospective data on the influence of surgeon volume and experience was reported. A study that focused on robot-assisted minimally invasive surgery reported less local recurrences for tumors smaller than 2 cm in the absence of adjuvant chemoradiotherapy in more experienced centers [82]. Cusimano and colleagues, however, still observed inferior survival after minimally invasive surgery for stage IB1 cases compared to open surgery, even after adjusting for surgeon volume [83]. Despite the large number of suggested explanations, we do hence not know the exact reasons for different survival outcomes after open or minimally invasive surgery in cervical cancer patients [84]. Until the problem is resolved, we will have to accept the retrograde step in oncological surgery and may even be compelled to review the surgical access for endometrial cancer.

The higher the substage of the cervical cancer, the more primary radiotherapy is an alternative for example in stage IB2 or even preferred to surgery as in stage IB3 (Table 2) [76]. The combination of surgery and radiotherapy causes excessive morbidity [85]. As higher stages may require adjuvant radiotherapy after initial surgery, and as primary radiotherapy results in at least equivalent survival rates, primary radiotherapy is usually preferred from stage II on [76,85–88]. Primary radiotherapy includes external beam radiotherapy, brachytherapy, and concomitant chemotherapy with cisplatin.

Whether a primary surgical or a primary radiotherapy-based approach should be given preference for stage IB2-IIB disease is a matter of active research and discussion. Neoadjuvant chemotherapy prior to surgery was superior to radiotherapy alone [89]. Radiotherapy alone, however, is outdated in most cases because the addition of concomitant chemotherapy significantly improves overall survival [67]. Two randomized phase-III-trials

recently reported outcomes of neoadjuvant chemotherapy plus surgery versus chemoradiotherapy in stage IB2-IIB disease [68,90]. The multicenter European study showed similar overall survival outcomes, but the surgical arm had significantly more acute toxicity levels of grade 3 or higher (35% vs. 21%; $p < 0.001$). In addition, 36% of patients in the surgical arm needed adjuvant radiotherapy, whereas only 3 % had additional surgery in the radiotherapy arm [68]. The single-center Indian trial also reported similar overall survival rates. The 5-year disease-free survival, however, was significantly better in the radiotherapy arm (69.3% vs. 76.7%; $p = 0.038$). At 24 months after treatment, there was no difference in toxicity except for vaginal toxicity, which was higher after radiotherapy (12% vs. 26%; $p > 0.001$) [90]. Viewed together, the results of these studies appear to favor a primary radiotherapy-based approach in stage IB2-IIB disease. Furthermore, it would be reasonable to state that current toxicity rates are lower than those observed in these trials, because intensity-modulated external beam radiotherapy and image-guided brachytherapy were either omitted altogether or not used on a routine basis [9].

The question as to whether neoadjuvant chemotherapy before primary chemoradiotherapy could improve outcomes was tested in a recent phase-III-trial. Surprisingly, overall survival was significantly poorer in the group that received neoadjuvant chemotherapy compared to chemoradiotherapy alone [91]. Therefore, concurrent chemoradiotherapy remains the standard of care for locally advanced disease.

Although the combination of surgery and radiotherapy is generally avoided in the treatment setting as mentioned above, it may be used for staging in the management of para-aortic lymph nodes. When clinical staging reveals the involvement of pelvic lymph nodes, the risk of para-aortic lymph node dissemination is high and is associated with a poorer prognosis [92,93]. Extension of the field of radiotherapy to the para-aortic lymph nodes up to the level of the renal vessels increases toxicity, albeit less so with intensity modulated radiotherapy [94]. Hence, if pelvic lymph nodes are affected but para-aortic spread is unclear or even negative per clinical staging, laparoscopic para-aortic lymph node staging may be performed prior to primary chemoradiotherapy, as stated in current guidelines [76,77,95]. The field of radiotherapy is usually only extended in cases of evident para-aortic lymph node disease; prophylactic extension of the field remains controversial [96–98]. This approach is supported by a study reporting favorable survival rates in locally advanced cases with a negative PET-CT for para-aortic involvement; the patients underwent laparoscopic staging and the field of radiotherapy was defined subsequently [99]. The laparoscopic approach was either extra- or transperitoneal and included lymphadenectomy from the aortic bifurcation to the left renal vein. The field of radiotherapy was extended to the para-aortic region if para-aortic involvement of any size was present per histology. This was the case in 12% (29/237) of the patients. Routine clinical staging versus laparoscopic lymph node dissection for FIGO (2009) IIB-IVA cases was investigated in just one randomized study [100]. In the arm of clinical staging, suspicious para-aortic lymph nodes were biopsied via CT-guidance. Biopsies revealed para-aortic lymph node metastases in 8% of the cases (9/114). In the arm of surgical staging, the surgical approach was mostly laparoscopic and extra- or transperitoneal. Of note, the field of lymphadenectomy encompassed pelvic lymph nodes as well as para-aortic lymph nodes up to the renal vessels. Lymphadenectomy resulted in an upstaging in 33% (39/120) and in the detection of positive para-aortic lymph nodes in 24% (29/120) of the cases. In histologically proven para-aortic involvement of any size, the field of radiation was extended to the para-aortic region in both arms. Patients did not undergo routine PET-CT imaging in this study. Although the acute toxicity profile was low after surgical staging, there was no statistically significant difference in overall survival per randomized arm [100,101]. Similarly, a recent retrospective cohort analysis suggested no survival benefit after surgical staging compared to clinical staging [102]. Depending on its availability, PET-CT is now the standard of care for staging in some countries. Therefore, we need randomized studies comparing surgical staging versus clinical PET-CT-based staging. Until

then, surgical staging remains an option for individualized treatment, especially if PET-CT imaging is not routinely available.

Local dose escalation to the cervix is an essential component of the primary radiotherapy-based approach. This is usually accomplished by intracavitary brachytherapy. Paralleling the premature adoption of minimally invasive surgery and in the absence of randomized data, advanced external beam radiotherapy techniques were used to an increasing extent as a substitute for brachytherapy [103]. Stereotactic external beam radiotherapy delivers high ablative doses to the tumor at steep dose gradients to surrounding normal tissue. Diverse data have been reported on dose escalation by stereotactic radiotherapy. While one population-based study reported equivalent survival rates, another showed poorer survival compared to brachytherapy [103,104]. In addition, a single-arm phase-II-trial of stereotactic radiotherapy for dose escalation was terminated early due to excessive toxicity [105]. Particle radiotherapy, including protons or carbon ions, is a further possible technology for radiation dose escalation and its outcomes continue to be investigated [106,107].

Another strategy for the local intensification of treatment was tested in a phase-III-trial in which brachytherapy was compared with radical hysterectomy after external beam radiotherapy. Additional surgery yielded no benefit in terms of local control or survival [108]. Taken together, brachytherapy remains the standard of care for dose escalation; its outcomes continue to improve with the implementation of image guidance for planning treatment [109].

In the postoperative adjuvant setting of early-stage cervical cancer, guidelines recommend observation alone or adjuvant radiotherapy with or without chemotherapy in the presence of risk factors (Table 1) [76,77]. Adjuvant external beam radiotherapy in FIGO IB2 patients with two additional risk factors (e.g., tumor size > 4 cm, deep stromal invasion) is associated with significantly fewer local relapses and significantly better progression-free survival, as shown in a randomized phase-III-trial [64]. However, when pathological staging after radical hysterectomy yields nodal involvement, positive resection margins or parametrial invasion, adjuvant chemoradiotherapy should be given preference because the risk of recurrent disease is high in these patients [76,77]. Moderate evidence suggests a survival benefit from the addition of concomitant chemotherapy to external beam radiotherapy in the adjuvant setting as well [110]. Additional vaginal brachytherapy is an option in patients with a high risk of vaginal recurrence [77]. Indeed, brachytherapy is associated with a significantly better overall survival, especially in the presence of positive resection margins [111]. However, when the initial work-up shows that the patient would probably need adjuvant radiotherapy, the guidelines recommend a primary radiotherapy-based approach rather than primary surgery [77].

In conclusion, primary surgery is the treatment of choice for early stages of cervical cancer, whereas primary chemoradiotherapy is recommended at least from FIGO stage II on. Brachytherapy is essential in a primary radiotherapy-based approach. Although the role of laparoscopic para-aortic nodal staging is unclear, it may be used to define the extent of the field of radiation.

3.4. Vaginal Cancer

With an incidence of 1/100,000 women, primary vaginal cancer is a rare entity [112,113]. Most cases are squamous cell carcinomas and 65% are associated with human papillomavirus infection [114]. According to the FIGO stages revised in 2009, the tumor may be confined to the vagina (FIGO I), invade the pelvis to a limited degree (FIGO II), invade the pelvis to a greater extent such as reach the pelvic wall and/or spread to lymph nodes (FIGO III), or invade adjacent organs and/or spread to distant organs (FIGO IV) [115]. Due to the rarity of primary vaginal cancer and the consequent lack of randomized data, the treatment approach is highly individualized and similar to that for cervical cancer. We have a small number of guidelines on the subject, mainly based on "expert consensus" [116,117].

Stage I vaginal cancer can be treated surgically by wide excision [118]. A radiotherapy-based approach is an alternative. In fact, from stage II on most cases are treated with

primary radiotherapy in order to achieve organ preservation [115]. A primary radiotherapy-based approach usually includes external beam radiotherapy, brachytherapy, and concurrent chemotherapy as in cervical cancer. The radiation field encompasses the pelvic lymph nodes and should be extended to the inguinal lymph nodes if the primary is located in the lower third of the vagina [115]. As in cervical cancer, brachytherapy is also an integral part of the primary radiotherapy-based approach for vaginal cancer. According to US-American guidelines, it should be used if the tumor exceeds 0.5 cm in thickness [117]. A large registry-based study confirmed the overall survival benefit of adding brachytherapy to external beam radiotherapy, regardless of tumor stage [119]. Furthermore, image-guidance is increasingly used for brachytherapy in vaginal cancer because it may be associated with better local control [120,121]. Retrospective data revealed that the concurrent administration of chemotherapy is associated with a survival benefit [122]. Therefore, cisplatin should be considered in a primary radiotherapy-based approach.

Data on toxicity and quality of life are scarce because of the retrospective nature of most studies. However, one retrospective single-center study reported overall grade 3 or 4 toxicity rates of 23% after primary radiotherapy [123]. This must be taken into account when planning treatment for the individual patient. Analogous to cervical cancer, minimally invasive surgical nodal staging may be performed prior to primary radiotherapy [115]. Minimally invasive surgery may also be offered for ovarian transposition in order to prevent radiation-induced dysfunction [115].

Taken together, the treatment approach for primary vaginal cancer is similar to that for cervical cancer because of the paucity of prospective data for this rare entity. Early stages can be treated by surgery. Primary chemoradiotherapy should be offered as an alternative or in more advanced stages in order to achieve organ preservation.

3.5. Vulvar Cancer

Vulvar cancer is uncommon and affects less than 2/100,000 women [124]. Two subgroups have been described. Vulvar cancer at a younger age is associated with human papillomavirus infection, whereas this association is less frequent in older women [125]. The 2000's witnessed an increase in the incidence of the disease in younger patients [124]. Most cases are of squamous cell histology [125]. The most prominent prognostic factor is nodal status because the 5-year overall survival is 84% in node-negative cases, compared to 30% in cases with three or more positive lymph nodes [126].

Early stages are usually treated surgically with superficial or radical (partial) vulvectomy, depending on tumor size and location, as stated in the guidelines [127,128]. In cases of positive resection margins of the primary tumor, re-excision is recommended if feasible. If this is not feasible due to imminent exenteration or if the resection margins remain positive, adjuvant radiotherapy to the primary tumor is recommended [127]. A large registry-based analysis supports this approach: a significant 3-year overall survival benefit was registered after adjuvant radiotherapy to the primary site compared to no radiotherapy (67.4% vs. 58.5%, $p < 0.001$) [65].

Due to its impact on prognosis, the assessment and management of regional lymph nodes is also important in early-stage disease with a clinically negative nodal status. Nodes should be assessed by surgery; either an inguinofemoral lymphadenectomy or a sentinel lymph node biopsy should be performed [127,128]. The latter should be restricted to smaller (<4 cm) and unifocal primary tumors without clinical evidence of nodal spread [128]. Surgical lymph node evaluation may be ipsilateral or bilateral, depending on the size and location of the primary tumor. The optimal adjuvant treatment approach concerning radiotherapy in cases of positive lymph nodes is a debated issue because the data on the subject is largely retrospective in nature (Table 1) [129].

When the sentinel lymph node biopsy reveals a singular micrometastasis (<2 mm), a US-American guideline recommends radiotherapy as an alternative to inguinofemoral lymphadenectomy [127]. Conversely, a less recent European guideline solely suggests inguinofemoral lymphadenectomy in this scenario [128]. However, a multicenter phase-II

trial recently reported only two inguinal recurrences in 129 patients treated with radiotherapy alone after the detection of a micrometastasis by sentinel lymph node biopsy [69]. Given the favorable toxicity profile of only 4.2% grade 3 toxicity, radiotherapy appears to be an appropriate alternative in the presence of a singular micrometastasis after sentinel lymph node biopsy, although randomized data on the subject are lacking. When a singular metastasis larger than 2 mm is detected per sentinel lymph node biopsy, guidelines recommend complete inguinofemoral lymphadenectomy [127,128].

In cases of two or more positive lymph nodes per lymphadenectomy or extracapsular extension, US-American and European guidelines suggest adjuvant radiotherapy to inguinal and pelvic lymph nodes in order to reduce local recurrences and improve survival [127,128]. The role of adjuvant radiotherapy was confirmed in a prospective trial in which patients with inguinal lymph node involvement were randomized either to adjuvant radiotherapy encompassing the groin and pelvis, or to pelvic lymphadenectomy [66]. The radiotherapy group had a significant survival benefit in cases of upfront clinically suspected and/or more than two affected lymph nodes. Similarly, a large multicenter cohort study showed an overall survival benefit after adjuvant radiotherapy when two or more nodes were positive [130]. Concurrent chemotherapy may be added when the risk of recurrence is rated very high due to bulky disease, extracapsular extension, or residual tumor [127]. Conversely, retrospective data revealed that adjuvant radiotherapy was not associated with better overall survival in cases of a single lymph node metastasis without extracapsular extension [130,131]. Therefore, adjuvant radiotherapy is usually not recommended in the latter scenario, although used quite often [127,128,130].

In locally advanced cases, neoadjuvant or definitive chemoradiotherapy are appropriate alternatives when complete resection is not feasible (Table 2) [127]. The field of radiotherapy should include the primary tumor as well as pelvic lymph nodes. If surgical lymph node staging was performed in the groin and yielded no evidence of nodal spread, this site may be omitted from the radiotherapy field; otherwise the treating physician should include inguinal lymph nodes in the field of radiotherapy [127]. Cisplatin is given preference in concurrent chemotherapy [127]. Prospective and retrospective data support the use of primary chemoradiotherapy in this setting. A prospective phase-II trial assessed the rate of complete clinical and pathological response after primary chemoradiotherapy in unresectable T3/T4 cases [70]. Sixty-four percent (37/58) of patients achieved a complete clinical response and, of those who had a confirmatory biopsy, 78% (29/34) experienced a complete pathological response. A retrospective study of 26 women treated with intensity-modulated radiotherapy and concomitant cisplatin reported a high complete response rate of 80.7% [132]. Complete response after chemoradiotherapy is associated with fewer recurrences and longer overall survival [132,133]. A large registry-based study of locally advanced cases reported similar survival rates in women treated with primary chemoradiotherapy compared to neoadjuvant chemoradiotherapy followed by surgery [134]. Although primary chemoradiotherapy appears to be effective, the associated toxicity must be taken into account. In the afore-mentioned phase-II-study, 15.5% (9/58) of the patients discontinued the treatment early due to toxicity [70]. In a retrospective study, 19% of patients had grade 3 or 4 toxicity after primary chemoradiotherapy [132]. We lack patient-reported quality of life data in this setting.

In vulvar cancer, radiotherapy is an alternative to inguinofemoral lymphadenectomy in the presence of a singular lymph node micrometastasis. Furthermore, adjuvant radiotherapy improves overall survival in cases of positive resection margins of the primary or extensive nodal spread. Neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy are effective in advanced disease.

4. Conclusions

Women with newly diagnosed gynecological malignancies require a multidisciplinary care team to ensure optimal treatment. This comprehensive review aimed to explore the manifold intersections between surgery, including minimally invasive surgery, and

radiotherapy in the light of recent advances and challenges. As radiotherapy and surgery are both local treatments, they do complement one another in some clinical scenarios, but also compete in others.

Adjuvant radiotherapy after surgery is generally indicated for many gynecological malignancies in the presence of risk factors for adverse oncological outcomes. Adjuvant radiotherapy reduces local relapses and ideally improves overall survival. Primary radiotherapy instead of surgery is a well-accepted and extensively investigated alternative for many patients with cervical or vaginal cancer. Minimally invasive surgery can complement this treatment approach for example by protective ovarian transposition or by determining the field size of radiotherapy after para-aortic nodal staging. Concerning endometrial and vulvar cancer, primary radiotherapy is the preferred option in localized but unresectable disease. Furthermore, modern radiotherapy techniques have reduced treatment-related toxicity, whereas concomitant chemotherapy improves overall survival in many scenarios. Any attempt to further improve the therapeutic ratio of a modality should be approached with caution, as proven by the premature adoption of minimally invasive surgery or stereotactic radiotherapy for cervical cancer prior to the attainment of high-quality data on the subject [79,80,103]. Our review highlighted the absence of patient-reported quality of life data, especially in the treatment of rare entities that require further comparative study. The latter holds true for surgery, including minimally invasive surgery, as well as radiotherapy.

To conclude, advances in surgery as well as radiotherapy contribute to improved outcomes in the treatment of gynecological malignancies if implemented carefully. The number of life years lost, however, is still significant and justifies ongoing efforts from all members of the scientific and clinical team in the field of gynecologic oncology.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/1/93/s1. Table S1: Search strategy—PubMed/MEDLINE.

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Surgical Performance Is Not Negatively Impacted by Wearing a Commercial Full-Face Mask with Ad Hoc 3D-Printed Filter Connection as a Substitute for Personal Protective Equipment during the COVID-19 Pandemic: A Randomized Controlled Cross-Over Trial

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Abstract: (1) Background: During the COVID-19 pandemic, shortages in the supply of personal protective equipment (PPE) have become apparent. The idea of using commonly available full-face diving (FFD) masks as a temporary solution was quickly spread across social media. However, it was unknown whether an FFD mask would considerably impair complex surgical tasks. Thus, we aimed to assess laparoscopic surgical performance while wearing an FFD mask as PPE. (2) Methods: In a randomized-controlled cross-over trial, 40 laparoscopically naive medical students performed laparoscopic procedures while wearing an FFD mask with ad hoc 3D-printed connections to heat and moisture exchange (HME) filters vs. wearing a common surgical face mask. The performance was evaluated using global and specific Objective Structured Assessment of Technical Skills (OSATS) checklists for suturing and cholecystectomy. (3) Results: For the laparoscopic cholecystectomy, both global OSATS scores and specific OSATS scores for the quality of procedure were similar (Group 1: 25 ± 4.3 and 45.7 ± 12.9, $p = 0.485$, vs. Group 2: 24.1 ± 3.7 and 43.3 ± 7.6, $p = 0.485$). For the laparoscopic suturing task, the FFD mask group needed similar times to the surgical mask group (3009 ± 1694 s vs. 2443 ± 949 s; $p = 0.200$). Some participants reported impaired verbal communication while wearing the FFD mask, as it muffled the sound of speech, as well as discomfort in breathing. (4) Conclusions: FFD masks do not affect the quality of laparoscopic surgical performance, despite being uncomfortable, and may therefore be used as a substitute for conventional PPE in times of shortage—i.e., the global COVID-19 pandemic.

Keywords: COVID-19; sars-cov-2; laparoscopy; surgical performance; 3D printing; skill assessment; snorkel mask

1. Introduction

As the COVID-19 pandemic has spread, various delivery bottlenecks have become apparent. Not only has there been a shortage of everyday objects, but also shortages of many medical products, especially in the field of respiratory and personal protective equipment (PPE), such as filtering facepiece (FFP) masks. In response to that, inventive minds soon found a promising alternative—full-face diving (FFD) masks, which are suitable for everyday clinical practice after minor adjustments [1–6]. Using an ad hoc 3D-printed adapter, a common heat and moisture exchange (HME) respiratory filter could be installed

on top of the mask to filter pathogens and allow a clean airflow (Figure 1). Ad hoc 3D printing has enabled the rapid prototyping of solutions in different situations in surgical research with a quick production, highly adaptive modelling, and independence from industrial partners [7]. This has become a popular subject during the COVID-19 pandemic, due to the shortages of PPE and other material in hospitals.

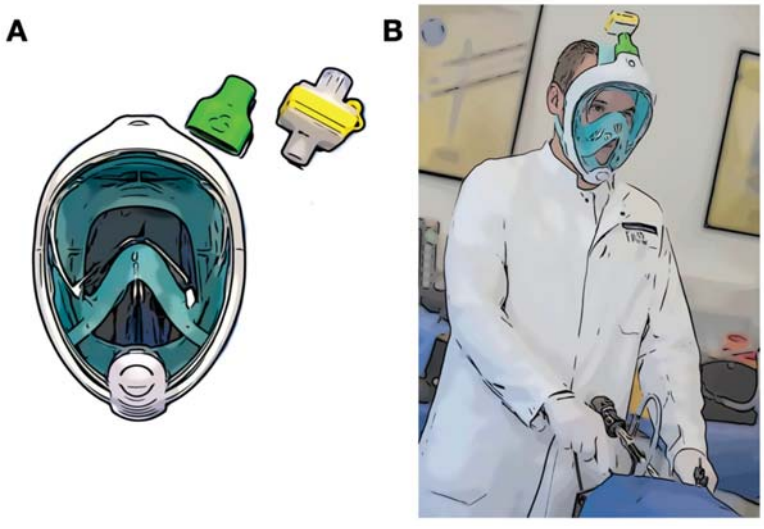

Figure 1. Schematic representation. (**A**) A full-face diving mask with a 3D-printed adapter (green) and air filter (yellow); (**B**) A participant.

FFD masks have been proposed as a solution for both shortages of conventional non-invasive ventilation material and also the lack of PPE for health care workers. The FFD masks can be reused after a thorough but easy disinfection with a combination of disinfectant wipes for flat surfaces and a liquid disinfectant agent for the breathing channels. The idea quickly became popular through (social) media and was rapidly spread around the world. The principal is particularly appealing to the medical community, especially surgeons and other health care workers in the operative and interventional fields, who work in close proximity to patients' bodies and are directly exposed to bodily fluids and aerosols. The practicality of such an approach tempted us to dive into clinical implementation. The idea, which may first sound like a joke, has suddenly become a reality—extreme circumstances require extraordinary measures. However, it is not clear if wearing an FFD mask may alter performance during everyday work and therefore compromise patient safety, especially while performing complex surgical tasks. Factors such as the limited view through the visor, the heat, and the restricted air circulation within the mask might greatly affect surgeon's wellbeing and lead to concentration issues and low performance. To our knowledge, the impact of the use of an FFD mask on the quality of surgical performance has not been evaluated yet. We therefore aimed to assess laparoscopic surgical performance while wearing an FFD mask in a dedicated randomized controlled trial in standardized settings with a homogenous group of participants.

2. Experimental Section

2.1. Study Design and Tasks

This was a randomized controlled cross-over trial recruiting 40 laparoscopically naive medical students with no known health issues or history of respiratory illnesses. Each participant participated in the study on a voluntary basis and signed an informed consent form. All the participants were recruited from the medical faculty of the University of

Heidelberg as part of a clinical elective course over a two-month period. The study took place in the Training Center for Minimally Invasive Surgery (MIC) in the Department for General, Visceral, and Transplant Surgery at Heidelberg University Hospital, Germany. The study was approved by the local ethics committee at Heidelberg University (S-436/2018). After completing a basic laparoscopic training based on the Fundamentals of Laparoscopic Surgery Manual (FLS), the participants were randomized into two groups (with an allocation ratio of 1:1): the FFD mask group and the standard surgical mask group. As PPE, we used the Easybreath© full-face diving mask (Subea^{TM}, Decathlon, France). The breathing valve of the mask was fitted with a 3D-printed adapter made out of polylactide (PLA), to the top of which a conventional breathing air filter (HME-Filter) was connected (Figure 1). The adapter was printed according to the freely accessible stereolithography (stl-) files provided by the engineering company Custom Surgical® [8]. The masks were disinfected and prepared according to in-house protocol.

The students underwent laparoscopic suturing training on standard surgical suture pads until predefined proficiency levels were reached [9,10] and then were asked to perform a laparoscopic cholecystectomy on cadaveric porcine gall bladders [11–13]. As the method of instruction, we followed Peyton's Four-Step Approach (demonstration, deconstruction, comprehension, and execution), as described elsewhere [14,15]. Depending on the assigned group, the participants would only wear the FFD mask for either the cholecystectomy or the suturing task (Figure 2). Global and specific Objective Structures Assessments of Technical Skills (OSATS) checklists were used for the evaluation of suturing and cholecystectomy. The OSATS is a validated assessment tool for rating a student's skills in laparoscopic cholecystectomies [15]. The global subscale deals with general performance during surgical procedures, such as the handling of instruments and respect for tissue. The specific subscale assesses specific aspects of a laparoscopic cholecystectomy, such as the preparation of the Calot Triangle or the prepping of the gall bladder. Because of its higher construct validity [16], the performance was directly rated by a trained expert using the respective OSATS criteria. For the knot-tying task, the total time needed to reach proficiency and the number of attempts were collected. In addition, all the participants were asked to answer a questionnaire on their personal experience while wearing the FFD mask, with an emphasis on comfort and subjective impact on performance.

2.2. Randomization

Upon the completion of the basic laparoscopic training, all the participants were randomized 1:1 into two groups. The randomization numbers were assigned to the participants according to the order of registration for the study. The randomization was conducted through the Research Randomizer program (http://www.randomizer.org) by an independent employee otherwise unconnected to the project. The results of the randomization were sealed in opaque envelopes labeled with consecutive numbers until they were given to the tutor. The envelopes were only opened directly at the beginning of the study for each participant.

2.3. Blinding

There was no double blinding during this study. The performance was rated by a trained expert while the participant was completing the task. The participants were instructed not to exchange experiences and information with other participants until the end of the study.

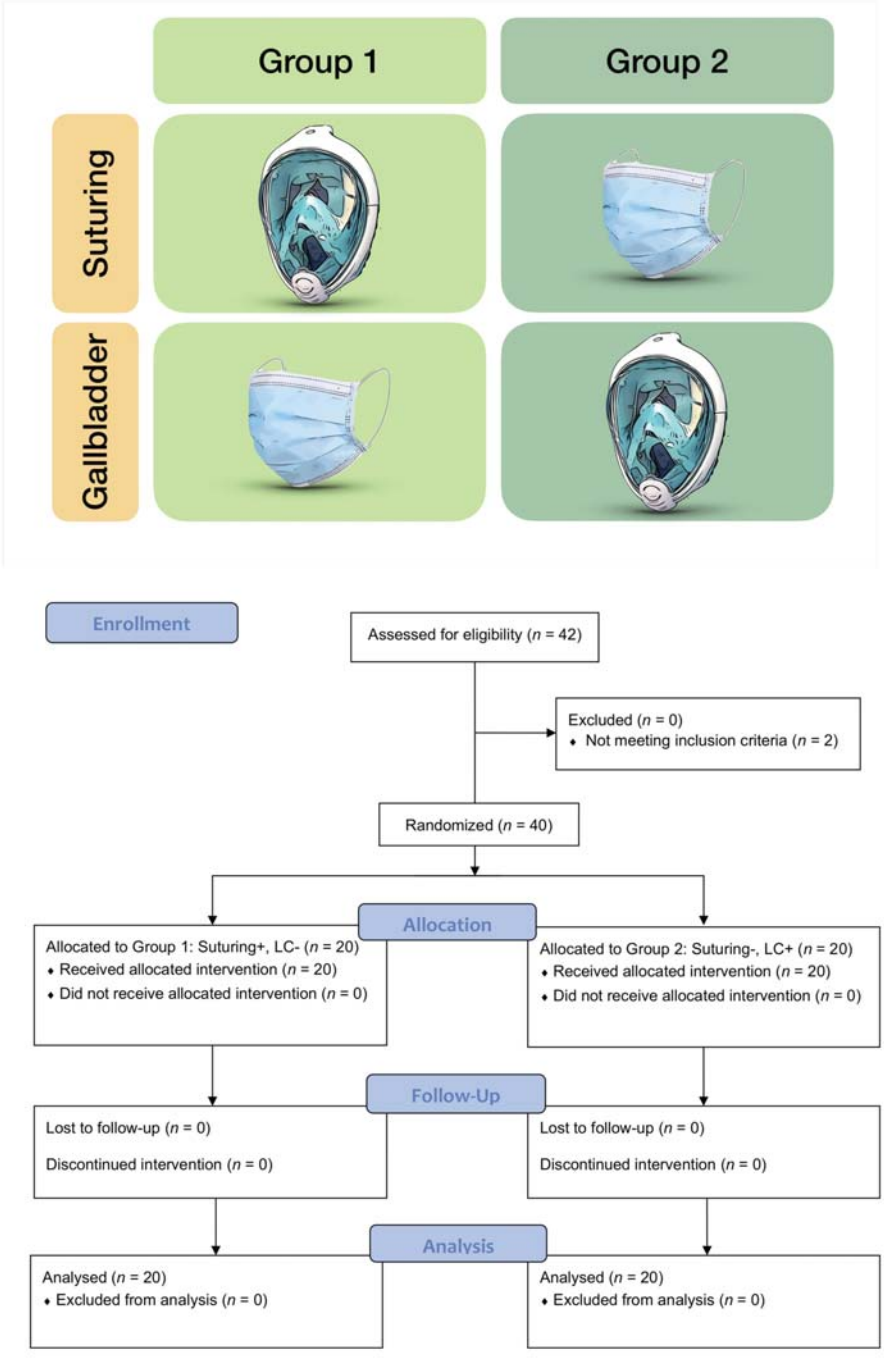

Figure 2. Study design and CONSORT 2010 flow diagram. Group 1 performed the suturing task while wearing the full-face diving mask (+), whereas Group 2 was wearing the surgical mask (−). For cholecystectomy, the masks were swapped.

2.4. Sample Size

The sample size determination was based on previous studies with identical endpoints, hypothesizing that the surgical masks would be superior to FFD [10].

2.5. Statistical Methods

An independent statistician who was otherwise not involved in the study performed the statistical analysis. All the data were entered into a spreadsheet and the statistical evaluation was carried out with R software, Version 3.6.2 [17]. For group comparisons, the non-parametric Mann–Whitney test was applied for continuous and ordinal data. Binary data were analyzed using the Chi^2 test. Continuous data are reported as medians and ranges. Binary data are reported as absolute and relative frequencies. A p-value of less than 0.05 was considered statistically significant.

2.6. Harms

Should a participant have, at any point of the study, experienced physical or mental impairments, the training was to be stopped immediately. For personal safety reasons, affected participants would have been excluded from further participation in the study.

3. Results

3.1. Study Population

A total of 40 laparoscopically naive medical students (out of 42 students screened) were recruited over a two-month period (March to April 2020). They were randomized into the two groups with an allocation of 1:1 and completed the study in June 2020. Group 1 had a mean age of 23.2 ± 3.1 and Group 2 of 22.5 ± 1.9 years. A total of 18 (45%) male and 22 (55%) female students participated (Table 1). Further, we did not include students (n = 2) requiring prescription glasses who were unable to switch to contact lenses, as glasses did not fit underneath the snorkel mask. The recruitment period of two months was from March until April 2020.

Table 1. Participants' general characteristics.

	Total	Group 1	Group 2
n, (%)	40 (100)	20 (50)	20 (50)
Age			
Mean (SD)		23.2 (3.1)	22.5 (1.9)
Gender			
Male, *n* (%)	18 (45)	9 (45)	9 (45)
Female, *n* (%)	22 (55)	11 (55)	11 (55)
Other, *n* (%)	0 (0)	0 (0)	0 (0)
Dropouts, *n* (%)	0 (0)	0 (0)	0 (0)

3.2. Laparoscopic Performance Outcomes

The suturing task was performed until the participant reached proficiency. Proficiency was defined as making a laparoscopic knot within a two-minute time frame and of a good quality, which was measured with a suturing-specific OSATS checklist [9,10,14]. The mean time until proficiency did not significantly differ between the snorkel mask and surgical mask group (3009 ± 1694 s vs. 2443 ± 949 s; p = 0.20). The mean number of attempts until proficiency in suturing was also not significantly different (snorkel mask 12.3 ± 5.45 vs. surgical mask 10.8 ± 3.65; p = 0.313). The participants with the highest and lowest number of attempts were featured in the snorkel mask group (n = 27 and n = 3, respectively). (Figure 3).

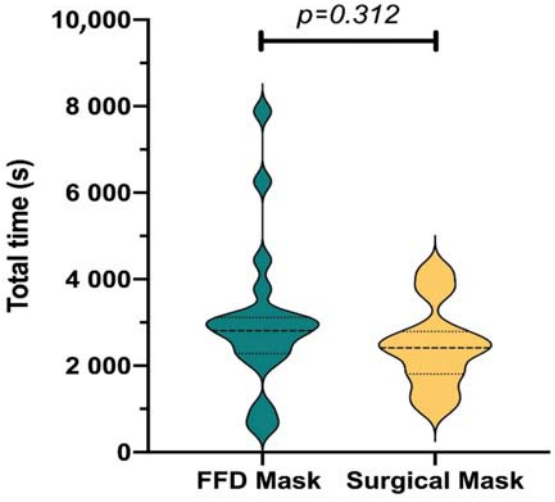

Figure 3. Total time needed to reach proficiency in the laparoscopic knot tying task. s, second.

For the laparoscopic cholecystectomy task, the medians of the global OSATS scores, with the highest possible score being 35, were not significantly different (snorkel mask 25 (IQR 22.5–26.3) vs. surgical mask 27 (IQR 23.3–28.0); $p = 0.259$). The medians of the task-specific OSATS scores, with the highest possible score being 70, were not significantly different either (41.0 (IQR 37.5–48.5) and 51.0 (IQR 33.5–56.0); $p = 0.290$) (Figure 4). There was no difference in mean time for cholecystectomy between groups (FFD mask 80.3 ± 12.7 min vs. surgical mask 77.8 ± 18; $p = 0.607$).

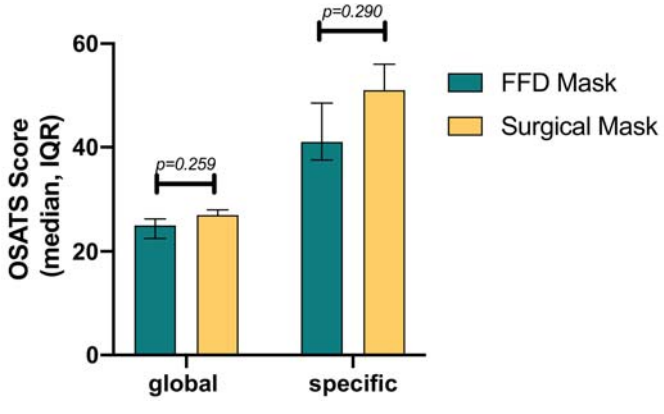

Figure 4. Global and procedure-specific Objective Structured Assessment of Technical Skills (OSATS) score results for laparoscopic cholecystectomy. The median of the OSATS scores and *p*-values are shown. IQR, interquartile range.

3.3. Full-Face Diving Mask Questionnaire

Concerning the aspect of the comfort of the FFD mask, the participants reported some difficulties in breathing and exhaustion after wearing the FFD mask. However, restriction of view or wearing the FFD mask for longer periods of time were not reported as problems. There was no distinct agreement on whether the FFD mask influenced the participants' performance. Still, wearing the FFD mask in the OR on a regular basis could have a negative impact according to participants (Figure 5).

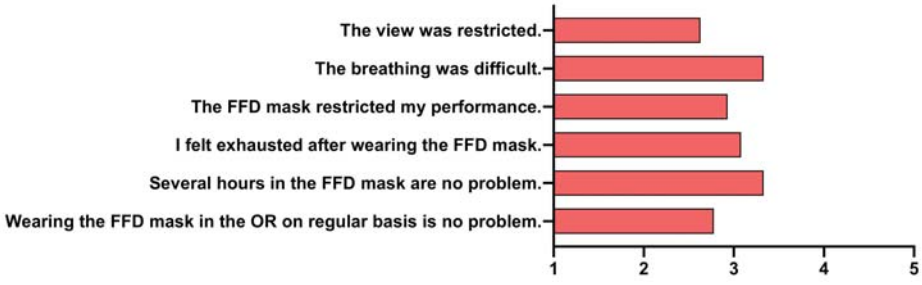

Figure 5. Full-face diving mask questionnaire. Mean Likert score values for each question are shown as bars. FFD, full-face diving.

4. Discussion

The present study did not show any difference between the group wearing an FFD mask with an HME filter and the group wearing a standard surgical mask in terms of the time and number of attempts needed until proficiency in laparoscopic suturing was reached. There was also no significant difference between groups in terms of their mean OSATS scores, completion time, and afflicted damage for the laparoscopic cholecystectomy task. Laparoscopic suturing and laparoscopic cholecystectomy were chosen as representative tasks because intracorporeal suturing is considered an advanced skill indispensable for minimally invasive surgery [18] and cholecystectomies are amongst the most common laparoscopic procedures to be completed in both elective and emergency settings.

Furthermore, the participants did not perceive the FFD mask as a detrimental restriction of performance. However, this observation was restricted only to shorter procedures and the effect of the FFD mask on surgical performance during longer laparoscopic procedures needs to be assessed in further studies. Conversely, Yánez et al. described that wearing conventional PPE, such as FFP2 masks, face shields, and two pairs of surgical gloves, was considered to be uncomfortable and impacted the personal perception of surgical performance negatively [19]. Since the participants in the present study were medical students with little prior experience in the OR, the assessment of the FFD mask could potentially differ when asking practicing surgeons. However, this lack of experience could also suggest that with the frequent use of the FFD mask, its inconveniences could be acclimated to. In some respects, the present study is limited. Since the evaluation of participants' performance was not blinded and conducted through direct observation, detection bias cannot be completely ruled out. Video-recorded analysis of performance could have been conducted in a blinded fashion, but this was not considered for practical reasons on the one hand. On the other hand, video assessment was not considered because of the superior validity of direct ratings over video ratings, which has been shown in previous studies [16], as well as the inability to assess the amount of help needed, which is an important factor in student trainees.

Further, the environmental influence factors specific to the OR—e.g., machine noises and chatter—did not occur in the training center, which might bias the hearing ability though the mask. Nevertheless, our training center reliably simulates most aspects of the OR, including specific light settings and real instruments. As a limitation of the FFD mask, we found that the voice is muffled by it, making conversations (which are such an indispensable tool during surgery!) harder to understand. Furthermore, surgeons who wear prescription glasses would need to switch to contact lenses. Lastly, the FFD mask did not fully accommodate every face shape despite the three different available sizes. These limitations might require more unconventional solutions. Auditory problems could be mitigated by wearing a small microphone underneath the mask. The improved fitting of the mask could, in critical times, be achieved by using adhesive material. On the other

hand, in times of shortage, standard PPE could be reserved to the health care workers not able to use FFD masks.

Presumably, wearing an FFD mask for an extended period of time leads to habituation and diminishes subjective feelings of discomfort. Moreover, the participants stated that they would take into consideration using the FFD mask in the OR even on a regular basis.

In the present study, using an FFD mask as PPE did not significantly affect the quality of laparoscopic surgical performance. The implication of an impairment of patient safety can therefore not be derived from the present study, nor has the equivalence of both masks been definitively proven yet. For this purpose, a larger study population might be considered to test for non-inferiority. Further, this study did not aim to evaluate any of the safety features of the FFD mask, and additional studies concerning the true value of using the FFD mask as PPE during the COVID-19 pandemic need to be conducted.

5. Conclusions

Full-face diving masks with ad hoc 3D-printed connections to HME filters do not seem to affect the quality of laparoscopic surgical performance, despite being uncomfortable, and may therefore be used as a substitute for conventional PPE in times of shortage—i.e., during the global COVID-19 pandemic—after confirming its protective features in further studies. This easy-to-assemble PPE might offer a solution to the ethical dilemma of PPE rationing during the COVID-19 pandemic.

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Intercostal Catheters for Postoperative Pain Management in VATS Reduce Opioid Consumption

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Abstract: Background: Postoperative pain after video-assisted thoracoscopic surgery (VATS) affects patients' recovery, postoperative complications, and length of stay (LOS). Despite its relevance, there are no guidelines on optimal perioperative pain management. This study aims to analyse the effects of an additional intercostal catheter (ICC) in comparison to a single shot intraoperative intercostal nerve block (SSINB). Methods: All patients receiving an anatomic VATS resection between June 2019 and May 2020 were analysed retrospectively. The ICC cohort included 51 patients, the SSINB cohort included 44 patients. Results: There was no difference in age, gender, comorbidities, or duration of surgery between cohorts. Pain scores on the first postoperative day, after chest drain removal, and highest pain score measured did not differ between groups. The overall amount of opioids (morphine equivalent: 3.034 mg vs. 7.727 mg; $p = 0.002$) as well as the duration of opioid usage (0.59 days vs. 1.25 days; $p = 0.005$) was significantly less in the ICC cohort. There was no difference in chest drain duration, postoperative complications, and postoperative LOS. Conclusions: Pain management with ICC reduces the amount of opioids and number of days with opioids patients require to achieve sufficient analgesia. In conclusion, ICC is an effective regional anaesthesia tool in postoperative pain management in minimally invasive thoracic surgery.

Keywords: minimally invasive; VATS; pain; postoperative pain control; thoracic surgery; lung cancer; intercostal catheter; opioid; regional anaesthesia

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1. Introduction

Comparing post-operative pain regimens for video-assisted thoracoscopic surgery (VATS) across the literature, a wide variety and combinations of different drugs and techniques is found to be used without a universal standard. Currently, single shot intraoperative intercostal nerve block (SSINB)—also referred to as paravertebral block (PVB) or thoracic epidural analgesia (TEA)—is considered the gold standard for pain management after thoracotomy; however, guidelines are lacking for a VATS approach [1–4].

TEA catheter placement is an effective method for postoperative pain control, but also carries specific risks (e.g., epidural hematoma or spinal cord injury) and is also time consuming, not only because of the procedure itself but also because of the management of frequently occurring hypotension, which develops in 36–75% of patients [5–7]. Additionally, reported failure rates of placed catheters range from 5.6% to 30% [8,9]. An optional technique of pain management for VATS patients is the placement of an intercostal catheter (ICC). Recent studies of ICC seem to provide inconclusive results across institutions. This may be owed to most of the studies being of retrospective character or having a small sample size [10,11].

In the presence of Enhanced Recovery After Surgery® (ERAS) protocols to improve outcome after surgery, thoracic surgery clearly needed to improve postoperative pain. Minimally invasive thoracic surgery significantly reduced postoperative pain in comparison to anterolateral thoracotomy in a controlled randomized trial [12]. However, a VATS approach is not free of pain. To further improve, there is a need to establish guidelines for reliable and effective pain management after VATS. This might not only impact patient satisfaction, but also help compete against the rising budgetary pressure for health care providers experienced worldwide, as the needed rehabilitation phase and rate of postoperative chronic pain might be decreased [13–15]. Moreover, in the current wave of the opioid epidemic, it is especially important to also focus on the role of opioids in postoperative pain management and possibilities to reduce their usage [16,17].

The aim of our study was to analyse the effect of an ICC in addition to PVB on post-operative pain, amount of opioid usage, and length of stay after surgery.

2. Experimental Section

2.1. Patient Selection

All patients from June 2019 to May 2020 receiving an anatomical VATS resection (lobectomy and segmentectomy) for primary lung cancer at our surgical institution were analysed retrospectively. Exclusion criteria were contraindications for opioid usage (one patient). Permission for analysis was granted by the local ethics committee (registration number: UN4424, 303/4.10).

A total of 95 consecutive patients were included in our database for further analysis. ICC placement was introduced in September 2019. Placement of an ICC was only attempted if the patient gave informed consent (one patient refused ICC placement). Four patients with primary non-function of the ICC (i.e., intraoperatively detected malposition of the catheter) were analysed in the PVB cohort. Furthermore, ICC placement intraoperatively was left at the discretion of the surgeon (15 patients after September 2019 without ICC).

2.2. Data Collection

Patients' data were collected in a prospectively maintained database. Recorded data included patients' age, gender, comorbidities (coronary artery disease, chronic obstructive pulmonary disease, and diabetes mellitus), type of operation, length of operation, length of stay, placement of an ICC, duration until chest drain removal, postoperative opioid usage, postoperative complications, and pain scores.

2.3. Definitions

2.3.1. Study Endpoints

Primary study endpoint was defined as opioid consumption. Secondary study endpoints were defined as amount of opioid usage, duration of opioid usage, length of operation, chest drain duration, length of stay (LOS), and postoperative complications. Patient characteristics were also analysed.

2.3.2. Surgical Technique

VATS resections follow a standardized procedure with a three-port approach using the Copenhagen technique and have been described elsewhere [18]. One camera incision is made in the seventh intercostal space, an auxiliary port incision is made in the eighth intercostal space, and a utility port incision is made in the fourth or fifth intercostal space. Thoracic drain was inserted in the camera incision at the end of the procedure.

2.3.3. Analgesic Technique

All patients received general anaesthesia based on an in-house standard, which consists of either a combination of propofol and remifentanil (total intravenous anaesthesia, TIVA) or balanced anaesthesia using sevoflurane and remifentanil, depending on patient comorbidities. At the end of the operation, patients received 1 to 2 g of metamizole, 0.5

to 1 g of paracetamol, and 4.5 to 7.5 mg of piritramide for pain control, all depending on each patient's weight. All patients received single-shot intercostal injections of bupivacaine 2.5 mg/mL under visual control at the end of the procedure covering the intercostal nerves III–IX. Postoperative pain management consisted of paracetamol and metamizole on a fixed schedule. Piritramide was only administered on request at numeric rating scale (NRS) > 5, administration of rescue medication was documented in the patient chart (time and amount). In case of repeated opioid request, other opiates might have been prescribed according to the preference of the surgeon. For statistical analysis, all prescribed opioids were converted to their morphine equivalent. Duration of opioid usage was defined as the time from surgery until the time of last opioid request during hospital stay.

At the end of surgery ICCs were placed following a standardized technique. We used a regular 16G Tuohy needle and a catheter also used for peridural anaesthesia. The ICC was inserted in the same intercostal space as the chest drain, as can be seen in Figure 1A,B. Through the ICC, 2 mg/mL of ropivacaine was applied at a fixed rate of 6 mL/h with the same pumps as for epidural administration. ICCs were removed at the time of chest drain removal, or on pod 3 if the chest drain was kept in place because of an air leak.

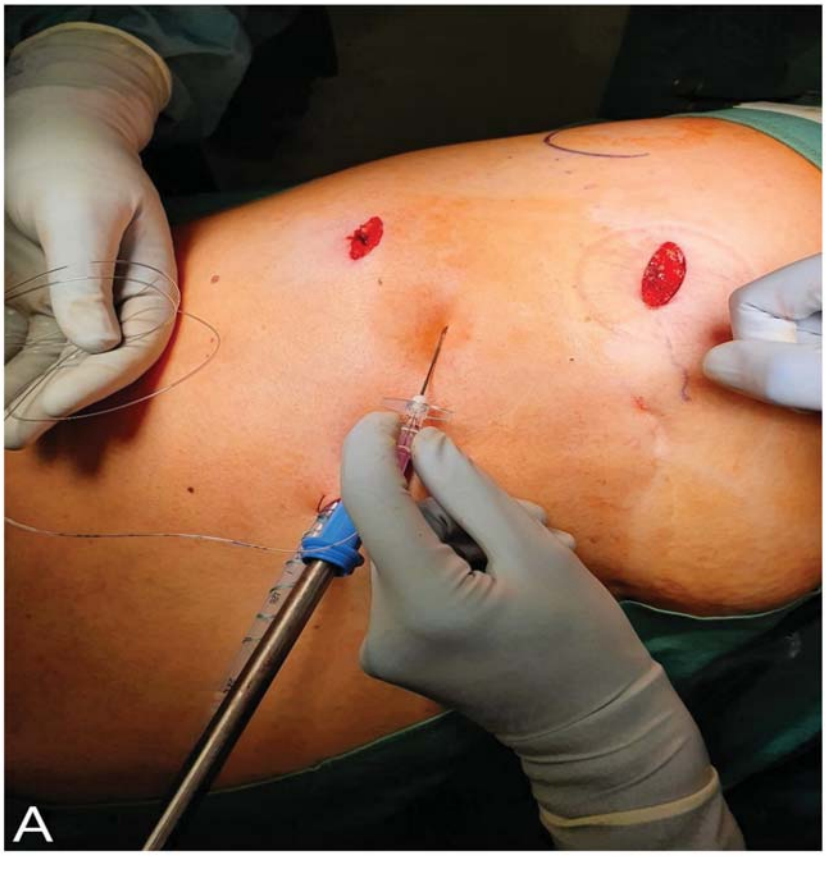

Figure 1. *Cont.*

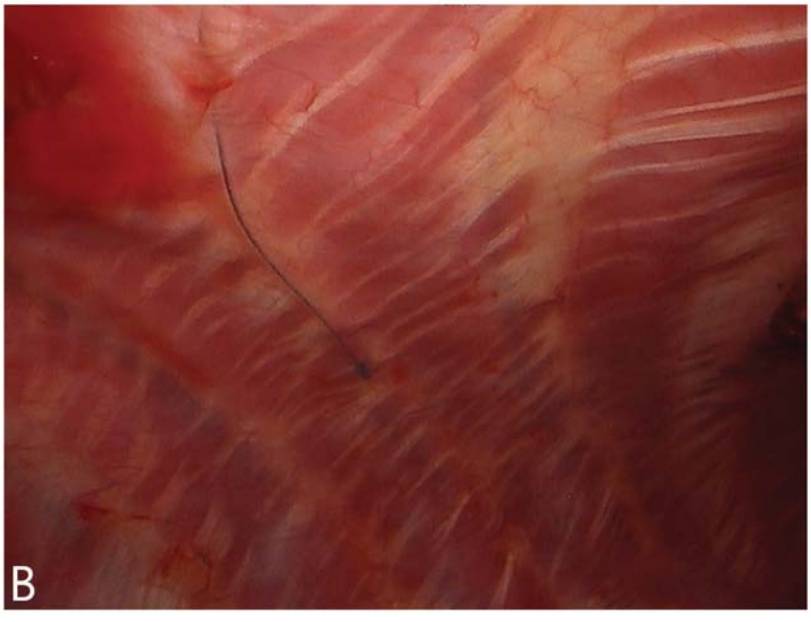

Figure 1. (**A**) View of the intercostal catheter (ICC) after insertion using a 16 Gauge Tuohy needle and a standard peridural catheter. (**B**). Visual control of the ICC. The ICC is placed in the same intercostal space as the chest drain. In the projection of the ICC, the corresponding intercostal nerve and vessels can be seen.

2.3.4. Pain Scoring

Pain Scoring by NRS was performed by staff nurses at least three times daily and was guided by the same cutpoints as described by Serlin et al. [19] with 0 meaning no pain, 1–4 indicating mild pain, 5–6 indicating moderate pain, and 7–10 indicating severe pain. Pain scores were documented in the hospital information system.

2.3.5. Postoperative Complications

Postoperative complications were graded according to the Clavien–Dindo classification by Dindo et al. [20] and also split in pulmonary and non-pulmonary complications.

2.3.6. Statistical Analysis

A *t*-test was performed for analysing means and Pearson's chi-squared test was used to calculate correlations between categorical variables. A Kolmogorov–Smirnov test was used for analysing distribution; Mann–Whitney U test was used for comparing medians. Statistical significance was assumed for a p-value < 0.05. SPSS 26 (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis.

3. Results

A total of 95 consecutive patients were analysed, with 51 (53.68%) being in the ICC and 44 (46.32%) in the SSINB cohort. Patients' characteristics are shown in Table 1.

All patients received a primary VATS anatomic resection. There was no difference in age, gender, or number of drains placed between the two groups (p = 0.777/1.000/1.000, respectively). The median length of the operation was 2.5 min longer in the ICC group (ICC vs. SSINB: 145.00 vs. 142.50 min, respectively, p = 0.474 using the exact sampling distribution of U), which was attributed to the placement of the ICC; the difference was not significant. Mean length of operation also did not differ (153.84 vs. 144.27 min, respectively,

$p = 0.153$). There was no injury to the intercostal vessels or nerve during the placement of the ICC.

Median chest drain duration and median postoperative LOS did not differ between groups (3.00 vs. 3.00 days, $p = 0.766$ using the exact sampling distribution of U; 6.00 vs. 6.00 days, $p = 0.172$ using the exact sampling distribution of U). There was no difference in the amount or type of postoperative complications (overall: $p = 0.479$; pulmonary complication vs. non-pulmonary complication: $p = 0.675$).

Table 1. Patient characteristics.

Factor	ICC, $n = 51$	SSINB, $n = 44$	p-Value
Age (years), median (range)	65 (28–83)	65 (37–80)	0.993
Gender (%)			1.000
Female	26 (51.0)	23 (52.3)	
Male	25 (49.0)	21 (47.7)	
Side (%)			1.000
Left lung	16 (31.4)	14 (31.8)	
Right Lung	35 (68.6)	30 (68.2)	
Lobe (%)			1.000
Upper Lobe	24 (47.1)	21 (47.7)	
Middle Lobe	5 (9.8)	4 (9.1)	
Lower Lobe	21 (41.2)	19 (43.2)	
Multilobar	1 (2.0)	0 (0.0)	
Comorbidities (%)			
Coronary Artery Disease	7 (13.7)	7 (15.9)	0.780
Chronic Obstructive Pulmonary Disease	12 (23.5)	13 (29.5)	0.641
Diabetes Mellitus	5 (9.8)	7 (15.9)	0.537
Postoperative Complications (%)			0.721
Clavien-Dindo I–II	8 (15.7)	9 (20.5)	
Clavien-Dindo III–IV	3 (5.9)	4 (9.1)	
No Complication	40 (78.4)	31 (70.5)	

Abbreviations: SSINB: Single Shot Intraoperative Intercostal Nerve Block; ICC: Intercostal Catheter.

Opioid Usage

To avoid statistical misinterpretation, both median and mean values were compared for opioid usage between the groups. The median total opioid usage was 0.000 mg morphine equivalent in the ICC cohort and 5.000 mg in the SSINB cohort ($p = 0.012$ using the exact sampling distribution of U, $r = 0.256$), as can be seen in Figure 2. The ICC cohort showed a significantly lower mean total opioid usage (morphine equivalent: 3.034mg vs. 7.727mg; $p = 0.002$). The median duration of opioid usage was 0 days in the ICC cohort and 1 day in the SSINB cohort ($p = 0.014$ using the exact sampling distribution of U, $r = 0.251$) (Figure 3). The mean duration of opioid usage was significantly lower in the ICC cohort (0.59 days vs. 1.25 days; $p = 0.005$).

The number of patients needing opioids was lower in the ICC cohort (43.1% vs. 59.1%, $p = 0.151$), but did not prove to be statistically significant. However, only 11.8% in the ICC group needed opioids for longer than one day, in contrast to 38.6% in the SSINB group ($p = 0.010$).

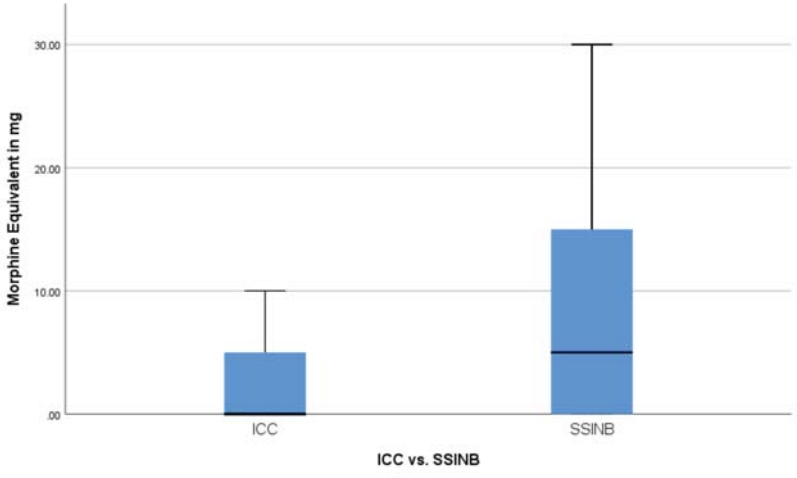

Figure 2. Distribution of morphine equivalent consumption between the ICC (intercostal catheter) and SSINB (single shot intercostal nerve block) group.

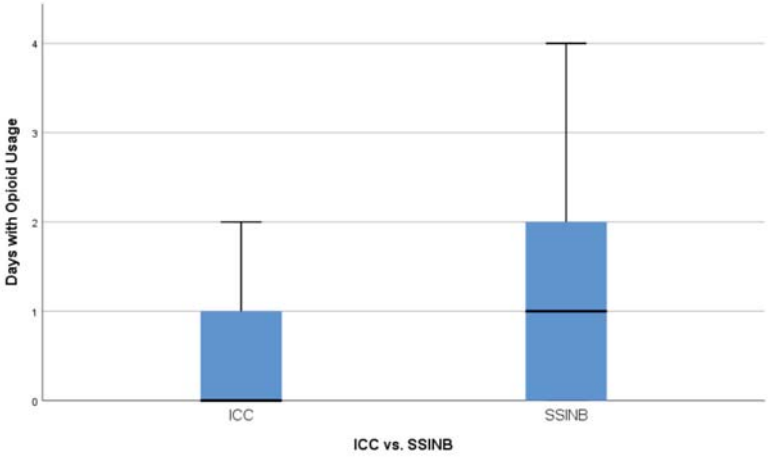

Figure 3. Distribution of days with opioid usage between the ICC (intercostal catheter) and SSINB (single shot intercostal nerve block) group.

4. Discussion

Up to 40% of patients suffer from persistent pain as a result of acute postoperative pain in thoracotomy patients [1,21]. The introduction of minimally invasive surgery has significantly improved the outcome of patients undergoing lung surgery in contrast to thoracotomy, with reduced postoperative pain, improvement of respiratory function and quality of life, and shorter length of stay [12,22]. Despite this evidence, a VATS approach is not pain free. Sufficient pain control in the postoperative period is known to decrease postoperative morbidity and mortality and reduces the rate of chronic postsurgical pain after thoracic procedures [1]. However, there is no evidence for an ideal pain management regimen after VATS resections, and a variety of different treatment algorithms have been described in the literature with or without the use of regional anaesthesia.

Driven by the Enhanced Recovery After Surgery® concept, we wanted to reduce the amount of opioids by introducing regional anaesthesia, thereby also reducing the amount

of associated complications such as nausea, emesis, or hypotension. As opioids act as respiratory depressant, a lower opioid usage might also mitigate the risk of developing postoperative atelectasis and possible pneumonia [23,24].

In the search for an ideal regional anaesthetic procedure, we were specifically looking for an easy-to-perform and time-saving procedure with a low risk for associated complications. While epidural anaesthesia achieves good pain control, it is time-consuming, difficult to perform, and has the risk of damaging the spinal cord and postoperative hypotension [5–7]. Therefore, the use of peridural analgesia in minimally invasive thoracic surgery remains a matter of debate [25].

We introduced the technique of ICC at our department in September 2019. The catheter can easily be placed at the end of the procedure. It can be performed under visual control, thereby reducing the risk of direct damage to the intercostal vessels or nerve. Local anaesthetic is directly administered to the site of maximum pain in the postoperative period, which in most cases is the area of the chest drain [26]. According to our data, placing the catheter takes a median of approximately 2.5 min and does not result in ICC-related haematoma or nerve damage.

In our study, we were able to demonstrate a reduction of the total amount of postoperative opioids and the overall duration of opioid usage through placement of an ICC by 60.74% and 52.80%, respectively. Moreover, the rate of single-day opioid usage in contrast to multiple days was significantly less in the ICC group, pointing at better overall pain control with only little benefit experienced with rescue medication. This finding is in accordance with various ERAS protocols and pain management regimens by trying to limit the use of opioids and their potential side effects [27,28]. With regard to the ongoing opioid crisis, ICCs have been shown to be an appropriate adjuvant therapy for postoperative pain management [16,17]. Although our cohort consisted only of VATS resections, ICCs have also proven to be a feasible alternative to TEA in thoracotomy patients, as described by Luketich et al. [29], reducing the duration of supplemental opioid usage. In comparison to our described procedure, Luketich et al. [29] performed the catheter insertion by creating a tunnel over a minimum of two intercostal spaces above and below the thoracotomy, using a Stern clamp (Scanlon, St Paul, MN, USA) and pulling the catheter through. Further prospective investigations at our department might evaluate the combination of our ICC insertion procedure with the approach to cover more than one intercostal space in VATS and thoracotomy cohorts.

Possible confounders were ruled out, as we analysed a consecutive patient cohort without a selection bias, and statistical analysis showed no differences in comorbidities, age, or gender. Also, the time until removal of the thoracic drain did not differ between groups and therefore cannot explain the reduced duration of opioid usage.

Implementation of ICCs in our surgical standard proved to be rather frictionless, because it did not add significant delay to the operative time. Postoperative monitoring of the used pumps is performed by our in-house anaesthetists and simplified by using the same pump as for epidural administration, so there was no need for any additional investment/acquisition of medical devices.

Unfortunately, the improved pain management did not translate into reduced postoperative complications or reduced length of stay in this group with low overall morbidity of 25.3%. This might be explained by the still adequate pain control in the SSINB group using rescue medication. However, side effects of opioid usage are not routinely documented and due to the retrospective nature of the study are impossible to identify.

Our results suggest the additional use of regional anaesthesia through ICCs for optimizing postoperative recovery and pain management. Through the combination of ICC, intraoperative single-shot intercostal injections of bupivacaine, oral pain medication, and physical therapy, patients' postoperative pathway can be optimized, resulting in better pain control, reduced breakthrough pain, presumably improved recovery and quality of life, and less opioid consumption.

Limitations

This study was performed in a retrospective and non-randomized setting. The placement of ICCs at our department was started in September 2019 and thus the respective learning curve might have had an impact on the outcome. As the postoperative rate of complications and length of stay did not differ between groups, it is important to also focus on the patients' quality of life and return to work after they are discharged from hospital. In regard to the surging budgetary pressure in the public health care sector and the rising number of resectable lung cancer diagnoses, it is important to prioritize this topic to reduce the strain on mentioned public health care providers [30,31]. Quality of life was not assessed in our study; however, this should be an integral part of any future prospective trials in the field of postoperative pain management.

5. Conclusions

As demonstrated in our study, through the standardized use of ICCs the postoperative need and duration for opioids can be minimized. ICCs represent an easy-to-perform procedure of adjuvant pain management for VATS anatomic lung resections. Further studies investigating combinations of various treatment modalities need to be performed in order to optimize postoperative pain management regimens and improve length of stay, return to daily routine, and rehabilitation.

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Long-Term, Health-Related Quality of Life after Open and Robot-Assisted Ivor-Lewis Procedures—A Propensity Score-Matched Study

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Abstract: Esophagectomies are among the most invasive surgical procedures that highly influence health-related quality of life (HRQoL). Recent improvements have helped to achieve longer survival. Therefore, long-term postoperative HRQoL needs to be emphasized in addition to classic criterions like morbidity and mortality. We aimed to compare short and long-term HRQoL after open transthoracic esophagectomies (OTEs) and robotic-assisted minimally invasive esophagectomies (RAMIEs) in patients suffering from esophageal adenocarcinoma. Prospectively collected HRQoL-data (from the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 (EORTC QLQ-C30)) were correlated with clinical courses. Only patients suffering from minor postoperative complications (Clavien–Dindo Classification of < 2) after R0 Ivor-Lewis-procedures were included. Age, sex, body mass index (BMI), American Society of Anesthesiologists physical status-score (ASA-score), tumor stage, and perioperative therapy were used for propensity score matching (PSM). Twelve RAMIE and 29 OTE patients met the inclusion criteria. RAMIE patients reported significantly better emotional and social function while suffering from significantly less pain and less physical impairment four months after surgery. The long-term follow up confirmed the results. Long-term postoperative HRQoL and self-perception partly exceeded the levels of the healthy reference population. Minor operative trauma by robotic approaches resulted in significantly reduced physical impairments while improving HRQoL and self-perception, especially in the long-term. However, further long-term results are warranted to confirm this positive trend.

Keywords: esophagectomy; esophageal cancer; Ivor-Lewis procedure; robotic surgery; health-related quality of life

1. Introduction

Esophageal cancer (EC) is, with increasing incidence, becoming among the most common malignancies worldwide [1,2]. The therapy of choice for locally-resectable EC still is surgery [3,4]. If indicated, additional perioperative radio chemotherapy is applied [3,4]. Depending on the localization of the tumor, surgery is performed as a two- or three-cavity approach with an intrathoracic (Ivor-Lewis) or cervical (McKeown) anastomosis, respectively [5–8]. Since the procedure involves at least two cavities, the surgical approach is important. Perioperative surgical and oncological results, as well as the physical and psychological burden of surgery, highly influence the long-term, postoperative, health-related quality of life (HRQoL), postoperative course, and outcomes [5,9–13].

Since the 1940s, open transthoracic esophagectomies (OTEs) have been the gold standard for EC, achieving solid oncological results but also causing high postoperative complication rates, prolonged postoperative courses, major physical impairments, and long-lasting physical deterioration for up to ten years after surgery [3,6,11–14]. In the 1990s, minimally-invasive esophagectomies (MIEs) and so-called hybrid-MIEs (HMIEs) were introduced to overcome the shortcomings of OTE [4,13]. While achieving fewer postoperative complications and comparable oncological results, MIE and HMIE are associated with risks, complications, and limitations of their own [3–5,15–19]. For the first time in 2003, Kerstine described a robot-assisted MIE (RAMIE) [20], which appeared to overcome the limitations of not only OTE but also MIE and HMIE [3,7,20]. The advantages of RAMIE range from less intraoperative trauma, shorter hospital stays, and cosmetically more-appealing surgical incisions to more comfortable positions for the operating surgeon, a better visualization of the operative field, and greater degrees of freedom for the instruments during surgery, especially in narrow spaces like the mediastinum [7,17,21,22]. In specialized surgical centers with robotic systems and consecutive experience, RAMIE has become a standard surgical procedure for patients with EC [4,7,22,23]. Postoperative courses and oncological radicalness after RAMIE have been shown to be comparable to OTE [3,4,10,15,16].

However, no clear definition of the surgical gold standard for EC exists, and different techniques are still applied worldwide [5,24–28]. Therefore, OTE is often used to as reference procedure, even in large trials like the TIME-, MIRO- and ROBOT-trials [4,7,13,26,27,29,30]. Furthermore, terms for esophagectomies, e.g., MIE, HMIE, RAMIE, Ivor-Lewis, and McKeown, are used variably in the literature [11,25,31,32]. Additionally, no surgical approach has unambiguously been proven to be superior compared to the others [33,34].

However, EC patients not only suffer from the diagnosis of cancer but must also cope with the insecurity, physical changes, and impairments associated with the disease. Severe fear of surgery, physical impairments, and the reduction of HRQoL after unavoidable surgery must be managed. EC patients even choose reduced survival time over postoperative complications, accepting alternative, potentially non-curative treatments with fewer complications to avoid surgery [35]. Such therapies, including watchful waiting, radio chemotherapy, and brachytherapy, are physically and psychologically challenging, reduce HRQoL for up to five years after application, and are associated with risks of tumor progression, perforation, bleeding, and post-interventional fistula, among others [36–41].

Though RAMIE has led to promising short-term postoperative results [3,7,31], little is known about its long-term influence on physical functions, oncological outcomes, and, especially, HRQoL. Long-term improvements in HRQoL after esophagectomy are gaining importance alongside traditional outcome measures such as improved oncological results, the Clavien–Dindo Classification, and long-term survival. HRQoL is increasingly being used to evaluate new surgical techniques [3,7,14,17,21,22,42–44]. However, to the best of our knowledge, no study has analyzed and evaluated long-term HRQoL after RAMIE. Therefore, we aimed to compare postoperative courses in EC patients undergoing OTE and RAMIE with curative intention in a German tertiary referral center, with a special focus on the short- and long-term effects on HRQoL. As the presence of complications can negatively or positively influence the subjective perception of the postoperative course, only patients without major postoperative complications (Clavien–Dindo Classification of < 2) were included and compared in a propensity score matching (PSM) analysis for up to 18 months after surgery [44].

2. Material and Methods

2.1. Data Collection

A database prospectively collecting the HRQoL-data of all patients undergoing surgery is maintained at the Department of General, Visceral, Transplant, Thoracic, and Pediatric Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Germany. In brief, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and a tumor-specific module that cover different aspects of physical function and psychological status are

used [21]. Patients receive the questionnaire prior to surgery and four and 18 months postoperatively. Questionnaires are returned in pre-stamped envelopes, at no cost to the patients. The EORTC QLQ-C30 is an internationally-validated questionnaire covering different functional aspects of self-perception (such as physical, cognitive, emotional, role, and social function) and QoL (including global health status, postoperative function, and impairments such as pain, insomnia, appetite loss, vomiting, constipation, diarrhea, and financial difficulties). Items are classified in four ("not at all" to "very much") and seven categories ("very poor" to "excellent"), respectively. High scores in the functional aspects represent high levels of functioning (i.e., good QoL), whereas low scores in the impairment categories represent few side effects [45]. Results are compared to a healthy reference population [46]. The data of the healthy reference population are provided by the European Organization for Research and Treatment of Cancer [46].

Demographic data and clinical courses of EC patients were retrospectively retrieved from hospital's in-house patient files. All patients gave written informed consent for inclusion in this study and the use of their data. The local ethics committee provided written approval (AZD421/13, D451/19). The study adhered to the principles of the Declarations of Helsinki and Istanbul. Only de-identified data were used for further analysis. Patient data included age, gender, body mass index (BMI), American Society of Anesthesiologists physical status-score (ASA score), and comorbidities such as coronary heart disease, heart insufficiency, myocardial infarction, arterial hypertension, chronic obstructive pulmonary disease (COPD), diabetes, history of smoking, and alcohol consumption. These comorbidities have been shown to be associated with an increased risk of EC.

2.2. Inclusion Criteria

Patients with adenocarcinoma of the esophagus who underwent Ivor-Lewis OTE (2005–2010) or RAMIE (2013–2017) at the Department of General, Visceral, Thoracic, Transplantation, and Pediatric Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Germany, were included. A complete HRQoL follow-up was mandatory to achieve a valid statement on postoperative courses. Exclusion criteria were age <18 years, any other procedure than Ivor-Lewis esophagectomy, the conversion of robotic procedures, any type of carcinoma other than adenocarcinoma, complications Clavien–Dindo Classification ≥ II, and R1- or R2-resections.

2.3. Surgical Procedures

Because OTE has long been the surgical gold standard for EC, it was used as the reference procedure against which RAIME patients were compared. We aimed to achieve homogenous and comparable study populations and to exclude the influence of the learning curve on a new technique.

The OTE was performed as previously described [3,6,23]. In brief, a median incision was made, followed by the transhiatal mobilization of the stomach and D2-lymphadenectomy before the formation of a gastric tube. If necessary, omentectomy or further lymphadenectomy were performed. After the completion of the abdominal part, the patient's position was changed to the prone position, and a right thoracotomy between the 5th and 6th rib was achieved while performing one-lung ventilation. The mobilization and resection of the esophagus were completed with an en-bloc lymphadenectomy, and a hand-sewn or stapler-based anastomosis was performed [3,6].

For the abdominal and thoracic approaches in RAMIE, the da Vinci Si® (2013–2014) or da Vinci Xi®(2014–2017) systems were used [22,23]. Patients were initially put in a supine or French position and later changed to swimmer's position for the thoracic part. For the abdominal part, four ports were placed; after liver retraction and mobilization, D2-lymphadenectomy was performed before the mobilization of the stomach and the opening of the hiatus to release the esophagus prior to construction of the gastric tube. Since 2017, feeding tubes have been implanted in the first jejunal loop to secure enteral nutrition. For the thoracic approach, four trocars were positioned using a left thoracic approach. The esophagus was dissected from the surrounding tissue at the level of the hiatus down to the

pericardium and cranially at the level of the azygos vein using a linear stapler. The gastric tube was then carefully pulled up, and a stapler-based anastomosis was performed transorally [20,22,23,47].

Postoperatively, all patients were transferred to the intensive care unit (ICU) and extubated as soon as possible. A histopathological analysis of the resected specimens was performed by a board of specialized pathologists. Pre- and post-operative presentation in an interdisciplinary tumor board was mandatory, and adjuvant (radio)chemotherapy was given if recommended. Postoperative courses were documented in the in-house patient files. Postoperative complications were classified according to Clavien–Dindo Classification [48]. The time of surgery, type of anastomosis, use and type of stapler, size of tumor and lymph node harvested, and (neo)adjuvant (radio)chemotherapy were assessed. The Union for International Cancer Control (UICC) TNM-staging version 8 was used to classify tumor stage (UICC-guidelines for EC, version 8).

2.4. Outcome Measures

The primary endpoint was the completion of OTE or RAMIE and a postoperative course without complications (Clavien–Dindo Classification ≥ II). Secondary endpoints included the overall HRQoL for up to 24 months postoperatively and overall and disease-free survival.

2.5. Statistical Analysis

Qualitative data are presented as means ± standard deviations (SD) and ranges, evaluated using the Chi-square test. Quantitative data are presented as percentages, evaluated using Student's t-test. Survival data were analyzed and interpreted using the Kaplan–Meier method and log-rank tests [49]. Survival was defined from surgery to last contact or death, whichever occurred first. HRQoL data were pooled for 4 months (3 and 6 months) and 18 months (12 and 24 months) postoperatively and analyzed according to the EORTC-scoring manual, as previously described [21]. Student's *t*-test was used to compare the cohorts. p-values < 0.05 were considered significant. Age, sex, BMI, TNM-stage, ASA-classification, and (neo)adjuvant radio- and chemotherapy were used as matching criteria to perform the PSM analysis. The propensity matching score was 0.1. All statistical analyses were performed using IBM®SPSS Statistics Version 25 for Windows (IBM, Somers, NY, USA). Graph Pad Prism was used to present data.

3. Results

Between 2005 and 2017, 29 OTE patients and 12 RAMIE patients met the inclusion criteria and were included in the final analysis (Figure 1). Cohorts were comparable regarding demographic data, with no significant differences (Table 1). Most patients were male (83.3%and 86.2%, respectively) and overweight (BMI 26.5 ± 4.6 and 28.3 ± 4.5 kg/m^2, respectively). The average age was 64.5 ± 9.1 vs. 61.5 ± 8.2 years, respectively). Though the differences were not significant, RAMIE patients smoked more often than OTE patients (41.7% vs. 24.1%, respectively), suffered more often from COPD (16.7% vs. 10.3%, respectively), and had been classified as sicker according to the ASA-classification. OTE patients suffered more often from arterial hypertension than RAMIE patients (55.2% vs. 25.0%, respectively) and diabetes mellitus (17.2% vs. 0%, respectively). Furthermore, RAMIE patients more often received both neoadjuvant chemo- and radiotherapy and adjuvant chemotherapy.

Surgical times, postoperative complications, UICC-stage of tumors resected, and length of stay at the hospital were comparable (Table 2). Interestingly, tumors resected by RAMIE tended to be larger (diameter of 31.9 ± 11.7 mm for RAMIE patients vs. 20.6 ± 20.9 mm for OTE patients). In addition, RAMIE achieved a significantly higher lymph node yield (31.0 ± 10.0 for RAMIE patients vs. 18.7 ± 12.1 for OTE patients; $p = 0.004$). Overall and disease-free survival were comparable between the RAMIE and OTE cohorts ($p = 0.279$ and $p = 0.510$, respectively) (Figure 2). The follow-up for RAMIE patients was shorter due to the more recent inclusion period.

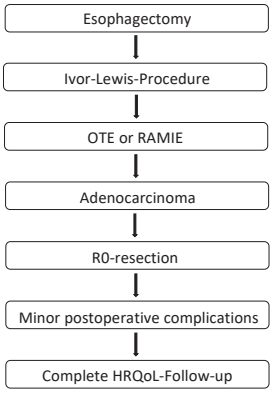

Figure 1. Flow chart of patient inclusion into the study. OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy; HRQoL: health-related quality of life.

Table 1. Baseline comparison of all patient characteristic—cohorts stratified by surgical approach (RAMIE vs. OTE).

	RAMIE (*n* = 12)	**OTE (*n* = 29)**	***p*-Value**
Age (years), mean ± SD (range)	64.5 ± 9.1 (50–75)	61.5 ± 8.2 (51–81)	0.332 [a]
Gender, % male	83.3	86.2	0.813 [b]
BMI (kg/m^2), median ± SD (range)	26.5 ± 4.6 (21.6–34.0)	28.3 ± 4.5 (19.8–44.2)	0.264 [a]
Comorbidities, %			
Arterial hypertension	25.0	55.2	0.078 [b]
Coronary heart disease	16.7	6.9	0.337 [b]
Myocardial infarction	0	0	
Heart failure	8.3	6.9	0.872 [b]
Diabetes	0	17.2	0.965 [b]
COPD	16.7	10.3	0.574 [b]
Alcohol consumption	8.3	6.9	0.872 [b]
Smoking	41.7	24.1	0.262 [b]
ASA-classification, %			0.136 [b]
I	0	0	
II	25.0	50.0	
III	66.7	50.0	
IV	8.3	0	
Additional treatment, %			
Neoadjuvant chemotherapy	75.0	62.1	0.472 [b]
Neoadjuvant radiotherapy	16.7	10.3	0.574 [b]
Adjuvant chemotherapy	58.3	40.0	0.295 [b]
Adjuvant radiotherapy	8.3	7.1	0.896 [b]

Data presented as mean ± standard deviation (SD), median, min, and max or relative frequencies. Continuous variables were compared using [a] Student's *t*-test, while categorical variables were compared using [b] Chi square test. *p*-values of less than 0.05 were considered statistically significant. ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

Table 2. Surgery-associated characteristics of all patients—cohorts stratified by surgical approach (RAMIE vs. OTE).

	RAMIE (*n* = 12)	**OTE (*n* = 29)**	***p*-Value**
Total time of surgery (min), mean ± SD (range)	357.8 ± 86.7 (232–524)	394.5 ± 101.1 (245–589)	0.278 [a]
Type of anastomosis, %			**0.014** [b]
End-to-end	8.3	7.1	
End-to-side	33.3	78.6	
Hand-sewn	58.3	14.3	
Postoperative complications, %			
0	58.3	62.1	
I	0	27.6	
II	41.7	10.3	
Histopathological results, %			0.283 (T) 0.317 (N) 0.125 (M) 0.355 (R) TNM 0.430
pT0	25.0	10.3	
pT1	0	20.7	
pT2	25.0	20.7	
pT3	50.0	48.3	
pN0	50.0	48.3	
pN1	25.0	37.9	
pN2	25.0	6.9	
pN3	0	6.9	
pM0	100.0	82.8	
pM1	0	17.2	
pR0	91.66	93.1	
pR1	8.33	6.9	
Postoperative tumor stage (UICC), %			
0	25.0	10.3	
IA	0	17.2	
IB	0	0	
IIA	16.7	6.9	
IIB	0	3.4	
IIIA	25	17.2	
IIIB	33.3	27.6	
IVA	0	3.4	
IVB	0	13.8	
Size of tumor (mm), mean ± SD (min-max)	31.9 ± 11.7 (17–46)	20.6 ± 20.9 (2.5–65)	0.164 [a]
Lymph nodes harvested, n	31.0 ± 10.0 (20–46)	18.7 ± 12.1 (7–47)	0.004 [a]
Positive lymph nodes harvested, n	1.4 ± 1.9 (1–5)	1.9 ± 2.7 (1–10)	0.609 [a]
Length of stay in hospital (days), mean ± SD (min-max)	18.9 ± 8.6 (12–42)	15.3 ± 3.5 (9–24)	0.180 [a]

Data presented as mean ± standard deviation (SD), median, min, and max. Continuous variables were compared using [a] Student's *t*-test (normally distributed), while categorical variables were compared using [b] Chi square test. *p*-values of less than 0.05 were considered statistically significant. N: number; OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy; UICC: Union for International Cancer Control.

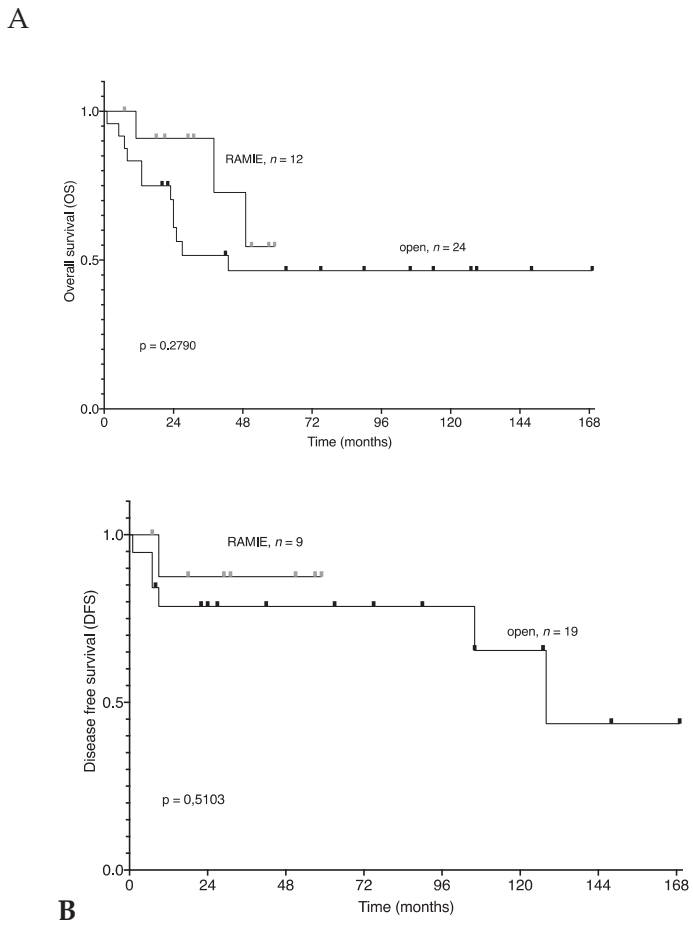

Figure 2. Survival stratified by the cohorts—RAMIE (red) vs. OTE (green). (**A**) overall survival; (**B**) disease-free survival. Kaplan–Meier survival curves and the log-rank test were used to compare survival. DFS: disease-free survival; OS: overall survival; OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

HRQoL was assessed four and 18 months after surgery and compared to a healthy reference population. As this was an inclusion criterion, follow-up was 100%. The results for the different items used to describe QoL, HRQoL, and self-perception and self-esteem in the EORT QLQ-C30 can be seen in Figure 3A–E and Figure 4A–J. As expected, surgery influenced QoL and symptoms in both cohorts, and patients perceived symptoms to be stronger than the general population (Figure 4A–J). However, four months after surgery, the overall QoL was better after RAMIE than after OTE (Figure 4A). Additionally, RAMIE patients reported less fatigue, nausea, vomiting, pain, dyspnea, appetite loss, and diarrhea in the early postoperative follow-up (Figure 4B–I). In the long-term, RAMIE patients seemed to recover better than OTE patients, reporting lower levels of impairment and deterioration up to 18 months after surgery. Interestingly, RAMIE patients suffered from fatigue significantly less often in the long-term (Figure 4B). Neither cohort reported a change in financial difficulties after esophagectomy in the short- or long-term (Figure 4J). It is noteworthy that RAMIE patients reported QoL levels that were similar to the healthy reference population in the long-term, while the QoL

in OTE patients was still reduced 18 months after surgery; only a small improvement in QoL was reported during the postoperative course. Other body functions, such as dyspnea, diarrhea, fatigue, nausea/vomiting, and postoperative pain, were almost at the level of the healthy reference population after RAMIE.

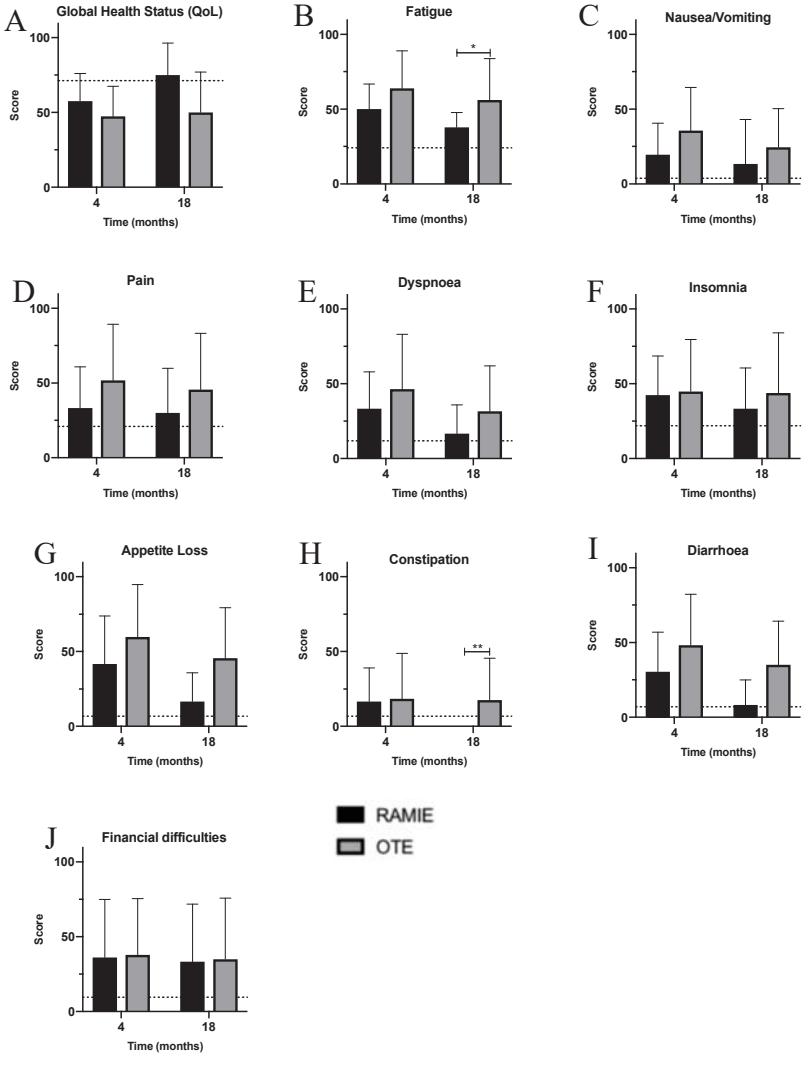

Figure 3. Quality of life and symptoms stratified by cohorts—RAMIE (black) vs. OTE (grey). (**A**) Global health status; (**B**) fatigue; (**C**) nausea/vomiting; (**D**) pain; **E**: dyspnea; (**F**) insomnia; (**G**) appetite loss; (**H**) constipation; (**I**) diarrhea; and (**J**) financial difficulties. OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

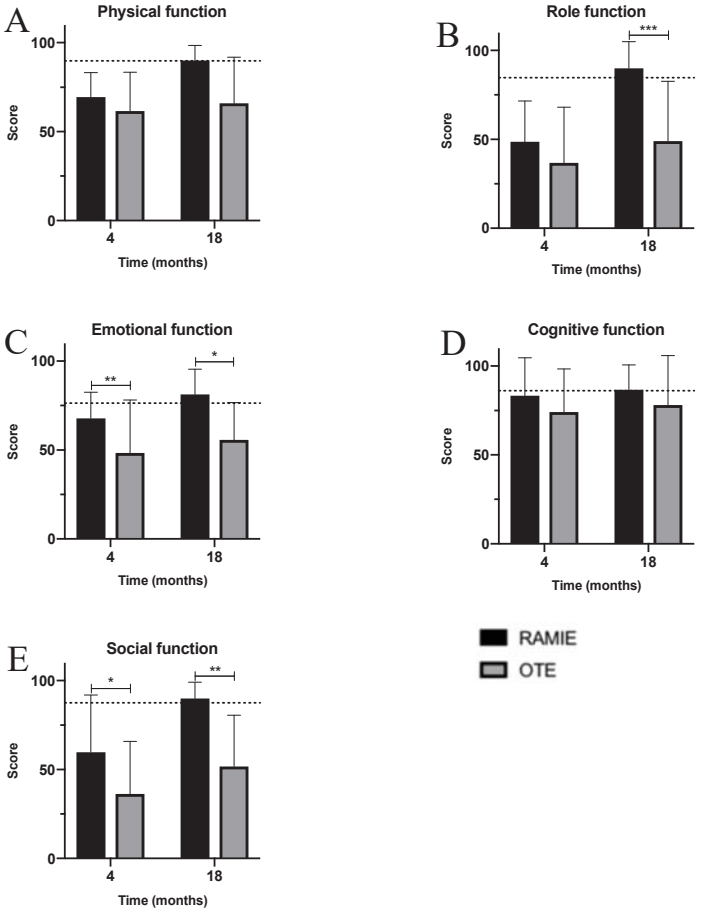

Figure 4. Function stratified by cohorts—RAMIE (black) vs. OTE (grey). (**A**) Physical function; (**B**) role function; (**C**) emotional function; (**D**) cognitive function; and (**E**) social function. OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

In the early postoperative follow-up, patients in both cohorts felt impaired regarding all physical functions, reporting levels beneath those of the reference population (Figure 3A–E). Nonetheless, emotional and social function were significantly better after RAMIE, with emotional function almost reaching the level of the reference population (Figure 3C,E). Furthermore, RAMIE patients tended towards higher physical, role, and cognitive functions (Figure 3A,B,D). At the long-term, 18-month follow-up, RAMIE patients reported highly-improved physical, role, emotional, and social functions, even feeling recovered to the level of the reference population (Figure 3A–E). In contrast, OTE patients only showed moderate improvements during the same follow-up period. In particular, role function was highly and significantly better after RAMIE, with additional significant differences regarding social and emotional function in favor of RAMIE.

A PSM analysis was performed to achieve a more precise comparison of the influence of the surgical approach on HRQoL. Out of 29 OTE and 12 RAMIE patients, 22 patients, eleven from each cohort, were included according to the matching criteria chosen. The PSM cohorts were comparable regarding demographic data, with few significant differences between RAMIE and OTE patients

(Table 3). Most patients were male (81.8% vs. 72.7%, respectively) and of similar age (64.4 ± 9.5 vs. 63.2 ± 6.0 years, respectively). RAMIE patients smoked more often than OTE patients, whereas OTE patients reported a tendency towards more arterial hypertension. Furthermore, RAMIE patients received more adjuvant chemotherapy. It is noteworthy that all anastomoses in OTE were stapler-based, whereas 54.5% of the anastomoses in RAMIE were hand-sewn. Again, tumors tended to be larger in RAMIE patients, and their lymph node yield was significantly higher compared to OTE patients (29.9 ± 9.8 vs. 18.1 ± 13.8, respectively; $p = 0.031$). The length of surgery and hospital stay were comparable (Table 4).

Regarding HRQoL, the PSM revealed more obvious differences between RAMIE and OTE patients. Early in the postoperative course, RAMIE patients reported significantly better QoL and significantly less pain (Figure 5A,D). Additionally, RAMIE patients showed a tendency towards less physical impairment regarding other symptoms (Figure 5B–I), with an improvement in QoL and the amelioration of symptoms over time (Figure 5A–I). Eighteen months after surgery, the QoL of RAMIE patients improved further and was comparable to that of the general population (Figure 5A). At this time, appetite loss was significantly reduced in RAMIE patients compared to OTE patients (Figure 5G). Interestingly, there was little change in postoperative pain levels in the long-term among RAMIE patients, potentially already reflecting low postoperative pain levels after RAMIE and improved compared to OTE patients. The type of procedure, however, did not influence the financial situation in the long-term in either cohort.

Table 3. Baseline comparison of patient characteristics in the propensity score-matched cohorts stratified by surgical approach (RAMIE vs. OTE).

	RAMIE ($n = 11$)	**OTE ($n = 11$)**	***p*-Value**
Age (years), mean ± SD (range)	64.4 ± 9.5 (48–75)	63.2 ± 6.0 (51–73)	0.732 [a]
Gender, % male	81.8	72.7	0.611 [b]
BMI (kg/m^2), median ± SD (range)	27.0 ± 4.5 (19.8–29.3)	27.8 ± 4.3 (23.1–30.9)	0.651 [a]
Comorbidities (yes), %			
Arterial hypertension	27.3	63.6	0.087 [b]
Coronary heart disease	18.2	0	0.138 [b]
Heart failure	0	9.1	0.306 [b]
Myocardial infarction	0	0	
Diabetes mellitus	18.2	27.3	0.611 [b]
COPD	18.2	0	0.138 [b]
Alcohol consumption	9.1	9.1	1.000 [b]
Smoking	36.4	18.2	0.338 [b]
ASA-classification, %			0.647 [b]
I	0	0	
II	27.3	36.4	
III	72.7	63.6	
IV	0	0	
Additional treatment, %			
Neoadjuvant chemotherapy	72.7	72.7	1.000 [b]
Neoadjuvant radiotherapy	18.2	9.1	0.534 [b]
Adjuvant chemotherapy	54.5	25.0	0.198 [b]
Adjuvant radiotherapy	9.1	0	0.329 [b]

Data presented as mean ± standard deviation (SD), median, min, and max. Continuous variables were compared using [a] Student's *t*-test, while categorical variables were compared using [b] Chi square test. *p*-values of less than 0.05 were considered statistically significant. ASA: American Society of Anesthesiologists; BMI: body mass index; COPD: chronic obstructive pulmonary disease; OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

Table 4. Surgery-associated characteristics of propensity score-matched cohorts stratified by surgical approach (RAMIE vs. OTE).

	RAMIE (n = 11)	OTE (n = 11)	p-Value
Total time of surgery (min), mean ± SD (range)	357.7 ± 91.0 (232–524)	369.4 ± 83.1 (205–460)	0.757 [a]
Type of anastomosis, %			0.190 [b]
End-to-end	9.1	10.0	
End-to-side	36.4	90.0	
Hand-sewn	54.5	0	
Type of stapler, %			
Circular stapler	45.5	100	**0.004** [b]
Stapler	54.5		
Postoperative complications, %			
0	54.5	54.5	
I	0	27.3	
II	45.5	18.3	
Postoperative tumor stage (UICC), %			0.881 (T) 0.330 (N) 0 (M) 0.384 (R) TNM 0.952
0	27.3	27.3	
I A	0	0	
I B	0	0	
II A	18.2	18.2	
II B	0	0	
III A	27.3	36.4	
III B	27.3	18.2	
IV A	0	0	
IV B	0	0	
Size of tumor (mm), mean ± SD (min-max)	31.8 ± 11.7 (7–48)	16.0 ± 22.24 (3–60)	0.156 [a]
Lymph nodes harvested, n	29.9 ± 9.8 (19–46)	18.1 ± 13.8 (4–40)	0.031 [a]
Tumor-positive lymph nodes harvested, n	1.3 ± 2.0 (1–10)	1.8 ± 3.3 (2–5)	0.640 [a]
Length of stay in hospital (days), mean ± SD (min-max)	19.3 ± 8.9 (12–42)	14.2 ± 2.4 (9–17)	0.082 [a]

Data presented as mean ± standard deviation (SD), median, min, and max. Continuous variables were compared using [a] Student's t-test (normally distributed), while categorical variables were compared using [b] Chi square test. p-values of less than 0.05 were considered statistically significant. N: number; OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy; UICC: Union for International Cancer Control.

Four months after surgery, both cohorts reported deterioration regarding body functions (Figure 6A–F). However, RAMIE patients reported less impairment, with function levels closer to those of the general population. In addition, social and emotional functions were significantly better among RAMIE patients (Figure 6C,F). In both cohorts, functions improved over time. However, long-term improvements were much stronger among RAMIE patients, with physical, role, and social functions reaching 90% (90.0 ± 8.6%, 90.0 ± 14.9%, and 90.0 ± 9.3%, respectively; Figure 6A,B,E). These body and emotional functions overtook function levels reported by the general population and were significantly better than those reported by OTE patients (Figure 6A–C,E).

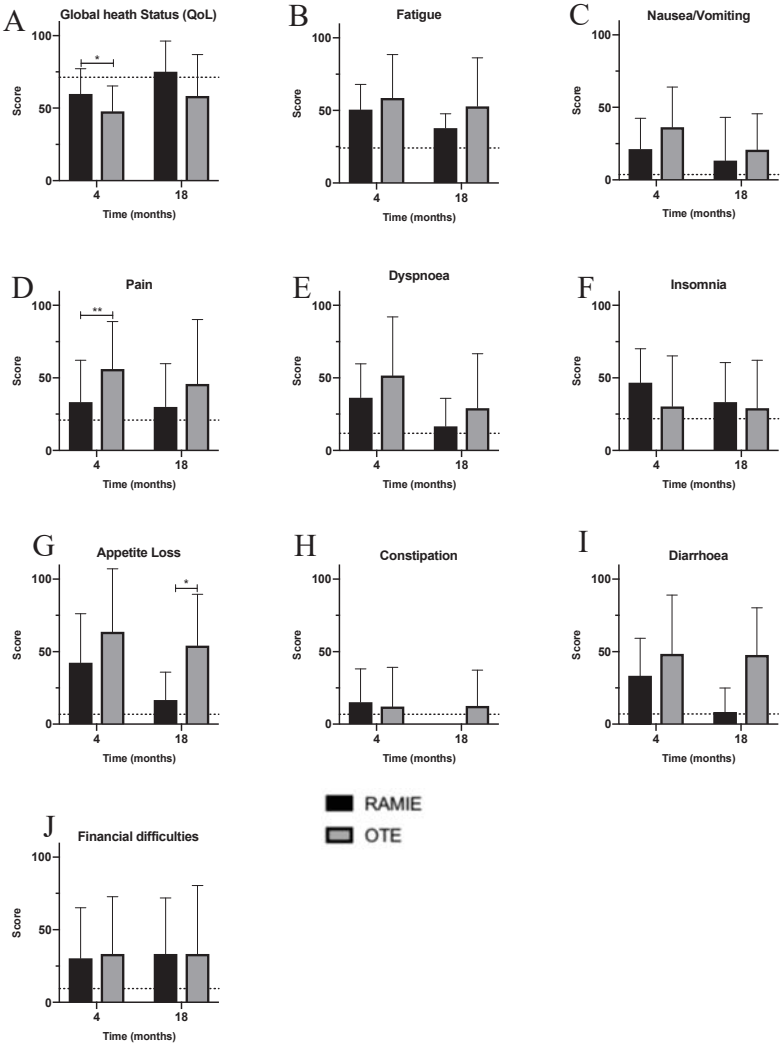

Figure 5. Quality of life and symptoms in the propensity score matching (PSM) analysis stratified by cohorts—RAMIE (black) vs. OTE (grey). (**A**) Global health status; (**B**) fatigue; (**C**) nausea/vomiting; (**D**) pain; (**E**) dyspnea; (**F**) insomnia; (**G**) appetite loss; (**H**) constipation; (**I**) diarrhea; and (**J**) financial difficulties. OTE: open transthoracic esophagectomy; RAMIE: robot-assisted minimally-invasive esophagectomy.

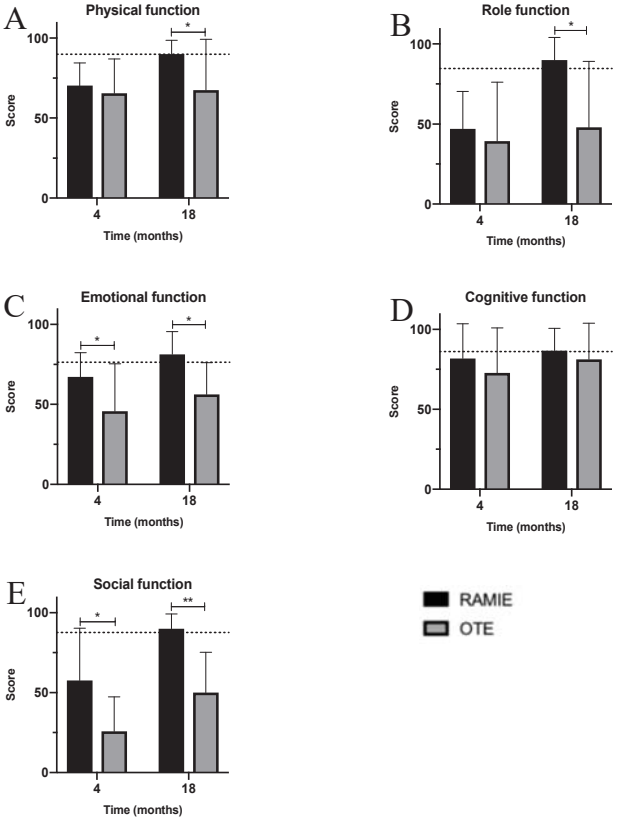

Figure 6. Function in the PSM analysis stratified by cohorts—RAMIE (black) vs. OTE (grey). (**A**) Physical function; (**B**) role function; (**C**) emotional function; (**D**) cognitive function; and (**E**) social function. RAMIE: robot-assisted minimally-invasive esophagectomy; OTE: open transthoracic esophagectomy.

4. Discussion

The diagnosis of EC is still troubling, and esophagectomies are among the most challenging surgical procedures, potentially causing many physical changes and impairments [3,14,42]. It was hoped that the introduction of RAMIE would lead to improved postoperative courses compared to conventional and MIE procedures [7,20]. From a surgical point of view, RAMIE offers major additional technical advantages in the narrow mediastinum that can enable, for example, high lymph node yields, the more comfortable and technically easier creation of intrathoracic anastomoses using smaller thoracic incisions, and less severe post-thoracotomy syndromes [3,7,16–18,20,22,23]. Using tissue- and nerve-sparing surgery, functional impairments and, thus, impairments of body function are assumed to result in fewer long-lasting impairments and thereby improved long-term body function after RAMIE [11].

Our study aimed to compare the postoperative HRQoL after traditional OTE and RAMIE Ivor-Lewis procedures. To obtain an homogenous cohort of patients and eliminate the influence of comorbidities and perioperative complications, we chose to only include patients who suffered from adenocarcinoma of the esophagus, had experienced only minor complications after surgery, and who presented with complete postoperative HRQoL data for up to 18 months after surgery. To further exclude other biases, included patients were matched for age, sex, BMI, tumor stage, and application of

perioperative radio chemotherapy. This analysis further focused on short- and long-term postoperative functions and different body functions after OTE and RAMIE. Since OTE is a well-established procedure and the introduction of novel techniques and procedures always has to deal with a learning curve, we only included full OTE procedures and, for better comparison, full RAMIE procedures in our analysis [25,26,29,32]. Since complications with a Clavien–Dindo Classification > II are often used as a stopping point, we chose to use it as one of our inclusion criteria [7,30].

Our analysis in patients with minor postoperative complications clearly identified better HRQoL four months after RAMIE compared to OTE. The 1:1 PSM analysis further emphasized this result and revealed significantly better HRQoL and reduced postoperative pain after RAMIE in the short-term follow-up. We consider this to be the result of the less harmful surgical approach, the comparably few and small postoperative reductions in the different body functions, and reportedly lower postoperative pain. Early after surgery, RAMIE patients even reported an HRQoL that was comparable to the healthy reference population, thus not considering surgery the major issue that it has traditionally been. The ROBOT study was the first to compare postoperative HRQoL and perioperative pain after OTE and RAMIE procedures [7], and it found a higher postoperative HRQoL, better body functions, and greater functional recovery immediately and six weeks after hybrid-RAMIE. However, the procedures included in the ROBOT trial consisted of hybrid procedures combining laparoscopic abdominal and robot-assisted thoracic approaches. The ROBOT study was therefore only partly suitable for a comparison of HRQoL after full RAMIE, as performed in our analysis. Recently, Sakaria et al. compared early postoperative HRQoL after full RAMIE and OTEand reported better HRQoL with RAMIE at four months after surgery [31]. However, they included thoracoabdominal, Ivor-Lewis, and McKeown RAMIEs, and they only reported results for a four-month follow-up, during which 20% of patients were lost [31]. To the best of our knowledge, no further study has analyzed or compared HRQoL after RAMIE versus OTE. Since terms, e.g., MIE, HMIE, and RAMIE, are often mixed and heterogeneous cohorts, including Ivor-Lewis, McKeown, Sweet, and other types of surgical approaches are often mixed, we consider our approach, which compared full RAMIE to the established gold standard OTE while only including Ivor-Lewis-procedures, appropriate. Furthermore, most studies have reported on hybrid procedures and avoided the full laparoscopic approach due to the limitations of laparoscopic surgery [28]. Our RAMIE cohort, on the other hand, underwent a full robotic approach after having completed the learning curve in hybrid RAMIE [22].

Early postoperative HRQoL is mainly influenced by the postoperative impairments of body functions, such as swallowing problems, a loss of appetite, and vomiting, as well as postoperative pain. After OTE, but also after HMIE using open thoracic approaches, strong and persistent thoracic pain—the so-called post-thoracotomy syndrome—significantly influences postoperative QoL [50,51]. Postoperative pain is mainly caused by the open approach, when rips and damage to intercostal nerves spreads [51]. In our analysis, which included a robotic thoracic approach, RAMIE patients reported significantly less pain compared to OTE patients in the PSM analysis. Both the MIRO and ROBOT trials reported reduced postoperative pain after MIE or robotic thoracic approaches, clearly attributing the main pain to the transthoracic approach [4,7]. Reduced postoperative pain has also been reported for up to one year after MIE, and this has been attributed to the significantly smaller and less invasive surgical approaches, reduced intraoperative trauma, and, thus, a lower incidence of post-thoracotomy syndromes [15,16]. In line with this, Sakaria et al. also reported a reduction in postoperative pain for up to four months after full RAMIE [31]. A surrogate for reduced postoperative thoracic pain may be dyspnea. Patients unambiguously reported less dyspnea after RAMIE in our analysis, which may suggest less postoperative thoracic pain.

While body functions are best used to evaluate short-term results, self-esteem and self-perception are the best surrogates for long-term recovery after esophagectomy [52]. Postoperative HRQoL, self-esteem, and self-perception have gained importance in recent years and have become other factors when evaluating a procedure, especially when considering improved oncological results and longer survival rates [7,21,44]. Even early after surgery in our study, RAMIE patients reported

superior postoperative HRQoL but also significantly better emotional and social functions. We assume that the latter were attributable to reduced intraoperative trauma, fewer postoperative impairments, and, therefore, better body functions and superior HRQoL. The early, positive postoperative trend of improved HRQoL after RAMIE persisted over time and was again reported 18 months after surgery. RAMIE patients in both the whole cohort and in the PSM analysis clearly stated a higher postoperative HRQoL in the long-term follow-up. Furthermore, an unambiguous improvement in physical, role, emotional, and social functions was detectable among RAMIE patients. In particular, role, emotional and social functions were significantly better compared to OTE patients and even overtook levels reported by the healthy reference population. The PSM analysis underlines the results of the whole cohort.

As RAMIE is a relatively new surgical procedure, no long-term HRQoL follow-up data have yet been reported, including the ROBOT study and that by Sakaria et al. Therefore, our analysis is the first to report the impact of the robotic procedure on HRQoL. However, severe and long-lasting impairments regarding HRQoL, physical function, self-perception, and self-esteem have been reported for up to 10 years after OTE [14,42,53]. Mariette et al. further reported reduced social function for up to two years after HMIE [4]. In contrast, Taioli et al. identified superior social and emotional function in the long-term follow-up after MIE compared to OTE [15], while Mantoan et al. reported improved role function after HMIE compared to the healthy reference population [11]. A full recovery of HRQoL and physical and emotional function was reported by Qi et al. two years after an MI Ivor-Lewis procedure for squamous cell carcinoma [54]. Interestingly, they even demonstrated an "over recovery" of emotional and social function after surgery, with both functions being reported as superior to preoperative levels [54]. Klevebro et al., on the other hand, reported no differences in HRQoL when comparing OTE to MIE and HMI for up to one year after surgery [55]. These studies only allowed for a partial comparison to our results due to different surgical approaches, tumor entities, and study designs. Despite these limitations, they are the only existing potential comparisons. In addition to the improvements in self-perception, physical function and postoperative impairments were found to improve in the long-term follow-up in our RAMIE patients, who reported less pain and physical impairments such as vomiting, nausea, dyspnea, diarrhea, and loss of appetite or sleep compared to OTE patients. Fatigue, which highly influences postoperative courses, was reported significantly less often after RAMIE in the long-term. This may also be attributable to the improved postoperative HRQoL and self-perception. Additionally, not only surgery and the surgical approach chosen influence postoperative HRQoL, because complications also influence the latter. Heits et al. reported on the so-called "response shift" after prolonged postoperative courses due to major complications, while Scarpa et al. mentioned impaired postoperative HRQoL on the long-term in patients suffering from postoperative complications [50,56]. Most studies have only reported on major complications or have not differentiated between minor and major complications [34,56,57]. Rutegard et al. also reported on impaired HRQoL after major surgical complications in patients undergoing OTE [58]. Kaupilla et al., on the other hand, reported on the influence of medical complications for up to 10 years after surgery and surgical complications for up to five years after surgery [59]. By our inclusion criteria, we aimed to exclude this vagueness and the response shift influencing the results. Our inclusion criteria voluntarily only included patients suffering from minor complications in order to avoid response shift, an extensive influence of major complications following extensive or long therapy, e.g., esosponge-therapy, stent, and reoperation, on HRQoL [28,34,57,59]. However, in this context, it would be especially interesting to see if major complications differently influence HRQoL in RAMIE patients compared to OTE patients, especially in the long-term.

In our study, RAMIE was superior to the established OTE regarding body and physical functions in the short- and long-term follow-up. Due to the smaller surgical approaches, less-obvious scars, and fewer visible bodily changes during RAMIE, there is less of an impact on physical function, self-perception, and role function, and there is therefore a smaller influence on social and emotional function, which results in improved self-esteem [4].

Postoperatively, all oncological patients at our department are offered both tailored psycho-oncological therapy and rehabilitation after surgery. In addition to the surgical changes, this may further influence postoperative courses, HRQoL, self-perception, and self-esteem, especially in the long-term. Considering the understanding of Wikmann et al. regarding worse clinical courses after esophagectomy in patients with new-onset depression [10], we place special emphasis on postoperative HRQoL and self-perception after esophagectomy, and we consider our results to be encouraging. Our patients unambiguously reported better postoperative HRQoL and role function, as well as fewer impairments with regard to body functions after RAMIE, especially in the long-term follow-up.

However, there were several limitations to our study. Due to the small number of patients fulfilling the inclusion criteria and the partly retrospective character of the study, the statistical power was limited. On the other hand, inclusion criteria were made quite strict to ensure two homogenous cohorts and thus achieve a more valuable comparison. Small demographic differences should have had only a minor, if any, influence on the results. Secondly, not all patients had been treated neoadjuvantly. Since we used neoadjuvant therapy as one of the matching criteria in the PSM, we excluded the influence of neoadjuvant radio chemotherapy on symptoms and function. Due to the relative novelty of the procedure, there were no valid long-term follow-ups (>18 months) regarding HRQoL or oncological outcomes after RAMIE. We also could not provide preoperative data on HRQoL. However, it is known that the diagnosis of a malignant tumor, the associated stress and fear, and neoadjuvant treatment negatively influence physical and psychological well-being [11,14,44]. We therefore do not consider preoperative HRQoL data as representative and feel that comparing patients to a healthy reference population is more useful. It is also well-known that postoperative complications influence postoperative courses, especially the perception of the postoperative course and HRQoL [4,21,50]. Patients learn to live with and adapt to problems and limitations. After a certain period of time, impairments are no longer perceived as such and may even be considered positively [36,43,50]. To exclude this bias, we only included patients with a Clavien–Dindo Classification of < II and are well-aware that our cohorts do not represent a normal cohort after esophagectomy.

Patients who underwent robot-assisted esophagectomy reported fewer physical impairments and better HRQoL and body functions in short- and long-term (18 months) follow-ups compared to open esophagectomy patients, and they did so without experiencing a reduction in oncological outcomes. We therefore consider RAMIE to be a safe and, regarding its positive impact on long-term HRQoL and self-perception, preferable procedure for patients with adenocarcinoma of the esophagus. However, further long-term analyses are needed to verify this positive trend.

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Incidence, Diagnosis and Repair of a Diaphragmatic Hernia Following Hepatic Surgery: A Single Center Analysis of 3107 Consecutive Liver Resections

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Abstract: Diaphragmatic hernia (DH) after a liver resection (LR) is an uncommon but potentially severe complication. In this retrospective study, we aim to share our experience with DH in our hepatic surgery center. We retrospectively analyzed 3107 patients who underwent a liver resection between January 2012 and September 2019. The diagnosis of DH was based on clinical examination and radiological imaging and confirmed by intraoperative findings during surgical repair. Five out of 3107 (0.16%) patients after LR developed DH. Especially, all five DH patients had a major right-sided LR before (n = 716, 0.7%). The mean time interval between initial LR and occurrence of DH was 30 months (range 15 to 44 months). DH exclusively occurred after a right or extended right hepatectomy. Two patients underwent emergency surgery, three were asymptomatic, and DH was diagnosed in follow-up imaging. Three of these five treated patients (60%) developed DH recurrence: two of three (67%) patients after suture repair alone and the only patient after suture repair in combination with an absorbable mesh. The patient who was treated with a composite mesh implant did not show any signs of DH recurrence after 52 months of follow-up. In patients who develop DH after liver surgery, a mesh augmentation with nonresorbable material is generally recommended. In order to diagnose these patients in an early state, we recommend that special attention be paid and a prompt and targeted diagnostic examination of patients with abdominal complaints after right-sided liver resections take place.

Keywords: diaphragmatic hernia; liver resection; hernia repair; mesh; enterothorax

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1. Introduction

An acquired diaphragmatic hernia (DH) is a rare condition, occurring either due to trauma or after major liver resections. When resulting from a blunt or penetrating trauma, they are usually located on the left side because on the right side, the liver covers the diaphragm and thus protects it from injury [1,2]. The incidence of DH following trauma is 3.4% for blunt trauma and 2.1% for penetrating trauma [3]. Hence, a right-sided hernia can occur after liver resections, especially following a right-sided extended hepatectomy [4–9]. There are also some cases of DH after living donor transplantation described in the literature [10]. Other iatrogenic diaphragmatic hernias have been reported following esophagogastrectomies, hiatus hernia repairs, radiofrequency ablation of liver tumors or due to endometriosis [11–14]. Altogether, it remains a rare postoperative complication after hepatic resections [15]. Clinical appearance ranges from completely asymptomatic to bowel obstruction or even bowel perforation with severe peritonitis [16]. In this study, we present a cohort of patients with a right-sided diaphragmatic hernia following liver resection who underwent conventional or laparoscopic

hernia repair. The aim was to present patient-related data, the surgical therapy and the postoperative course of this uncommon but potentially severe complication after major liver resection.

2. Materials and Methods

The Department of Surgery Campus Charité Mitte/Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, Germany is a high-volume hepatobiliary center with an average of more than 400 cases per year [17]. We retrospectively analyzed 3017 patients who underwent liver surgery between January 2012 and September 2019. Patient's demographics, operative details and circumstances as well as time to diaphragmatic hernia occurrence and the surgical outcome were examined. The study was conducted in accordance with the requirements of the Institutional Review Board of the Charite–Universitätsmedizin Berlin, the current version of the Declaration of Helsinki, and the guidelines for good clinical practice.

The initial liver resection of all DH cases was performed using an open approach. Liver resection was carried out in accordance with common clinical standards. The right liver lobe was fully mobilized before parenchymal transection and was performed by cutting of the right triangular ligament and the right diaphragmatic adhesions to the liver. This step was performed with either a monopolar cautery or scissors. Hemostasis on the right side of the diaphragm was achieved with a bipolar clamp or an infrared coagulator.

Diagnosis of DH was either an accidental finding, a finding during planned follow-up examinations or found in an emergency consultation. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used to prove the diagnosis.

For DH repair, either an open (n = 4, 80%) or a laparoscopic approach (n = 1, 20%) was used, and the defect was treated with a primary repair using a nonabsorbable suture only or in combination with placement of a prosthetic mesh implant (Table 1).

Table 1. Characteristics of the patients with diaphragmatic hernia after liver surgery.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	54	56	58	49	69
Gender	m	f	f	f	f
BMI	26.1 kg/cm^2	27.9 kg/cm^2	35.7 kg/cm^2	20 kg/cm^2	29.4 kg/cm^2
Etiology of LR	CRLM	CCC	CRLM	HCC	cholecystitis
Procedure	ext. right hepatectomy	Right hepatectomy	Right hepatectomy	ext. right hepatectomy	ext. right hepatectomy
Open or laparoscopic approach	open	open	open	open	open
Size Of Tumor	multiple leasons	10 cm	multiple leasons	18 cm	parenchymal abscess
Resection Of Diahpragm in the Course Of The LR	no	no	no	no	no
DH Occurence: Time after Liver Resection	21 months	15 months	34 months	44 months	36 months
Symptoms/Reason of Presentation	ileus	shortness of breath	colon stenosis during coloscopy	HCC recurrence in Follow-up, asymptomatic in respect of DH	enterothorax with jejunal perforation and peritonitis
Diagnostic Study	CT	CT	CT	CT/MRI	CT
Herniated organ	right colon flexure, omentum	colon and small bowell	colon and omentum majus	colon	colon
Side of hernia	right-sided	right-sided	right-sided	right-sided	right-sided
Size of Hernia	4 cm	<5 cm	4 cm	5 cm	7 cm
Elective/Emergent	emergent	elective	elective	elective	emergent/elective
DH Repair Approach	Open	Open	Lap.	Open	Open
DH Procedure	primary repair	repair with mesh BioA 10 × 7 cm	repair with composite IPOM	primary repair	primary repair/BioA Mesh at recurrence

Table 1. *Cont.*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Chest Drain During DH Repair	yes	yes	yes	yes	yes
Complications after DH Repair	recurrence	recurrence	none	none with regard to DH	recurrence
Hospital Stay after DH Repair	9 days	8 days	5 days	15 days	21 days
Follow up after DH Repair	36 months	41 months	52 months	14 months	62 months
Recurrence after DH Repair	yes	yes	no	no	yes
Time After DH Repair Till Diagnosis of Recurrence	12 months	12 months	-	-	22 months

Statistical analysis in this study was carried out using the Statistical Package for Social Sciences software (IBM SPSS). For categorical variables analysis, Fisher's exact test was applied. The level of significance was set to $p < 0.05$, and p-values are given for two-sided testing. Analyses were performed using SPSS Statistics 25 (IBM Corp., Armonk, NY, USA).

3. Results

Out of 3017 identified liver resections from a prospectively maintained database from January 2012 to September 2019 ($n = 3107$), five (0.16%) patients developed postoperative DH (Figure 1).

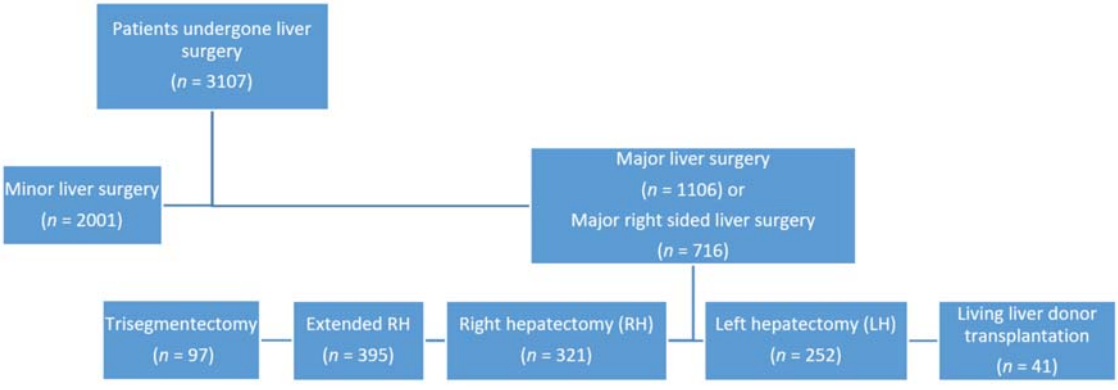

Figure 1. Flowchart of the 3107 cases of liver resections at Department of Surgery at Charité – Universitätsmedizin Berlin from January 2012 to September 2019.

DH only occurred in patients who underwent major right-sided liver resections (anatomical right-sided or extended right-sided hepatectomy). During this period, 716 elective major right-sided liver resections were performed for benign, malignant tumors and infective remnants.

The incidence following major right-sided liver resection was 0.7% ($n = 5$). Two patients received liver resections because of colorectal metastasis (40%), one because of cholangiocarcinoma (20%) and one because of hepatocellular carcinoma (20%). Only one hepatectomy was performed without prior tumor diagnosis: one severe case of cholecystitis with huge liver abscess (20%). In less extensive surgeries such as wedge resections, segmental or anatomical left resection, there was no incidence of DH. No case of DH after living liver donation was found at our center.

The average patients' age at time of DH diagnosis was 57.5 years. The median BMI was 27.9 kg/cm^2. Only one of them was male (20%). On average, 30 months passed between

the operation and the clinical occurrence of the hernia, ranging between 15 and 44 months. Three patients (60%) with DH presented with a symptomatic condition (abdominal pain, shortness of breath or bowel obstruction symptoms). Only two (40%) DH patients received emergency surgical treatment, one of them because of an ileus and the other one because of peritonitis due to a jejunal perforation, needing concomitant bowel resection. In the remaining three patients (60%), DH were random findings in the course of a routine follow-up. The diagnosis was mainly made with CT. In one case, an additional MRI was performed because of hepatocellular carcinoma (HCC) recurrence in order to obtain the most possible information about tumor progress. One of the patients received laparoscopic repair (20%), and four (80%) were carried out with an open approach because of intra-abdominal adhesions. Three of the patients were treated with a nonabsorbable suture and two received a prosthetic mesh implant (BioA®, Gore, 7 × 10 cm and Parietex Composite®, Medtronic, 20 × 15 cm). In all patients, a pleural drainage (≥20 Ch) was placed.

The perioperative period regarding DH was uneventful in all patients. Three patients (60%) showed a recurrence in the follow-up. One patient had ileus symptoms one year after primary DH repair, and was then treated with implantation of a mesh (Bio-A®, Gore). The other two recurrent patients were diagnosed in routine follow-up radiological examinations one year after DH repair. Surgical repair of DH recurrence had not been performed yet.

We analyzed the recurrence rate after DH repair. For this reason, the patients were divided into two groups: group one, with primary repair only or in combination with a resorbable mesh, and group two, with nonresorbable mesh augmentation. No significant difference was found ($p = 0.4$).

The characteristics of the patients are shown in summary in Table 1. Preoperative and recurrence CT scans of one DH patient are shown in Figure 2.

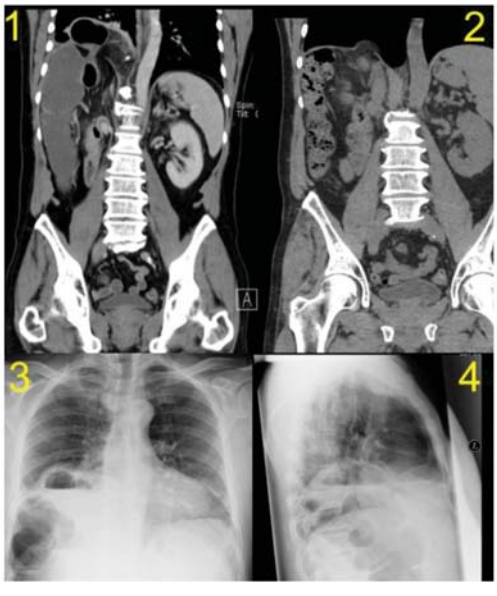

Figure 2. Pre- and postoperative CT scans of one of the patients with diaphragmatic hernia (DH) after right liver resection: (**1**) preoperative computed tomography (CT) scan, (**2**) follow-up CT scan showing the recurrence of DH after primary suture repair, (**3**) and (**4**) chest X-ray images before DH repair.

4. Discussion

Diaphragmatic hernia constitutes a rare but potentially severe complication following major liver resection. As a high-volume hepatobiliary center, we seek to stress the role of

DH, its importance in the differential diagnoses of right upper abdominal pain and ileus symptoms in patients who underwent liver resection. A variety of additional presenting symptoms are described, such as respiratory distress, abdominal distension, constipation, spasmodic hiccup with chronic right upper abdominal pain and acute or chronic bowel obstruction symptoms being the common ground [4,5,15,16,18,19].

The reasons for the occurrence of DH after liver surgery have not yet been sufficiently clarified. The resection or opening of parts of the diaphragm in primary surgery as well as the initial tumor size are suggested as possible risk factors in the literature. This observation was also made in our cohort, as DH occurred after liver resections due to larger lesions, such as multifocal tumors, larger tumor diameter or an abscess needing extensive parenchymal resection. Additionally, cautery-related thermal injury is most often mentioned in this context. Nevertheless, the etiology seems to be multifactorial [4,5,7,20–22].

In our cases, the diagnosis was made based on CT scan findings. In general, two radiological methods could be used to confirm the diagnosis. As CT scan is a part of most cancer follow-up examinations and at the same time the most effective procedure, it should take center stage in routine diagnostics, while sonography, being even easier to perform, could be used as first-line in an emergency situation or in outpatient clinic consultations by experienced examiners [23]. Although in synopsis of the studies it is shown that the sensitivity of chest X-ray (CXR) for diaphragmatic injuries varies between 40% and 81%, with some studies also speaking of an error rate of 40%, in our opinion, CXR is not a meaningful method, while ultrasound is superior, being proven in several studies as a reliable method of diagnosing diaphragmatic hernias [24–30].

In the literature, the recommended follow-up is 24 months [15]. The median time interval between the initial liver resection in our study was 30 months, longer than the 19 months described in the literature [15]. Based on our experience with the occurrence of a DH 44 months after LH, we recommend at least 48 months of follow-up. Oh et al. recommended that clinicians and radiologists should not overlook DH after living-donor right hepatectomy [19]. We would like to endorse the thesis and propose, in addition to the standardized follow-up for carcinomas, a targeted diagnostic examination of patients with abdominal complaints after right-sided liver resections.

Our retrospective study showed a lower incidence of diaphragmatic hernias after liver resection than previously reported in the literature. The figures described in the literature range from 1% to 2.3% and are thus higher than the 0.16% and 0.7% reported in our study [4,5,15]. To this day, the number of publications on this topic is low. Our department carries out a high number of liver resections every year, so we believe that a lower incidence of DH is a logical consequence of this expertise. More specifically, when mobilizing the right liver lobe, care is taken not to injure the diaphragm. For this purpose, only the ligamentum triangulare dextrum is dissected. This also includes avoiding severe bleeding of the diaphragm during dissection, which could lead to extensive thermocoagulation and secondary damage to the diaphragm [15].

Regarding the surgical treatment of DH, some authors recommend that a hernia smaller than 10 cm should be treated with a primary suture and a hernia larger than 10 cm with mesh [4,5,7]. Based on our experience, we do not recommend primary suture repair but prefer mesh augmentation, because the treatment of a small hernia without mesh led to a recurrence, which had negative influence on the clinical outcome and morbidity of the patient (Table 1). This opinion has already been reflected in literature for DH after a blunt trauma [31].

In our opinion, prompt treatment of the diaphragmatic hernia and augmentation by means of mesh are indispensable to avoid possible complications and thus reduce morbidity [4,5]. In this context, it should also be mentioned that early diagnosed DH defects are small or moderate in size and could therefore be repaired more easily [5].

Although our analysis did not show statistical significance, the numbers are quite obvious—80% of the patients not treated with a nonresorbable mesh showed a recurrence of DH. Therefore, we recommend an augmentation with a nonresorbable and intraperitoneal

suitable mesh for all DH after LR because in our opinion, this is the best method to avoid recurrence. Right now, no data exist about DH and repair with long-term resorbable meshes.

In this study, only abdominal approaches were chosen. If technically possible, this should always be preferred to the thoracic approach, in order to avoid a two-cavity procedure [5,7,8]. On the other hand, Tabrizian et al. suggested that a thoracic approach is useful for recurrence of DH after repair by an abdominal approach [5].

Furthermore, a laparoscopic approach is superior to an open approach with regard to convalescence, especially with regard to postoperative pain and mobilization. The postoperative complication rate is lower at experienced centers after laparoscopic liver resection than after conventional open surgery [17]. Further studies may also verify this for a diaphragmatic hernia after a liver resection. Finally, advances in laparoscopic and robotic surgery will show in the future whether the incidence of DH after liver resection will change or can also be reduced by, for example, a more detailed dissection [17,32,33].

5. Conclusions

Due to the severity of complications in patients with diaphragmatic hernia, we recommend (if possible) defect closure by nonresorbable suture with mesh augmentation of every diaphragmatic hernia after liver resection. Mesh repair can be performed laparoscopically in IPOM technique or as open mesh implantation. We suggest that this maximal reinforcement of the diaphragmatic defect reduces the risk of recurrence and consecutive morbidity. Hernia repair under elective conditions would improve the clinical outcome of patients compared to emergency surgery. Therefore, we recommend, in addition to the standardized follow-up of carcinomas, a targeted diagnostic examination of patients with abdominal complaints after right-sided liver resections, especially in cases of extensive preparation or dissection of the diaphragm, in order to diagnose a DH at the earliest possible state and certainly not in an emergency situation. Special attention should be given to the few noncancer patients after right-sided liver resections in case of hernia-related symptoms, since they do not have standardized follow-up.

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Predicting the Risk of Postoperative Complications in Patients Undergoing Minimally Invasive Resection of Primary Liver Tumors

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Abstract: Minimal-invasive techniques are increasingly applied in clinical practice and have contributed towards improving postoperative outcomes. While comparing favorably with open surgery in terms of safety, the occurrence of severe complications remains a grave concern. To date, no objective predictive system has been established to guide clinicians in estimating complication risks as the relative contribution of general patient health, liver function and surgical parameters remain unclear. Here, we perform a single-center analysis of all consecutive patients undergoing laparoscopic liver resection for primary hepatic malignancies since 2010. Among the 210 patients identified, 32 developed major complications. Several independent predictors were identified through a multivariate analysis, defining a preoperative model: diabetes, history of previous hepatectomy, surgical approach, alanine aminotransferase levels and lesion entity. The addition of operative time and whether conversion was required significantly improved predictions and were thus incorporated into the postoperative model. Both models were able to identify patients with major complications with acceptable performance (area under the receiver-operating characteristic curve (AUC) for a preoperative model = 0.77 vs. postoperative model = 0.80). Internal validation was performed and confirmed the discriminatory ability of the models. An easily accessible online tool was deployed in order to estimate probabilities of severe complication without the need for manual calculation.

Keywords: laparoscopic liver surgery; hepatocellular carcinoma; cholangiocarcinoma; risk score

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1. Introduction

Liver resection is the primary option for the curative treatment of hepatic malignancies [1–3]. While in some disease entities local ablative techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA) can be effectively deployed to treat small tumors, they rapidly lose efficacy with increasing nodule size [4,5]. Until recently, liver surgery has been thought of as a classical domain of open surgery with the need for large incisions and inherent protracted postoperative courses. This is particularly evident in the case of malignancies, where concerns regarding oncologic outcomes have dampened the widespread application of minimal-invasive techniques. These concerns have been disproven, and laparoscopic liver resection (LLR) is, in select centers, applied as the mainstay treatment option independent of tumor size, entity or location [6–8]. Indeed, LLR has been

shown to be an effective method to treat the most common primary hepatic malignancies, hepatocellular carcinoma (HCC) [9] and intrahepatic cholangiocarcinoma (iCC) [10,11].

Incremental improvements in technology and instruments as well as increasing experience in tailored surgical training [12] have contributed to LLR being regarded as mature for several distinct resection types [1,13]. The overarching theme of studies on LLR is that the minimal-invasive approach is associated with less intraoperative bleeding [14] and overall fewer complications [15–17] when compared to open resection, which is still burdened by potentially life-threatening complications [9,18]. Few reports, however, have identified risk factors for postoperative complications among patients undergoing LLR. Instead, emphasis has been placed on defining risk factors for conversion and subsequent prolonged courses [19,20]. Validated scoring systems appraising the expected difficulty of a resection type [21–24] are used in clinical practice, but available predictive systems that have been developed for the occurrence of complications have key shortcomings. First, some scores were developed using subjective interpretation by individual surgeons and have not been formulated in an unsupervised analysis [21]. Other groups focused on the type of resection without giving patient-dependent factors enough consideration [23]. Similarly, a recent comprehensive report generating and validating a model using objective criteria expanded the scope by considering all types of indications but did not factor in the general health of the patient. Thus, in these reports, the premise of the occurrence of complications shifts from being a complex interplay of patient history, surgical technique and experience to being a plain readout of the operative procedure.

The present study aimed to address this shortcoming by reporting risk factors for major complications in patients undergoing hepatectomy for primary malignancies. We herein define a logistic regression model factoring in solely preoperative variables as well as one that also considers intraoperative variables. Models are validated using a bootstrapping approach. Finally, in order to address the intrinsic shortcoming of logistic models, a lack of clinical utility due to the need for complex scoring, we deployed an online application providing probabilities for the occurrence of major complications.

2. Materials and Methods

Clinical courses of all consecutive patients undergoing LLR between January 2010 and May 2020 at the Department of Surgery, Campus Charité Mitte and Campus Virchow-Klinikum, Charité–Universitätsmedizin Berlin, Germany were analyzed for this retrospective study. Patients who had undergone resection for lesions other than primary liver malignancies were excluded from the analysis. The study was approved by the local Ethics Committee (EA2/006/16).

2.1. Patient Evaluation and Surgical Approaches

In all patients, preoperative workup included imaging with either triphasic contrast-enhanced computed tomography or magnetic resonance imaging as well as platelet count, liver and kidney function tests and, in the case of cirrhosis or planned major hepatectomy, maximum liver function capacity (LiMAx) testing. Indication for resection was given through a multidisciplinary hepatobiliary tumor board consisting of surgeons, hepatologists, medical oncologists and radiologists. Laparoscopic surgery was performed in the French position. Three different techniques were applied as described elsewhere [25–27]: standard multiport laparoscopy (MILL), single-incision laparoscopic surgery (SILS) or hand-assisted laparoscopic surgery (HALS). All resections were performed with curative intent.

2.2. Data Collection and Study Endpoints

Pre- and intraoperative variables were collected in a prospective database. For the purpose of the study, imaging from included patients was evaluated for signs indicative of liver cirrhosis and portal hypertension.

Complications were defined by the Clavien–Dindo classification system (CD) [28]. The primary endpoint was the occurrence of major postoperative complications defined as grade 3 and above. Mortality was assessed as a secondary endpoint. As the CD system defines the given grade as the most severe complication that occurred, patients that decease during hospitalization by default also have complications of grades 3 or 4. We therefore included these patients for the primary endpoint and analyzed them separately for the secondary endpoint. In accordance with the original classification system, morbidity and mortality were defined as complications and death occurring within 90 days after the procedure. Analysis was based on the intention-to-treat principle and, therefore, any procedure planned laparoscopically was included. Conversion was defined as switching from any laparoscopic technique to laparotomy.

2.3. Statistical Analysis

Analysis was performed using SPSS V22.0® (IBM, Armonk, NY, USA) and R software, version 4.02. The distribution of continuous variables was evaluated with the Shapiro–Wilk test. A comparison of continuous variables in the case of nonparametric distribution was performed with the Mann–Whitney test. Continuous variables with a Gaussian distribution were compared with ANOVA. Categorical variables were compared using the Chi-square or Fisher exact test. A two-tailed value of $p < 0.05$ was considered statistically significant. Continuous variables are stated as the mean with the 95% confidence interval, whereas categorical variables are reported as counts with percentages in brackets unless stated otherwise.

Missing variables ranged from 0% up to 41% for AFP. A granular view of missing variables is shown in Figure S1. Multiple imputations using a regression-switching approach was applied in order to avoid omitting cases from the analysis (R package *mice*, with m = 20). Imputations were performed under the missing-at-random assumption for missing variables, using the ppm method for continuous variables and logreg for categorical variables. Imputed datasets were combined to generate estimates using Rubin's rules. The stability of imputed variables was ensured through density plotting.

The model was constructed using intraoperative and preoperative variables and testing the association with the above-defined complication categories along with a bivariate logistic regression model with odds ratios (ORs) to capture differences between cases with major complications from those without. The integrated continuous variable had a linear relationship with the outcome and was applied as a linear term. Categorical and continuous variables associated with the occurrence of major complications in a univariate model ($p < 0.1$) were included in a multivariate logistic regression model with proportional OR using a removal significance of $p = 0.05$. We constructed a preoperative and postoperative model including respective variables.

Ultimately, the performance of the two models was evaluated by ascertaining the area under the ROC curve (AUC) to discriminate major complications (CD 3-5) from no or minor complications (CD 0-2). Pre- and postoperative models were compared using the bootstrap test. We defined a threshold of an AUC greater than 0.6 to capture acceptable performance. The goodness of fit of the model was tested using the Hosmer–Lemeshow test. Finally, internal validation of the models was performed by bootstrapping 3000 datasets.

3. Results

3.1. Cohort Characteristics

Screening of patients undergoing LLR between January 2010 and May 2020 identified 210 out of 572 patients with a primary hepatic malignancy as an indication. Expectedly, the majority of resections were performed for HCC (73.8%) and iCC (20.0%). Most cases presented without viral hepatitis as a cause of the underlying liver disease (63.8%). Liver function was well compensated in the included patients, as accounted for by Child–Pugh scores up to B7 in all cases and a median MELD score of 8 (95% CI = 7.81–8.50). Preoperative imaging was suspicious for liver cirrhosis in 69.5% of cases, whereas radiographic signs of

portal hypertension were observed in 29.9%. Major hepatectomy was performed in 24.8% of all patients, and MILL was the most frequently applied surgical approach (76.6%). Baseline patient characteristics as well as intraoperative data are presented based on the occurrence of major complications (CD 3-5) in Table 1. As no data were available on blood loss, we used the number of perioperatively transfused red blood cell (RBC) concentrates as a surrogate. Overall morbidity comprising all CD stages was 31.4%, whereas 32 patients (15.2%) had major complications. Four patients (1.9%) succumbed to postoperative complications. The most common indication for reoperation was a burst abdomen, which occurred in three patients (two HALS cases, one MILL case). Major complications are detailed in Table 2.

Table 1. Patient characteristics based on the occurrence of major complications.

	Complication Grading According to Clavien–Dindo			
	CD 0-2 (*n* = 178)	**CD 3-5 (*n* = 32)**	**Odds Ratio (95% CI)**	***p***
General Variables				
Age in years	67.1 (65.6–68.7)	65.9 (61.6–70.1)	0.981 (0.949–1.016)	0.26
Male gender	121 (68.0)	22 (68.8)	1.036 (0.471–2.421)	0.93
BMI in kg/m^2	26.8 (26.1–27.5)	26.5 (24.7–28.4)	0.999 (0.92–1.082)	0.98
Diabetes	49 (27.7)	14 (43.8)	2.047 (0.934–4.425)	0.07
HCC	136 (76.4)	19 (59.4)	0.451 (0.207–1.0)	0.047
HCV	37 (21.3)	11 (36.7)	2.144 (0.914–4.847)	0.07
HBV	23 (13.2)	3 (10.0)	0.729 (0.165–2.288)	0.63
Previous hepatectomy	8 (4.6)	4 (13.3)	3.935 (1.119–12.712)	0.02
Previous abdominal surgery	84 (47.2)	17 (53.1)	1.268 (0.596–2.723)	0.54
ASA 3/4	97 (55.4)	22 (68.8)	1.769 (0.791–3.956)	0.16
Surgical variables				
Number of previously performed LLRs	279 (255–302)	268 (210–326)	1.0 (0.997–1.002)	0.72
Major hepatectomy	40 (22.7)	12 (37.5)	2.04 (0.899–4.489)	0.08
Simultaneous ablation	5 (2.8)	3 (9.4)	3.579 (0.704–15.402)	0.09
MILL	143 (80.3)	17 (54.8)	0.315 (0.143–0.701)	0.004
HALS	31 (17.4)	12 (38.7)	1.362 (0.535–3.183)	0.49
SILS	4 (2.2)	2 (6.5)	2.9 (0.390–15.552)	0.23
Length of surgery (LOS) in min.	226.9 (213.6–240.1)	296.7 (260.4–333.0)	1.008 (1.004–1.012)	<0.001
Conversion	1 (0.6)	2 (6.3)	11.8 (1.097–258.613)	0.046
R1 Status	15 (8.6)	10 (31.3)	4.818 (1.891–12.011)	<0.001
Perioperative RBCs transfused	0.11 (0.0–0.21)	0.31 (0.0–0.65)	3.821 (0.736–16.915)	0.18
Maximum tumor diameter in cm	4.5 (4.0–4.9)	4.2 (3.4–5.1)	0.974 (0.848–1.10)	0.69
Liver function variables				
ALT, U/L	41.3 (33.8–48.9)	52.1 (26.8–77.3)	1.008 (1.0–1.016)	0.037
AST, U/L	48.4 (38.9–58.0)	56.7 (22.7–90.7)	1.004 (0.997–1.01)	0.25
Thrombocytes	192.1 (173.8–210.5)	200.5 (139.9–261.22)	1 (0.995–1.004)	0.98
Thrombocytes <100/uL	18 (10.3)	7 (23.3)	2.638 (0.941–6.809)	0.052
Albumin mg/dl	41.2 (40.0–42.4)	40.0 (38.4–42.7)	0.979 (0.901–1.070)	0.62
Bilirubin mg/dl	0.67 (0.59–0.76)	0.63 (0.51–0.75)	0.772 (0.249–1.59)	0.59
INR	1.1 (1.08–1.13)	1.1 (1.07–1.16)	3.772 (0.098–107.931)	0.45
ALBI score	−2.85 (−2.97–(−2.74))	−2.76 (−3.06–(−2.48))	1.278 (0.516–2.935)	0.575
FIB−4	3.24 (2.83–3.66)	3.28 (2.25–4.3)	1.005 (0.853–1.145)	0.95
LiMAX µg/kg/h	322 (289–355)	379 (306–451)	1.002 (0.999–1.005)	0.15
Cirrhosis in imaging	119 (70.8)	18 (62.1)	0.674 (0.30–1.570)	0.35
Cirrhosis in pathology	98 (58.0)	14 (46.7)	0.634 (0.287–1.385)	0.25
Advanced fibrosis (grade III-IV)	115 (68.0)	20 (66.7)	0.939 (0.412–2.143)	0.88
Portal Hypertension in imaging	50 (29.8)	9 (31.0)	1.062 (0.434–2.435)	0.89
MELD	8.2 (7.7–8.6)	9.1 (6.9–11.3)	1.077 (0.922–1.234)	0.30
Preoperative ascites	2 (1.3)	1 (3.8)	3.14 (0.142–33.970)	0.36

Variables are expressed as the mean with the 95% CI for continuous variables and as counts with percentages in brackets for categorical variables. An overview of missing data is shown in Figure S1. For continuous variables, the odds ratios are per one unit increase.

Table 2. Description of major complications.

Clavien–Dindo Grade	Frequency
3a	17 (8.1%)
Biliary leakage	6
Intraabdominal abscess	5
Pleural effusion	3
Pneumothorax	2
Wound infection	1
3b	11 (5.2%)
Biliary leakage	2
Burst abdomen	3
Ileus	1
Intraabdominal abscess	2
Postoperative hemorrhage	1
Wound infection	2
4	0 (0%)
5	4 (1.9%)
Congestive heart failure	1
Pneumonia	1
Pulmonary embolism	1
ISGLS C post hepatectomy liver failure	1

3.2. Model Generation for the Prediction of Major Complications

Out of the 10 preoperative variables associated with major complications in the univariate analysis, 5 variables were retained for the preoperative risk model after the multivariate analysis (Table 3): preoperative alanine aminotransferase (ALT) levels, history of previous liver resection (yes/no), diabetes (yes/no), resection performed as MILL (yes/no) and whether or not the malignancy was an HCC (yes/no). Major complications were associated with high ALT levels, previous hepatectomies, diabetes, application of techniques other than MILL and non-HCC lesions.

Table 3. Variables retained after the multivariate analysis.

	Odds Ratio	*p* Value
Preoperative model		
Diabetes	2.74 (1.13–6.63)	0.026
Rehepatectomy	5.79 (1.46–22.92)	0.013
ALT	1.01 (1.0–1.02)	0.033
Non-HCC	3.27 (1.28–8.36)	0.014
Standard multiport approach	0.26 (0.11–0.63)	0.003
Postoperative variables		
Length of surgery (LOS)	1.01 (1.0–1.01)	0.002
Conversion	23.4 (1.57–350.1)	0.023

For the postoperative setting, duration of surgery and the need for conversion to laparotomy, both associated with an adverse safety outcome, were included in the model as well. The entity of the diagnosis was dropped from the model as it did not retain statistical significance. Model calibration parameters are shown in Figure S2 and the regression coefficients per variable in Table S1.

3.3. Prediction of Pre- and Postoperative Model for Primary and Secondary Endpoints

The preoperative model was capable of discriminating CD 3-5 from CD 0-2 patients with a mean AUC across imputations of 0.73 (Figure 1A). Applying the same model to the endpoint of mortality, it retained its predictive ability at an AUC of 0.85 (Figure 1B). Likewise, the AUC for the postoperative model to identify major complications was 0.79 (Figure 1C) and 0.87 when considering mortality as an endpoint (Figure 1D). Bootstrap

testing revealed the postoperative model to be significantly more accurate for both the primary and secondary endpoints ($p < 0.0001$ and $p < 0.01$, for major complications and mortality, respectively).

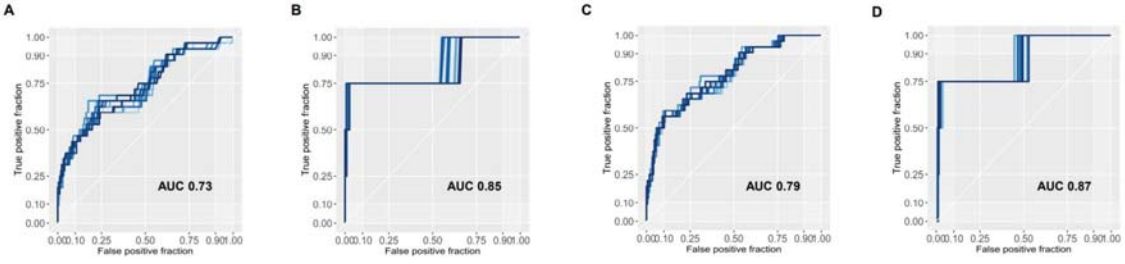

Figure 1. Performance of preoperative and postoperative models across imputed datasets Areas under the curves are shown for the preoperative model as well as the postoperative model for the primary endpoint of occurrence of major complications (**A**,**C**) and the secondary endpoint of mortality (**B**,**D**). Every curve represents one iteration of 20 imputed datasets for missing variables. The mean AUC for each model is depicted.

To address the evident risk of overfitting the model to the data, we performed internal validation by bootstrapping (random sampling with replacement) 3000 datasets with replacement. After correction for overoptimism, the AUC for the preoperative model was 0.72 and 0.76 for the postoperative model. The Hosmer–Lemeshow test revealed an acceptable goodness of fit for the preoperative model ($p = 0.22$) and the postoperative model ($p = 0.59$).

3.4. Predictive Ability of the Two Models in Patients Undergoing Major Hepatectomy

Fifty-two patients (24.8%) underwent major hepatectomy (33 right (extended) hemihepatectomies, 19 left (extended) hemihepatectomies). Applying the models created in the entire cohort to these patients, the AUC for predicting major complications of the preoperative model was 0.67, whereas the AUC for the postoperative model was 0.77. The bootstrap test revealed, for the entire dataset, the postoperative model to be significantly more accurate in predicting morbidity. When considering the secondary endpoint of mortality, the AUC of both the preoperative and the postoperative model was 0.75.

3.5. Comparison of Predictive Models with Previously Reported Model

The discriminatory ability of both the preoperative and the postoperative model prompted us to compare the predictive ability with the Southampton Laparoscopic Liver Difficulty Score, a recently published scoring system from a multicenter cohort that, of note, predicts intraoperative complications [24]. The application of this system yielded an AUC of 0.63 as compared to the median AUC of 0.77 from our preoperative model and 0.80 of our postoperative model, in which nonimputed data are used for model generation (Figure 2). In accordance with this, the superior accuracy of the present models was maintained when mortality was used as the endpoint (AUC = 0.58 vs. 0.82 vs. 0.88 for the Southampton score, preoperative model and postoperative model, respectively).

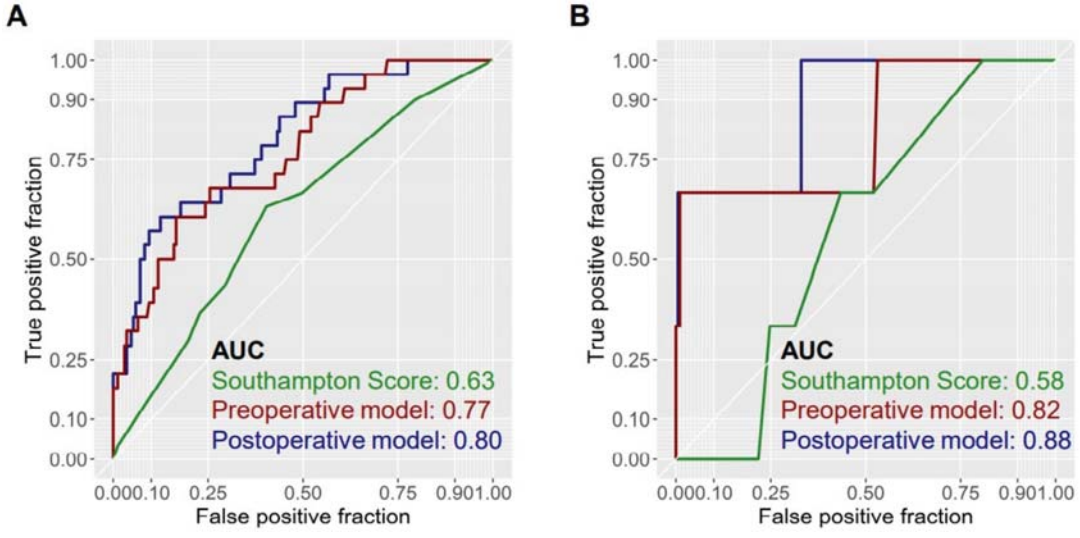

Figure 2. Comparison of predictive models. Comparative analysis of the AUC of the preoperative (red) and postoperative (blue) models compared to the Southampton score (green) both for the primary endpoint of major complications (**A**) and the secondary endpoint of mortality (**B**) reveals the two defined models to have a higher predictive value. AUC computation and model generation are based on the dataset, omitting cases with missing variables.

4. Discussion

The rise of minimal-invasive techniques in hepatobiliary surgery is in full swing. More and more centers are adopting various approaches in their clinical practice, no longer being constrained by reservations regarding intraoperative safety and oncological outcome. With increasing experience, our understanding of the benefits of minimal-invasive techniques has evolved, and it is commonly regarded as settled knowledge that LLR is able to elicit faster functional recovery, reducing hospital stay and lowering morbidity rates while achieving noninferior outcomes from an oncological perspective. The application of LLR has opened up curative resections to patients who previously might have been considered inoperable due to impaired liver function or poor general health. In a very recent study, laparoscopy has been shown in a French multicenter cohort to reduce the risk of posthepatectomy liver failure [29]. The spectrum of potential complications after liver surgery, of course, goes beyond hepatic dysfunction. Indeed, preoperative patient health and liver function are critical, but likewise, the amount of tissue resected, type of resection and tumor entity are critical factors. Moreover, intraoperative decision making impacts outcome, and some complications may be attributable to low experience. In this regard, a structured curriculum to obtain necessary experience, as recently suggested, is vital [12]. With growing surgeon experience, however, other factors drive the occurrence of complications.

In the present study, we have examined resections of primary hepatic malignancies and developed two simple robust scoring systems, capable of predicting the occurrence of major complications. While similar approaches have been undertaken by other studies [21,24], they are limited by either biased model development or by placing disproportionate focus on technical factors rather than the patient or are only predicting intraoperative complications. The tools developed in the present report integrate parameters of general patient health, liver function and operative course that have been shown to be independently associated with an adverse outcome. Inclusion of operative time and the need for conversion, information immediately obtainable after surgery, improved the predictive ability substantially. Specifically, operative time is a powerful readout of aggressiveness of the

surgical approach and highly predictive of the occurrence of postoperative complications. Likewise, conversion can be regarded as a surrogate of procedure complexity. By defining patients at risk of developing potentially life-threatening events after surgery, the models may help to improve patient selection for resection and identify patients requiring close monitoring in the postoperative period. Moreover, the model can be applied in the process of training, as patients at high risk, where margins of error decrease, could be operated by fellows at later training stages.

Interestingly, no statistically meaningful correlation was observed between the presence of cirrhosis and the occurrence of major complications. This was the case both for preoperative imaging-based assessment as well as postoperative pathology. Moreover, factors associated with cirrhosis such as higher serum bilirubin, lower albumin and low thrombocyte counts showed no significant correlation with CD 3-5 complications. This may be, at least in part, attributable to the limited spectrum of hepatic dysfunction in included patients and the low likelihood of major resection carried out in these at-risk cases [30]. Except for one patient with a Child–Pugh B7 score, all patients were within Child–Pugh A. It should be considered, however, that the decreased magnitude of harm inflicted by LLR clouds the relationship between hepatic dysfunction and occurrence of complications in this patient subset and a trend might be more evident in (a) patients undergoing laparotomy or (b) patients with less compensated hepatic function, i.e., Child–Pugh B7 patients that undergo major hepatectomy.

The use of logistic regression models in clinical practice is constrained by the need to fill out complex formulas. Any models are therefore regarded with caution due to limited practicality. To address this, we have deployed our tool as an easily accessible online application providing an instant estimation of risk based on the provided input [31].

The limitations of this study are certainly its retrospective design and the single-center nature of the report. Moreover, as validation is only performed internally, the tools are still to a certain extent subjected to overfitting and thus external prospective validation is required. The lack of perfect prediction by the tools also shows that other factors, unaccounted for by either model, impact the outcome.

5. Conclusions

Predicting major morbidity has implications for surgical training, selecting the appropriate operative approach and postoperative clinical management. In this large-scale single-center study, we defined a robust logistic regression model, capable of predicting major postoperative complications, that incorporates individual data on lesion characteristics, patients' general health, liver function and the surgical approach. The addition of intraoperative information significantly improves the predictive ability. This system outperforms previously reported scores that have failed to account for risk factors on the side of the patient as well as the operative procedure.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/4/685/s1, Figure S1. Missing data. Figure S2. Model calibration. Table S1. Model coefficients are depicted for the preoperative and postoperative model.

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Minimal-Invasive Versus Open Hepatectomy for Colorectal Liver Metastases: Bicentric Analysis of Postoperative Outcomes and Long-Term Survival Using Propensity Score Matching Analysis

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Abstract: Minimal-invasive hepatectomy (MIH) has been increasingly performed for benign and malignant liver lesions with most promising short-term results. However, the oncological role of MIH in the treatment of patients with colorectal liver metastases (CRLM) needs further investigation. Clinicopathological data of patients who underwent liver resection for CRLM between 2012 and 2017 at the Department of Surgery, Charité-Universitätsmedizin Berlin, and the Inselspital Bern were assessed. Postoperative outcomes und long-term survivals of patients following MIH were compared with those after conventional open hepatectomy (OH) after 1:1 propensity score matching. During the study period, 229 and 91 patients underwent liver resection for CRLM at the Charité Berlin and the Inselspital Bern, respectively. Patients who underwent MIH in one of the two centers ($n = 69$) were compared with a matched cohort of patients who underwent OH. MIH was associated with lower complication rates (23% vs. 44%, $p = 0.011$), shorter length of intensive care unit stay (ICU, 1 vs. 2 days, $p = 0.043$), shorter length of hospital stay (7 vs. 11 days, $p < 0.0001$), and a reduced need for intraoperative transfusions (12% vs. 25%, $p = 0.047$) compared to OH. R0 status was achieved in 93% and 75% of patients after MIH and OH, respectively ($p = 0.005$). After a median follow-up of 31 months, MIH resulted in similar five-year overall survival (OS) rate (56% vs. 48%, $p = 0.116$) in comparison to OH. MIH for CRLM is associated with lower postoperative morbidity, shorter length of ICU and hospital stay, reduced need for transfusions, and comparable oncologic outcomes compared to the established OH. Our findings suggest that MIH should be considered as the preferred method for the treatment of curatively resectable CRLM.

Keywords: colorectal liver metastases; laparoscopic liver surgery; minimal invasive surgery

1. Introduction

The most common site of metastatic tumor spread in patients with colorectal cancer is the liver. At time of diagnosis, 20% of patients present with synchronous colorectal liver metastases (CRLM) [1], and up to 25% of patients are at risk to develop metachronous CRLM over time [2]. Liver resection remains the mainstay of a multimodal curative therapeutic approach for CRLM, enabling long-term survivals. In the last decades, advances in the multimodal treatment of patients with CRLM have achieved five-year overall survival rates of up to 58% after hepatectomy [3,4].

Since the introduction of laparoscopic liver surgery in the early 1990s [5,6], minimal-invasive hepatectomy (MIH) has been widely adopted for benign and malignant lesions of the liver, including hepatocellular carcinoma [7,8] and CRLM [9]. Doubts about laparoscopic liver resection concerning the general complexity of the technique and cost-effectiveness are gradually declining, since benefits in short-term outcomes have been reported in several retrospective studies and were confirmed in meta-analyses [10,11]. MIH for CRLM has been associated with less intraoperative blood loss, lower need for transfusion, lower postoperative morbidity rates, and shorter length of hospital stay in comparison to open hepatectomy (OH) [10,12,13]. Reports on oncologic results have already demonstrated the non-inferiority of MIH in terms of the rate of patients with tumor-free resection margins (R0 resection), overall survival (OS), and disease-free survival (DFS) [9,14]. These findings have indicated that MIH is a valid alternative to OH in the most recent Southampton guidelines for laparoscopic liver surgery [15].

Scientific evidence on the feasibility of MIH for CRLM is mostly based on retrospectively collected data. To date, only one randomized controlled study (RCT) from Norway has been conducted showing benefits for minimal-invasive CRLM resection concerning postoperative morbidity and length of hospital stay [13]. However, this study was single-center and included only patients with minor resections, thus may not be widely applicable for patients with extended disease.

Although long known [16], propensity-score matching (PSM) analysis gained popularity in recent years as a statistical method to adjust for known confounding factors and thus reduce the impact of selection bias in retrospective studies [17]. PSM has been often used for the comparison of surgical techniques in an effort to create comparable treatment groups [10]. Using propensity-score based analysis, previous European multi-center studies have given insight into the short- and long-term outcomes of MIH in comparison to OH for CRLM [18,19]. In this study, we aimed to share the current experience of two major hepatobiliary centers that regularly perform MIH.

The objective of this study was to evaluate the postoperative and oncologic outcomes of patients undergoing MIH for CRLM compared to those of patients undergoing OH in a bi-centric setting using PSM analysis. In addition, the inter-center comparison of postoperative and long-term outcomes between two major hepatobiliary centers in Berlin, Germany, and Bern, Switzerland, intended to provide further insight into each center's approach to the treatment of patients with CRLM.

2. Experimental Section

2.1. Patient Inclusion Criteria

Approval for this study was obtained from the Ethics Commission of Charité-Universitätsmedizin Berlin (EA2/006/16) and the Ethics Commission of the Canton of Bern (2018-01576). Clinicopathological data on 229 and 91 consecutive patients who underwent resection for CRLM from 2012 to 2017, at the Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité-Universitätsmedizin Berlin, and the Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, respectively, were collected.

Inclusion criterion was a curative intended resection, defined as the ability to remove all radiologically evident disease. Patients were excluded from the analysis if they were <18 years old, if extended hemihepatectomies were performed, and if microwave ablations or other surgical procedures (e.g., resection of the primary tumor) were concomitantly performed with hepatectomy.

2.2. Preoperative Assessment

Patients with CRLM presenting in each department routinely underwent a standardized preoperative evaluation protocol that included medical history, physical examination, serum laboratory tests, and an anesthesia evaluation. Tumor staging and the estimation of the future liver remnant (FLR) volume was determined via cross-sectional imaging (triphasic contrast-enhanced computed tomography or magnetic resonance imaging with liver-specific contrast agents) as needed.

An institutional multidisciplinary tumor board in each center consisting of surgeons, hepatologists, oncologists, and specialized radiologists discussed each case and recommended the best individual treatment strategy for each patient.

2.3. Surgical Procedure

Surgical procedures were performed as previously described [20–23]. At the beginning of every procedure, following laparotomy or laparoscopy, the peritoneal cavity was examined to rule out any previously undiagnosed tumor spread. Intraoperative ultrasound of the liver was used to validate the exact location and extent of CRLM as determined by imaging studies. Conventional OH was initiated with a modified Makuuchi incision [24]. For MIH in both centers, patients were kept in a supine position with legs spread apart (French position) [25]. MIH was performed either via multiport laparoscopic surgery (MLS, transumbilical 12 mm optical trocar and further 5 mm and 12 mm trocars), single-incision laparoscopic surgery (SILS; GelPort®, Applied Medical, Rancho Santa Margarita, CA, USA, via 4–5 cm midline incision for three trocars, additional 5 mm port in upper left abdominal quadrant, if needed), or hand-assisted laparoscopic surgery (HALS; handport via 5 cm supraumbilical incision and 2–3 additional 12 mm ports). Specimen were retrieved via a Pfannenstiel incision, extension of the umbilical incision or by using an existing scar. Total or selective hepatic vascular exclusion was utilized for major parenchymal transections, as needed. For MIH in both centers, liver parenchyma dissection was performed using a combination of following devices and instruments: energy devices (Thunderbeat®, Olympus K.K., Tokyo, Japan, or Harmonic Ace®, Ethicon Inc., Somerville, NJ, USA), laparoscopic cavitron ultrasonic surgical aspirator (CUSA®, Valleylab Boulder, CO, USA), Waterjet (ERBEJET®, ERBE Tübingen, Germany), and vascular stapler (Echelon™, Ethicon, Somerville, NJ, USA) or Endo GIA™ (Medtronic, Dublin, Ireland).

The resection of ≥ 3 contiguous liver segments defined major hepatectomy according to Couinaud's classification [26]. Location of CRLM was stratified by technical difficulty in segments II, III, IVb, V, and VI, and segments I, IVa, VII, and VIII. The latter was defined as technical more difficult.

2.4. Postoperative Management

After surgery, patients were occasionally admitted to a surgical intensive care unit (ICU) if needed, where they were monitored for postoperative complications such as intra-abdominal bleeding, infection, biliary fistula, wound infection, pneumonia, pleural effusions, and liver failure. After routine removal of the nasogastric tube on the same day, oral intake and mobilization was anticipated on postoperative day 1. Intra-abdominal drains were either not used at all or removed as soon as the discharge was unremarkable. Blood tests were postoperatively regularly performed to assess liver function and cholestasis and rule out the development of an infectious collection. Any complication or death within 90 days after surgery defined postoperative morbidity and mortality, respectively. Postoperative complications were graded according to the classification of Clavien and Dindo and major complications were defined as ≥3a [27]. After surgery, all cases were re-evaluated in our multidisciplinary tumor board and postoperative treatment was recommended according to current guidelines [28].

2.5. Histological Evaluation

Resected specimens were evaluated by a pathologist to confirm the diagnosis of CRLM and to determine the resection margin status (R). R0 was defined as a surgical margin of ≥1 mm free of malignant cells [29].

2.6. Statistical Analysis

Propensity score analysis was used to match patients who underwent MIH for CRLM with a cohort of patients who were treated with OH in each center separately. A 1:1 PSM was performed using a logistic regression model with a match tolerance of 0.1 based on the following matching parameters: patient age, sex, ASA (American Society of Anesthesiologists) status, comorbidities (diabetes, hypertension, coronary heart disease, pulmonary disease, and/or renal disease), presence of solitary or multiple CRLM, sequence of hepatic tumor spread (synchronous or metachronous), preoperative chemotherapy, and resection extent (including major or minor hepatectomy). Matched cohorts from both centers were then merged for a pooled comparison of MIH with OH.

Quantitative and qualitative variables were expressed as medians (range) and frequencies. The chi-square or Fisher's exact test for categorical variables, and the Wilcoxon signed-rank test for continuous variables, were used as appropriate to compare between groups. Patient characteristics and postoperative outcomes were compared between the matched MIH and OH cohorts as well as between the MIH patients in Berlin and Bern.

Using the Kaplan-Meier method, overall survival (OS) was calculated from the date of resection to the date of death or last follow-up and disease-free survival (DFS) was calculated from the date of resection to the date of first recurrence or last follow-up. Comparisons between survival rates were performed using log-rank tests.

p values < 0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software package, version 25 (IBM, Armonk, NY, USA).

3. Results

3.1. Patient Characteristics

During the study period, 229 and 91 consecutive patients underwent hepatectomy for CRLM at the Department of Surgery, Campus Charité Mitte and Campus Virchow-Klinikum, Charité Berlin, and the Department of Visceral Surgery und Medicine, Inselspital, Bern, respectively, and were included in this study. OH was performed in 251 patients (78%) (n = 185 in Berlin, n = 66 in Bern) and 69 patients (22%) were treated with MIH (n = 44 in Berlin, n = 25 in Bern).

Patient cohorts in Berlin differed significantly before matching (MIH vs. OH) regarding the rate of patients presenting with CRLM > 50 mm including 35% and 16% in the OH and MIH group, respectively (p = 0.016). Additionally, the extent of liver resection was significantly different between the two groups (p < 0.0001), since there were more open major hepatectomies during the study period. Before matching MIH with OH in Bern, there were significant differences between the two groups regarding the proportion of patients presenting with single CRLM (76% vs. 42%, p = 0.003) and CRLM > 50 mm (12% vs. 36%, p = 0.023). In addition, the N stage of the primary tumor was more advanced in the OH group (p = 0.048). Significantly less major hepatectomies (4% vs. 33%, p = 0.004) and less anatomic resections (4% vs. 55%, p < 0.0001) were performed in the MIH cohort compared to the OH group.

After PSM, pooled analysis of MIH (n = 69 patients) versus OH (n = 69 patients) is summarized in Table 1. Both groups (MIH vs. OH) were comparable regarding sex (male: 68% vs. 55%, p = 0.115), median age (65 vs. 63 years, p = 0.210), median BMI (25 vs. 25 kg/m^2, p = 0.718), ASA physical status (p = 0.470), and location of the primary tumor (colon and rectum: 54% vs. 61% and 46% vs. 39%, p = 0.390). Moreover, no significant differences regarding the sequence of liver tumor spread (synchronous: 46% vs. 45%, p = 0.864), and the proportion of patients presenting with CRLM > 50 mm (15% vs. 27%,

$p = 0.074$) or solitary CRLM (51% vs. 44%, $p = 0.439$) were found. However, CRLM were more frequently located in segments I, IVa, VII, and VIII in the OH group ($p = 0.005$). The rate of patients treated with preoperative chemotherapy was comparable between both groups (60% vs. 62%, $p = 0.727$). Anatomic resections were performed in 39% and 51% in the MIH and OH group, respectively ($p = 0.171$). Both groups had equal amounts of major resections (33% vs. 33%, $p = 1$), and the extent of hepatectomy was comparable ($p = 0.660$) between the two groups. The median duration of surgery was similar between the groups (218 vs. 250 min, $p = 0.078$). Positive resections margins were found in 7% and 25% after MIH and OH, respectively ($p = 0.005$). A comparable number of patients were monitored on the ICU postoperatively (83% vs. 88%, $p = 0.370$). The length of ICU stay (1 vs. 2 days, $p = 0.043$) and length of hospital stay (7 vs. 11 days, $p < 0.0001$) were significantly shorter after MIH than after OH. The need for blood transfusions was reduced after MIH (12% vs. 25%, $p = 0.047$).

Table 1. Characteristics of propensity-score matched patients who underwent hepatectomy for CRLM in Berlin and Bern ($n = 138$).

Variable	OH ($n = 69$)	MIH ($n = 69$)	p
Gender, *n* (%)			0.115
Female	31 (45)	22 (32)	
Male	38 (55)	47 (68)	
Age, years, median (range)	63 (30–86)	65 (27–89)	0.210
Age > 65 years, *n* (%)	32 (46)	35 (51)	0.609
BMI, kg/m^2, median (range)	25 (18–46)	25 (18–40)	0.718
BMI > 30 kg/m^2, *n* (%)	11 (16)	14 (21)	0.480
ASA physical status, *n* (%)			0.470
1	2 (3)	0 (0)	
2	34 (49)	32 (46)	
3	32 (47)	35 (51)	
4	1 (1)	2 (3)	
Comorbidities, *n* (%)			
Diabetes	10 (15)	12 (17)	0.642
Hypertension	29 (42)	29 (42)	1
Coronary heart disease	4 (6)	7 (10)	0.346
Pulmonary disease	4 (6)	4 (6)	1
Renal disease	4 (6)	6 (9)	0.511
Localization of primary, *n* (%)			0.390
Colon	42 (61)	37 (54)	
Rectum	27 (39)	32 (46)	
Synchronous CRLM, *n* (%)	31 (45)	32 (46)	0.864
Size of biggest CRLM > 50 mm, *n* (%)	18 (27)	10 (15)	0.074
Solitary CRLM, *n* (%)	30 (44)	35 (51)	0.439
CRLM in segments II, III, IVb, V, and VI, *n* (%)	56 (81)	63 (91)	0.084
CRLM in segments I, IVa, VII, and VIII, *n* (%)	52 (75)	36 (52)	0.005
Preoperative chemotherapy, *n* (%)	43 (62)	41 (60)	0.727
T stage of primary, *n* (%)			0.360
1	4 (6)	3 (5)	
2	4 (6)	8 (13)	
3	43 (64)	41 (67)	
4	16 (24)	9 (15)	
N stage of primary, *n* (%)			0.038
0	23 (34)	33 (54)	
1	33 (49)	16 (26)	
2	11 (16)	11 (18)	
3	0 (0)	1 (2)	

Table 1. *Cont.*

Variable	OH (*n* = 69)	MIH (*n* = 69)	*p*
UICC stage of primary, *n* (%)			0.031
1	5 (7)	7 (11)	
2	7 (10)	14 (21)	
3	23 (34)	9 (14)	
4	33 (49)	36 (54)	
Tumor grading of primary, *n* (%)			0.443
G1	2 (4)	0 (0)	
G2	47 (82)	38 (84)	
G3	8 (14)	7 (16)	
Postoperative ICU stay, *n* (%)	59 (88)	57 (83)	0.370
Length of ICU stay, days, median (range)	2 (0–37)	1 (0–23)	0.043
Length of hospital stay, days, median (range)	11 (4–109)	7 (2–59)	<0.0001
90-day complications, *n* (%)	30 (44)	16 (23)	0.011
90-day major complications, *n* (%)	17 (25)	12 (17)	0.296
90-day mortality, *n* (%)	2 (3)	1 (1)	0.559
Anatomic resection, *n* (%)	35 (51)	27 (39)	0.171
Major resection, *n* (%)	23 (33)	23 (33)	1
Positive resection margins, *n* (%)	17 (25)	5 (7)	0.005
Resection margin width in R0 resected patients, mm, median (range)	2 (1–20)	3 (1–40)	0.430
Surgical technique, *n* (%)			0.660
right hepatectomy	13 (19)	12 (17)	
right hepatectomy and wedge resections or segmental resections	6 (9)	8 (12)	
left hepatectomy	4 (6)	1 (1)	
left hepatectomy and wedge resections or segmental resections	0 (0)	2 (3)	
left lateral hepatectomy	4 (6)	4 (6)	
segmentectomy/wedge resection	30 (43)	30 (43)	
bisegmentectomy	12 (17)	12 (17)	
Need for transfusion, *n* (%)	17 (25)	8 (12)	0.047
Duration of operation, minutes, median (range)	250 (106–513)	218 (46–602)	0.078
Postoperative chemotherapy, *n* (%)	22 (32)	22 (32)	1

CRLM, colorectal liver metastases; OH, open hepatectomy; MIH, minimal-invasive hepatectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; UICC, Union internationale contre le cancer; ICU, intensive care unit.

3.2. Postoperative Morbidity and Mortality

Postoperative morbidity was significantly lower after MIH than after OH (23% vs. 44%, $p = 0.011$). Postoperative mortality was not significantly different between the two techniques (1% vs. 3%, $p = 0.559$).

3.3. Overall Survival and Disease-Free Survival

After a median follow-up time of 31 months, the 5-year OS rates were 56% and 48% after MIH and OH, respectively ($p = 0.116$; Figure 1). Five-year DFS rates were 46% and 27% after MIH and OH, respectively ($p = 0.018$).

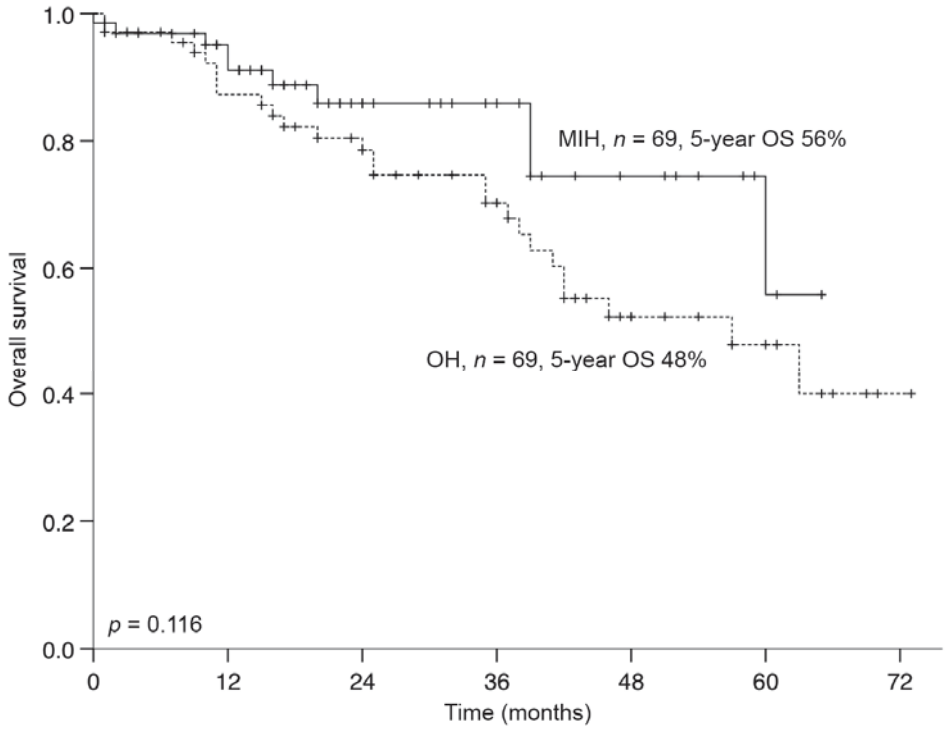

Figure 1. Overall survival of propensity-score matched patients who underwent hepatectomy for CRLM in Berlin and Bern (n = 138). MIH, minimal-invasive hepatectomy; OS, overall survival; OH, open hepatectomy; CRLM, colorectal liver metastases

3.4. Comparison of Clinicopathological Characteristics and Outcomes of Patients Who Underwent MIH in Berlin vs. Bern

Characteristics of patients who underwent MIH in Berlin (n = 44) were compared with those of patients in Bern (n = 25) (Table 2). Patient-related parameters were comparable between the two centers. No significant differences were found concerning age (p = 0.453), BMI (p = 0.513), ASA status (p = 0.163), or presence of comorbidities. The rate of patients with CRLM > 50 mm (16% vs. 12%, p = 0.657) and synchronous CRLM (43% vs. 52%, p = 0.480) was equivalent between the two centers. CRLM were equally located in segments II, III, IVb, V, and VI (p = 0.180), and segments I, IVa, VII, and VIII of the liver (p = 0.306). However, patients presented with solitary CRLM more frequently in Bern than in Berlin (76% vs. 36%, p = 0.002). More major (50% vs. 4%, p < 0.0001) and anatomic resections (59% vs. 4%, p < 0.0001) were performed in Berlin than in Bern. In general, the extent of MIH was different between Berlin and Bern (p = 0.002). Whereas a large part of minimal-invasive resections in Berlin were hemihepatectomies, the majority of laparoscopic treated patients in Bern underwent wedge resections or segmentectomies, thus also resulting in significant differences regarding the median duration of the operation (290 vs. 125 min, p < 0.0001), postoperative morbidity rates (32% vs. 8%, p = 0.024), and length of hospital stay (9 vs. 5 days, p < 0.0001). There were more patients in intensive care in Berlin than in Bern (91% vs. 68%, p = 0.022); however, length of ICU stay was comparable between the centers (1 vs. 2 days, p = 0.283). Postoperative mortality after MIH was comparable in both centers (p = 1). Additionally, there were no significant differences regarding positive resection margins (p = 0.151), and the need for transfusions (p = 1).

Table 2. Comparison of characteristics and outcomes between patients who underwent minimal-invasive hepatectomy for CRLM in Berlin or Bern (n = 69).

Variable	Berlin (n = 44)	Bern (n = 25)	p
Gender, n (%)			0.110
Female	17 (39)	5 (20)	
Male	27 (61)	20 (80)	
Age, years, median (range)	65 (27–89)	66 (29–84)	0.453
Age > 65 years, n (%)	21 (48)	14 (56)	0.509
BMI, kg/m^2, median (range)	25 (18–40)	26 (19–34)	0.513
BMI > 30 kg/m^2, n (%)	8 (19)	6 (24)	0.630
ASA physical status, n (%)			0.163
1	0 (0)	0 (0)	
2	21 (48)	11 (44)	
3	23 (52)	12 (48)	
4	0 (0)	2 (8)	
Comorbidities, n (%)			
Diabetes	8 (18)	4 (16)	1
Hypertension	19 (43)	10 (40)	0.797
Coronary heart disease	3 (7)	4 (16)	0.225
Pulmonary disease	1 (2)	3 (12)	0.132
Renal disease	4 (9)	2 (8)	1
Localization of primary, n (%)			0.423
Colon	22 (50)	15 (60)	
Rectum	22 (50)	10 (40)	
Synchronous CRLM, n (%)	19 (43)	13 (52)	0.480
Size of biggest CRLM > 50 mm, n (%)	7 (16)	3 (12)	0.657
Solitary CRLM, n (%)	16 (36)	19 (76)	0.002
CRLM in segments II, III, IVb, V, and VI, n (%)	42 (96)	21 (84)	0.180
CRLM in segments I, IVa, VII, and VIII, n (%)	25 (57)	11 (44)	0.306
Preoperative chemotherapy, n (%)	23 (52)	18 (72)	0.109
T stage of primary, n (%)			0.086
1	1 (2)	2 (8)	
2	8 (22)	0 (0)	
3	23 (62)	18 (75)	
4	5 (14)	4 (17)	
N stage of primary, n (%)			0.437
0	18 (49)	15 (63)	
1	12 (32)	4 (17)	
2	6 (16)	5 (21)	
3	1 (3)	0 (0)	
UICC stage of primary, n (%)			0.919
1	5 (12)	2 (8)	
2	8 (20)	6 (24)	
3	6 (15)	3 (12)	
4	22 (54)	14 (56)	
Tumor grading of primary, n (%)			0.412
G1	0 (0)	0 (0)	
G2	24 (89)	14 (78)	
G3	3 (11)	4 (22)	
Postoperative ICU stay, n (%)	40 (91)	17 (68)	0.022
Length of ICU stay, days, median (range)	1 (0–23)	2 (0–3)	0.283
Length of hospital stay, days, median (range)	9 (3–59)	5 (2–10)	<0.0001
90-day complications, n (%)	14 (32)	2 (8)	0.024
90-day major complications, n (%)	11 (25)	1 (4)	0.027
90-day mortality, n (%)	1 (2)	0 (0)	1

Table 2. *Cont.*

Variable	Berlin (n = 44)	Bern (n = 25)	p
Anatomic resection, n (%)	26 (59)	1 (4)	<0.0001
Major resection, n (%)	22 (50)	1 (4)	<0.0001
Positive resection margins, n (%)	5 (11)	0 (0)	0.151
Resection margin width in R0 resected patients, mm, median (range)	4 (1–40)	3 (1–20)	0.519
Surgical technique, n (%)			0.002
right hepatectomy	11 (25)	1 (4)	
right hepatectomy and wedge resections or segmental resections	8 (18)	0 (0)	
left hepatectomy	1 (2)	0 (0)	
left hepatectomy and wedge resections or segmental resections	2 (4)	0 (0)	
left lateral hepatectomy	4 (9)	0 (0)	
wedge resection	13 (30)	17 (68)	
bisegmentectomy	5 (11)	7 (28)	
Need for transfusion, n (%)	5 (11)	3 (12)	1
Duration of operation, minutes, median (range)	290 (121–602)	125 (46–235)	<0.0001
Postoperative chemotherapy, n (%)	13 (30)	9 (36)	0.580

CRLM, colorectal liver metastases; BMI, body mass index; ASA, American Society of Anesthesiologists; UICC, Union internationale contre le cancer; ICU, intensive care unit.

Five-year OS rates (Berlin vs. Bern: 52% vs. 59%, p = 0.091; Figure 2) and DFS rates (Berlin vs. Bern: 47% vs. 44%, p = 0.577) were statistically equivalent between the two centers.

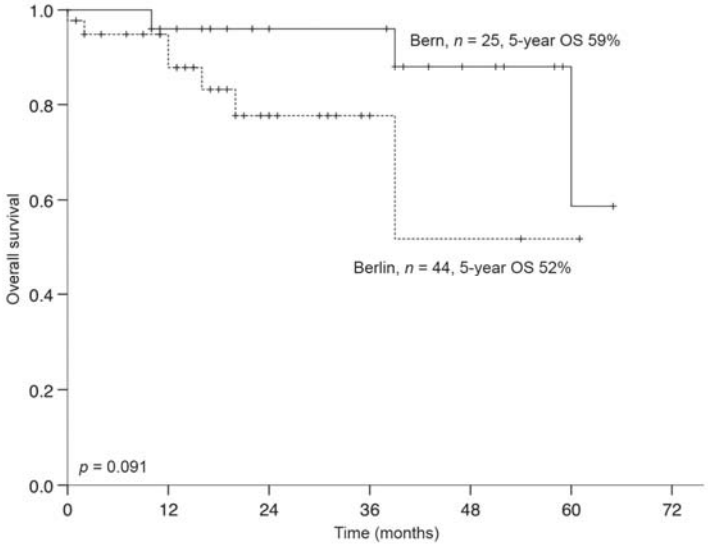

Figure 2. Overall survival of patients who underwent minimal-invasive hepatectomy for CRLM in Berlin or Bern (n = 69). OS, overall survival; CRLM, colorectal liver metastases

Forty-three percent (n = 3/7) and 67% (n = 2/3) of patients who deceased following MIH in the observed time period in Berlin and Bern, respectively (p = 1), died due to cancer progression including intrahepatic recurrence. Two of the three patients suffering cancer-related death in Berlin had initially underwent major MIH because of extended liver tumor burden, and none of these three patients were selected for repeat hepatectomy due to extended recurrent disease burden or insufficient FLR.

Instead of re-resection, one patient underwent local brachytherapy, one patient was administered palliative chemotherapy, and the third was lost to follow-up. In Bern, both patients, who died of cancer progression following laparoscopic hepatectomy underwent initially minor liver resections (bisegmentectomy and wedge resection) and were able to undergo repeat MIH for limited intrahepatic recurrence. After diagnosis of intrahepatic recurrence, patients lived for another 6, 9, and 10 months in Berlin, and for another 27 and 28 months in Bern, respectively.

4. Discussion

Our study on a bicentric experience from the Charité Berlin (Campus Charité Mitte and Campus Virchow-Klinikum) and the Inselspital Bern compared the postoperative and oncologic outcomes of patients who underwent MIH for CRLM with those of propensity-score matched patients treated with OH. In comparison to conventional OH, our results indicated lower postoperative complication rates, shorter length of ICU and hospital stay, and lower rates of intraoperative blood transfusions for patients undergoing MIH. MIH was associated with oncologic outcomes equivalent to those after OH.

The advantages of MIH over OH for CRLM have been previously reported in the literature. Recent studies found benefits regarding postoperative morbidity, length of hospital stay, blood loss, and the need for transfusions with equivalent oncologic outcomes in comparison to OH [10,12,14,30–32]. These findings have been mainly derived from retrospective data since RCTs are often faced with methodical and patient-recruitment related challenges [33]. So far, only one RCT has been completed evaluating MIH for CRLM [13] while another had to be cancelled early due to a slow accrual process [34]. For this reason, PSM analysis has been introduced aiming to overcome treatment bias in retrospective studies by assembling patient cohorts with minimal differences in clinicopathological features allowing for a meaningful comparison [35,36]. To date, consensus regarding the optimal parameters that should be included in PSM is lacking. Since our objective was to eliminate all patient- and tumor-related factors that could influence outcomes after surgery, we decided to include all variables concerning the general condition of the patient, the tumor characteristics, the administration of preoperative chemotherapy, and the extent of hepatectomy. Various studies performed PSM to compare the outcomes of laparoscopic versus open resection for CRLM, most recently coming from Italy [12], and the USA [14]. Earlier studies were analyzed in a meta-analysis which is entirely based on propensity-score matched data [10].

Within the framework of our PSM analysis, we report on a comparably high rate of major MIH for CRLM with 50% in Berlin and 33% in the entire cohort, respectively [12]. Of note, Fretland et al. defined parenchymal-sparing liver resections in the design of their RCT with the switch to major hepatectomy if needed [13]. To our knowledge, only few groups performed >50% major hepatectomies in the laparoscopic group [31,37]. Due to the influence of the extent of hepatectomy on postoperative outcomes, these findings need to be acknowledged when comparing the results of our study with others. However, our study confirmed the findings of previous studies, which have shown that MIH is associated with lower morbidity after surgery compared to OH [13,14,32]. Postoperative morbidity (23% vs. 44%, $p = 0.011$) was significantly reduced after MIH, whereas major postoperative morbidity was comparable between MIH and OH (17% vs. 25%, $p = 0.296$).

Moreover, our results showed at least equivalent oncologic outcomes between MIH and OH (5-year OS: 56% vs. 48%, $p = 0.116$; 5-year DFS: 46% vs. 27%, $p = 0.018$). Previous studies reported comparable survivals after open and laparoscopic hepatectomy for CRLM [12]. Patient- and tumor-related factors that may have an influence on survival after surgery are comorbidities, size, and number of CRLM, rate of preoperative chemotherapy, and extent of hepatectomy. These parameters were comparable between the groups after PSM, supporting our opinion that MIH may provide oncologically sufficient outcomes.

Furthermore, oncologic outcomes are generally known to be influenced by the presence of malignant cells in the surgical margins (R1) allowing for early tumor recurrence [29]. Notably, positive resection margins were significantly decreased after MIH in comparison to OH in this study

(7% vs. 25%, $p = 0.005$). However, median resection margin width in R0 resected patients was comparable between OH and MIH, as previously shown [38]. Margin width following MIH was also comparable between the two centers. The implementation of standardized and routinely performed intraoperative ultrasound both in MIH and OH has allowed for higher rates of R0 resections in the recent years. However, the possibility that the surgeon might evaluate and determine the resection margins more conservatively when performing MIH [9], especially due to the different tactile feedback and during the learning curve could explain the improved R0 resection rate after MIH. Additionally, despite thorough PSM taking into consideration numerous cancer-related characteristics we could probably not entirely eliminate bias in the selection of the matched OH cases resulting in the inclusion of some more advanced disease. Furthermore, CRLM were more frequently located in segments I, IVa, VII, and VIII of the liver in the OH group compared to the MIH group. Hepatectomy on these segments are known to be more difficult to perform [39], and this may have translated into a higher R1 rate in this group, and may have negatively influenced the oncologic outcome among OH patients [40]. In addition, more extensive tumor burden requiring OH may also be reflective of unfavorable tumor biology, which, in turn, may be responsible for higher R1 resection rates [41–43].

Currently, perioperative chemotherapy has been widely adapted as an integral component in the multimodal treatment of patients with CRLM [44]. The establishment of modern chemotherapy regimens was one reason to exclude patients treated before 2012. Guidelines recommend the use of preoperative systemic therapy to downsize the hepatic tumor burden and consequently convert patients with unresectable disease to a resectable state [45,46]. Additionally, patients with initially resectable CRLM may profit from preoperatively administered chemotherapy by reducing the presence of malignant cells in the resection margins resulting in prolonged progression-free survival [44]. Our data suggest that patients in both cohorts (MIH and OH) may have benefited equally from the positive effects of chemotherapy as it was administered to equivalent percentages of patients preoperatively. However, possible side effects of neoadjuvant cytotoxic agents (e.g., steatosis, steatohepatitis, or sinusoidal changes) need to be taken into consideration, impairing the function and regenerative capacity of the otherwise healthy remaining liver tissue [47].

Finally, in an effort to elucidate the improved OS for patients after MIH, postoperative morbidity following liver resection for CRLM may have played a role as it has been proven to affect OS and DFS negatively [48–52]. It is hypothesized that postoperative morbidity prolongs a phase of immunosuppression allowing residual tumor cells to proliferate and to induce local recurrence [53]. We found a significantly reduced incidence of overall complications after MIH in comparison to OH in our study, suggesting a positive impact on long-term survival after MIH. Moreover, postoperative complications may have delayed the onset of adjuvant chemotherapy as part of the multimodal treatment concept further contributing to diminished overall survival, as seen in patients after colorectal cancer surgery [54].

Another interesting finding of our study was that MIH correlated with a shorter length of ICU and hospital stay compared to OH. Laparoscopic techniques are considered to diminish the stress that surgical procedures exert on the human body, and thus help to preserve and eventually restore organ function after surgery in an accelerated timeline. Benefits of MIH include earlier postoperative oral intake, optimized postoperative pain control, and earlier mobilization after surgery. In addition to the reduced morbidity, these factors may have also contributed to an earlier discharge for patients after MIH.

In this study, we compared the results of patients, who underwent MIH, in the Charité Berlin und the Inselspital Bern. Both groups were equivalent regarding patient-related characteristics but differed significantly in tumor-specific features. In Bern, MIH was mostly selected for patients with solitary CRLM, and segmental resections were predominantly performed. This resulted in reduced morbidity (8% vs. 32%, $p = 0.024$) and shorter length of hospital stay after MIH in comparison to Berlin (5 vs. 9 days, $p < 0.0001$) without diminishing R0 resection rates. In contrast, more patients in Berlin presented with higher tumor burden making more extensive hepatic resections necessary. These major

MIHs for multiple CRLM were then followed by higher complication rates and longer length of hospital stay in comparison to Bern. However, the results from both centers showed comparable low mortality rates, and prolonged long-term survivals.

When deciding for a liver resection strategy, surgeons are confronted with two conflicting objectives; on the one side, extensive hepatic disease requires an adequate resection extent in order to achieve R0 resection and prevent tumor recurrence. On the other side, as much non-tumorous liver tissue as possible needs to be preserved aiming to avoid postoperative liver insufficiency. This is further aggravated by the aforementioned risks of preoperatively administered chemotherapy on the histopathological and functional integrity of the residual liver parenchyma. An initially major hepatectomy may impede the selection of patients for repeat liver resection in case of intrahepatic recurrence. Additionally, extended tumor burden requiring hemihepatectomy or more is a surrogate factor for advanced disease with a higher risk for earlier and disseminated recurrence. In our study, patients who died of intrahepatic recurrence following MIH in Berlin, presented with high tumor burden in the first place making extended hepatectomy necessary. Repeat hepatectomy for recurrence could not be offered and these patients died within the first year after recurrence. In contrast, patients who died of intrahepatic recurrence following minor MIH in Bern could undergo repeat parenchymal-sparing liver resection for single CRLM and lived for another two years. The fact that more patients in Berlin than in Bern died without recurrence from non-cancer related causes, could be one reason for the higher DFS but lower OS in Berlin (not statistically significant differences).

In the current literature, the optimal extent of hepatic resection remains unclear. Often, no differences were found between parenchymal-sparing and anatomic resections [55,56], but the current trend moves towards parenchymal-sparing resections [57]. In this regard, CRLM needs to be acknowledged as a chronic disease. By limiting hepatectomies to parenchymal-sparing resections whenever possible, re-resections for recurrent CRLM are made possible [58]. Interestingly, improved oncologic outcomes were not associated with an increase in margin width for R0 resections [59] leading to the recommendation in the current Southampton guidelines that parenchymal-sparing resections should be preferably conducted for patients with CRLM [15], which was implemented in both centers if this was allowed by the extent of the tumor burden. Nevertheless, prolonged OS could be achieved in both centers in our study, and especially DFS was not compromised by parenchymal-sparing resections. In summary, despite of favorable short-term and comparable long-term outcomes after MIH found in this study, the decision for either MIH or OH should be individually made for each patient and should be based on patient- and tumor-related factors.

Our present retrospective study has also several limitations. Firstly, conclusions should be carefully drawn due to the rather small cohorts and the retrospective nature of data collection. We tried to challenge this issue by establishing a bi-centric cohort pooling data from two specialized centers with large experience in hepatobiliary surgery. Surgeon- and center-related bias have been eliminated by matching MIH with OH for each center separately. Thus, we could assure that same number of OH and MIH were included from each center, respectively. In addition, it was our objective to create a meaningful statistical comparison by performing PSM to eliminate known covariates. Nevertheless, unused and especially unknown confounders could have influenced our results. Of note, the investigation of somatic gene mutations gains increasingly importance in the treatment of CRLM [60–62]; however, this was not within the scope of this study. The introduction of laparoscopic surgery for CRLM during the study period is associated with a possible learning curve, which may have influenced the outcomes [63,64]. However, standardized laparoscopic procedures performed by experienced hepatobiliary surgeons in both high-volume centers resulted in favorable short- and long-term outcomes underling the advantages of MIH for CRLM.

5. Conclusions

MIH for CRLM was associated with lower overall postoperative morbidity, and shorter length of ICU and hospital stay compared to OH. Oncologic outcomes after MIH were at least equivalent

compared to those after OH. Therefore, our results support our current approach that MIH should be preferred for patients presenting with resectable CRLM.

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Usability of Indocyanine Green in Robot-Assisted Hepatic Surgery

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Abstract: Recent developments in robotic surgery have led to an increasing number of robot-assisted hepatobiliary procedures. However, a limitation of robotic surgery is the missing haptic feedback. The fluorescent dye indocyanine green (ICG) may help in this context, which accumulates in hepatocellular cancers and around hepatic metastasis. ICG accumulation may be visualized by a near-infrared camera integrated into some robotic systems, helping to perform surgery more accurately. We aimed to test the feasibility of preoperative ICG application and its intraoperative use in patients suffering from hepatocellular carcinoma and metastasis of colorectal cancer, but also of other origins. In a single-arm, single-center feasibility study, we tested preoperative ICG application and its intraoperative use in patients undergoing robot-assisted hepatic resections. Twenty patients were included in the final analysis. ICG staining helped in most cases by detecting a clear lesion or additional metastases or when performing an R0 resection. However, it has limitations if applied too late before surgery and in patients suffering from severe liver cirrhosis. ICG staining may serve as a beneficial intraoperative aid in patients undergoing robot-assisted hepatic surgery. Dose and time of application and standardized fluorescence intensity need to be further determined.

Keywords: robotic surgery; indocyanine green; robotic liver resection; da Vinci; intraoperative imaging; hepatocellular cancer; real-life imaging; hepatic metastasis

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1. Introduction

Hepatobiliary surgery has made great technological progress over time, developing from open surgery to minimally-invasive approaches including laparoscopy and, more recently, robot-assisted procedures [1–4]. Advantages of the robotic platform compared to laparoscopic surgery include smaller incisions, clearer visualization of structures, higher degrees of freedom, avoidance of the fulcrum effect, and better access to segments IVa, VII, and VIII [1–5]. However, robot-assisted liver surgery is still partly in its infancy and hepatic resections have not yet been standardized [1,4–6]. Additionally, either some instruments are unavailable for the robotic platform or they are difficult to handle or change [1,6,7]. With the development of more suitable devices and surgical instruments, robot-assisted liver surgery will further improve [1,8]. Nonetheless, until now robot-assisted liver surgery has been proven to be safe and comparable to open surgery and laparoscopy from both a surgical and oncological point of view [1,5,9–13].

However, one major drawback of minimally-invasive surgery is the lack of haptic feedback, since palpation with laparoscopic or robotic forceps is limited [2,3,5,12,14,15]. The surgeon must rely on their own visual impressions, making parenchymal dissections particularly problematic [3,7]. As an additional intraoperative aid for strategic and intraoperative planning, the water-soluble dye indocyanine green (ICG) has been suggested [16–18]. ICG was approved by the Food and Drug Administration (FDA) in 1957 and has been used in various medical fields [19–21]. Since the 1980s, ICG has been used

to test liver function prior to hepatobiliary surgery. In this indication (LiMON test), ICG is administered intravenously days before surgery and the blood concentration and ICG plasma disappearance rates are measured noninvasively [14,22]. In healthy liver tissue, ICG is fully excreted after 72 h and no remnants should be detectable [1,14]. In this context, Ishizawa et al. noticed ICG accumulation in hepatocellular carcinoma (HCC) and hepatic metastasis (HM) of colorectal cancer up to 14 days after ICG application for liver function evaluation [16].

ICG accumulation can be visualized using a near-infrared (NIR) camera, which is currently often integrated into laparoscopic or robotic systems. The Firefly™ camera (Intuitive, Sunnyvale, CA, USA) is integrated in the da Vinci Surgical Systems (Intuitive, Sunnyvale, CA, USA) and can easily be used to intraoperatively visualize ICG accumulation [12]. In open surgery, additional NIR cameras and/or monitors are needed for ICG visualization, theater lights need to be switched off, and the operating surgeon must remove their focus from the operation field while performing crucial parts of the operation. In laparoscopic surgery, the NIR camera is integrated into some systems. Additionally, the quality of images highly depends on the systems used [15]. This results in a high risk for agitation within the theater at a vulnerable phase of surgery. Using the integrated Firefly™ camera, the surgeon operating using the robotic system can continue to focus on the operation field because the Firefly™ camera can easily be switched on and off and acquire real-life intraoperative ICG-based images that are directly projected onto the operation field. These may further be merged with intraoperative ultrasound (IOUS) images without changing instruments or monitors [7,12,23].

However, ICG is still mainly used to test liver function prior to hepatobiliary surgery or intraoperative bile leakage; it is not yet routinely applied to detect tumors or metastases [1]. Furthermore, reports on ICG-based tumor or metastatic resections mainly include open and laparoscopic procedures [12,15,16,19,23–28]. To our knowledge, only one group has reported on ICG-based, robot-assisted hepatic surgery for HCC and metastasis of colorectal cancer (CRC) [17,18]. Thus, we aimed to review our experiences regarding robot-assisted hepatic resections after ICG application in patients suffering from HCC and metastasis of CRC. Additionally, we wanted to evaluate the feasibility of preoperative ICG application in patients suffering from hepatic metastasis other than CRC metastasis.

2. Material and Methods

2.1. Data Collection

A prospective database collecting data for all patients undergoing robot-assisted hepatic surgery is maintained at the Dept. of General, Visceral, Transplant, Thoracic, and Pediatric Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Germany.

Demographic data and the clinical courses of included patients were prospectively retrieved from the hospital's in-house patient files. All patients provided written informed consent for inclusion in the study and use of their data. The local ethics committee provided written approval (D 610/20). The study adheres to the principles of the Declarations of Helsinki and Istanbul. Only de-identified data were used for further analysis. Patient data included age, gender, and body mass index (BMI), as well as tumor- and surgery-specific details.

2.2. Inclusion and Exclusion Criteria

The study included patients with primary HCC and HM of different origins, i.e., breast cancer, esophageal cancer, choroid coat melanoma, or neuroendocrine tumors, who were scheduled for robot-assisted hepatic liver resections between February 2019 and October 2020 at the Dept. of General, Visceral, Thoracic, Transplantation and Pediatric Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Germany. Exclusion criteria were age <18 years, hyperthyroidism and iodine allergy. Patients who were not considered eligible to undergo robot-assisted liver surgery were also excluded.

2.3. ICG Application

One vial of ICG (25 mg, Verdye®, Diagnostic Green GmbH, Aschheim, Germany) was dissolved in 50 mL sodium hydrochloride or water for injection according to the operator's manual and applied intravenously immediately after dilution the day before surgery.

2.4. Surgical Procedures Using the FireFly™ Camera

The da Vinci Xi® Surgical System (Intuitive, Sunnyvale, CA, USA) was used for all procedures in a standard fashion. All patients were operated on in a supine position. Five trocars were placed according to the tumor location. Usually, two 12 mm trocars and three 8 mm trocars were used. After the first entry, capnoperitoneum was established and maintained throughout the operation. After primary visual inspection of the abdominal cavity, with special attention to the liver, the ultrasound probe was inserted and the liver thoroughly examined by IOUS. Intraoperative findings were correlated with preoperative images. IOUS was repeated on demand during the procedure [5].

The Firefly™ camera is integrated into the da Vinci Xi® Surgical System, and is easily switched on and off by pushing a button. It is integrated into the normal camera, so that the NIR image is projected onto the normal camera image. The NIR image appears within seconds and the surgeon at the robotic console does not have to change monitors or vision, but can continue to perform surgery as planned while keeping their eyes on the operation field. ICG accumulation appears green on the screen, while the rest of the operation field appears in different shades of gray. A hybrid of the normal image with the NIR image can also be established. The NIR light can be activated and used on demand during the procedure to observe ICG enhancement. Three different types of ICG accumulation have been described by Ishizawa et al. [19]: Fully fluorescent, partly fluorescent, and the rim type. Different fluorescence patterns were attributed to impaired cellular excretion mechanisms, resulting in intracellular ICG accumulation [19]. Well-differentiated HCC therefore show homogenous fluorescence in the whole tumor, whereas dedifferentiated HCC only show partial accumulation [16]. HM, not consisting of hepatic tissue, do not metabolize ICG but compress cells at their rim, thereby hindering ICG excretion and causing the rim phenomena [7,12,17,22]. Furthermore, increased endothelial peritumoral leakage has been reported to contribute to the rim phenomenon [29]. In cirrhotic liver tissue, ICG accumulation may be less obvious.

Instruments usually used are curved Tip-Ups, monopolar curved scissors, Harmonic Ace® Curves Shears (Intuitive, Sunnyvale, CA, USA), and fenestrated bipolar forceps. Depending on the localization of the lesion, liver mobilization was realized afterwards and the tumor or metastasis, respectively, resected using a crush clamp technique. If larger vessels were near the resection margin or the lesion, Hemolok clips were applied. After resection, the Firefly™ camera was used to verify whether all potentially malignant tissues had been resected. The specimen was usually removed via one of the 12 mm incisions in a recovery bag. If necessary, an enlargement of one incision was performed. If thought to be useful, a drain was placed. Before closure and release of the capnoperitoneum, the resection margin and the whole abdominal cavity were checked for hemostasis using the Valsalva maneuver. Capnoperitoneum was released and standard abdominal closure performed. Patients were extubated immediately after surgery and usually returned to the normal ward after a short period in the recovery room.

2.5. Outcome Measures

The primary outcome measure was the feasibility and safety of preoperative intravenous ICG application. The secondary outcome measure was the intraoperative use of preoperatively-applied ICG and its advantages while performing R0 liver-sparing robot-assisted liver surgery.

2.6. Statistical Analysis

Qualitative data are presented as means ± standard deviations (SD) and ranges. Quantitative data are presented as percentages. Survival data were analyzed and interpreted using the Kaplan–Meier method [30]. Survival was defined from surgery to last contact or death, whichever occurred first. GraphPad Prism was used to present data. Statistics were performed using GraphPad Prism Version 8 and Microsoft Excel for Mac.

3. Results

During the study period (February 2019—November 2020), 147 patients underwent hepatic surgery at the Department of General, Abdominal, Transplant, Thoracic, and Pediatric Surgery, University Hospital Schleswig-Holstein, Campus Kiel. Twenty-seven patients were considered eligible for robot-assisted surgery and received ICG preoperatively, as described. No adverse events or allergic reactions occurred during or after ICG application. Robotic surgery was initiated as planned. Due to anatomical circumstances, the size of the tumor, or proximity to hepatic veins, conversion to open surgery was necessary in six cases (22.2%). One robotic procedure in a highly overweight patient (BMI = 38.1 kg/m^2) was stopped since the tumor located in segment VIII was deemed too difficult to expose and forced surgical resection would have caused more harm to the patient (who later underwent successful liver transplantation). ICG was not tested in these patients and they were excluded from the final analysis.

In total, 20 patients were included in the final analysis. The mean age was 64.0 ± 12.3 (40–82) years, and more patients were male (55.5%) and suffered from being overweight (median BMI 27.4 ± 6.7 (19.5–40.4) kg/m^2) (Table 1). HCC was the main diagnosis for surgery (n = 5), followed by hepatic metastasis of colorectal cancer (n = 5) and neuroendocrine tumor, breast cancer, focal nodular hyperplasia (n = 2 each), choroid coat tumor, esophageal and bladder cancer, and suspicion of cancer (n = 1 each) (Table 2).

Table 1. Demographic data of patients.

	(n = 20)
Age (years), mean ± SD (range)	64.0 ± 12.3 (40–82)
Gender, % male	55.5
BMI (kg/m^2), median ± SD (range)	27.4 ± 6.7 (19.5–40.4)

BMI, body mass index; SD, standard deviation.

Table 2. Surgery- and tumor-specific data.

	(n = 20)
Time of surgery (min), mean ± SD (range)	159.8 ± 72.3 (75–363)
Time of console (min), mean ± SD (range)	106.4 ± 40.7 (34–315)
Histopathological result (preoperative diagnosis/final diagnosis), n	
Hepatocellular carcinoma	7/5
Colorectal cancer	5/5
Neuroendocrine tumor	2/2
Breast cancer	2/1
Follicular nodular hyperplasia	1/2
Choroid coat melanoma	1/1
Urothelial carcinoma	1/1
Esophageal cancer	1/0
Unspecific	0/3
Size of tumor (mm), mean ± SD (range)	23.8 ± 11.5 (1–34)
Postoperative complications (Clavien-Dindo I/II/III/IV), n	2/0/0/1
Length of hospital stay (days), mean ± SD (range)	6.6 ± 5.4 (2–26)

n, number of patients; SD, standard deviation.

The duration of surgery was 159.8 ± 72.3 min. However, one patient received a complete robot-assisted proctocolectomy with a J-Pouch and protective stoma simultaneously to the atypical liver resection, prolonging the duration of surgery. If docking times were excluded, robotic surgery took 106.4 ± 40.7 min. Most tumors were located in segment VI, VII, and VIII. Three minor and one major hemihepatectomies and 16 atypical liver resections were performed. The average tumor size was 23.8 ± 11.5 (1–34) mm. In most patients, multiple segments were involved in the resection (Figure 1). These included patients suffering from metastasis of colorectal cancer (n = 4), hepatocellular carcinoma (n = 3), neuroendocrine tumors (n = 2), and urothelial carcinoma, choroid coat melanoma, and breast cancer (n = 1, each). No intraoperative complications occurred, and intraoperative blood loss was neglectable. Drains were placed in seven cases in patients with larger resection volume, or who were suffering from severe fibrosis or cirrhosis, or were undergoing an additional surgery within the same procedure. The length of stay (LOS) was 6.6 ± 5.4 days (median 5; range: 2–26) (Table 2). One patient suffered from postoperative hepatorenal failure and exacerbation of their chronic obstructive pulmonary disease. This prolonged LOS to 26 days. Another patient simultaneously underwent proctocolectomy and received a transarterial chemoembolization of parts of their liver remnant, which lengthened the LOS to 15 days. Minor complications were noted in two patients. Major complications occurred in one patient suffering from hepatorenal failure and exacerbation of chronic obstructive pulmonary disease after surgery.

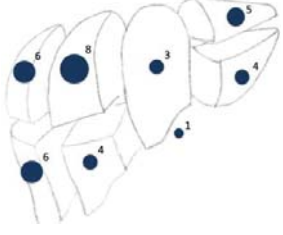

Figure 1. Scheme of location of tumors and metastasis resected.

Histopathological analysis confirmed preoperative suspicion in 85.0% of patients. In 15.0%, only necrotic tissue was detectable (Table 2). Two patients, one suffering from breast cancer and one from esophageal cancer, had been treated with chemotherapy preoperatively, explaining the necrotic tissue in two histopathological analyses (Table 2). Histopathologically-proven R0 resections were achieved in 85.0% of patients. All patients with R0 resections showed good intraoperative ICG staining. In one case, an extension was performed after a persistent ICG signal after lesion resection, achieving an R0 situation. ICG, combined with IOUS, was considered most helpful by the surgeon performing the procedure (Table 3). Two patients with an R1 situation suffered from progressive liver cirrhosis and did not show a helpful ICG signal (Table 4). All R1 situations were noted in patients showing unsuccessful ICG staining. Additionally, it is noteworthy that ICG did not help in patients who were mostly older than 70 years, suffering from different types of hepatic metastasis, and mainly suffered from liver cirrhosis and fibrosis, respectively (Table 4).

Table 3. Intraoperative indocyanine green (ICG) use (according to surgeon's perception).

	(*n* = 20)
Dose of ICG applied (mg/kg) mean ± SD (range)	0.32 ± 0.08 (0.22–0.50)
Duration between ICG application and surgery (h:min) mean ± SD (range)	21:24 ± 4:52 (7:39–47:05)
Intraoperative ICG signal [a]	2.4 ± 1.4 (1–6)
The intraoperative ICG signal helped during surgery (yes), % (*n*)	60.0 (12)
ICGA was clear and unequivocal (yes), % (*n*)	60.0 (12)
IOUS was used (yes), % (*n*)	100 (20)
Did IOUS and ICGA correlate? (yes), % (*n*)	75.0 (15)
Which intraoperative support helped the most? *n*	
ICGA	3
IOUS	4
Combination	8
None	4
None necessary because of macroscopic detection	1

ICG, indocyanine green; ICGA, ICG accumulation; IOUS, intraoperative ultrasound; n, number of patients. [a] 1 = excellent signal, 2 = good signal, 3 = moderate signal, 4 = sufficient, 5 = insufficient signal, 6 = no signal at all.

Table 4. Patients showing unsuccessful ICG staining.

	1	2	3	4	5	6	7
Sex	m	f	f	m	f	m	f
Age (years)	61	70	40	76	74	79	82
Comorb. (liver)	Cirrhosis (grade IV)	cirrhosis	—	fibrosis	—	—	cirrhosis (grade IV)
Dose (mg/kg)	0.23	0.50	0.28	—	0.30	—	0.32
Timediff (h:min)	—	18:25	—	15:32	7:39	12:41	17:31
IOS	df	us	ns	ns	ns	us	ns
Histopath (Resection margin)	HCC (R1)	HCC (R1)	BC	HCC	NM, initally BC	UC (R1)	NM

BC, breast cancer; Comorb., liver-associated liver comorbidities; df, diffuse staining; HCC, hepatocellular carcinoma; Histopath., final histopathological results; IOS, intraoperative staining; NM, no malignancy; ns, no staining; Timediff, time difference between application and surgery; UC, urothelial carcinoma; us, ubiquitous staining.

The mean follow-up period was 9.4 ± 6.7 months. Cancer-specific survival was 100%, while the overall survival was 94.7%. The patient with the prolonged postoperative course died three months after surgery after a fall in a rehabilitation clinic. Recurrence-free survival was 8.7 ± 0.5 months. Recurrence occurred after a mean of 10.4 ± 2.6 months in seven patients (36.8%). Recurrences were newly-diagnosed metastasis of neuroendocrine tumor (lymph node), breast (hepatic), esophageal (brain), and colorectal cancer (hepatic), and choroid coat melanoma (ubiquitously). Patients with hepatic recurrence underwent ICG-based surgery again. Three patients without systemic metastasis successfully underwent liver transplants during their postoperative courses. However, due to the heterogeneity of patients included, survival analyses have limited meaning.

The ICG was administered on average 21 h 24 min ± 4 h 52 min (range: 7 h 39–47 h 05) before surgery. The amount of ICG used was on average 0.32 ± 0.08 (0.22–0.50) mg/kg (Table 2). Intraoperatively, ICG accumulation was obvious in 12 cases and correlated with the preoperative imaging and/or the IOUS (Table 3). As previously described by Ishizawa et al., we observed full fluorescence in HCCs, independent of grading, and rim phenomena in the other metastases [16] (Figures 2 and 3). In one case, ICG revealed one additional lesion that had been overlooked by preoperative imaging. In another case, two additional lesions (1 and 2 mm) were resected because of ICG staining. Histopathological analysis also revealed metastatic tissue. In seven cases, however, ICG application did not help as it either did not accumulate, stained the whole liver, or accumulated ubiquitously in the

cirrhotic liver (Table 4). One patient received ICG preoperatively, but as the tumor was clearly detectable macroscopically, the FireFly^{TM} camera was not used. Interestingly, ICG showed accumulation in a metastasis of esophageal cancer. However, the postoperative histopathological analysis could only provide proof of necrotic tissue.

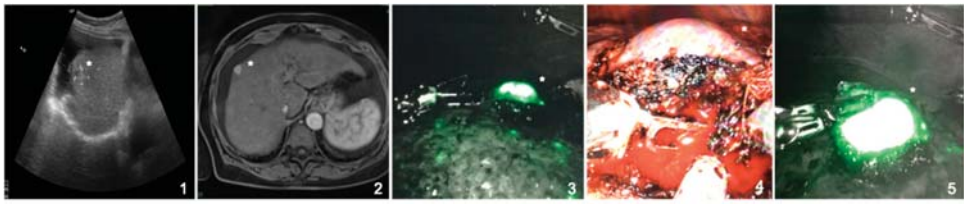

Figure 2. Pre- and intraoperative imaging of a 64-year-old female patient suffering from a hepatocellular carcinoma in liver cirrhosis (CHILD A). Indocyanine green accumulation in the hepatocellular carcinoma is clearly visible and shows full fluorescence (*). (**1**,**2**) Preoperative ultrasound and MRI-scan showing a hepatocellular carcinoma in segment VIII; (**3**) intraoperative, near infrared Firefly imaging showing indocyanine green accumulation in the tumor and the cirrhotic liver; (**4**) naive intraoperative image of the tumor; (**5**) intraoperative, near infrared Firefly imaging of the resected tumor.

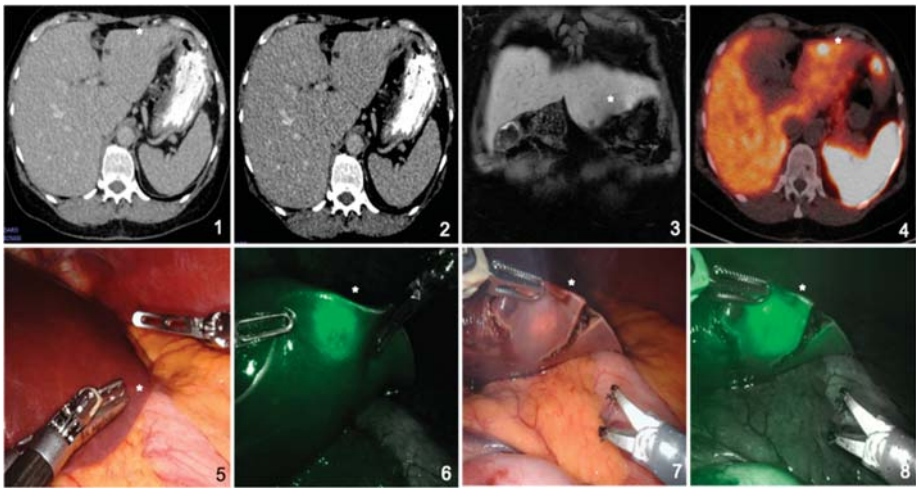

Figure 3. Pre- and intraoperative imaging of a 58-year-old female patient suffering from hepatic metastasis of a neuroendocrine tumor in a noncirrhotic liver. Indocyanine green accumulation at the rim of the metastasis is clearly visible and shows rim fluorescence, even after partial resection (*). (**1**–**3**) Preoperative computed tomography and magnetic resonance imaging scans do not show obvious metastasis; (**4**) preoperative DOTATATE-PET revealing subsuperficial metastasis in segment III (*); (**5**) naive intraoperative image not giving a macroscopic hint of the metastasis (*); (**6**) intraoperative, near infrared Firefly imaging showing indocyanine green accumulation at the rim of the metastasis; and (**7**,**8**) intraoperative, near infrared Firefly imaging showing indocyanine green accumulation at the rim of the partly resected metastasis (*).

4. Discussion

This prospective, single-center study reports on our experience regarding the feasibility and intraoperative use of intravenous ICG application in patients undergoing robot-assisted hepatic resections for HCC and HM of different tumors. In our experience, preoperative intravenous ICG application is easy to establish, simple and feasible, without complications, and serves as an additional supportive, real-life intraoperative aid. In most cases, it may help the operating surgeon to differentiate cancerous tissue from normal

hepatic tissue by means other than conventional preoperative imaging and IOUS, and thereby help with intraoperative strategic planning.

Due to in-house logistics, all included patients received 25 mg ICG dissolved in 50 mL NaCl or water for solution the day before surgery. Adapted to body weight, the patients received 0.22–0.50 mg/kg between 7:39–47:05 h before surgery (Table 3). The average time difference between application and surgery was 17:26 h. We noticed that for the patient who only received ICG 7:39 h before surgery, the whole liver showed green staining and ICG application did not help at all to perform surgery. The contrary was noted for the patient who had to be rescheduled to the next day due to in-house emergency surgery and therefore received ICG 38:05 h before surgery. Another patient received ICG 47:05 h prior to surgery as he had to undergo an additional preoperative CT scan two days before surgery. In both cases, the ICG signal was unequivocal and helped to perform liver-sparing, straightforward surgery.

The dose and time of ICG application is much discussed in the literature. Alfano et al. considered 0.5 mg/kg applied 24–48 h before surgery ideal to achieve reliable intraoperative staining [22]. Yet other reports regarding time of application ranged from 12 h to 10 days before surgery [15,18,22–26]. If applied too close to surgery, the false-positive rate of ICG accumulation can be quite high, leading to false, unnecessary resections [7,14,16]. Therefore, most authors recommend application intervals of 24–48 h [22,25]. Peyrat et al., even warranted 48–72 h between application and surgery, whereas van der Vorst et al., preferred 72 h if possible [25,26]. The advantage in this setting, unlike intraoperative identification of bile leakage or blood supply of a liver segment, is that patient-specific metabolic and physical properties such as heart rate and blood pressure, do not need to be considered, and a longer interval between application and surgery seems to be favorable [31].

Nonetheless, in fibrotic or cirrhotic liver tissue, hepatic metabolism is impaired. Therefore, impaired and slower hepatic elimination of ICG may lead to false positive or no results as we observed in our study [22,31]. In two patients with liver cirrhosis, the suspicious area or potential HCC, as well as the whole cirrhotic liver tissue, showed staining and small accumulations, respectively, which did not help to differentiate cirrhotic and tumorigenic liver tissue. Additionally, IOUS was difficult to perform in these patients. Perhaps one way to overcome this false positive staining may be a longer interval between ICG application and surgery [7,19]. Initially, Ishizawa et al. advocated at least a 48-h interval, especially in patients suffering from liver cirrhosis, before performing surgery [16]. Kawaguchi et al. even suggest an interval of seven days between ICG application and surgery in patients suffering from liver cirrhosis [27]. Nevertheless, no clear recommendation regarding perfect time point for ICG application for patients with normal or with cirrhotic liver tissue exists.

ICG has few reported side effects, and the lethal dose is estimated between 50–80 mg/kg [23,32]. The standard clinical dose used is between 0.1–0.5 mg/kg [7]. However, doses vary from indication to indication. In the setting of staining hepatic tumors and metastases, dose and timing are key to the avoidance of background fluorescence [25]. Kobayashi et al., like Alfano et al., performed titration experiments with different doses and concluded that either 3.75 mg ICG or 0.2 mg/kg, respectively, were favorable [15,22]. Moreover, Sucher et al. recommended a dose of 2.5–5 mg if only hepatic lesions needed to be visualized [7]. Van der Vorst et al. applied either 10 mg 24 h before surgery or 20 mg 48 h prior to surgery to obtain a clear contrast between tumor and normal liver tissue [25]. They thereby achieved concentrations between 0.13–0.26 mg/kg prior to surgery [25]. We applied an average dose of 0.33 mg/kg, which is a little above most recommendations. This, in combination with the relatively short time of application, may explain the ubiquitous staining in some of our patients. We also noticed that in general, ICG did not provide additional information in elderly patients with slower metabolisms. Some also suffered from liver cirrhosis. If the duration between application and surgery is short, smaller doses of ICG injection seem to be favorable, leading to fewer false positive results [7,25]. We would therefore rather stick to reduced doses and try to apply ICG a longer time (i.e., 48 h rather than 24 h) before surgery.

Parenchymal-sparing R0 resection is key to prolonged survival in oncological surgery [24,25]. Preoperative work-up—consisting of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) scans—therefore aims to identify as many lesions as possible to plan surgery accordingly and achieve the oncological best situation [12,23]. Nonetheless, some lesions, especially small, superficial ones, may be overlooked in pre- or intraoperative conventional imaging, thereby highly influencing the oncological prognosis [6,12,16,24,25,27,33,34]. After ICG application, substantially higher detection rates of additional lesions and even primary detection due to intraoperative ICG staining have been reported [14,17,18,23,25,26]. Kudo et al., identified another 17 lesions in 17 patients, whereas van der Vorst reported detection of additional metastases in five patients [12,25]. We can report ICG-based identification of additional nodules, i.e., in the patient suffering from choroid coat melanoma metastasis and one patient suffering from metastasis of a neuroendocrine tumor. In both cases, preoperative imaging and IOUS had not shown the additional foci, but intraoperative ICG did. Boogerd et al., even reported clear superiority of ICG in detecting nodules compared to preoperative CT, MRI, and IOUS [28]. Besides being highly user-dependent, IOUS has the problem of not detecting lesions that are just below the surface within the first cm of the liver [16,24]. In contrast, NIR light can only penetrate up to 1 cm into liver parenchyma and thereby fails to detect deeper tumors [18,33]. The combination of IOUS and ICG therefore seems to increase the detection rate of hepatic metastasis [31].

Along with a higher detection rate, Handgraaf et al., reported better survival after ICG-orientated liver resections due to the resection of additional nodules, which had been missed by pre- and intraoperative imaging [34]. Accordingly, Marino et al., compared robot-assisted liver resections with and without additional ICG application and reported significantly higher R0 resection rates after ICG application [17]. In our cohort, ICG staining helped to perform a R0 resection in one patient. After resection of the ICG-stained, ultrasonographically-verified lesion, the resection margin still showed ICG staining and an extended resection was immediately performed, finally achieving an R0 situation. Due to the visualization of ICG accumulation in around 200 cells, small lesions—which otherwise would have been missed—can be detected [16,31]. However, oncological long-term results comparing ICG-based surgery with conventional surgery have not yet been published [7].

Nevertheless, some authors have already called for mandatory preoperative ICG application in addition to IOUS, as each method seems to complement the other; in contrast, other experts suggest that it should only be used as an additional aid [16,18,24–27,33–35]. In our experience, ICG application can be easily implemented into daily practice at low cost, providing additional real time information during robotic surgery when haptic feedback is missing [23]. Furthermore, visualization of ICG accumulation can be shown continuously without having to change instruments or monitors during surgery—a great advantage over IOUS, for example, and helping to improve intraoperative navigation [7,23]. Therefore, ICG presently seems to be a helpful additional aid in robot-assisted liver surgery, making tailored liver parenchyma-sparing liver resections possible [18]. However, to our knowledge only two reports on the use of ICG in robotic surgery have been published, even though they considered preoperative ICG application to be useful [17,18].

The main limitation of our study is its design as a single-center, single-arm feasibility study that only included a small number of unselected patients suffering from different types of cancer, who received ICG at different doses and different points of time. Unfortunately, we cannot provide data for a comparative cohort. Additionally, ICG specific limitations must be considered, including low penetration depth (up to 13 mm), its non-quantifiable nature, and lack of reliability in patients suffering from liver cirrhosis [14,16,33]. Until now, no standardization of the intensity of fluorescence has been established [16,19,32]. Furthermore, the location of tumors and metastases, respectively, appear to be problematic due to the short penetration depths of NIR light.

5. Conclusions

Intraoperative hyperspectral imaging, artificial intelligence, deep machine learning, augmented reality, fusion of preoperative CT- or MRI-scans to IOUS and the operation field, and other technical developments will be possible in the near future using the robotic system, enabling new perspectives in hepato-biliary surgery and hopefully achieving better oncological results and patient survival [1,4,8,22,32,36–40]. Until then, ICG staining may serve as an additional helpful intraoperative aid in patients undergoing robot-assisted, atypical liver resection, providing real-time images and helping to plan intraoperatively and perform surgery in an individual, tissue-sparing way. In our experience, ICG is not only applicable to HCC and CRC metastasis, but also works for HM of other tumors. However, the operating surgeon should not only rely on ICG staining but integrate it into the repertoire of intraoperative planning tools. Further studies are needed to determine the exact dose and time of application and standardize fluorescence intensity. It would also be helpful to have a dye that specifically targets or accumulates in cancer cells.

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The Shift from Multiport to Single Port Increases the Amount of Bleeding in Laparoscopic Major Hepatectomy

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Abstract: Background: Bleeding is a negative outcome predictor in liver surgery. Reduction in the abdominal wall trauma in major hepatectomy is challenging but might offer possible benefits for the patient. This study was conducted to assess hemostasis techniques in single-port major hepatectomies (SP-MajH) as compared to multiport major hepatectomies (MP-MajH). Methods: The non-randomized study comprised 34 SP-MajH in selected patients; 14 MP-MajH served as the control group. Intraoperative blood loss and number of blood units transfused served as the primary endpoints. Secondary endpoints were complications and oncologic five-year outcome. Results: All resections were completed without converting to open surgery. Time for hepatectomy did not differ between SP-MajH and MP-MajH. Blood loss and number of patients with blood loss > 25 mL were significantly larger in MP-MajH ($p = 0.001$). In contrast, bleeding control was more difficult in SP-MajH, resulting in more transfusions ($p = 0.008$). One intestinal laceration (SP-MajH) accounted for the only intraoperative complication; 90-day mortality was zero. Postoperative complications were noted in total in 20.6% and 21.4% of patients for SP-MajH and MP-MajH, respectively. No incisional hernia occurred. During a median oncologic follow-up at 61 and 56 months (SP-MajH and MP-MajH), no local tumor recurrence was observed. Conclusions: SP-MajH requires sophisticated techniques to ensure operative safety. Substantial blood loss requiring transfusion is more likely to occur in SP-MajH than in MP-MajH.

Keywords: hepatectomy; single-port laparoscopy; radiofrequency pre-coagulation

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1. Introduction

The scientifically proven benefits of minimally invasive liver surgery justify the effort to further develop the technique [1]. Single-port laparoscopy (SP) is regarded as the most ambitious approach to minimize abdominal wall trauma in hepatic resection. The successful concept of aligning the entire procedure only via the incision that is necessary to retrieve the specimen has been scientifically evaluated in various organ systems such as colorectal and biliary surgeries [2,3]. In addition, the possibility to avoid vascular injury in portal hypertension by reducing the number of incisions and to alleviate repeated interventions for hepatic metastasis by preventing the formation of adhesions can be considered potential benefits in the group of these patients.

As compared to multiport laparoscopy, SP liver surgery is advantageous in terms of reduced blood loss while providing the same effectiveness and optimal patient safety and recovery [4].

Due to the technical obstacles encountered, such as the combination of different instruments that have to be delivered simultaneously through one single fulcrum to expose the operation field and to provide suction, flushing, coagulation or clipping, SP major hepatic resection (SP-MajH) is not performed at most liver centers. In particular, intraoperative bleeding control is at the center of interest as blood loss is one of the main adverse prognostic parameters for short-term and long-term outcomes [5,6]. Pre-coagulation by means of intraoperative radiofrequency-assisted transection of the hepatic parenchyma allows for ideal blood vessel sealing, without an increase in biliary complications [7]. We were previously able to demonstrate that SP minor liver resection benefits from the possibility to use inline pre-coagulation [8].

The study was conducted to evaluate the currently largest series of SP-MajH compared to multiport laparoscopic major hepatectomies (MP-MajH) with regard to bleeding control.

2. Materials and Methods

From September 2008 to November 2018, a total of 96 SP liver resections with inline pre-coagulation were performed at the surgical department of the St John of God Hospital, Salzburg, Austria. This accounts for 22.4% of all hepatic resections (n = 429) and 1.9% of the SP patient cohort (n = 5095) in that period of time.

Procedures were categorized as minor and major liver resection according to the 2nd International Consensus Conference for Laparoscopic Liver Surgery [9]. Major liver resection was defined as removal of >2 Couinaud segments or resections including at least one of the segments I, IVa, VII or VIII. Difficulty index, including tumor location, extent of liver resection, tumor size, proximity to major vessels and liver function, was calculated as proposed by Ban and colleagues [10].

A total of 34 single-port laparoscopic major hepatectomies (SP-MajH) were consecutively performed during the study period (study population).

At the same time, 14 multiport major hepatectomies (MP-MajH) with the identical procedural strategy were also performed (29.2% of all minimally invasive major liver resections) solely because of a lack of resources for SP surgery. These patients served as the control group in the comparison between SP and MP major hepatic resections.

All types of benign and malignant liver diseases requiring surgical treatment were considered for enrolment in the study. Prior abdominal surgery, higher age, obesity or unfavorable American Society of Anesthesiologists (ASA) scoring were not regarded as a contraindication for the SIL approach. Exclusion criteria for minimally invasive surgery were defined as follows: Child–Pugh B or C cirrhosis, future liver remnant volume <50%, tumor growth in close approximation to vital pedicles and as the only relative contraindication for SIL denial at the surgeon's discretion.

Preoperative routine testing, including CT and MRT, was performed according to international guidelines. Indication for the operation was confirmed by the local tumor board in all malignant cases. Informed consent was obtained from all patients following the standards of the Helsinki Declaration. The SP technique was approved by the local ethics committee. All SP procedures were performed by surgeons trained in both hepato-bilio-pancreatic surgery and advanced SP.

2.1. Procedure

Patients were placed in the reverse Trendelenburg position (20° head up) with their legs apart (French position). For posterior or right lateral resections, a 45° left lateral decubitus position alleviated exposure. Single-port access was obtained through the umbilicus, pre-existing scars in the upper abdomen (midline or subcostal) or a right subcostal incision in the midclavicular line (Figure 1).

The GelPort™ (n = 38; Applied Medical, Rancho Santa Margarita, CA, USA) and the OctoPort™ (n = 10; DalimSurgNET, Frankenman Group, Seoul, Korea) in combination with the AirSeal™ System (SurgiQuest, Milford, CT, USA) were used to maintain the pneumoperitoneum at 12 mmHg.

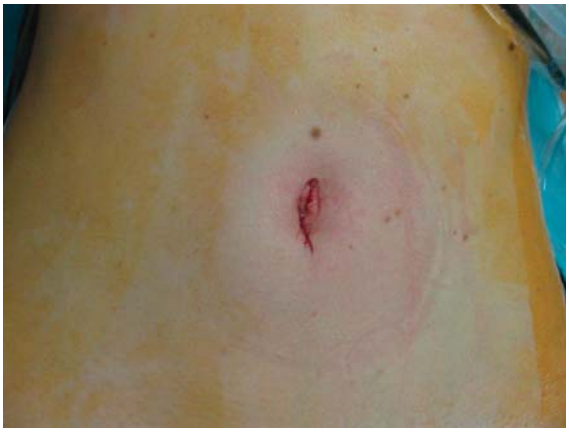

Figure 1. Image of the abdominal scar following single-port (SP) major hepatectomy (resections of segments VII and VIII).

A 10 mm, 30° extra-long optic and at least one articulating grasper were used throughout all procedures. Suction or retraction was controlled by the surgical assistant guiding the instrument through the same port. Suspending sutures for the triangular ligament were placed as needed. Laparoscopic ultrasound ensured the proper resection margin. The Pringle maneuver was not used routinely.

Exposure of central pedicles was mastered by means of bipolar cautery and clips. Prior to parenchymal transection, inline pre-coagulation was primarily accomplished with the HABIB 4X bipolar resection device (RITA Medical Systems, AngioDynamics, Latham, NY, USA). Liver packing was performed to prevent thermal injury to surrounding organs or the diaphragm. Parenchymal transection was subsequently performed with monopolar scissors or the LigaSureV™ (Medtronic, Dublin, Ireland) device. The CUSA (Cavitron Ultrasonic Surgical Aspirator; Medtronic, Dublin, Ireland), hemoclips, parenchymal sutures or vascular staplers served as second-line devices as needed.

Specimen retrieval was realized with a tear-proof bag (Espiner Medical, Clevedon, UK), allowing tissue compression to minimize the incisional length and guarantee correct pathohistological assessment.

Hemostatic matrix foam (Flowseal™, Baxter, Deerfield, IL, USA) or TachoSil™ fibrin sealant patch (Baxter, Deerfield, IL, USA) were applied at the surgeon's discretion. Wound closure was performed with monofilament, non-reabsorbing fascial running sutures and intra-cuticular stitches. No drainage was installed routinely.

Bleeding control served as the primary endpoint. As the smallest measurable unit of blood loss represents 25 mL in our routine protocol, this was set as the cut line for minimal blood loss in this study. Secondary endpoints were identified as intra- and postoperative complications as well as the appropriate histopathological outcome in malignancies with regard to free resection margins and local recurrence within a median follow-up of five years.

2.2. Statistics

Data were prospectively collected and documented in an Access database (Microsoft Corporation, Redmond, WA, USA). A mathematician (TH) not involved in data collection performed the statistical analyses using R, version 3.4.1 (https://www.r-project.org/). Continuous data are presented as mean ± SD with min–max; categorical data are represented as n (%). Differences between groups were assessed using Welch's two-sample T test for continuous variables and Fisher's exact test (where applicable) or Pearson's chi-squared test for categorical variables. A p value < 0.05 was considered statistically significant.

3. Results

Demographic parameters of patients undergoing SP-MajH and MP-MajH are summarized in Table 1 (Tab 1); procedural parameters are summarized in Table 2 (Tab 2). All major liver resections were able to be performed with the particular laparoscopic technique without converting to open surgery. One patient with simultaneous colorectal resection was converted to facilitate dissection in the narrow pelvis after successful SP hepatectomy. In SP-MajH, the transumbilical approach was used in 14 (41.2%) patients, whereas 19 (55.9%) resections were performed through a right subcostal incision. Additional trocars were delivered in 3/34 (8.8%) of SP-MajH for better exposure of the operating field. Suspending sutures were used in two patients for retraction on the falciform ligament.

Table 1. Demographics.

	SP-MajH	MP-MajH	Estimate with 95% CI	*p* Value
Number (*n*)	34	14		
Female gender (*n*)	13 (38.2%)	6 (42.9%)	1.21 (0.28 to 5.07)	1
Age (years) mean (SD)	63.4 (12.8)	62.4 (15.2)	0.9 (−8.7 to 10.5)	0.964
BMI (kg/m^2) mean (SD)	26.4 (3.9)	27.4 (4.9)	−0.9 (−4 to 2.1)	0.61
ASA > 2 (*n*)	19 (55.9%)	4 (28.6%)	0.32 (0.06 to 1.41)	0.117
Liver cirrhosis Child–Pugh A (*n*)	6 (17.6%)	6 (42.9%)	3.4 (0.7 to 17.08)	0.139
Previous surgery (*n*)	22 (64.7%)	9 (64.3%)	0.98 (0.23 to 4.63)	1
Malignant underlying disease	27 (79.4%)	13 (92.9%)	0.30 (0.01 to 2.79)	0.407
Future remnant liver volume (%, SD)	78.6 (14.7)	70.4 (11.7)	8.3 (0.1 to 16.5)	0.042

SP-MajH, single-port major hepatectomies; MP-MajH, multiport major hepatectomies; CI, confidence interval; ASA, American Society of Anesthesiologists.

Table 2. Procedural parameters.

	SP-MajH	MP-MajH	Estimate with 95% CI	*p* Value
Surgery time (min) mean (SD)	163.8 (80.3)	208.1 (93.1)	−44.2 (−103.4 to 15)	0.146
Difficulty index mean (SD)	6.6 (1.8)	8.7 (2)	−2.1 (−3.3 to −0.8)	0.004
Blood loss (mL) mean (SD)	354.4 (833.6)	564.3 (745.5)	−209.9 (−713 to 293.3)	0.001
Patients with blood loss > 25 mL (*n*)	11 (32.4%)	13 (92.9%)	25.33 (3.11 to 1195.26)	<0.001
RBC units (*n*)	7 (20.6%)	1 (7.1%)	0.3 (0.01 to 2.79)	0.407
Skin incision (cm) mean (SD)	4.8 (2.1)	5.7 (1.7)	−0.9 (−2.1 to 0.3)	0.027
Maximum specimen size (cm)	10.4 (5.1)	10.5 (4.3)	−0.1 (−3.1 to 2.9)	0.798
Minimum specimen size (cm)	5.2 (2.8)	5.1 (2.5)	0 (−1.7 to 1.7)	0.657

SP-MajH, single-port major hepatectomies; MP-MajH, multiport major hepatectomies; CI, confidence interval; RBC, red blood cell.

With respect to prior surgical interventions, limited and extended SP adhesiolysis was performed in 13 and 6 patients.

Numbers and type of hepatic resections for SP-MajH/MP-MajH were 4/2 right hepatectomies, 6/1 left hepatectomies, 7/5 right posterior bi-segment lateral resections and 17/6 single segmentectomies (Segment 7 or Segment 8). Intraoperative bleeding control during deep parenchymal dissection was achieved by pre-coagulation (Habib 4X) in 22 (64.7%) SP-MajH and 9 (64.3%) MP-MajH. In all other situations, additional thorough preparation with CUSA, bipolar energy, Hemoloc clips and staplers was necessary to ensure safety. Amount of blood loss and number of patients with intraoperative blood loss greater than 25 mL were significantly higher in the MP group. However, the individual amount of

blood lost in these patients during SP and MP surgery yielded in mean 1095.5 and 607.7 mL for SP-MajH and MP-MajH, respectively (p = 0.56, estimate with 95% CI 487.8 (−387.8 to 1363.4)). It is of note that 63.7% (7/11) of SP-MajH patients with bleeding during the procedure required red blood cell (RBC) packs, whereas only one out of 13 (7.7%) patients with bleeding during MP-MajH was given RBC units (p = 0.008, odds ratio (OR) 17.94 (1.59 to 1014.8)). One colon laceration during adhesiolysis accounted for the only intraoperative complication other than bleeding in the SP-MajH group. With regard to concomitant procedures in nine patients, the particular time for liver resection was calculated as mean ± SD 133 ± 53 min in SP-MajH. The surgical approach served as the retrieval site in all patients. The incisional length matched the minimum diameter of the specimen.

Wound closure was documented and evaluated by the surgeon as optimal (n = 48), suboptimal (with minor flaws, n = 0) or poor (with major flaws, n = 0) at the end of SP and MP procedures. Surgical site infections were not observed in any patient.

Postoperative complications classified as Grade 2 or higher according to Dindo-Clavien (DC) [11] were documented in seven (20.6%) and three (21.4%) patients in SP-MajH and MP-MajH, respectively (p = 1, estimate with 95% CI 1.05 (0.15 to 5.75)). Types of complications were pleural effusion (n = 4, DC 3a), abscess formation (n = 1, DC 3a), ascites (n = 1, DC 2) and bilioma (n = 1, DC 3a) in patients with SP-MajH and pleural effusion (n = 2, DC 3a) and acute cholecystitis (n = 1, DC 3b) in the MP-MajH group.

Postoperative stay was in mean ± SD 10.6 ± 5.5 days for SP-MajH and 11.6 ± 6.4 days for MP-MajH (p = 0.838, estimate with 95% CI −0.9 (−5 to 3.2)); 90-day mortality was zero in all patients.

Pathology

The underlying diseases are listed in Table 3 (Tab 3). Pathologic assessment yielded specimens without tumor lacerations in all patients with malignant disease. Histology revealed free resection margins in 27 (100%) of 27 specimens and 13 (100%) of 13 specimens in SP-MajH and MP-MajH patients, respectively. During a median oncologic follow-up of 61 and 56 months (SP-MajH and MP-MajH), four (14.8%) and five (38.5%) patients suffered from recurrent diseases (apart from the resection plane or metastatic disease), whereas two patients (7.4% and 15.4%) in either SP-MajH or MP-MajH died during the observation period.

Table 3. Underlying diseases.

	SP-MajH	MP-MajH
Benign diseases		
Giant hemangioma	5	-
Adenoma	-	1
Abscess formation	2	-
Malignant diseases		
• Primary liver tumors		
Hepatocellular carcinoma	8	7
Cholangiocellular carcinoma	1	-
• Liver metastases		
Colorectal cancer	8	6
Neuroendocrine tumors	4	-
Pancreatic cancer	4	-
Breast cancer	1	-
Ovarian cancer	1	-

4. Discussion

During the past decade, SP minor liver resection has been increasingly seen to make good surgical sense due to its proven benefits of minimal invasiveness and optimal cosmetic outcome [3,4,12–15]. Unfortunately, the SP concept is bothersome for the surgeon as it involves an uncommon type of triangulation and a limited number of deployed instruments. Bleeding control is crucial and technically demanding in all types of laparoscopic liver surgery as reduced bleeding can contribute to prolonged disease-free survival and overall survival [16]. Therefore, the possible high risks of intraoperative bleeding, longer procedural time and greater personal workload are the feared drawbacks of SP-MajH that make surgeons reluctant to offer this minimized approach technique to their patients. A meta-analysis evaluating patients with SP hepatectomies found a significant reduction in blood loss as compared to conventional laparoscopic liver resection [4]. This finding was confirmed in our study as the number of patients with intraoperative bleeding and the total amount of blood loss were significantly larger in the multitrocar population than in the SP cohort. However, this finding might be misleading: when substantial bleeding occurred in SP-MajH, almost two thirds of these patients required RBC transfusions. When more complex instrument manipulation is required during intraoperative emergencies in SP-MajH, meticulous dissection and hemostasis maneuvers, especially suture techniques, might be hampered. Delivering additional trocars for procedural safety in 8.8% of such interventions did not compensate this disadvantage in the study population. This unfavourable technical characteristic in SP surgery is of even more importance since the procedural difficulty index was significantly higher in MP-MajH in this study. With the intent to alleviate parenchymal transection, inline pre-coagulation by means of radiofrequency [7] did not meet the primary endpoint of sufficient bleeding control as a stand-alone technique in laparoscopic major hepatectomies (SP-MajH and MP-MajH) in about one third of procedures. When dealing with more challenging anatomical situations defined by a significantly higher difficulty index in comparison to minor hepatic resections, pre-coagulation techniques are therefore not regarded as the gold standard in parenchymal transection in minimally invasive major hepatectomy [9].

It is of note that a meta-analysis [17] documented better bleeding control but a higher rate of postoperative abscess formation but not biliary leakage or blood transfusion in the inline pre-coagulation group than for crush–clamp liver resections. The complication rates in SP-MajH and MP-MajH presented here reflect the complexity of the underlying disease and are more than acceptable in comparison to complication rates published for open or laparoscopic major hepatectomies (25.9% and 22.4%) [18]. The meta-analysis by Wang et al. showed no significant difference in terms of procedural time when comparing conventional laparoscopy and SP liver surgery [4]. When considering the fact that about two thirds of all study patients underwent combined procedures, the median operative time of less than three hours and the calculated median time for major hepatectomy of about two hours are comparable to procedural times published for laparoscopic and open liver resections [19,20]. The study presented here is embedded in our SP experience exceeding 5000 procedures. Having performed the first MP laparoscopic major hepatectomy and the first pure SP minor hepatectomy in 2008 [21], we further developed SP-MajH in a group of highly selected patients when overcoming an SP-specific learning curve of more than 1000 performed procedures. In addition to all intraabdominal manipulations, the incisional length allows adequate pathohistologic specimen harvest and an optimal cosmetic result in all patients with SP-MinH or SP-MajH. In MP-MajH, specimen retrieval is performed mostly via a Pfannenstiel incision for reduced wound complication rates and improved function and cosmesis [22]. Our standard of care in major hepatectomies includes an intensive care unit (ICU) treatment for the first two days and an observation at the normal ward for another eight days at least, regardless of an open or laparoscopic approach. This is closely related to national insurance policies and the resulting case-specific reimbursement, hampering any reasonable comparison between the groups. Remarkably, during a five-year follow-up, no wound complication occurred in the entire study population. As the SP concept itself

by no means confirms increased hernia rates, we currently aim for a total percentage of 2% late onset hernias in ten years of advanced SP surgery at our department. Due to the heterogeneity of our study collective with regard to tumor entity, it is difficult to assess oncological safety other than to document tumor lacerations, free resection margins and local recurrence. In contrast to non-ablative techniques, it is under debate whether margins extending into the ablation zone should be regarded as R1 resection (which did not occur in any of the study patients). Moreover, none of the patients developed local recurrence at the hepatic resection plane during the follow-up period, which speaks for both the accuracy of the SP technique and the value of inline pre-coagulation as an applicable transection mode. However, the authors are certain that meticulous anatomical preparation in all types of liver surgery with tumors adjacent to vital hepatic pedicles or the vena cava must be performed with instruments capable of more precise manipulation such as CUSA, hydro-jet and crush–clamp in combination with clips, staplers or sutures. The argument for the cost effectiveness (direct cost savings of 27.6% of disposables) enabling inline radiofrequency pre-coagulation is certainly not tenable in patients with SP-MajH when there is a substantial risk of perioperative bleeding. The literature has demonstrated convincingly that perioperative complications turned out to determine the financial burden [23]. It should be noted that certain factors might limit the study. The non-randomized study design and strict patient selection following the aforementioned exclusion criteria should be regarded as a limiting factor before generalizing these results. It must be emphasized that, if the required safety could not be guaranteed with SP, a decision for conventional surgery was made at the discretion of the surgeon. A significantly higher difficulty index in the MP-MajH group and a trend to a longer surgery time might be interpreted as a consequence of this. Hospital stay did not serve as a valid outcome parameter for patient recovery in order to compare groups, as hospital and insurance policies—instead of the patient condition alone—were determining factors in the duration of hospital stay. Quality of life was not assessed in this study, but it has been reported that SP results in better quality of life [11,12] than does conventional surgery. The evaluation of any additional benefit other than a reduction in abdominal wall trauma (shorter skin incisions) in the single-port versus the multiport approach was not scientifically targeted. This includes, but is not limited to, biomarkers, such as circulating tumor cells, circulating nucleic acids, extracellular vesicles and proteins. Targeting these biomarkers might have unravelled differences in some oncological entity more sophistically and represents an interesting future perspective. Emphasizing the calculated overall survival and disease-free survival would have no basis for justification due to the heterogeneity of the study population with malignancies and again was not the aim of this study. Therefore, we did not match open cohorts with the study population.

5. Conclusions

Intraoperative bleeding, although not common in minimally invasive liver resection, requires unrestricted immediate manipulation, which might be hampered in SP-MajH. Inline radiofrequency pre-coagulation failed to achieve sufficient hemostasis in laparoscopic major hepatectomies. With sufficient experience in both SP and liver surgery, a low complication rate and good oncologic outcome represented by surrogate parameters in strictly selected patients could be demonstrated in our study. However, SP-MajH should still be considered experimental at this time.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the hospital's privacy policy.

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Implementation of Robotic Assistance in Pancreatic Surgery: Experiences from the First 101 Consecutive Cases

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Abstract: Robotic assisted minimally invasive surgery has been implemented to overcome typical limitations of conventional laparoscopy such as lack of angulation, especially during creation of biliary and pancreatic anastomoses. With this retrospective analysis, we provide our experience with the first 101 consecutive robotic pancreatic resection performed at our center. Distal pancreatectomies (RDP, N = 44), total pancreatectomies (RTP, N = 3) and pancreaticoduodenectomies (RPD, N = 54) were included. Malignancy was found in 45.5% (RDP), 66.7% (RTP) and 61% (RPD). Procedure times decreased from the first to the second half of the cohort for RDP (218 min vs. 128 min, $p = 0.02$) and RPD (378 min vs. 271 min, $p < 0.001$). Overall complication rate was 63%, 33% and 66% for RPD, RPT and RDP, respectively. Reintervention and reoperation rates were 41% and 17% (RPD), 33% and 0% (RTP) and 50% and 11.4% (RPD), respectively. The thirty-day mortality rate was 5.6% for RPD and nil for RTP and RDP. Overall complication rate remained stable throughout the study period. In this series, implementation of robotic pancreas surgery was safe and feasible. Final evaluation of the anastomoses through the median retrieval incision compensated for the lack of haptic feedback during reconstruction and allowed for secure minimally invasive resection and reconstruction.

Keywords: robotic assisted surgery; pancreatic surgery; pancreaticoduodenectomy

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1. Introduction

Laparoscopic-assisted pancreatic surgery was initially only used for diagnostic purposes or palliative interventions like bypass procedures. In 1994, the first laparoscopic partial pancreaticoduodenectomy (LPD) was described [1]. In the following, several centres approached LPD. However, the results remained controversial. Some studies showed LPD to be either less safe or without display of the expected advantages like a shortened in-hospital stay or reduced blood loss compared to open surgery [2–4]. Other studies, on the other hand, confirmed comparable rates of perioperative morbidity and mortality [5] a reduction of length of stay [6,7], or even an advantage in oncologic outcome [8]. Overall, the general limitations of laparoscopy in the setting of complex reconstructions prevail, and therefore, robotic assistance arouses attention in pancreatic surgery after its implementation. It allows a three-dimensional, magnifiable view, up to seven degrees-of-freedom [9] and automatically reduces tremor transmission [10]. Additionally, the learning curve is shorter compared to laparoscopically assisted procedures [11–14].

Nevertheless, the main burdens of pancreatic surgery, including postoperative pancreatic fistula (POPF), postoperative pancreatic haemorrhage (PPH) and insufficiency of the implemented pancreatico-enteric or biliary anastomosis all apply to laparoscopic and robotic-assisted pancreatic surgery alike. As an important role is ascribed to the variable parenchymal texture of the gland, establishment and evaluation of the pancreatico-enteric anastomosis require a meticulous haptic examination for accomplishing adequate tactile

feedback. Therefore, in addition to a high-level of laparoscopic skills, extensive experience in open pancreatic surgery seems indispensable for a successful implementation of a minimally invasive pancreatic surgery program [15]. The main aims of laparoscopic as well as robotic-assisted surgery, in general, are reduction of in-hospital stays and enhanced recovery while providing comparable or reduced complication rates. However, the value of a treatment option is not only measured by complication rates but also by its oncologic outcome, including relevant parameters such as lymph node harvest or R0-resection rates.

With this analysis, we describe the implementation process of robotic-assisted pancreatic surgery in our centre and provide the data of our first 101 consecutive cases undergoing robotic-assisted pancreatic resections.

2. Materials and Methods

2.1. Data Collection and Exclusion Criteria

Data of patients who underwent either distal pancreatectomy (DP), total pancreatectomy (TP) or partial pancreaticoduodenectomy in a robotic-assisted procedure in the time between October 2017 and December 2019 were included in this analysis. All data were collected within the CARE-Study (surgical assistance by robotic support; originally Chirurgische Assistenz durch Robotereinsatz, ethical approval code E/A4/084/17; (DRKS00017229)). Procedures with conversion laparotomy before completion of resection were excluded from further analysis. Early conversion laparotomy was necessary in four patients due to tumour extent exceeding a safe minimally invasive approach, due to a bleeding complication in one patient and due to pneumoperitoneum related ventilation issues in two patients.

2.2. Perioperative Course

Patients were admitted to our surgical ward at least one day before surgery. The concept of enhanced recovery after surgery (ERAS) had been applied within the study period. Preoperative assessment included computed tomography or magnetic resonance imaging with contrast agents as well as if indicated, chest imaging and endosonography. Physical examination, basic laboratory testing, blood cell count and measuring of CEA and CA-19.9 alongside individual anesthesiological evaluation completed the preoperative assessment. Every case of suspected or confirmed malignancy was discussed in our specialised tumour board before and after surgery. All patients after PD and TP were admitted to the intensive care unit for at least one day. Patients undergoing DP were either admitted to intensive care or directly to the surgical ward depending on comorbidities as well as the surgical and anesthesiological course. Drainages were removed, if on POD3 lipase levels within the drainages were lower than three times the serum levels. Following PD with the implementation of a PG, a nasogastric tube remained at least until postoperative day five and was removed after a contrast swallow study confirmed regular gastric emptying. The ISGPS classifications for POPF, PPH and DGE, were applied [16–18]. Complications were classified according to the Clavien/Dindo classification [19].

2.3. Implementation Process and Procedures

The same team of two surgeons performed all procedures with the DaVinci® Xi surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA). Both were experienced in complex laparoscopic and open pancreatic surgery. Previous training consisted of computer-based lessons and intensive hands-on workshops. Figure 1 indicates the port placement, which is (a) suitable for RDP and (b) RPD and RTP.

Exclusion criteria for robotic assistance included (I) contraindication for creation of pneumoperitoneum (such as severe chronic obstructive lung diseases) and (II) multiple previous abdominal surgeries. Suspected extensive vessel involvements requiring additional resection (e.g., portal vein replacement) led to exclusion of the case and the patients underwent open surgery instead. In cases of underlying malignant disease or precancerous lesions, a standard lymphadenectomy was performed. Dissection of the pancreas was

either done by electrocautery or a stapling device. In cases of underlying malignant disease or precancerous lesions located in the body or tail of the pancreas, a splenectomy and standard lymphadenectomy was performed. Patients with benign lesions received a spleen-preserving distal pancreatectomy with preservation of the splenic vessels. Stapler closure of the pancreas remnant was performed using linear staplers with a 60-mm black cartridge (EndoGIA™, Medtronic, Minneapolis, MN, USA) reinforced by a bioabsorbable mesh (SEAMGUARD®, W.L. Gore, Flagstaff, AZ, USA).

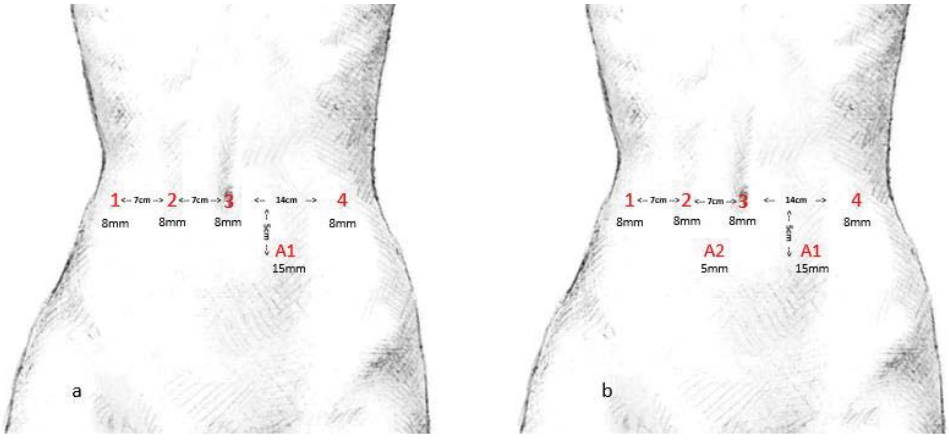

Figure 1. Port placement. (**a**) shows port placement for robotic assisted distal pancreatectomy. (**b**) shows port placement for robotic assisted pancreaticoduodenectomy and total pancreatectomy.

Early in the implementation phase, reconstruction following robotic-assisted PD (RPD) was carried out through the retrieval incision in the midline of the upper abdomen. Subsequently, we developed techniques for robotic-assisted hepaticojejunostomy and pancreatogastrostomy (PG). However, the retrieval incision remained essential for haptic reevaluation and, if indicated, correction of all anastomoses. In our centre, reconstruction following PD is in most cases carried out through a PG. During the implementation of a PG, suitable also for minimally invasive procedures, we developed a dorsal incision only PG for OPD that was subsequently also used for RPD. Every patient received at least one intra-abdominal drain (Degania Silicone Europe GmbH, Regensburg, Germany) to measure postoperative lipase levels and drain output in the postoperative course.

2.4. Statistical Analysis

Descriptive statistics and *t*-tests were used, and data were processed using SPSS version 25.0 (IBM, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

3. Results

This retrospective analysis included 101 consecutive patients, 44 of whom underwent DP, three underwent TP and 54 underwent PD. During the implementation process and this study period, 178 OPDs and no LPDs, 40 ODPs and six LDPs and 43 OTPs and no LTPs have been performed in our centre. Patient demographics are presented in Table 1.

Mean procedure time of the first 22 DPs was 217.9 min (minimum 142; maximum 353) with a standard deviation of 60 min. Mean procedure time of the second 22 DPs was 127.8 min (minimum 62; maximum 203) with a standard deviation of 34.6 min ($p = 0.02$).

Table 1. Patient's demographics.

Characteristics N (%)	Pancreaticoduodenectomy (N = 54)	Total Pancreatectomy (N = 3)	Distal Pancreatectomy (N = 44)
		Sex N (%)	
Male	32 (59.3)	1 (33.3)	22 (50)
Female	22 (40.7)	2 (66.7)	22 (50)
		Age (year)	
Minimum	27	41	22
Maximum	82	54	87
Mean	60.9	47.7	59.5
		BMI (kg/m^2)	
Minimum	19.7	23	18
Maximum	39.8	26.6	41.9
Mean	25.3	24.6	26.8
		ASA-Score N (%)	
1	3 (5.9)	0	2 (4.8)
2	27 (52.9)	2 (66.7)	30 (71.4)
3	20 (39.2)	1 (33.3)	10 (23.8)
4	1 (2)	0	0 (0)
Malignancy N (%)	33 (61.1)	2 (66.7)	20 (45.5)

BMI: body mass index; ASA-Score: American Society of Anesthesiologists-Score.

Mean procedure time of the first 27 PDs was 378.3 min (minimum 284; maximum 535) with a standard deviation of 72 min. Mean procedure time of the second 27 PDs was 276.1 min (minimum 215; maximum 378) with a standard deviation of 36.2 min ($p < 0.001$). Development of the procedure time for RDP and RPD are shown in Figure 2.

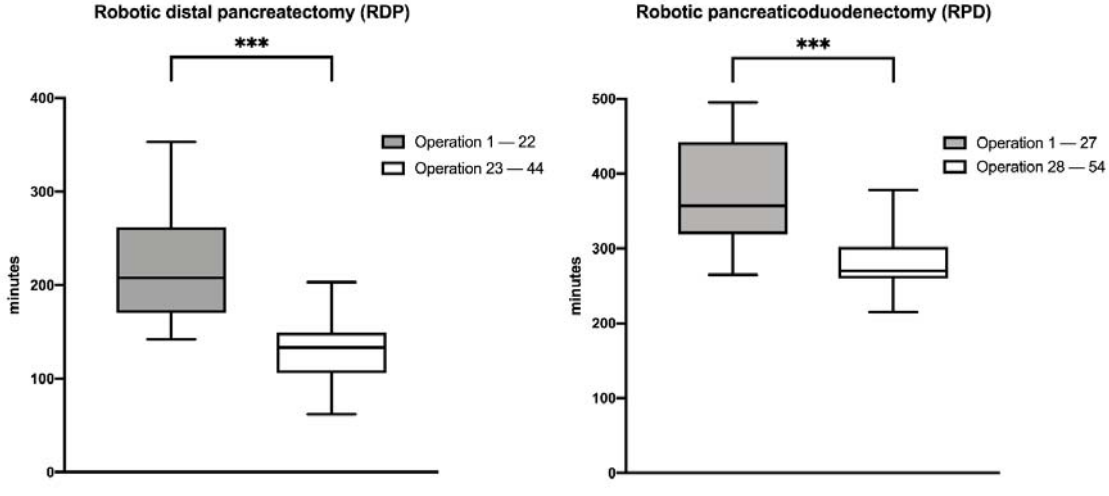

Figure 2. Development of procedure time. Decrease of procedure time comparing the initial and later series for RDP and RPD. *** $P \leq 0.001$.

The overall complication rate for RPD was 63%, 48% were classified as major complications (Clavien–Dindo $\geq$ 3a). Following RTP, the overall complication rate was 33.3% (all classified as $\geq$ 3a) and following RDP 65.9% (56.8% $\geq$ 3a). Nine patients underwent re-operation following RPD (16.7%), three of them underwent completion pancreatectomy (one due to necrotizing pancreatitis of the pancreatic remnant, two due to bleeding complications), two of them underwent revision of implemented PG, one of them underwent revision of hepaticojejunostomy (HJ), one of them underwent revision due to trocar hernia

and two patients underwent revision due to wound dehiscence or infection. Three patients following RDP underwent re-operation, two due to wound dehiscence and one due to colon perforation. Intraabdominal abscesses and persistent or recurrent fistula were treated with percutaneous or transgastric drainages. PG insufficiency was treated with re-operation in one case and transgastric drainage in the other cases. In cases of HJ-insufficiency either ERCP with stenting or PTCD was performed. All perioperative parameters are shown in Table 2.

Table 2. Perioperative parameters.

Characteristics N (%)	Pancreaticoduodenectomy (N = 54)	Total Pancreatectomy (N = 3)	Distal Pancreatectomy (N = 44)
Procedure Time (min)			
Minimum	215	258	62
Maximum	535	302	353
Mean	325.3	278	172.8
In-hospital stay (day)			
Minimum	3	10	5
Maximum	68	32	52
Median	15	11	11
ICU stay (day)			
Minimum	1	1	0
Maximum	55	6	12
Mean	6.6	2.6	1.9
Pancreatico-enteric anastomosis N (%)		None	None
Pancreaticojejunostomy	3 (5.6)		
Pancreatogastrostomy	51 (94.4)		
Overall complications N (%)	34 (63)	1 (33.3)	29 (65.9)
Clavien/ Dindo ≥3a N (%)	26 (48.1)	1 (33.3)	23 (52.3)
POPF N (%)			
Biochemical leakage	0 (0)	0 (0)	8 (18.1)
B	9 (16.7)	0 (0)	14 (31.8)
C	1 (1.9)	0 (0)	0 (0)
PPH N (%)			
A	3 (5.6)	0 (0)	2 (4.5)
B	4 (7.4)	0 (0)	3 (6.8)
C	4 (7.4)	0 (0)	0 (0)
SSI N (%)	5 (9.3)	0 (0)	1 (2.3)
DGE N (%)	10 (18.5)	0 (0)	1 (2.3)
Insufficiency pancreatico-enteric anastomosis N (%)	6 (11.1)	None	None
HJ-insufficiency N (%)	2 (3.7)	0 (0)	None
Pulmonary complications N (%)			
Pneumonia	5 (9.3)	0 (0)	3 (6.8)
Pulmonary embolism	0 (0)	0 (0)	2 (4.5)
Pleural effusion	4 (7.4)	0 (0)	3 (6.8)
Unplanned Re-Intubation	5 (9.3)	0 (0)	0 (0)
Intervention N (%)	22 (40.7)	1 (33.3)	22 (50)
Re-operation N (%)	9 (16.7)	0 (0)	5 (11.4)
30-day mortality N (%)	3 (5.6)	0 (0)	0 (0)

ICU: Intensive Care Unit; POPF: postoperative pancreatic fistula; PPH: postoperative pancreatic haemorrhage; SSI: surgical site infection; DGE: delayed gastric emptying; HJ: hepaticojejunostomy.

In six of the first seven cases following RPD, reconstruction was carried out through the retrieval incision including PG, hepaticojejunostomy and gastroenterostomy. In the following, revision of the PG through the retrieval incision appeared to be necessary in four cases due to exceptionally soft gland texture after haptic re-evaluation. PG-insufficiency appeared in 6 patients, two of them following open reconstruction. Insufficiency of hepaticojejunostomy occurred in two cases, one of them following open reconstruction. There was no significant difference for perioperative complications between early and later cases, whereas the amount of full robotic procedures increased in the latest series. Conversion laparotomy was necessary due to bleeding from the splenic artery in one case of RDP. In contrast, conversion in the later phase of RPD was required in two cases, one due to bleeding complication and one due to technical issues. Table 3 indicates postoperative histopathology for all specimen. None of the patients undergoing RPD or RTP underwent

neoadjuvant treatment and four patients underwent neoadjuvant chemotherapy prior to RDP.

Table 3. Tumour histopathology.

Characteristics N (%)	Pancreaticoduodenectomy (N = 54)	Total Pancreatectomy (N = 3)	Distal Pancreatectomy (N = 44)
Histology N (%)			
PDAC	12 (22.2)	2 (66.7)	15 (34.1)
NET	1 (1.9)		4 (9.1)
Periampullary carcinoma	10 (18.5)		
Distal cholangiocarcinoma	7 (13.0)		
IPMN	10 (18.5)		8 (18.2)
Chronic pancreatitis	7 (13.0)		9 (20.5)
Other	8 (14.8)	1 (33.3)	8 (18.2)
T. N (%)			
T1	7 (23.3)	0 (0)	6 (31.6)
T2	13 (43.3)	1 (50)	10 (52.6)
T3	10 (33.3)	1 (50)	3 (15.8)
T4	0 (0)	0 (0)	0 (0)
N. N (%)			
N0	15 (48.4)	1 (50)	8 (47.1)
N1	5 (16.1)	0 (0)	9 (52.9)
N2	11 (35.5)	1 (50)	0 (0)
Lymph node harvest (N)			
Minimum	4	17	2
Maximum	28	29	44
Mean	16.5	23	12.8
V. N (%)			
V0	28 (93.3)	1 (50)	16 (84.2)
V1	2 (6.7)	1 (50)	3 (15.8)
L. N (%)			
L0	19 (63.3)	1 (50)	12 (63.2)
L1	11 (36.7)	1 (50)	7 (36.8)
G. N (%)			
G1	1 (3.3)	0 (0)	5 (29.4)
G2	19 (63.3)	1 (50)	4 (23.5)
G3	10 (33.3)	1 (50)	8 (47.1)
Pn N (%)			
Pn0	7 (24.1)	0 (0)	5 (33.3)
Pn1	22 (75.9)	1 (100)	10 (66.7)
R. N (%)			
R0	26 (83.9)	1 (50)	15 (75)
R1	5 (16.1)	1 (50)	5 (25)
Tumour diameter (mm)			
Minimum	8	40	1
Maximum	47	50	95
Mean	23.6	45	33.1

PDAC: pancreatic ductal adenocarcinoma; NET: neuroendocrine tumour; IPMN: intraductal papillary mucinous neoplasm; T.: local tumour state; N.: nodal state; V.: vessel invasion; L.: lymphatic vessel invasion; G.: Grading; Pn: perineural invasion; R.: resection state.

4. Discussion

The learning curve for robotic assistance in pancreatic surgery is described to be quick and steep compared to laparoscopy. In our cohort, we achieved a significant decrease in OR time over the course of this series for both DP and PD. However, the learning process consisted not only of increased time savings but also of adoption of advantages as well as reaction to disadvantages of robotic assistance.

One of the main disadvantages of laparoscopic as well as robotic-assisted pancreatic surgery is the loss of direct haptic feedback, which is essential to examine the gland texture, the tumour extent and also the implemented anastomoses. For safety reasons, we therefore initially performed the restoration via PG, hepaticojejunostomy and gastrojejunostomy through the retrieval incision. After implementing a technique for robotic-assisted hepaticojejunostomy and PG, the retrieval incision remained essential for haptic re-evaluation of

all anastomoses. In our opinion, this increases safety and circumvents the remaining uncertainty coming along with the missing haptic feedback in robotic-assisted procedures. This may serve as an explanation of the comparability of complication rates in early and later patients from our cohort for RPD while the amount of full robotic procedures increased in the latest phase of implementation. Other authors, however, describe significantly decreased overall complication rates and significant complication rates after the first series of 15 and 30 cases, respectively [20], which equals a substantial amount of complications encountered in the early adoption phase. Compared to our experiences in open pancreatic surgery, mortality is increased in RPD in this initial series (2.9% vs. 5.3% 30-day mortality). Further data are necessary to verify these findings in a larger cohort.

In cases of underlying malignancy, the tumour extent may limit the applicability of robotic-assisted procedures as well. In our cohort, early conversion laparotomy had become necessary due to tumour extent. Such borderline resectable cases, in our opinion, also require haptic evaluation to examine resectability in the first place thoroughly. Nevertheless, vascular resections during RPD have been described to be feasible after enclosed learning curve for RPD without additional vascular resection [21,22].

Despite all technical improvements during the last decades, the pancreatico-enteric anastomosis can still be referred to as the Achilles' heel of current PD [23]. The superiority of neither reconstruction via pancreaticojejunostomy (PJ) nor PG in terms of complication rates and especially POPF incidence and severity for RPD is certain as, just like in open surgery, some studies advocate PG [24], while others prefer a PJ. PG-restoration via ventral gastrotomy, however, did not appear to be a technically feasible option for full robotic restoration. We, therefore, developed a dorsal-incision-only PG suitable for OPD and RPD alike.

Complication rates for robotic-assisted procedures in pancreatic surgery are comparable to open surgery [25]. Especially the main threats of modern pancreatic surgery, POPF, PPH and insufficiencies of pancreatico-enteric anastomoses seem equivalent [26,27]. In our cohort, we found a 30-day-mortality of 5.6% for RPD, and none of the patients following robotic-assisted DP died in the first 30 days after surgery. This has to be regarded with caution, as we aimed for careful patient selection, however, reflects in our opinion the cautious approach of our initial program, as these rates blend into other extensive experiences with open PD. We, therefore, found robotic assistance to be safe and feasible in our cohort. However, especially in the decision-making process of how far a minimally invasive approach can be pushed, we want to itinerate our impression of the surmount importance of extensive experience in both laparoscopy and open pancreatic surgery in order to safely embark on a robotic pancreas surgery program.

In our opinion, the structured step-by-step approach to the implementation of a robotic pancreas program with particular attention to a proper indication, port placement and reconstruction technique is essential. Considering the implementation of RPD in a two-step approach consisting of resection followed by reconstruction may be feasible.

Referring to the oncologic criteria, the amount of harvested lymph nodes is essential. Some studies suggest an increased number of harvested lymph nodes in minimally invasive procedures [28,29], whereas others did not find a difference between LPD, RPD and OPD [30]. The number of harvested lymph nodes in our cohort was comparable to other reports. Additionally, the rate of R0-resections is an important prognostic parameter, which is also said to increase with the use of robotic assistance [31]. As other authors already suggested, in our opinion, a structured training program, a sufficient volume and a close-knit quality assessment are essential for implementing a successful program for robotic-assisted pancreatic surgery [32].

A volume of at least 20 RPDs per year in a centre may maintain consistent training and complication rates [33]. However, despite insufficient training in a low-volume centre, cost-effectiveness decreases with low case numbers.

This descriptive analysis is limited to common biases, mainly due to its retrospective character and the deliberate patient selection in the investigated cohort. We are also

well aware that, as long-term results following robotic-assisted pancreatic surgery are still missing, more studies are mandatory to evaluate robotic assistance as an individual prognostic parameter in the future.

5. Conclusions

Robotic assistance is a feasible and safe option in modern pancreatic surgery if attention is paid to the lack of haptic feedback in minimally invasive techniques. Additionally, with respect to complication rates, further studies are mandatory to evaluate its oncologic and long-term outcomes. For safety reasons, the indication should be made with appropriate caution, and conversion laparotomy should be used without reservation at any step of the procedure to prevent life-threatening complications.

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Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author.

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Review

Bariatric Surgery–How Much Malabsorption Do We Need?—A Review of Various Limb Lengths in Different Gastric Bypass Procedures

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Abstract: The number of obese individuals worldwide continues to increase every year, thus, the number of bariatric/metabolic operations performed is on a constant rise as well. Beside exclusively restrictive procedures, most of the bariatric operations have a more or less malabsorptive component. Several different bypass procedures exist alongside each other today and each type of bypass is performed using a distinct technique. Furthermore, the length of the bypassed intestine may differ as well. One might add that the operations are performed differently in different parts of the world and have been changing and evolving over time. This review evaluates the most frequently performed bariatric bypass procedures (and their variations) worldwide: Roux-en-Y Gastric Bypass, One-Anastomosis Gastric Bypass, Single-Anastomosis Duodeno-Ileal Bypass + Sleeve Gastrectomy, Biliopancreatic Diversion + Duodenal Switch and operations due to weight regain. The evaluation of the procedures and different limb lengths focusses on weight loss, remission of comorbidities and the risk of malnutrition and deficiencies. This narrative review does not aim at synthesizing quantitative data. Rather, it provides a summary of carefully selected, high-quality studies to serve as examples and to draw tentative conclusions on the effects of the bypass procedures mentioned above. In conclusion, it is important to carefully choose the procedure and small bowel length excluded from the food passage suited best to each individual patient. A balance has to be achieved between sufficient weight loss and remission of comorbidities, as well as a low risk of deficiencies and malnutrition. In any case, at least 300 cm of small bowel should always remain in the food stream to prevent the development of deficiencies and malnutrition.

Keywords: malabsorption; Roux-en-Y gastric bypass; one-anastomosis gastric bypass; SADI-S; biliopancreatic diversion; weight regain

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1. Introduction

Obesity is an increasingly important disease considering the ever-growing numbers of patients worldwide. The World Health Organisation (WHO) has defined obesity as a body mass index (BMI) of >30 kg/m^2 [1]. It massively impairs patients' quality of life as well as their life expectancy, and has turned out to be a chronic disease that is difficult to cure [2]. The goal of a successful treatment is to achieve long-term weight loss and a remission or improvement of related comorbidities. Due to the chronic character of obesity, almost all conservative treatments for weight-loss are impermanent, and patients usually regain their body weight within a short period of time after an initial weight loss. Conservative treatments for obesity are dietary changes, behaviour therapy, physical activity or medication (e.g., Liraglutide, a glucagon-like peptide-1 receptor agonist). Furthermore, endoscopic

approaches, such as gastric balloons or endoscopic suturing techniques, are options as well. Nevertheless, currently, the best option for obese patients to achieve long-term weight loss is bariatric surgery [3].

Procedures combining restriction with malabsorption tend to be superior in the long-term follow-up when compared to restrictive procedures [4]. So far, studies with up to 20 years follow-up after various bariatric procedures have reported a relatively stable weight after surgery [5]. Nevertheless, up to 40% of the patients experience weight regain (WR) after bariatric surgery with the need of an additional intervention. The manifestation of WR depends on its definition, the chosen bariatric procedure and the length of the follow-up [6].

Therefore, it is important to find the right procedure for the individual patient to obtain long-term weight loss with only a small risk of WR [7]. Further considerations when selecting a bariatric procedure, or when choosing the individual limb lengths in bypass procedures, should focus on the patient's individual comorbidities. The choice of procedure always entails a balance between weight loss and remission of comorbidities on the one hand, and a risk of deficiencies (that should be minimal) on the other.

When talking about limb lengths in this context, it is important to consider that the total length of the human small bowel varies immensely between individuals. An analysis of ten studies measured the small bowel of 443 patients and found a mean length of 690 cm $\pm$ 93.7, with an enormous range of 350 cm to 1049 cm [8]. Not only sex and height of the patient, but also the technique of measurement, may influence the result [8,9].

2. Inclusion of Malabsorptive Bariatric Procedures

This article aims at reviewing the most frequently performed bariatric procedures worldwide that have been recognized by the International Federation for the Surgery of Obesity (IFSO) in terms of malabsorption. These procedures are Roux-en-Y-Gastric Bypass (RYGB), One Anastomosis Gastric Bypass (OAGB) and Single Anastomosis Duodeno-Ileal Bypass + Sleeve Gastrectomy (SADI-S). Biliopancreatic Diversion with Duodenal Switch (DPD + DS) was included as well, even though it only makes up to 0.5% of all bariatric procedures worldwide. However, it is the most common example of a procedure with a very strong malabsorptive component.

The present article also discusses the issue of revisional procedures that add malabsorption to reinitiate weight loss in patients with weight regain after primary bariatric procedures. Adding malabsorption to a primary procedure bears a potential risk of deficiencies alongside the advantage of further weight loss [10]. Most studies on this topic available today have looked at revisional procedures after RYGB.

The most common bariatric procedure, Sleeve Gastrectomy (SG), as well as the formerly very common Gastric Banding (GB), will not be discussed as both procedures are based on the principle of restriction instead of malabsorption. Endoscopic malabsorptive procedures, such as the Endobarrier®, GI-window®, among others, were not included either due to the small number of patients or the short lengths of follow-up in most studies available today [11].

This review article focusses on high-quality comparative studies of the discussed procedures. However, it does not claim to cover all studies available in the literature. In order to work out the impact of different limb lengths in a bypass procedure, even studies on extreme variants (i.e., DPD, DPD + DS) were included in this review article. As the heterogeneity of the included studies varied in terms of outcomes, type of study, length of follow-up etc., a common endpoint could not be defined for this article.

3. Roux-en-Y-Gastric Bypass

RYGB, the most common bariatric procedure relying on malabsorption, is a gastric bypass featuring a gastric pouch, a gastro-jejunostomy and a jejuno-jejunostomy (Figure 1). Various techniques have been used to perform a RYGB; differences mainly lie in the lengths of the alimentary limb (AL), the biliopancreatic limb (BPL) and the common limb (CL).

These variations are, e.g., Long-Limb Gastric Bypass, Short-Limb Gastric Bypass, classic (standard) RYGB, Distal Gastric Bypass, Very-Long-Limb Gastric Bypass and Diverted One-Anastomosis Gastric Bypass (D-OAGB). Even within these categories, limb lengths and pouch sizes are not strictly defined and vary from one study to another [12]. These differences may certainly complicate comparisons in terms of malabsorption. However, this chapter aims at discussing research on the lengths of AL, BPL and CL to highlight the proportions ensuring sufficient weight loss paired with a low risk of malnutrition.

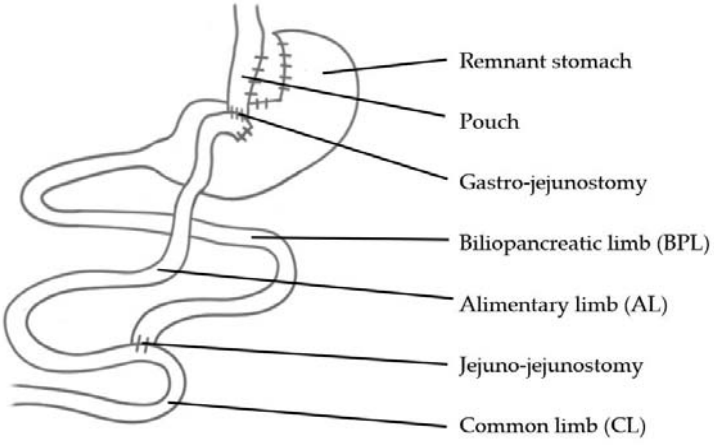

Figure 1. Roux-en-Y-Gastric Bypass (RYGB)/Diverted One-Anastomosis Gastric bypass (D-OAGB).

Classic (or standard) RYGB, which is the bypass procedure most studied in the literature, is performed creating an AL of 150 cm, a BPL of 40–70 cm and a CL varying in length. Traditionally, the pouch is small and short. The malabsorptive component of this RYGB is minor (similar to Short-Limb Gastric Bypass), since only 40–70 cm BPL is excluded completely from the food stream, whereas in the 150 cm of AL only the uptake of lipides and triglycerides is excluded [13]. RYGB is usually indicated for patients suffering from gastro-esophageal reflux disease [14].

Short-Limb Gastric Bypass was described to only include 10 cm of BPL and 40 cm AL, and Long-Limb Gastric Bypass as 100 cm BPL and 100 cm AL in a publication by Christou N. et al. [15]. The outcomes of these procedures were compared in 228 patients at a median follow-up of 11.4 years, with no differences found in terms of long-term weight loss between them. In the same study, both procedures reached an equal change in BMI of 17.8 and 18.1 kg/m^2 in the group of superobese patients (>50 kg/m^2) [15]. An early prospective randomized study by Brolin et al. with a shorter follow-up of 43 $\pm$ 17 months comparing Short-Limb Gastric Bypass (BPL: 15 cm; AL: 75 cm) to Long-Limb Gastric Bypass (BPL: 30 cm; AL: 150 cm) in 45 superobese patients found a significantly higher excess weight loss (EWL) in the long-limb group (64% vs. 50%) [16]. One may conclude that the longer BPL may also have affected patients' weight loss in the long-limb group.

Another study suggesting that the length of the AL may be of less consequence to weight loss results than the length of the BPL or CL, was published by Risstad H. et al. They compared the standard RYGB (AL: 150 cm; BPL: 50 cm; CL: variable) to a Distal Gastric Bypass (AL: variable; BPL: 50 cm; CL: 150 cm) in a randomized controlled trial (RCT) with 113 patients and found no difference in weight loss after two years between the two groups [17]. The variable AL in the Distal Gastric Bypass group must have been very long indeed in these patients, which contradicts an effect of the AL on weight loss.

Interestingly, another study by Süsstrunk J. et al. comparing a standard RYGB (AL: 150 cm; BPL: 60 cm; CL: variable) to a Very-Very Long-Limb Gastric Bypass (AL: variable; BPL: 60 cm; CL: 100 cm) in 232 patients after a follow-up of 9.4 years found a significant

difference in weight loss and weight regain in favor of the Very-Very Long Limb Bypass. The authors reported no significant difference in the frequency of reoperations between both groups. However, while there were two patients with malnutrition/malabsorption in need of revisional surgery (reverse bypass) in the RYGB group, there were six patients suffering from malnutrition/steatorrhea that needed to be reversed (proximalization, reversed bypass) in the Very-Very Long-Limb Gastric Bypass group [18]. Considering the length of the CL in the Very-Very Long-Limb Gastric Bypass group (100 cm), fat malabsorption and possible loss of bile acids can be assumed in these patients. As Risstad et al.'s [17] and Süsstrunk et al.'s [18] studies appear to be quite similar in terms of surgical technique, the main reason for the difference in the outcomes seems to have been the length of the follow-up period.

Another variation of RYGB relying on a long BPL is D-OAGB, which features the creation of a long and narrow pouch (similar to OAGB) and the exclusion of 150 cm of BPL. By performing a jejuno-jejunostomy, an AL of 70 cm is created to prevent backflow of biliary fluids to the pouch [19]. An RCT by Nergaard B. J. et al. compared a standard RYGB (AL: 150 cm; BPL: 60 cm; CL: variable) to a D-OAGB (AL: 60 cm; BPL: 200 cm; CL: variable) in 187 patients in terms of excess BMI loss. After seven years, a significant difference was achieved, with 78.4% of BMI loss in the long BPL group and 67.1% in the group with the long AL [20]. Darabi S. et al. studied the length of both the AL and BPL in RYGB after one and three years. Three hundred and thirteen patients in three groups (group 1: BPL 50 cm, AL: 150 cm; group 2: BPL: 150 cm, AL: 50 cm; group 3: BPL: 100 cm, AL: 100 cm) were compared. After one year no difference in %EWL was observed. However after three years patients with a longer BPL achieved a higher %EWL [21].

The length of the BPL also plays an important role in the postoperative development of deficiencies. Robert M. et al. [22] compared 129 OAGB (BPL: 200 cm) to 124 RYGB patients (BPL: 50 cm, AL: 150 cm) in an RCT with a noninferiority design. OAGB was not inferior to RYGB regarding weight loss and metabolic outcomes after two years. Nevertheless, 21.4% of severe nutritional complications in the OAGB group vs. none in the RYGB group ($p = 0.0034$) were found. Again, the main factor was the length of BPL, since no digestion takes place in this part, as opposed to the AL. Therefore, the risk of developing deficiencies after a standard RYGB is slightly lower than after OAGB [23].

Finally, a meta-analysis by Mahawar K. et al., which compared different limb lengths for RYGB, concluded that 100 cm to 200 cm of BPL + AL combined may lead to optimal results [24].

Thus, it may be concluded that the BPL length is more important in terms of weight loss and improvement of comorbidities than the length of the AL. Therefore, a D-OAGB may be superior to a standard RYGB. Nevertheless, if a BPL of more than 150 cm is considered, the total small bowel length should be measured intraoperatively to prevent deficiencies.

4. One-Anastomosis Gastric Bypass

OAGB (synonyms are Mini-Gastric Bypass or Omega-Loop Gastric Bypass) is an efficient and relatively safe bariatric procedure considering weight loss and postoperative development of deficiencies. As opposed to RYGB, OAGB does not feature an AL. Instead, it relies on a BPL and a CL [25] (Figure 2). It should be noted that (perhaps confusingly) a few publications refer to the CL as AL.

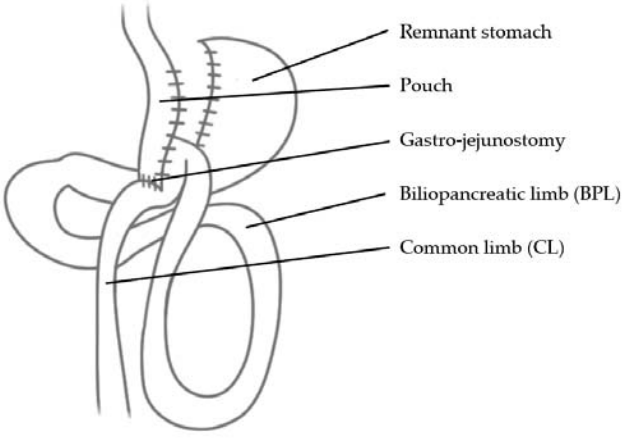

Figure 2. One-Anastomosis Gastric Bypass (OAGB).

OAGB was first described by Rutledge R. et al. in 2001 as a bariatric procedure in 1274 patients with a BPL length of 200 cm. The patients achieved an EWL of 77% after two years with a low complications rate [26]. Liagre A. et al. studied 115 patients eight years after OAGB with a 150 cm BPL and found an EWL of 84.8%. Interestingly, these results are not inferior to those mentioned above, despite the fact that a shorter BPL had been created. None of the patients were suffering from malnutrition, but high rates of Vitamin A and D deficiencies (54%; 33%) were found [27].

Several studies have compared different BPL lengths in OAGB patients to find an ideal balance between sufficient weight loss and a low risk of deficiencies. For example, comparing OAGB with a BPL of 150 cm to a BPL of 200 cm in 343 patients after two years, Boyle M. et al. found equal results in terms of EWL (74%; 75%). They reported no differences in albumin and hemoglobin levels [28]. In another study by Pizza F. et al., three groups of BPL lengths (150 cm, 180 cm, 200 cm) of 60 patients each were compared. After two years, no differences in terms of EWL, remission of type 2 diabetes (DMII) and arterial hypertension were found between the groups. Nevertheless, significant differences in iron and ferritin deficiencies were observed between the 150 cm and the 200 cm groups. Therefore, the authors concluded a BPL length of 150 cm–180 cm to be the safest and most effective option even in patients with a BMI > 50 g/m^2 [29]. Ahuja A. et al. compared OAGB with BPL lengths of 150 cm, 180 cm and 250 cm. In the third group, 15% were reported to suffer from severe malnutrition and anemia [30]. Jedamzik J. et al. found that nutritional deficiencies were generally increased after OAGB with a tendency towards higher rates in longer BPL lengths, without improved weight loss [31].

By contrast, Charalampos M. et al. did not find any correlations between the BPL length (comparing 200 cm, 250 cm, and 300 cm BPL) and deficiencies after three years [32].

Some studies have compared a fixed BPL of 200 cm with a BPL of variable length. A recently published RCT by Nabil T. et al., for example, compared two groups of OAGB: group 1: BPL: 200 cm; group 2: CL: 400 cm (with a mean BPL of 301 cm). No significant differences in terms of weight loss were found, however, group 2 showed greater albumin, iron and hemoglobin deficiency rates [33]. Komaei I. et al. also compared fixed 200 cm BPL in the first group to a BPL of 40% of the small bowel in the second group and found less deficiencies of vitamins A, D, B12, iron and albumin one year after OAGB in the tailored BPL group, despite the fact that some patients in the tailored BPL group had a CL length of only 250 cm [34].

Lee W. J. et al. presented a different approach by tailoring BPL lengths to patients' preoperative BMI. They compared these tailored BPL lengths (150 cm for BMI > 40 kg/m^2, 250 cm for BMI 40–50 kg/m^2, 350 cm for BMI > 50 kg/m^2) in 644 patients. The mean

BMI reduction was staggered as expected: 10.7, 15.5 and 23.5 kg/m^2, respectively. Severe anemia was detected more frequently in the group with the lowest BMI [35].

In conclusion, the results of studies comparing different BPL lengths after OAGB are diverse. It appears that differences regarding the length of the BPL tend to impact the risk of deficiencies more strongly than weight loss and remission of comorbidities. Therefore, the recent IFSO Consensus Conference recommends a BPL of 150–180 cm for OAGB as effective and safe. If a BPL of more than 200 cm is created, the entire small bowel length should be measured intraoperatively to ensure that the CL is long enough [36]. A CL of at least 300 cm will likely prevent patients from developing malnutrition and deficiencies.

5. Single-Anastomosis Duodeno-Ileal Bypass with Sleeve Gastrectomy (SADI-S)

SADI-S (Figure 3) is a single-anastomosis procedure and may also be described as a combination of SG and a gastric bypass. Synonyms are: One-Anastomosis Duodenal Switch (OADS), Stomach Intestinal Pylorus Sparing (SIPS) or Loop-Duodenal Switch (Loop DS). After performing an SG, the duodenum is transected 3–4 cm post pylorus and an anastomosis is sutured between the duodenum and the ileum at a distance of 200–300 cm from the ileocecal valve [37]. The IFSO position statement of 2018 supported SADI-S as a recognized bariatric and metabolic procedure, even though studies with long-term follow-up in terms of safety and efficiency, as well as RCTs, have yet to be published [38].

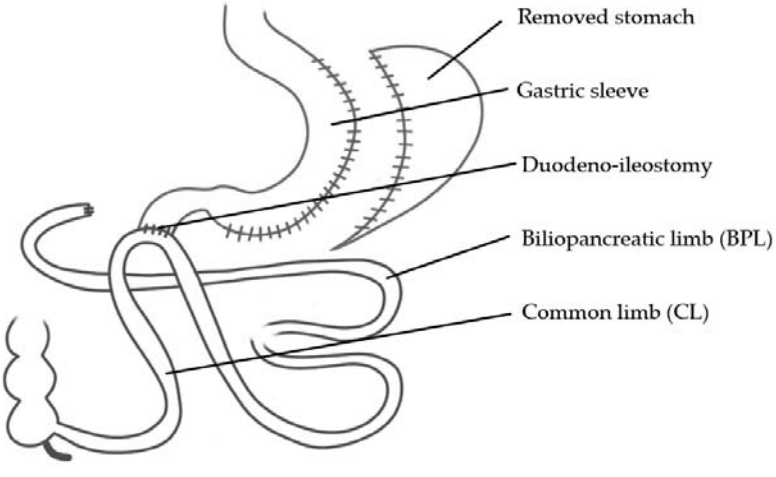

Figure 3. Single-Anastomosis Duodeno-Ileal Bypass + Sleeve Gastrectomy (SADI-S).

By comparing the results of high-quality comparative studies on SADI-S, the aim of this chapter is to shed some light on the question: how much of the small bowel should remain in the food stream (CL) to maintain good weight loss results, yet keep the risk of deficiencies at an acceptable level? The development of the most effective and safe technique may, for example, be observed in a series of studies by A. Torres and A. Sanchez-Pernaute. Sanchez-Pernaute A. et al. first reported one to three years follow-up in 50 patients with a CL length of 200 cm. The EWL was 94.7% after one year and over 100% after three years, with 100% DMII remission and 91.3% remission of arterial hypertension. Patients with anemia (10%) and hypoalbuminemia (8%) after the first postoperative year recovered by the third year [37]. However, four patients (8%) had to be revised due to malnutrition, so that the authors then adjusted their technique by elongating the CL to 250 or 300 cm [39]. In a subsequent study with a total follow-up of up to four years, the next 50 patients were operated creating a 250 cm CL length and were analyzed together with the previously published patients. The EWL was stable >95% over the years with 90% DMII and 58% arterial hypertension remission rates [40].

In a more recent study of 65 patients after SADI-S (CL: 250 cm) and two years of follow-up, Moon R.C. et al. reported an EWL of 74.3% and 100% DMII remission rate. However, it was claimed that close monitoring of liver enzymes and nutritional status were necessary to avoid long-term complications [41]. The majority of studies published later performed a CL of 300 cm and also found an EWL between 70% and 90% with a low risk of malnutrition [42–45].

Midterm results of SADI-S are very satisfactory as well. Zaveri H. et al. published a large series of SADI-S with 300 cm CL in 437 patients at a four-year follow-up. The EWL after this period was 85.7% with 81.3% remission of DMII and 70.7% remission of arterial hypertension [46]. The most recent study on SADI-S was published by Surve A. et al. and included 750 SADI-S patients (CL: 300 cm) and a follow-up of six years. The authors reported 80.7% EWL and 77% DMII remission. Nutritional deficiencies were acceptable after five years. However, levels of albumin, total protein, calcium, parathormone and vitamin E had lowered significantly in these patients [47].

There are only a few case series reporting revisional procedures in cases of severe deficiencies or malnutrition after SADI-S. In those rare cases, revisions are lengthening of the CL or a conversion to RYGB. Horsley B. et al. collected nine cases of revisions (lengthening of the common limb) after SADI-S due to hypoproteinemia or chronic diarrhea. The CL before the revision was between 160 and 400 cm and was lengthened to 450–870 cm in the procedure. All patients with chronic diarrhea before the revision had normal bowel movement postoperatively, and the patients with hypoproteinemia improved their protein levels [48]. Vilallonga et al. published a case-series of five patients after SADI-S (CL between 170 and 250 cm). Some were converted to RYGB, others had lengthening of the CL due to malnutrition [49].

To conclude, SADI-S is one of the most effective bariatric procedures regarding weight loss and may be performed especially in patients with a very high BMI as well as patients with good compliance. One of the advantages of SADI-S is that the exact length of the small bowel in the food stream is known in each patient. The studies published so far have shown that a CL of 300 cm may achieve excellent %EWL with an acceptable risk of vitamin and micronutrient deficiencies [46]. Nevertheless, SADI-S is still a relatively new procedure and should therefore be performed in bariatric centers with good expertise and the capacity for sufficient aftercare.

6. Biliopancreatic Diversion (with Duodenal Switch)

BPD was first described in 1979 by Scopinaro N. et al. in 18 patients with different lengths of the CL [50]. In 1993 Marceau P. et al. published an alteration of this procedure named BPD-DS, which included the creation of a gastric Sleeve instead of a partial stomach resection. They compared 156 BPD-DS with a CL of 100 cm to patients with BPD and a CL of 50 cm, and found equal weight loss results but also a lower rate of undesirable side effects [51].

Studies on BPD-DS have commonly found very good to excellent weight loss results, yet high rates of deficiencies. However, a longer CL may lower the deficiency rates. An RCT by Lebel S. et al. comparing a classic BPD- DS (Figure 4) featuring 100 cm of CL to a variation with a CL of 200 cm initially, found similar weight loss results but significantly more weight regain in the 200 cm CL group. On the other hand, the second group had a lower albumin deficiency rate, lower hyperparathyroidism and a lower number of daily bowel movements [52].

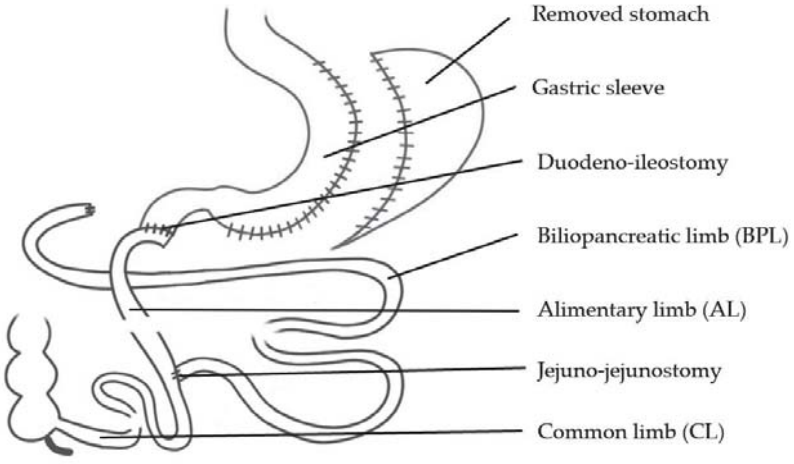

Figure 4. Biliopancreatic Diversion with Duodenal Switch (BPD-DS).

Another RCT by Risstad H. et al., comparing a classic RYGB (BPL: 50 cm; AL: 150 cm) to a classic BPD-DS (AL: 200 cm; CL: 100 cm) in superobese patients >50 kg/m^2 after five years, found greater weight loss and improvement of hyperlipidemia and glucose levels in BPD-DS, but also a higher rate of surgical, nutritional and gastrointestinal adverse events.

The results of long-term studies on BPD-DS are also quite homogenous. Again, they report excellent weight loss results but also high to extremely high rates of deficiencies. Topart P. et al. reported the outcome of BPD-DS after a follow-up of ten years. The EWL of 73% was excellent after this period. Nevertheless, high rates of fat-soluble deficiencies, hyperparathyroidism and a 14% revision rate due to nutritional complications were found [53]. Another long-term follow-up (>10 years) study by Bolckmans R. et al. also found excellent outcomes in terms of weight loss but at the cost of protein and nutritional deficiencies [54]. Finally, a long-term study nine years after BPD-DS reported dramatically high deficiency rates even in patients given adequate vitamin supplementation, as well as protein deficiencies in 30% of the patients and anemia in 40%. Therefore, the authors suggested continuous measurement of blood levels and clinical monitoring of these patients [55].

Despite the well-known potential of bariatric procedures to improve nonalcoholic steatohepatitis (NASH), there is a certain risk of total liver failure after strong malabsorptive procedures [56,57]. A nationwide Belgian survey collected ten patients listed for liver transplantation after bariatric surgery, nine of whom had BPD [58].

In conclusion, BPD is an operation with excellent results in terms of weight loss and remission of comorbidities, at the price of a high risk of postoperative deficiencies, malnutrition and adverse gastrointestinal events. As suggested by the studies referred to in this review, a CL length of only 100 cm may, in fact, be too short to equal a balanced operation. Therefore, BPD and BPD-DS currently only play a minor part as bariatric procedures worldwide. However, these procedures may be indicated for superobese patients. In any case, there is a clear contraindication of these methods for any noncompliant patient lacking lifelong commitment to vitamin supplementation.

7. Revisional Procedures for Weight Regain

Patients experience their nadir weight about 6–18 months after the bariatric procedure [22]. While most patients are able to maintain this weight, or experience a very slow reincrease in the long-term follow-up, about 5–10% suffer from significant WR, indicating a reoperation. On the one hand, a revisional procedure may include improving/re-

establishing the restriction of the pouch (pouch-resizing, pouch-banding, restriction of the gastro-jejunostomy, etc.) or, on the other, malabsorption may be added [10].

Two studies described early experiences with WR operations. Sugerman H.J. et al. described five patients with a distalization for WR after RYGB and shortened the CL to only 50 cm. All patients developed malnutrition and were revised. Nevertheless, two of them died due to hepatic failure. In a second step, the CL was then increased to 150 cm in 22 patients. Besides good additional weight loss results, again, three patients were reoperated due to malnutrition. The authors concluded that a CL of only 50 cm meant an inacceptable level of morbidity and mortality, and that even patients with a CL of 150 cm would need continuous nutritional support thereafter. [59]. The other publication by Fobi M. et al. reported 65 patients that were converted from a Fobi pouch operation to a Distal Gastric Bypass for insufficient weight loss. Due to malnutrition in 15 patients, six of them had to be converted to a Short-Limb RYGB [60].

In a more recent study on WR after RYGB presented by Caruana J.A. et al., ten patients were bypassed more than 70% of the small bowel length and ten were bypassed less than 70%. The additional EWL was 47% in the first and 26% in the second group. However, the authors reported diarrhea in five patients and revision due to malnutrition in three patients of the first group [61]. Felsenreich et al. studied 30 patients who had shortening of the CL to only 100 cm due to WR after RYGB. Nine patients (30%) had to be reoperated (lengthening of the CL to 250 cm) for malabsorption in the follow-up [10].

Buchwald H. et al. published 53 patients that suffered from WR and insufficient weight loss after RYGB. In 47 patients, both the AL and CL were shortened to 75–100 cm, and in six patients the total length (CL + AL) was shortened to 250 cm. While the BMI decreased from 47.2 to 31.4 kg/m^2 after five years, the complication rate was high, with 23 patients (43.4%) in need of total parenteral nutrition and 14 (26.4%) patients needing a revisional procedure [62].

In a current study, Ghiassi S. et al. presented 96 patients after three years. Patients with a total small bowel length of 400–450 cm were less likely to develop nutritional issues than patients with 250–300 cm in the food passage [63].

To conclude, adding malabsorption by decreasing the length of the CL should always be done very carefully. Patients chosen for this approach need to show very good compliance in terms of a commitment to vitamin supplementation and routine aftercare. It is important that these patients do not suffer from dysphagia or vomiting due to a stenosis or ulcer of the gastro-jejunostomy, as these increase the risk of postoperative malnutrition [57]. In every reoperation for weight regain, the entire small bowel must be measured and documented [64]. The CL, or the CL + AL lengths, respectively, should not be shortened below 300–350 cm to minimize the risk of deficiencies and malnutrition [65,66].

8. Conclusions

It is hard to assess how much malabsorption the individual patient needs; as we have seen, the length of the small bowel differs in each individual. It is necessary to find a balance between sufficient weight loss and remission of comorbidities on the one hand, and a low risk of possible deficiencies and malnutrition on the other. The larger the part of the small bowel removed from the food stream, the higher the importance of the patient's compliance with daily vitamin supplementation as well a thorough aftercare program.

In fact, the reasoning behind the choice of procedure varies to a great extent worldwide. However, one may use the following suggestions as a possible algorithm for choosing an appropriate malabsorptive procedure: Patients suffering from gastro-esophageal reflux disease may benefit most from RYGB, whereas SADI-S or BPD-DS are recommended for super-obese patients (>50 kg/m^2) and OAGB may be performed in any patients without reflux.

Studies have pointed out that the effect of a BPL (in RYGB or BPD-DS) removed from the food stream completely has more impact than an AL, where protein and carbohydrate digestion is continued. In patients with a BPL longer than 150 cm, the entire small bowel should be measured to ensure that the CL is long enough. A rule of thumb for any

malabsorptive procedure should be maintaining at least 300 cm of small bowel (CL or CL + AL) in the food stream to prevent the development of deficiencies and malnutrition.

If nutritional deficiencies and malabsorption cannot be treated conservatively in an adequate way, a reoperation should be considered early on to increase the length of small bowel in the CL. In patients with a critical body condition, the placement of a flow-care tube to the remnant stomach (in OAGB or RYGB) may be considered as a first step to start enteral nutrition of the BPL.

The initial question, "how much malabsorption do we need?", cannot be answered in definitive terms but must be answered for each patient individually, as it is multilayered and depends on several individual factors, such as preoperative weight, comorbidities and the patient's compliance.

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Review

Three and Five-Year Mortality in Ovarian Cancer after Minimally Invasive Compared to Open Surgery: A Systematic Review and Meta-Analysis

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Abstract: As regards ovarian cancer, the use of minimally invasive surgery has steadily increased over the years. Reluctance persists, however, about its oncological outcomes. The main objective of this meta-analysis was to compare the three and five-year mortality of patients operated by minimally invasive surgery (MIS) for ovarian cancer to those operated by conventional open surgery (OPS), as well as their respective perioperative outcomes. PubMed, Cochrane library and CinicalTrials.gov were systematically searched, using the terms laparoscopy, laparoscopic or minimally invasive in combination with ovarian cancer or ovarian carcinoma. We finally included 19 observational studies with a total of 7213 patients. We found no statistically significant difference for five-year (relative risk (RR) = 0.89, 95% CI 0.53–1.49, $p = 0.62$)) and three-year mortality (RR = 0.95, 95% CI 0.80–1.12, $p = 0.52$) between the patients undergoing MIS and those operated by OPS. When five and three-year recurrences were analyzed, no statistically significant differences were also observed. Analysis in early and advanced stages subgroups showed no significant difference for survival outcomes, suggesting oncological safety of MIS in all stages. Whether the surgery was primary or interval debulking surgery in advanced ovarian cancer, did not influence the comparative results on mortality or recurrence. Although the available studies are retrospective, and mostly carry a high risk for bias and confounding, an overwhelming consistency of the evidence suggests the likely effectiveness of MIS in selected cases of ovarian cancer, even in advanced stages. To validate the use of MIS, the development of future randomized interventional studies should be a priority.

Keywords: ovarian cancer; laparoscopy; minimally invasive surgery; survival; mortality

1. Introduction

Ovarian cancer is the most lethal of common tumours in women, and represents the fifth most frequently diagnosed neoplasm among women [1]. Surgery, together with chemotherapy, are the pillars of the management of ovarian cancer. For early stages, the main objective is to establish the stage of the disease with the purpose of confirming the indication of adjuvant chemotherapy. For advanced tumors, the mainstay of the curative treatment is radical cytoreduction without any residual disease, followed by chemotherapy [2]. Whenever this finality is unachievable with upfront surgery, neoadjuvant chemotherapy and interval debulking surgery were accepted as valid alternatives.

The standard surgical approach is open surgery (OPS). In selected cases, minimally invasive surgery (MIS) has been shown to be safe in terms of postoperative complications and short term mortality [3,4]. Reluctance persists, however, about its oncological outcomes in the longer term.

Over the last ten years, multiple studies have compared survival in ovarian cancer after MIS and OPS without showing any clear differences between the approaches, but each of these studies had a limited sample size. Meta-analyses of ovarian cancer have recently been published [5–12] showing similar operative and clinical outcomes between patients treated by MIS and those operated by OPS. However, none of them compared three or five-year survival or performed an overall analysis (early and advanced stages). There is a need to evaluate and pool the relevant data together in a systematic review and meta-analysis to provide more robust evidence regarding survival after MIS versus OPS.

The main objective of this meta-analysis was to compare the survival of patients operated by laparoscopy for ovarian cancer to those operated by conventional open surgery, as well as their respective perioperative outcomes.

2. Experimental Section

This was a systematic review and meta-analysis which followed a detailed a priori study protocol. It has been registered in PROSPERO (CRD42020183284). It was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines [13] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] (Table S1).

PubMed, Cochrane library and CinicalTrials.gov were systematically searched, using the terms laparoscopy, laparoscopic or minimally invasive in combination with ovarian cancer or ovarian carcinoma. The literature search was limited to articles published in the last ten years (from January 2009 to April 2020).

Using these search criteria, we identified all English language original studies comparing outcomes of patients with ovarian cancer who had a staging procedure for early stages, and primary or interval debulking surgery for advanced stages by laparoscopy or open surgery. Only comparative studies between laparoscopy and laparotomy were included in the present review. References of the included papers were further searched to identify other potentially relevant studies. Exclusion criteria included duplicate publications, nonEnglish language literature, abstracts, letters, editorials and reviews not reporting original data, studies with less than 10 patients and studies including patients treated for recurrent disease or fertility-sparing surgery only. Studies including patients treated by robot-assisted laparoscopy were also included if it was possible to distinguish their data from patients treated by laparoscopy. Additionally, we excluded studies that included borderline tumors when it was not possible to discern data related to women with invasive cancer. The Methodological Index for Nonrandomized Studies (MINORS) [15] was used to conduct quality evaluation for the studies.

In each report, we sought to extract oncologic outcomes, surgical details and baseline demographic data. Oncologic outcomes included five and three-year mortality rate and five and three-year recurrence rate. Surgery-related details included the following surgical related outcomes: mean operative time, mean blood loss, intraoperative complication rate, length of hospital stay and postoperative complications rate (all grades first, then we considered separately complications of grade ≥ 3 according to the Clavien-Dindo classification [16]). Demographic data were also searched: proportion of patients with adjuvant therapy, proportion of patients with neoadjuvant therapy and proportion of complete debulking surgery.

Studies were selected and data were extracted by two reviewers (FJ and MV), and any discrepancy between reviewers was resolved through discussion.

The main outcome measures were all-cause mortality within five and three years. Secondary outcomes measures were five and three-year recurrence, as well as the above-mentioned surgical outcomes. Data were presented as median values and ranges and were converted to mean values and standard deviations using the formula proposed by Wan et al. [17]. Survival data only available in Kaplan-Meier curves were extracted using the software Digitizeit (https://www.digitizeit.de). R 3.6.2 software was used to carry out the meta-analysis and the effect measures were presented with relative risk (RR)/mean difference (MD) and 95% confidence interval (CI). A random effect was used in the overall analysis due to the variability of the population included in each study. Subgroup analyses were conducted based on the initial characteristics of the study population: early stage only versus advanced ovarian cancer, and conducted

using a mixed-effects model [18] in which subgroup effect sizes were pooled using a random-effects model, and subgroup differences were assessed using a fixed-effect model. Heterogeneity between studies was assessed using the Higgins I^2 test, with levels of heterogeneity defined as not important (I^2 = 0–40%), moderate (I^2 = 30–60%), substantial (I^2 = 50–90%), or considerable (I^2 = 75–100%) [19]. If $I^2 \geq 75\%$, data were considered to have considerable heterogeneity and could not be combined [19]. The χ^2 test was used for the same purpose, with a statistical significance level of $p < 0.05$ indicating presence of statistical heterogeneity. A metaregression analysis was performed for survival outcomes to determine factors that had an influence on heterogeneity using the baseline demographics data mentioned above. The proportion of neoadjuvant therapy and the proportion of complete debulking were analyzed only in the advanced stage subgroup. Outcomes were given as the exponentiated slope coefficient and 95% CIs. Variables with $p < 0.05$ were regarded as significant influential factors on heterogeneity. Egger's test [20] was utilized to evaluate publication bias. When there was a substantial publication bias, a Duval and Tweedie nonparametric trim and fill procedure was performed to assess the possible effects of the publication bias and to suggest the adjusted overall values. To conclude, a sensitivity analysis was conducted by detecting outliers in each meta-analysis. A study was defined as an outlier if the study's confidence interval did not overlap with the confidence interval of the pooled effect. In that case, the study was removed from the analysis to examine the effect removal of the study had on the pooled effect.

3. Results

3.1. Literature Search

In this study, we enrolled 19 observational studies (Figure 1) [6,11,21–37]. In total, 7213 patients were included in this meta-analysis: 2285 (32%) in the minimally invasive surgery group and 4928 (68%) in the open surgery group. The design of each study, with the baseline demographic data, are provided in Table 1. The quality scores of the studies according to MINORS varied between 16 and 20 with a median value of 18.

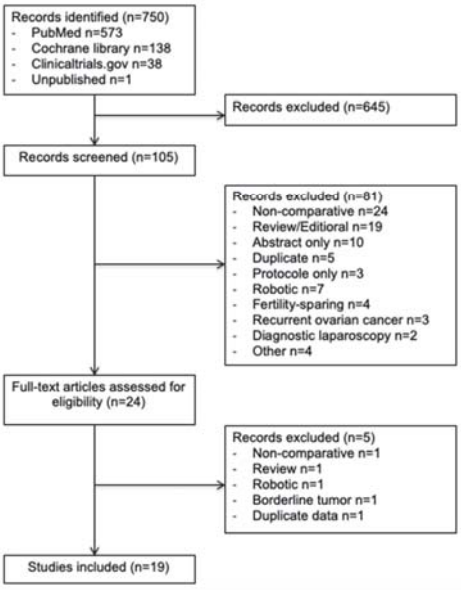


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

Table 1. Study design and demographic data.

Study	Period	Study Design	Total MINORS *	Location	Histological Type	Number of Patients	Follow-Up, Months	Adjuvant Therapy, *n* (%)	Neoadjuvant Therapy, *n* (%)	Complete Resection, *n* (%)
Early ovarian cancer										
Bergamini et al., 2018	1965–2017	Retrospective	18	Multicenter Italy	Granulosa cells	MIS = 93 OS = 130	81 (10–450)	25 (11%)	-	-
Bogani et al., 2014	2003–2010	Retrospective	18	Monocentric Italy	Epithelial	MIS = 35 OS = 32	64 (37–106) 100 (61–287)	56 (84%)	-	-
Ditto et al., 2016	2005–2015	Retrospective and prospective	19	Monocentric Italy	Epithelial	MIS = 50 OS = 50	49.5 (64) 52.6 (31.7)	59 (59%)	-	-
Gallotta et al., 2016	2000–2013	Retrospective	17	Monocentric Italy	Epithelial	MIS = 60 OS = 120	38 (24–48)	126 (70%)	-	-
Koo et al., 2014	2006–2012	Retrospective	18	Multicenter Korea	All types	MIS = 24 OS = 53	31.7 (20.7) 31.1 (19.1)	69 (90%)	-	-
Lee et al., 2011	2005–2010	Retrospective	18	Monocentric Korea	All types	MIS = 26 OS = 87	12 (1–42) 25 (1–74)	82 (73%)	-	-
Liu et al., 2014	2002–2012	Retrospective	16	Monocentric China	All types	MIS = 35 OS = 40	36 to 84	66 (88%)	-	-
Lu et al., 2016	2002–2014	Retrospective	19	Monocentric China	Epithelial	MIS = 42 OS = 50	82 (16–152) 82 (16–152)	-	-	-
Melamed et al., 2016	2010–2012	Retrospective	20	Multicenter USA	Epithelial	MIS = 1096 OS = 1096	28.7 (20.4–38.9) 29.3 (20.6–39.3)	1230 (56%)	-	-
Minig et al., 2016	2006–2014	Retrospective	17	Multicenter Spain and Argentina	Epithelial	MIS = 50 OS = 58	25.9 (11.2–38.5) 34.3 (32.8–49)	66 (61%)	-	-
Wu et al., 2009	1984–2006	Retrospective	18	Multicenter Taiwan	Epithelial	MIS = 34 OS = 174	48.5 (3–174.5) 67 (2–276)	152 (78%)	-	-
Advanced ovarian cancer										
Alletti et al., 2016	2010–2014	Retrospective	17	Monocentric Italy	High grade serous	MIS = 30 OS = 65	28	95 (100%)	95 (100%)	91 (96%)
Brown et al., 2018	2006–2017	Retrospective	19	Monocentric USA	Epithelial	MIS = 53 OS = 104	-	-	157 (100%)	76 (48%)

Table 1. *Cont.*

Study	Period	Study Design	Total MINORS *	Location	Histological Type	Number of Patients	Follow-Up, Months	Adjuvant Therapy, *n* (%)	Neoadjuvant Therapy, *n* (%)	Complete Resection, *n* (%)
Ceccaroni et al., 2017	2007–2015	Prospective	19	Monocentric Italy	All types	MIS = 21 OS = 45	47.3 (12–72) 52.3 (5–117)	66 (100%)	0	58 (88%)
Favero et al., 2015	2011–2014	Prospective	20	Monocentric Brazil	High grade serous	MIS = 10 OS = 11	20 (12–26) 36 (24–48)	21 (100%)	21 (100%)	21 (100%)
Jochum et al., 2020	2010–2018	Retrospective	19	Monocentric France	Epithelial	MIS = 41 OS = 41	31.0 (16.0–52.0) 32.0 (23.0–61.0)	67 (82%)	45 (55%)	82 (100%)
Magrina et al., 2011	2002–2008	Retrospective	17	Monocentric USA	Epithelial	MIS = 27 OS = 119	52.8 (2.4–110.4) 34.8 (0–128.4)	106 (73%)	36 (25%)	92 (63%)
Melamed et al., 2017	2010–2012	Retrospective	19	Multicenter USA	Epithelial	MIS = 540 OS = 2621	32.0	-	3161 (100%)	919 (49%)
Tozzi et al., 2016	2008–2016	Prospective	19	Multicenter Italy and United Kingdom	All type	MIS = 18 OS = 32	- -	-	50 (100%)	49 (98%)

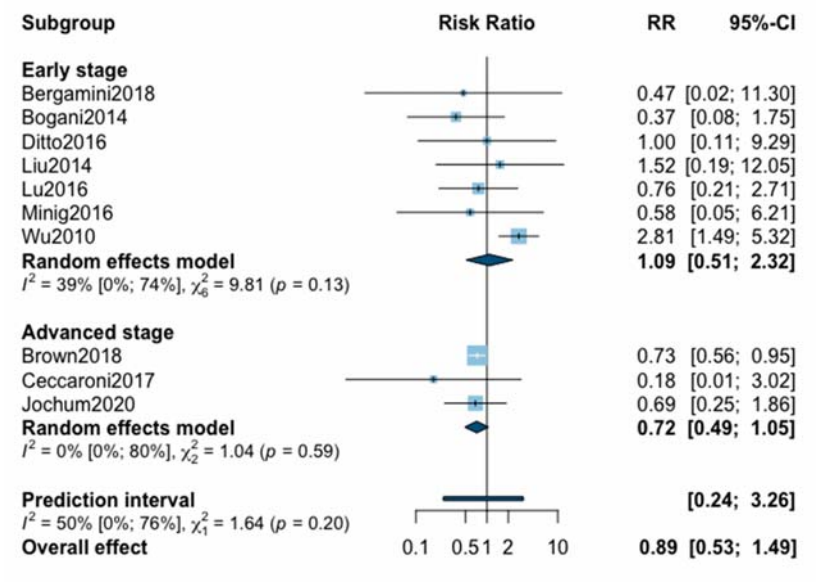
* Methodological Index for Nonrandomized Studies.

3.2. Overall Mortality

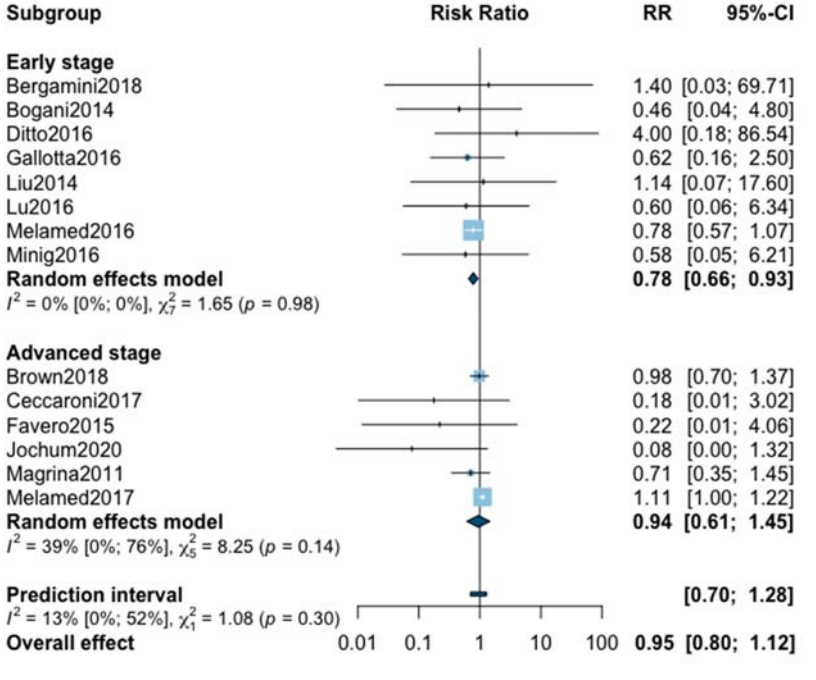
A total of 10 studies reported all-cause five-year mortality (Figure 2). The meta-analysis revealed no significant difference for overall survival after MIS compared with OPS at five years (RR = 0.89, 95% CI 0.53–1.49, $p = 0.62$). No significant difference was observed between the early and advanced stage subgroups ($p = 0.20$). The statistical heterogeneity of the studies shows moderate heterogeneity in the early stage subgroup ($I^2 = 39\%$, 95% CI 0–74%, $p = 0.13$) and no heterogeneity in the advanced stage subgroup ($I^2 = 0\%$, 95% CI 0–80%, $p = 0.59$) with an overall heterogeneity of 50% (0–76%), $p = 0.20$. The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.97$), arguing against small-study effects or publication bias. Metaregression found no significant result in subgroup analysis and overall (Table 2). In the advanced stage subgroup, the metaregression was not realized for adjuvant therapy due to the presence of only two studies. No outlier was detected in the sensitivity analysis.

Table 2. Metaregression analysis.

Metaregression	k	Exponentiated Slope Coefficient (95% CI)	*p* Value
Five-year mortality			
Metaregression by adjuvant therapy, %			
Early stage	6	0.01 (−0.04 to 0.07)	0.55
Overall	8	−0.00 (−0.05 to 0.05)	0.99
Metaregression by neoadjuvant therapy, %			
Advanced stage	3	0.01 (−0.08 to 0.09)	0.51
Metaregression by complete resection, %			
Advanced stage	3	−0.00 (−0.12 to 0.11)	0.77
Three-year mortality			
Metaregression by adjuvant therapy, %			
Early stage	7	−0.01 (−0.04 to 0.02)	0.53
Advanced stage	4	−0.05 (−0.20 to 0.09)	0.24
Overall	11	−0.02 (−0.04 to 0.00)	0.06
Metaregression by neoadjuvant therapy, %			
Advanced stage	5	0.01 (−0.01 to 0.02)	0.21
Metaregression by complete resection, %			
Advanced stage	6	−0.04 (−0.06 to −0.02)	0.01
Five-year recurrence			
Metaregression by adjuvant therapy, %			
Early stage	6	0.00 (−0.02 to 0.03)	0.69
Overall	8	0.00 (−0.01 to 0.01)	0.78
Metaregression by neoadjuvant therapy, %			
Advanced stage	3	−0.01 (−0.04 to 0.03)	0.25
Meta-regression by complete resection, %			
Advanced stage	3	0.01 (−0.02 to 0.03)	0.14
Three-year recurrence			
Metaregression by adjuvant therapy, %			
Early stage	6	−0.01 (−0.03 to 0.02)	0.58
Advanced stage	3	0.03 (−0.04 to 0.10)	0.12
Overall	9	−0.00 (−0.02 to 0.01)	0.66
Metaregression by neoadjuvant therapy, %			
Advanced stage	4	−0.00 (−0.02 to 0.02)	0.73
Metaregression by complete resection, %			
Advanced stage	4	0.01 (−0.03 to 0.04)	0.55



(**a**)



(**b**)

Figure 2. Forrest plot for relative risk (RR) for five-year mortality (**a**) and three-year mortality (**b**).

Three-year mortality was reported in 14 studies (Figure 2). Three-year mortality for MIS compared with OPS was not significantly improved (RR = 0.95, 95% CI 0.80–1.12, p = 0.52). No significant

difference was observed between the early and advanced stage subgroups ($p = 0.30$). The statistical heterogeneity of the studies showed no heterogeneity in the early stage subgroup ($I^2 = 0\%$, 95% CI 0–0%, $p = 0.98$), and moderate heterogeneity in the advanced stage subgroup ($I^2 = 39\%$, 95% CI 0–76%, $p = 0.14$), with an overall heterogeneity of 13% (0–52%), $p = 0.30$. The funnel plot appeared asymmetrical with a statistical testing significant (Egger test $p = 0.01$), indicating some level of small-study effects or publication bias. Relative risk was corrected using the trim and fill procedure and revealed an adjusted value of 0.97 (0.80–1.18) (Figure 3). As a result of metaregression, three-year survival was not associated with the proportion of neoadjuvant and adjuvant therapy (Table 2). From the advanced stage subgroup, the RR for three-year mortality was significantly reduced with a higher proportion of complete resection ($p = 0.01$ with r2 = 100%) (Figure 4). The sensitivity analysis found no outlier.

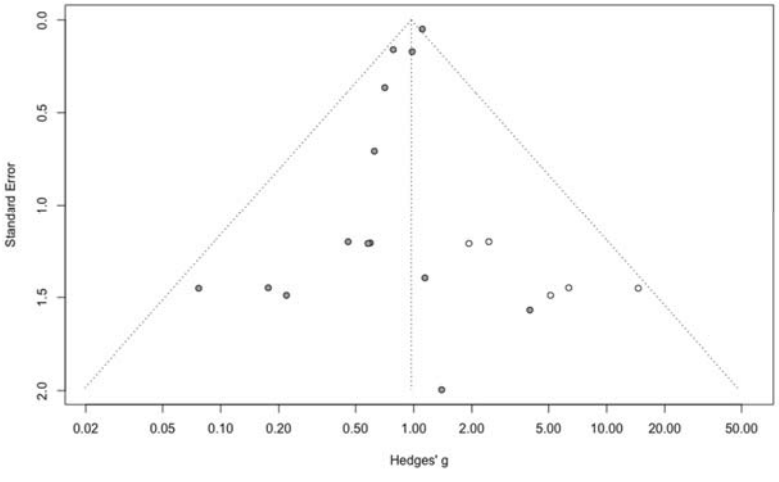


Figure 3. Corrected funnel plot for three-year mortality outcome.

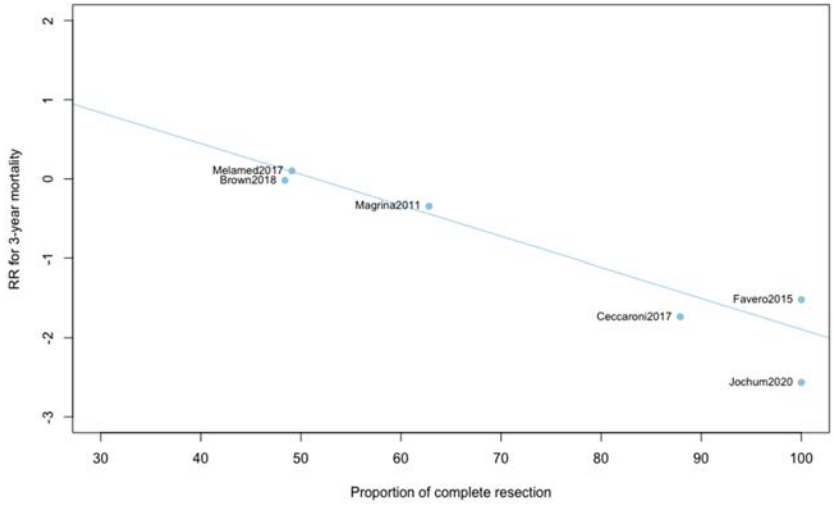


Figure 4. Metaregression of RR for 3-year mortality by proportion of complete resection. $y = 2.01 - 0.04x$.

3.3. Secondary Outcomes

A total of nine studies reported five-year recurrence (Appendix A). The pooled analysis found no significant difference when comparing MIS with OPS (RR = 0.97, 95% CI 0.72–1.31; $p = 0.84$). No significant difference was observed between the early and advanced stage subgroups ($p = 0.23$). The statistical heterogeneity of the studies showed not important heterogeneity in the early stage subgroup ($I^2 = 22\%$, 95% CI 0–66%, $p = 0.27$), and in the advanced stage subgroup ($I^2 = 51\%$, 95% CI 0–86%, $p = 0.13$), with an overall heterogeneity of 41% (0%; 73%), $p = 0.23$. The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.14$), arguing against small-study effects or publication bias. Metaregression overall, and in subgroups, found no significant result (Table 2). Meta-regression in the advanced stage subgroup for adjuvant therapy was not realized due to the presence of only two studies. No outlier was detected in the sensitivity analysis.

Three-year recurrence was reported in 10 studies (Appendix A). The pooled analysis showed no significant difference between MIS and OPS for three-year recurrence (RR = 0.94, 95% CI 0.73–1.22, $p = 0.60$). No significant difference was observed between the early and advanced subgroups ($p = 0.23$). The statistical heterogeneity of the studies showed no important heterogeneity in the early stage subgroup ($I^2 = 4\%$, 95% CI 0–76%, $p = 0.39$) and in the advanced stage subgroup ($I^2 = 20\%$, 95% CI 0–88%, $p = 0.29$, with an overall heterogeneity of 16% (0%; 57%), $p = 0.23$. The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.21$), arguing against small-study effects or publication bias. Metaregression found no significant result (Table 2). No outlier was detected in the sensitivity analysis.

For estimated blood loss, 12 studies were initially included in the analysis (Appendix B). The statistical heterogeneity of the studies showed considerable heterogeneity in the early stage subgroup ($I^2 = 76\%$, 95% CI 51–89%, $p < 0.01$) and in the advanced stage subgroup ($I^2 = 95\%$, 95% CI 92–97%, $p < 0.01$), with an overall heterogeneity of 90% (85%; 94%), $p < 0.001$. A significant difference was observed between the early and advanced subgroups ($p = 0.02$). The sensitivity analysis found one outlier in the early stage subgroup and three outliers in the advanced stage subgroup. These studies were removed from the analysis. The statistical heterogeneity of the remaining eight studies showed moderate heterogeneity in the early stage subgroup ($I^2 = 33\%$, 95% CI 0–73%, $p = 0.19$), and not important heterogeneity in the advanced stage subgroup ($I^2 = 14\%$, $p = 0.28$). A significant difference was still observed between the two subgroups ($p < 0.001$) with, in the early stage subgroup, an MD for estimated blood loss at −187.99 (−239.91; −134.07) and in advanced stage subgroup at −1167.84 (−1673.25; −662.42). The pooled analysis could not be realized due to high heterogeneity ($I^2 = 73\%$, 95% CI 45–97%, $p < 0.01$).

A total of 14 studies were initially included in the meta-analysis for operating time (Appendix B). The statistical heterogeneity of the studies showed considerable heterogeneity in the early stage subgroup ($I^2 = 89\%$, 95% CI 80–94%, $p < 0.01$), and moderate heterogeneity in the advanced stage subgroup ($I^2 = 33\%$, 95% CI 0–71%, $p = 0.18$) with an overall heterogeneity at 80% (67%; 88%), $p = 0.37$. No significant difference was observed between the early and advanced stage subgroups ($p = 0.37$). One outlier was removed from each subgroup in the sensitivity analysis. The pooled analysis of the remaining 12 studies showed no significant difference for operative time between MIS and OPS (MD = 8.89, 95% CI −0.01 to 17.8, $p = 0.05$; $I^2 = 43\%$, 95% CI 0%–71%, $p = 0.33$). The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.64$), arguing against small-study effects or publication bias.

Mean hospital stay was reported in 16 studies (Appendix B). The statistical heterogeneity of the studies showed considerable heterogeneity in the early stage subgroup ($I^2 = 95\%$, 95% CI 93–97%, $p < 0.01$), and in the advanced stage subgroup ($I^2 = 93\%$, 95% CI 88–96%, $p < 0.01$) with an overall heterogeneity at 94% (92%; 96%), $p = 0.10$. No significant difference was observed between the early and advanced stage subgroups ($p = 0.10$). The sensitivity analysis removed seven outliers. The pooled analysis of the remaining nine studies showed a significant reduction of hospital stay when patients were treated with MIS (MD = −2.59, 95% CI −3.22 to −1.97, $p < 0.01$; $I^2 = 57\%$, 95% CI 9–80%, $p = 0.64$).

The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.71$), arguing against small-study effects or publication bias.

As for intraoperative complication rate, 11 studies were included in the meta-analysis (Appendix B). The pooled analysis revealed no significant difference between MIS and OPS (RR = 0.77, 95% CI 0.51–1.16, $p = 0.18$). No significant difference was observed between the early and advanced stage subgroups ($p = 0.88$). The statistical heterogeneity of the studies showed no heterogeneity in the early stage subgroup ($I^2 = 0\%$, 95% CI 0–0%, $p = 0.95$) and in the advanced stage subgroup ($I^2 = 0\%$, 95% CI 0–66%, $p = 0.66$) with an overall heterogeneity at 0% (0%; 0%), $p = 0.88$. The funnel plot appeared asymmetrical according to visual observation, even if statistical testing was not significant (Egger test $p = 0.06$), indicating the possibility of small-study effects or publication bias. The relative risk was corrected using the trim and fill procedure and revealed an adjusted value of 0.97 (0.61–1.52) (Appendix C). No outlier was detected in the sensitivity analysis.

Finally, postoperative all grade complication rate was analyzed in nine studies (Appendix B). The meta-analysis showed an almost significant reduction of postoperative complication in favor of MIS (RR = 0.65, 95% CI 0.40–1.05, $p = 0.07$). No significant difference was observed between the early and advanced stage subgroups ($p = 0.31$). The statistical heterogeneity of the studies showed no heterogeneity in the early stage subgroup ($I^2 = 4\%$, 95% CI 0–85%, $p = 0.37$) and substantial heterogeneity in the advanced stage subgroup ($I^2 = 57\%$, 95% CI 0–69%, $p = 0.05$, with an overall heterogeneity at 33% (0%; 69%), $p = 0.31$. The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.22$), arguing against small-study effects or publication bias. No outlier was detected in the sensitivity analysis. As for postoperative complication rate grade ≥3, only five studies recorded it. The low number of studies can be explained by the high number of different definitions of perioperative complications. The pooled analysis showed, again, no significant difference between MIS and OPS (RR = 0.67, 95% CI 0.25–1.80, $p = 0.32$). No significant difference was observed between the early and advanced stage subgroups ($p = 0.76$). The statistical heterogeneity of the studies showed no heterogeneity in the early stage subgroup ($I^2 = 0\%$, $p = 0.70$) and not important heterogeneity in the advanced stage subgroup ($I^2 = 21\%$, 95% CI 0–92%, $p = 0.76$), with an overall heterogeneity at 0% (0%; 69%), $p = 0.09$. The funnel plot was symmetrical both according to visual and statistical testing (Egger test $p = 0.56$), arguing against small-study effects or publication bias. No outlier was detected in the sensitivity analysis.

4. Discussion

This report is, to our knowledge, the only quantitative meta-analysis to date to compare the five-year survival between MIS and OPS in ovarian cancer. We found that patients diagnosed with ovarian cancer undergoing MIS presented similar five-year (RR = 0.89, 95% CI 0.53–1.49, $p = 0.62$) and three-year mortality (RR = 0.95, 95% CI 0.80–1.12, $p = 0.52$). When five-year and three-year recurrences were analyzed, no statistically significant differences were observed. Analyses in subgroups show no significant difference for survival outcomes, suggesting an oncological safety of MIS in both early and advanced stages. Metaregression found no impact of the proportion of neoadjuvant and adjuvant chemotherapy on survival outcomes. Whether the surgery was primary or interval debulking surgery in advanced ovarian cancer, it did not influence the comparative results on mortality or recurrence. Metaregression on three-year mortality found, however, a significant influence of the proportion of complete resection in advanced ovarian cancer. When the proportion of complete resection is higher, the three-year mortality is lower with MIS compared to OPS. This result reinforces the idea that, if patients are correctly selected, minimally invasive surgery can be a very effective treatment. Unfortunately, these selection criteria have yet to be precisely defined, which is currently one of the main barriers to the acceptance of laparoscopic management of ovarian cancer.

In all the studies included, no specific criteria were used to select patients for laparoscopy, and there was great heterogeneity in the way the groups were set up. Minimally invasive surgery should be reserved only in centers that might guarantee the possibility of complete cytoreduction when judged to

be feasible. The analyses of perioperative outcomes showed a decrease in morbidity with a reduction in the length of hospital stay with MIS. Although estimated blood loss could not be aggregated overall, the subgroups analyses showed a significant reduction of blood loss with MIS. No significant differences were observed for operative time, intraoperative complications and postoperative complications, even if the all grade complications analyses were at the borderline of significance (RR = 0.65, 95% CI 0.40–1.05, $p = 0.07$).

These findings must be interpreted in the context of several important caveats. First, no randomized clinical trials comparing MIS and OPS in ovarian cancer were identified, and so our meta-analysis included only observational studies, which were mostly retrospective. This can lead to the presence of potential bias. Therefore, conclusions should only be regarded as hypothetical conclusions and not as absolute truth. However, few publication biases were identified in our study. Second, in many of the studies included, the MIS and OPS cohorts differed with respect to prognostically important variables. The metaregression was adjusted for important prognostic factors, yet residual confounding cannot be excluded. Patients in the laparoscopy group often had fewer complex procedures, which could be an indirect expression of lower burden of disease. Unfortunately, we were not able to extract patient-level data regarding these variables, especially the surgical complexity. Biases in the individual studies might have affected the results of the meta-analysis. Should data of this type become available, a more robust analysis based on these variables could be performed.

5. Conclusions

Although the available studies are retrospective, and mostly carry a high risk for bias and confounding, an overwhelming consistency of the evidence suggests the likely effectiveness of MIS in selected cases of ovarian cancer, even in advanced stages. In light of the existing evidence, we further recommend that additional retrospective cohort trials will not contribute additional useful data. In order to validate this conclusion on the oncological safety of MIS, conducting a feasibility study followed by a randomized clinical trial should be a priority.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/8/2507/s1, Table S1: PRISMA 2009 checklist.

Author Contributions: Conceptualization, F.J. and C.A.; methodology, F.J.; software, F.J.; validation, E.F., T.B., L.L., and C.A.; formal analysis, F.J.; investigation, F.J and M.V.; resources, F.J. and M.V.; data curation, F.J.; writing—original draft preparation, F.J. and M.V.; writing—review and editing, E.F., T.B., L.L. and C.A.; visualization, E.F., T.B., L.L. and C.A.; supervision, C.A.; project administration, C.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Meta-Analysis for Recurrence

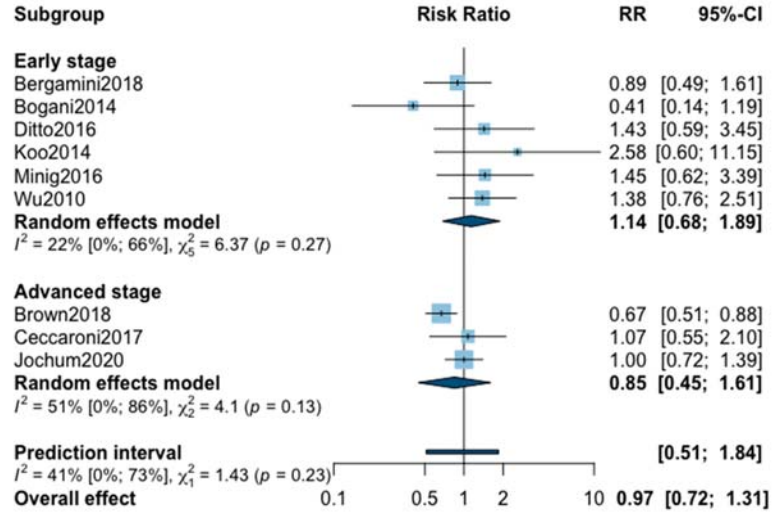

Figure A1. Meta-analysis for five-year recurrence.

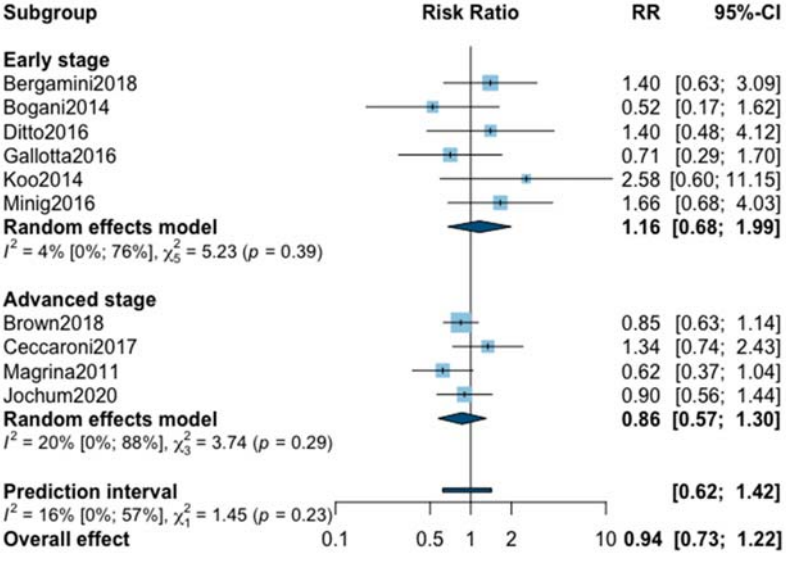

Figure A2. Meta-analysis for three-year recurrence.

Appendix B. Meta-Analysis for Perioperative Outcomes

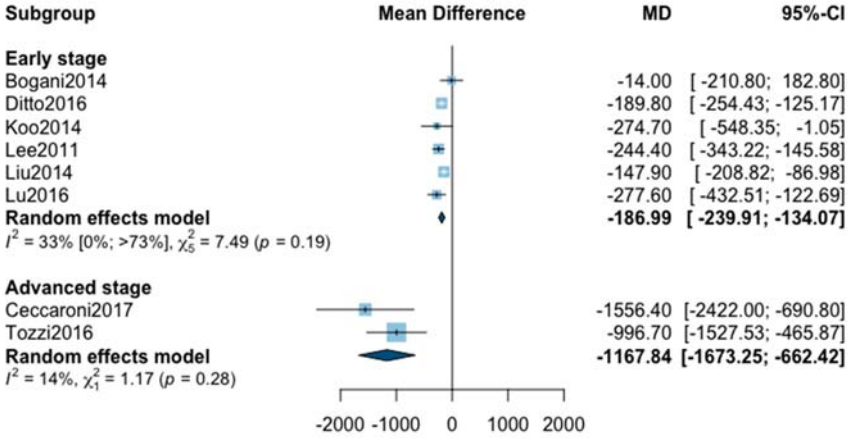

Figure A3. Meta-analysis for estimated blood loss.

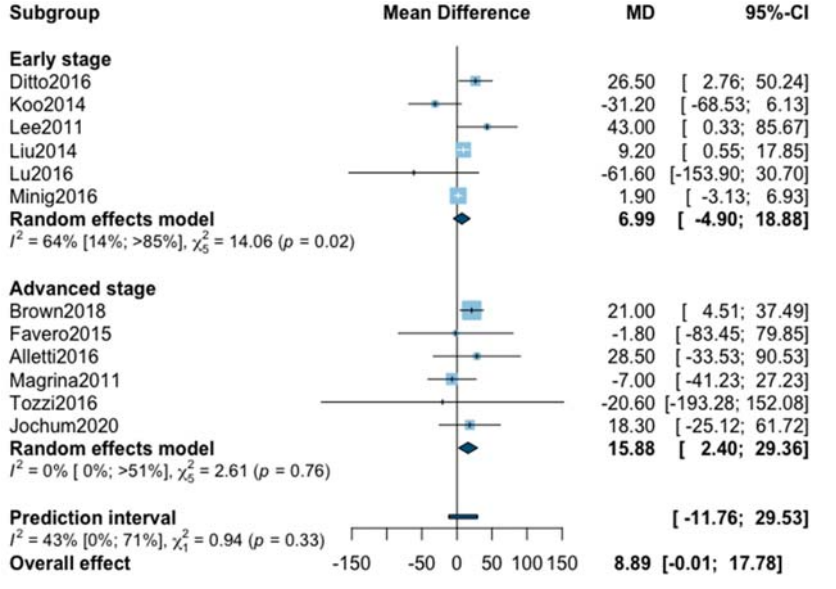

Figure A4. Meta-analysis for operative time.

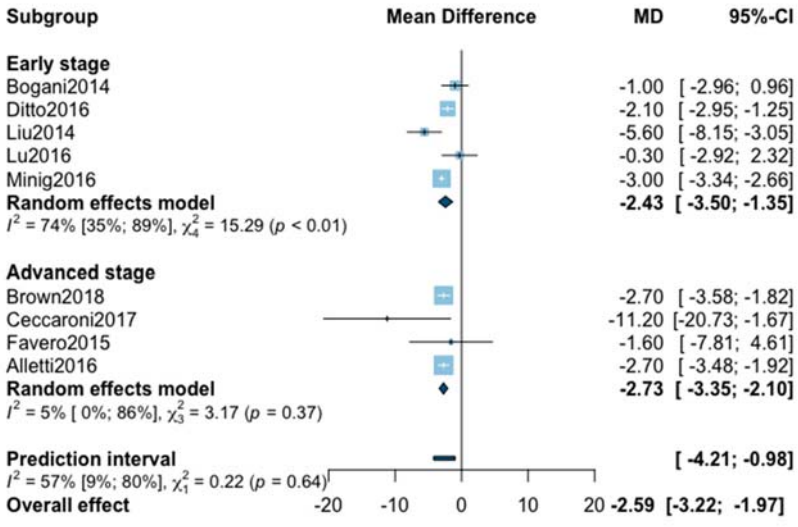

Figure A5. Meta-analysis for hospital stay.

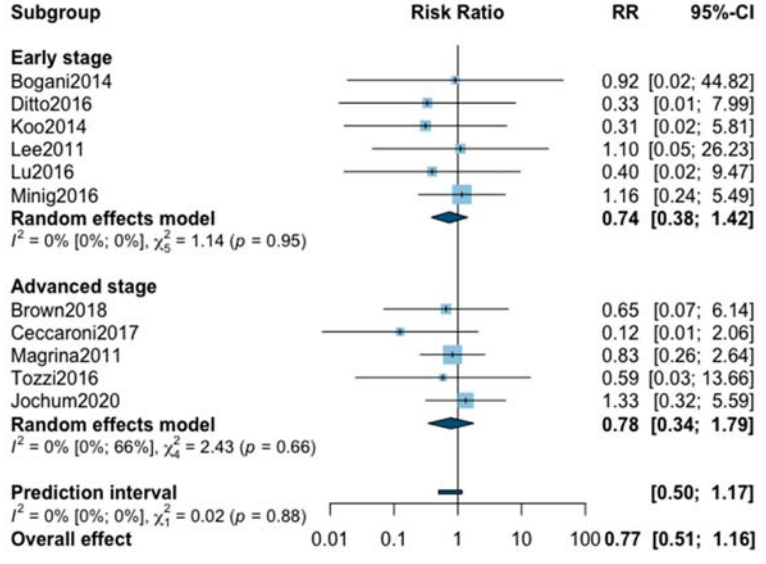

Figure A6. Meta-analysis for intraoperative complications.

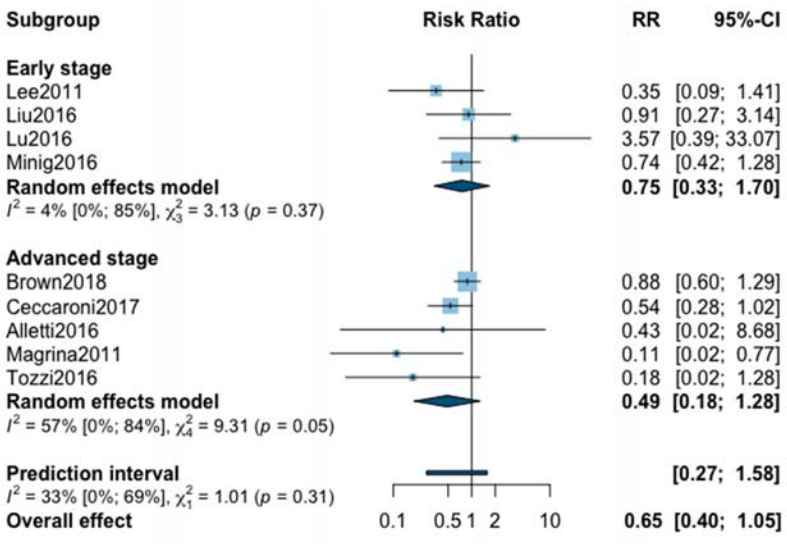

Figure A7. Meta-analysis for postoperative complications all grade.

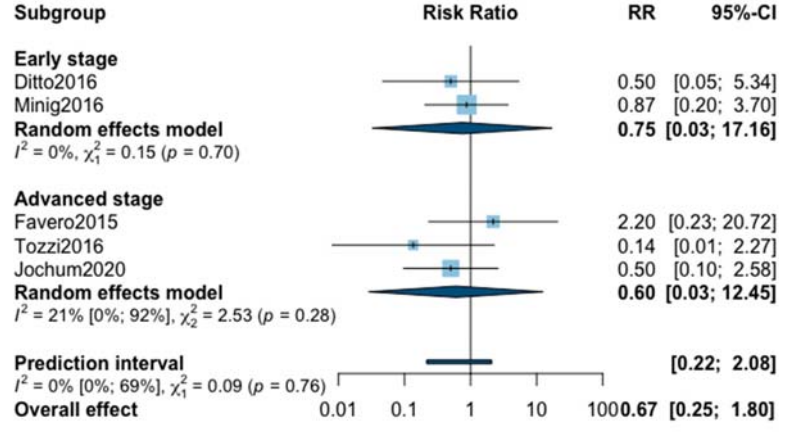

Figure A8. Meta-analysis for postoperative complications grade ≥ 3.

Appendix C.

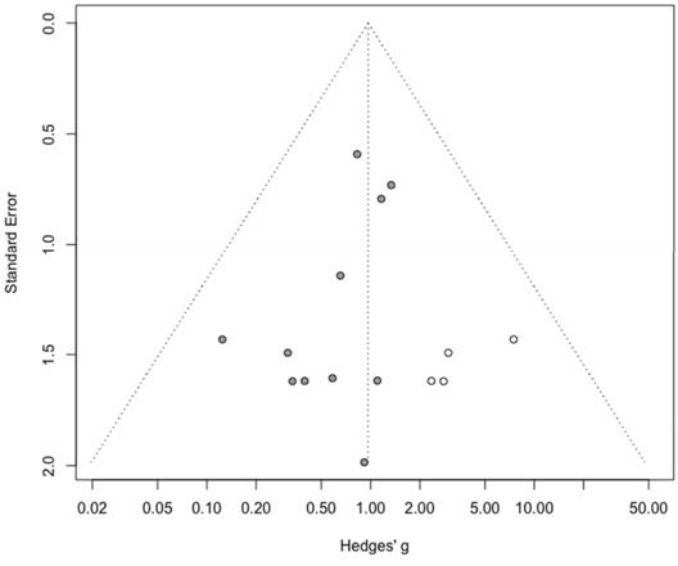

Figure A9. Corrected funnel plot for intraoperative complication outcome.

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Postoperative Telephone-Based Questionnaire on Quality of Life after Robotic-Assisted Laparoscopic Hysterectomy versus Conventional Total Laparoscopic Hysterectomy

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Abstract: *Aim*: The objective of the study was to evaluate the benefits of robotic-surgery for hysterectomy compared to conventional laparoscopy for benign indications. A specially prepared telephone-based questionnaire was used postoperatively. *Method*: All women (n = 155) undergoing total laparoscopic hysterectomy for benign indications either by the robotic-assisted procedure (RALH) or conventional laparoscopy (CL) between 1 January 2013 and 31 December 2017 at the Department of the Gynecology, University Hospitals, Campus Kiel, Germany, were eligible for analysis. Intra-operative and postoperative parameters affecting the patients' quality of life were assessed by a telephone-based questionnaire. The latter addressed postoperative pain, limitations of basic hygiene, daily activity, active pursuit of hobbies, sexual intercourse, and days of sick leave. All patients received the questionnaire by post at least three weeks prior to being contacted on the phone. *Results*: 78% of the contacted patients responded to the questionnaire; 96% (n = 115) of the patients said they would recommend the operation to other patients. Both groups needed 42 days to resume their regular hobbies. In whole 90.8% (n = 108) were total satisfied with the cosmetic result of the abdominal incision; the numbers in the respective groups were 80% (80% n = 36) in RALH and 97.3% (n = 72) in CL. The difference was significant on the Chi-square test (p = 0.002). 5% (n = 7) were dissatisfied with the scar (13.3%; n = 6) in the RALH group, and 1.4% (n = 1) in CL. In all 1.7 % of patients were dissatisfied with the position of the incisions; the respective numbers were 4.4 % (n = 2) in the RALH group and no patient in the CL group. 33% of patients experienced no limitations in regard of sexual intercourse after the operation. The median number of days taken to resume sexual intercourse after the operation was 56 days in the CL group, and 49 days in the RALH group. Nearly 30% (n = 25) were hesitant to resume intercourse. The median operating time was 145 min in the RALH group, which was significantly longer than the 117 min taken in the CL group ($p < 0.001$). *Conclusions*: The RALH procedure was associated with some minor advantages for the patients according to the results, however it does not have major significant advantages, especially in regard of early restoration of sexual function, while the CL shows shorter operating times and similar limitation. Postoperative counseling of patients should be aligned to their fears and expectations in regard of sexual function.

Keywords: robotic surgery; sexuality; laparoscopic hysterectomy; learning curve; quality of life; counseling; patient-doctor-relationship

1. Introduction

Hysterectomy is one of the most commonly performed surgical procedures in women. At all university hospitals in Germany, about 4338 hysterectomies were performed for benign indications in 2016.

Although hysterectomy is a standard treatment for gynecologic malignancies, many hysterectomies are performed for benign gynecologic disease [1]. In the last decade, a number of national trends have influenced surgical practices [2,3]. The rapid developments of the technology in the instruments and telemedicine have influenced the development of surgery. Vaginal hysterectomy has been performed for several decades. If feasible, it is still recommended as the treatment of choice by the German national guideline and the most recent Cochrane analysis [4]. Laparoscopically-assisted hysterectomy and conventional total laparoscopic hysterectomy (CL) have been used since the 1990s [5]. Minimally invasive surgical techniques are now used for many procedures. More recently, robotic assisted laparoscopic hysterectomy (RALH) has also become an established technique [6].

The potential benefits of robotic-assisted laparoscopic surgery include a larger range of motion with the instruments, three-dimensional stereoscopic visualization, and improved ergonomics during surgery [7]. Unlike procedures such as prostatectomy or colorectal surgery, for which robotic assistance is the sole alternative to the open approach, both laparoscopic and vaginal hysterectomies are widely performed without significant problems [8]. However, the benefits of robotic-assisted laparoscopic surgery are still not clearly established. In women with benign disease, RALH did improve outcomes, was associated with longer operating times and higher costs compared to hysterectomy by CL [9].

Prospective trials comparing CL with RALH have failed to demonstrate significant improvements in clinical outcomes in women with benign gynecologic disease [10,11]. Therefore, we conducted a telephone-based postoperative survey on quality of life and convalescence among patients undergoing RALH with a matched cohort with conventional total laparoscopic hysterectomy to assess the benefits of RALH in comparison to CL for benign indications. The purpose was to determine whether the variables addressed in the questionnaire play a significant role in the treatment choice based on a shared decision-making. Furthermore, we determined the patients' level of satisfaction with abdominal scars after RALH and their limitations in regard of sexual intercourse after surgery.

Objective

The objective was to compare peri- and postoperative outcomes, focusing on the patients' satisfaction with the treatment and their limitations, including: convalescence, sick leave, sexual intercourse, perioperative morbidity, postoperative pain, the number and positions of scars.

2. Method

All women undergoing total laparoscopic hysterectomy for benign indications by RALH between 1 January 2013 and 31 December 2017 at the Department of the Gynecology, University Hospitals, Campus Kiel, Germany, were eligible for analysis. Patients who underwent TLH by CL during the same period, matched for age, indication for hysterectomy, comorbidities, body mass index, uterine weight and histopathology, served as controls. The study was approved by the ethics committee of the University of Kiel (574/17). Written informed consent was obtained from all patients.

2.1. Design of Questionnaire

Postoperative parameters affecting the patients' quality of life were addressed in a postoperative telephone interview. The latter was focused on postoperative pain, limitations of basic hygiene, daily activities, active pursuit of hobbies, sexual intercourse, and days of sick leave.

The questionnaire (Appendix A) was designed on the basis of the following: (a) a validated German version of King's health questionnaire for assessing quality of life in women [12], (b) the EQ-5D (a standardized health-related quality of life questionnaire developed by the EuroQol Group

to provide a simple generic measure of health for clinical and economic appraisal) [13], and (c) the validated Female Sexual Function Index (FSFI; a brief multidimensional scale for assessing sexual function in women) [14].

Postoperative pain scores were recorded at one and four weeks after the operation. Pain was determined on a numeric rating scale (NRS) as recommended by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) [3]. Patients rated their pain on a scale from 0 to 10 (0 = no pain; 10 = worst imaginable pain). To avoid bias resulting from different cognitive levels, we used construct-specific questions for a satisfaction scale from 1 to 6 [15]; 1 indicated extreme satisfaction and 6 indicated dissatisfaction.

All patients received the questionnaire by post at least three weeks before they were contacted by phone; an appointment for the telephone interview was suggested in the questionnaire sent by post. We contacted 155 patients and received a reply from 122 (78.7%). Three patients were excluded due to the lack of ability to answer the questioner due to limited cognitive functions. The ethics committee to avoid any violation to the patient's privacy suggested a three weeks interval between the sending the mail and contacting the patients per telephone and we were only allowed to contact the patients per phone after receiving the written informed consent per Post.

2.2. Telephone Interview

Based on former QOL investigations of our study group [16], the telephone interview was designed as an interactive measure. Data published by the University of Heidelberg, Germany, showed that responses to an interactive interview are more explicit and critical, which makes the interview more suitable for quality control [17]. We minimized the influence of disruptive factors by conducting a standardized interview and avoiding any open conversation with the patient. To avoid any bias, the standardized telephone interviews were conducted by the same operator (SS).

2.3. Material

The study was designed to investigate parameters affecting the clinical outcome of RALH and CL, list the various indications for the procedures, the development of the procedures, compare complication rates and outcomes, and their association with the route of surgery.

Cases were also matched for the surgeon, who performed 56 operations by RALH and 99 by CL. The surgeon is a highly trained surgeon certified as MIC III surgeon for minimally invasive surgery held by the German society of gynecological laparoscopic surgery (*Arbeitsgemeinschaft Gynäkologische Endoskopie*, AGE). The surgeon who performed the procedures had attended a robotic training course and was then proctored by experienced robotic surgeons.

RALH was performed using the four-arm da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA). Patient data were entered into a Microsoft Excel database. The total operating times were derived from the operating theatre database for TLH by CL, and the da Vinci surgical procedure database for RALH. The total operating time included: (a) installation of the uterine manipulator; (b) 'skin-to-skin' operating time, defined as the time from the first skin incision to skin closure and (c) console time, defined as the time from the start of operating the console to de-docking of the surgical cart.

Intra- and postoperative complications until 20 weeks after surgery and the length of hospital stay were noted. The Clavien Dindo classification system for grading surgical complications was used [18]. Complications were further classified into intraoperative (urinary tract, gastrointestinal tract, vascular injury) and postoperative complications (revision, wound healing, thromboembolic events, mortality, systemic inflammatory response associated with fever, urinary tract infection, Clostridia infection, transient paresthesia, and hemoptysis).

2.4. Statistical Analysis

Data were entered on a spreadsheet in the computer. The IBM SPSS statistics program (IBM Corp IBM, NY, USA) was used to log and analyze the data. Professional statistical guidance was provided by the Medistat GmbH office. Differences between groups in regard of the analyzed parameters were subjected to statistical analysis. The following tests were used: (a) Chi-square test for the analysis of differences between two proportions, (b) T-test to determine the significance of differences between two proportions or percentages, and (c) The Mann-Whitney U-test and Wilcoxon's signed rank test to compare one quantitative value between two groups of patients. Demographic and surgical data were analyzed by analysis of variance (ANOVA), Kruskal-Wallis, Chi-square, or Fisher's test. A p value less than 0.05 was considered statistically significant. We also used the Lilliefors significance correlation when a significant correlation R-value of more than 0.2 was considered to be statistically correlated.

3. Results

3.1. Patient Characteristics

One-hundred and fifty-five women underwent hysterectomy during the study period. Ninety-nine women had a conventional total laparoscopic hysterectomy (CL) and 56 underwent a robotic-assisted laparoscopic hysterectomy (RALH).

Indications for surgery were the following in the CL and RALH groups: uterine myomas in 43 (43.4%) and 28 (50%) patients, respectively; premalignant lesions such as diffuse hyperplasia of the endometrium and intracervial neoplasia in 26 (26.3%) and nine (16.1%) patients, respectively; endometriosis in 17 (17%) and 13 (23.2%) patients, respectively; abnormal uterine bleeding in nine (9.1%) and six (10.7%) patients, respectively; and other indications such as completed family planning, carcinophobia and transgender transformation in four (4.9%) and one (1.8%) patients, respectively.

The main indications for TLH by CL and RALH were similar; no statistical difference was noted between groups. The same was true of the patients' age and body mass index. We registered concomitant gynecologic procedures, including adhesiolysis, salpingo-oophorectomy, ureterolysis, endometriosis resection, and others such as filling the bladder with colored dye, suturing the bladder wall, suturing the serosa of the intestine, cyst enucleation, adhesion prophylaxis, transient abdominal ovariopexy, and colposuspension. Demographic data and indications for surgery are summarized in Table 1.

Table 1. Characteristics of the study population, indications and complications by the hysterectomy operation.

Characteristics	CL (n = 99)	RALH (n = 56)	p-Value
Age (years), Mean	49,00	49.09	
Median (range)	47.0 (42.0–54.0)	47.0 (43.0–52.0)	0.907
BMI (kg/m^2), Mean	27.78	29.53	
Median (range)	26.66 (22.65–32.42)	27.71 (24.16–31.98)	0.265
Operative time (min.), Mean	162.73	131.31	
Lenghts of stay (nights), Mean	4.44	4.13	
Median (range)	4.0 (3.0–5.0)	4.0 (4.0–4.0)	0.514
Uterine weight (g), Mean	210.14	185.64	
Median (range)	150.0 (86.0–262.0)	141.0 (94.0–206.25)	0.804
Indications			
benign, n (%)	73 (73.3%)	48 (85.7%)	0.083
leiomyomas, n (%)	43 (43.4%)	28 (50.0%)	0.431
gynecologic (pre)cancer, n (%)	26 (26.3%)	9 (16.1%)	0.145
abnormal bleeding, n (%)	9 (9.1%)	6 (10.7%)	0.743
endometriosis, n (%)	17 (17.2%)	13 (23.2%)	0.36
other indications, n (%)	4 (4.0%)	1 (1.8%)	0.654

3.2. Operating Time

The median operating time was significantly longer in the RAHL group (145 min) than in the CL group (117 min) ($p < 0.001$). The operating time for RALH fell markedly in 2016: 132.50 min was the shortest operating time registered for RALH during the study. The median time taken to perform CL in 2016 was 159.00 min (Figure 1).

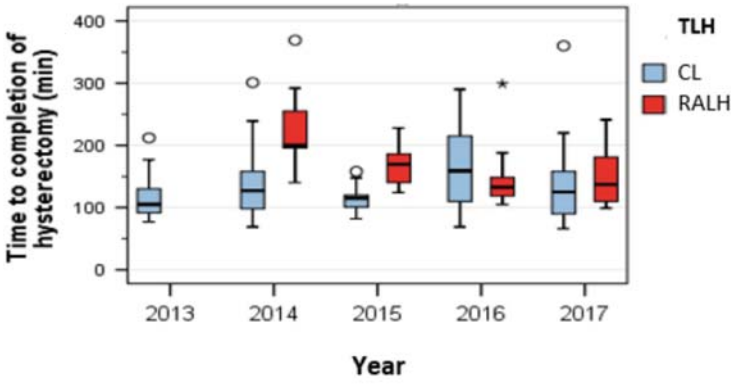

Figure 1. Operating times during the study: the shortest operating time for RALH was noted in 2016.

3.3. Learning Curve

In the RALH group we noted a significant fall in median operating time after the first 30 cases (Figure 2). The mean operating time fell by 38.5 min from 168 min (cases 1–30) to 129.50 min (cases 30–56).

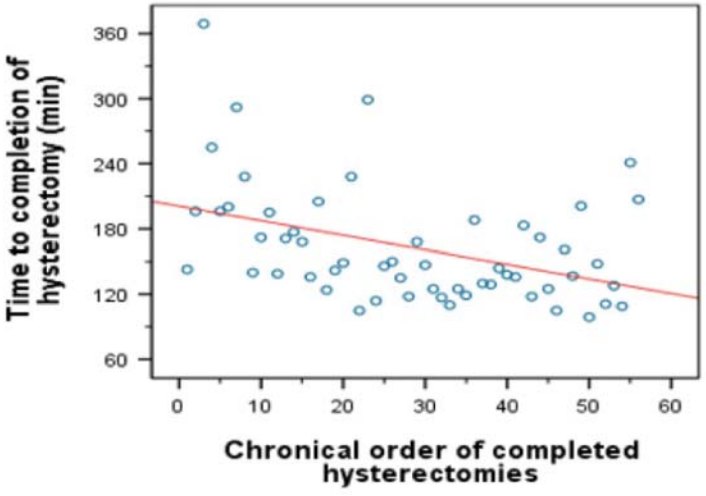

Figure 2. Linear regression for operating time.

Linear regression showed a significant reduction until case number 30 ($p = 0.012$), and no regression thereafter ($p = 0.108$) (Figure 3). No notable learning curve was observed for conventional laparoscopy because the surgeon had performed more than 1.000 surgical laparoscopies before the investigation was started.

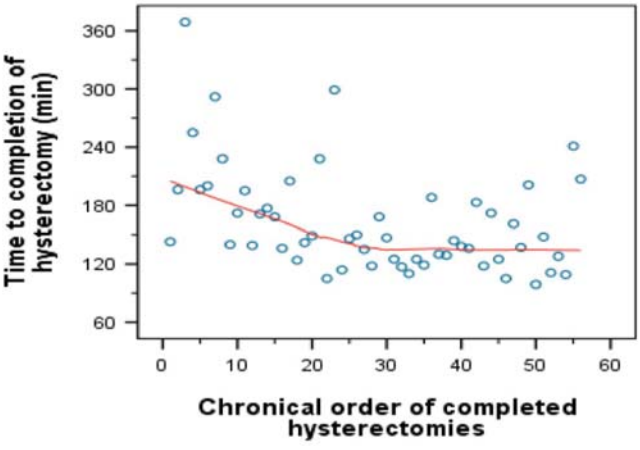

Figure 3. The linear regression for operating time according to Loess.

3.4. Intra- and Postoperative Complications

Two patients in the RALH group and four patients in the CL group sustained iatrogenic bladder injuries ($p > 0.999$). Although there was no significant difference between groups, the total number of bladder injuries was rather high; this was due to the presence of dense pelvic adhesions in these cases. One patient experienced an iatrogenic intestinal injury in the RALH group and three in the CL group. Vascular injury in the CL group was due to the umbilical trocar entry site, and vaginal bleeding occurred in the RALH group. However, hemostasis was achieved immediately. Intraoperative blood loss did not differ between groups, and no patient required a transfusion (Table 2). A conversion to laparotomy was not performed in either group.

Table 2. Intraoperative and postoperative complications.

Complications Number (%)	**CL 15 (15.2%)**	**RALH 12 (21.4%)**	***p*-Value 0.322**
Intraoperative	8 (8.1%)	5 (8.9%)	0.999
Injuries of the urinary tract, *n* (%)	4 (4.0%)	2 (3.6%)	>0.999
Injuries of the gastrointestinal tract, *n* (%)	3 (3.0%)	1 (1.8%)	>0.999
Vascular injuries, *n* (%)	1 (1.0%)	3 (5.4%)	0.135
Other complications, *n* (%)	1 (1.0%)	0	>0.999
Postoperative	8 (8.1%)	9 (16.1%)	0.126
Revision surgery, *n* (%)	2 (2.0%)	1 (1.8%)	>0.999
Wound complications, *n* (%)	2 (2.0%)	2 (3.6%)	0.62
Thromboembolic complications, *n* (%)	0	1 (1.8%)	0.361
Mortality, *n* (%)	0	0	>0.999
Other complications, *n* (%)	5 (5.1%)	5 (8.9%)	0.497

According to the Clavien-Dindo classification, two first-grade complications occurred in the CL group and five first-grade complications in the RALH group. Of second-grade complications, five were recorded in the CL group, and three in the RALH group. Of third-grade complications, 11 occurred in the CL group and seven in the RALH group.

Postoperatively only one patient in the RALH group needed a revision in the operating room due to the formation of an abscess at the site of vaginal closure. Two patients in the CL group required a revision: one due to acute peritonitis as a result of iatrogenic intestinal injury, and the second as a result of abscess formation at the site of vaginal closure.

Fever was registered in six patients due to various reasons such as urinary tract infection, Clostridium difficile infection, or unknown causes. Paresthesia was recorded in two patients of the RALH group due to the long operating time and probably unsuitable positioning of the patients.

3.5. Length of Hospital Stay, Pain Scores, and Postoperative Intake of Painkillers

The mean duration of the patients' hospital stay was 4.44 days (SD 3.214) in the RALH group and 4.13 days (SD 1.096) in the CL group. The mean postoperative pain score at one and four weeks after the operation were similar in the two groups: 3.26 (SD 2.809) and 1.19 (SD 1.733) in the CL group, and 2.73 (SD 2.136) and 1.11 (SD 1.385) in the RALH group, respectively.

Both groups consumed oral non-steroidal anti-inflammatory drugs for a similar period of time (median 4.00 days). No statistically significant difference was noted between groups with regard to any of these outcomes (Table 3).

Table 3. Postoperative pain scores and intake of painkillers.

Postoperative	CL	RALH	*p*-Value
Pain score at week 1 (mean)	3.26 (SD 2.809)	2.73 (SD 2.136)	
Median (range)	3.00 (0.75–5.00)	3.00 (1.00–4.00)	0.519
Pain score- week 4 (mean)	1.19 (SD 1.733)	1.11 (SD 1.385)	
Median (range)	0.00 (0.00–2.00)	1.00 (0.00–2.00)	0.693
Intake of painkillers (days) (mean)	11.92 (SD 43.043)	8.44 (SD 10.874)	
Median (range)	4.00 (1.00–7.00)	4.00 (2.50–7.00)	0.471

3.6. Postoperative Satisfaction and Dissatisfaction

Ninety-six percent (n = 115) of the patients would recommend the operation to others under similar circumstances; RALH fared slightly better (100% n = 45) than CL (94.6% n = 70) in this regard. On a satisfaction score, 68% (n = 81) of all patients were highly satisfied with the treatment while 23.5% percent (n = 28) were satisfied. Six percent were moderately satisfied and one patient (0.8%) was dissatisfied. Seventy percent (n = 52) and 64% (n = 29) were highly satisfied in the CL and RALH groups, respectively. No significant differences between groups were noted with regard to any of these outcomes (Table 4).

Table 4. Patient's satisfaction-score with the outcome of the treatment based on a construct-specific satisfaction scale from 1 to 6; 1 indicated extreme satisfaction and 6 indicated dissatisfaction.

			Surgical Procedure		Total
			CL	RALH	
Satisfaction with the outcome of treatment	1	Number (Percentage)	52 (70.3%)	29 (64.4%)	81 (68.1%)
	2	Number (Percentage)	15 (20.3%)	13 (28.9%)	28 (23.5%)
	3	Number (Percentage)	5 (6.8%)	3 (6.7%)	8 (6.7%)
	4	Number (Percentage)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	5	Number (Percentage)	1 (1.4%)	0 (0.0%)	1 (0.8%)
	6	Number (Percentage)	1 (1.4%)	0 (0.0%)	1 (0.8%)
Total		Number (Percentage)	74 (100.0%)	45 (100.0%)	119 (100.0%)
Statistical test		Chi-square test			0.823

3.7. Dissatisfaction with the Abdominal Incision

In whole 90.8% (n = 108) were total satisfied with the cosmetic result of the abdominal incision; the numbers in the respective groups were 80% (80% n = 36) in RALH and 97.3% (n = 72) in CL. The difference was significant on the Chi-square test (p = 0.002).

The detailed interview with the patients showed that 5.9% (n = 7) were dissatisfied with the scar; this was true of 13.3% (n = 6) in the RALH group and 1.4% (n = 1) in the CL group. The position of the incisions was a source of dissatisfaction for 1.7% (n = 2), which was true of 4% (n = 2) in the RALH group and no patient in the CL group (Table 5).

Table 5. Satisfaction- and dissatisfaction- score with the abdominal incision.

			Surgical Procedure		Total	Statistical Test
			CL	RALH		Chi-Square Test
Total satisfaction		Number (Percentage)	72 (97.3%)	36 (80.0%)	108 (90.8%)	
Main cause of cosmetic dissatisfaction	Position of the incisions	Number (Percentage)	0 (0.0%)	2 (4.4%)	2 (1.7%)	0.002
	Number of scars	Number (Percentage)	0 (0.0%)	1 (2.2%)	1 (0.8%)	
	Scar	Number (Percentage)	1 (1.4%)	6 (13.3%)	7 (5.9%)	
	Painful/sensitive scars	Number (Percentage)	1 (1.4%)	0 (0.0%)	1 (0.8%)	
Total		Number (Percentage)	74 (100.0%)	45 (100.0%)	119 (100.0%)	

3.8. Limitation of Sexual Intercourse

Only 33% (n = 28) experienced no limitation of sexual intercourse after the operation. The two groups needed a similar period of time to resume sexual intercourse after the operation; the median time was 56 days for CL and 49 days for RALH.

Nearly 30% (29.8% n = 25) were afraid to resume intercourse after the operation; no percentile difference was noted between groups. Pain was reported as a limitation by 22.6% (n = 19) in both groups. RALH was slightly superior to CL in regard of pain during sexual intercourse (15.2% n = 5, and 27.4% n = 14, respectively) (Figure 4).

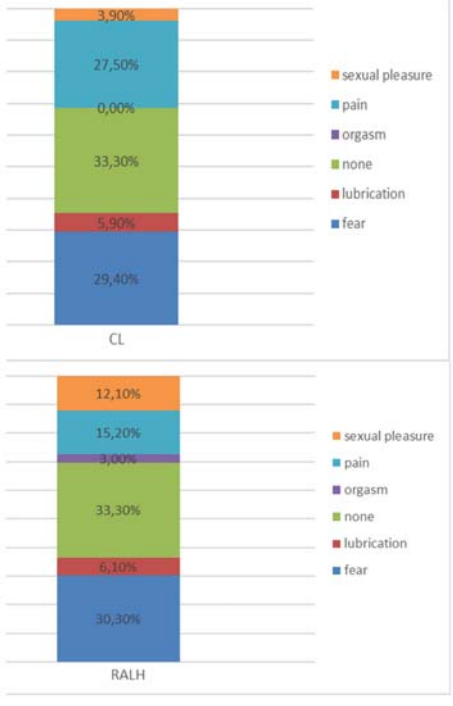

Figure 4. Limitation of sexual intercourse after the operation. Fear and pain were the most frequent limitations.

3.9. Convalescence

The median number of days before starting to work after the operation was 42 days in both groups. The same numbers of days were needed by both groups to resume their hobbies. No statistical significance was noted between groups.

4. Discussion

The two groups investigated in the present study were similar in regard of age, body mass index, and indications for surgery. We also observed no significant differences in postoperative pain, the use of painkillers, intraoperative and postoperative complications.

We focused our analysis on clinical factors rather than economic aspects of the operation. The cohort studies published by Rosero and Wright report similar morbidity profiles for laparoscopic and robotic-assisted hysterectomy, with slightly higher costs for the latter procedure. However, other factors such as body mass index, uterine weight, and previous abdominal surgery were not addressed in earlier studies [19,20].

We maintained a three-week interval between sending the questionnaires and contacting patients on the phone for the interview. To minimize the possibility of patients trying to please the surgical team, the person conducting the telephone interview was not a member of the department.

The present study revealed that 20% of patients were dissatisfied with the abdominal incision in the RALH group, and a mere 2.7% in the CL group. This was most likely due to the rigidity of the RALH trocars compared to the disposable trocar used for CL. We conclude that greater attention should be given to counseling patients about the number of the scars and their positions. It might be feasible to develop a single incision port for robotic surgery and use a limited number of trocars.

Quality of life parameters such as pain scores at 1 and 4 weeks postoperatively, the period of taking painkillers, and the duration of convalescence were similar in the two groups. This concurs with a meta-analysis of prospective trials [21]. The question as to whether the patients would recommend the operation to others yielded a score of 100% for RALH and 94.6% for CL.

Difficulties in resuming sexual intercourse after the operation were experienced by 66.7% of our patients. Anxiety about resuming sexual intercourse was experienced by 30% in both groups. The time period from surgery to the resumption of sexual intercourse was four months. We conclude that patients should be counseled in detail about this aspect postoperatively. Recent studies published by Berlit show that the patients' expectations concerning sexual function appear to influence postoperative outcomes. Therefore, this aspect as well as other personal factors should be considered when counseling patients [22,23].

Less invasive surgical methods of hysterectomy, such as those by the vaginal and laparoscopic approach tend to have a less destructive effect on sexual function [24]. Ercan suggested that, probably because of the positive effects of less invasive procedures on the patients' self-esteem and quality of life, the procedures may be associated with no visible abdominal scar and a shorter recovery period [24]. Bastu and co-workers studied patients who underwent laparoscopic hysterectomy and those who underwent vaginal cuff closure; the authors found that although sexual function did not differ significantly preoperatively and three months postoperatively, vaginal lengths were significantly longer in the laparoscopic group [25]. In 2014 De La Cruz published a comparison of 38 total vaginal hysterectomies and 46 robotic hysterectomies, both of which were accompanied by pelvic support surgery, with regard to vaginal length and postoperative sexual functions. The authors registered no difference in sexual function, but a greater reduction in vaginal length after vaginal hysterectomy [26]. Therefore, when planning a laparoscopic hysterectomy, it would be advisable to opt for the laparoscopic cuff closure technique rather than the vaginal route in order to preserve vaginal length, to avoid alterations in the female sexual function [27].

In our study population, the median operating time was significantly longer in patients undergoing RALH compared to CL. This agrees with a Cochrane review published by Lawrie, which reported observational data on robotic-assisted and laparoscopic hysterectomy; operating times of about 1 to

2.5 h were noted for CL, and 3 h for RALH [4]. However, recently Lönnerfors registered data at university hospitals in Sweden and reported similar operating times for CL and RALH; the procedures were performed by a highly experienced robotic surgeon [28].

A variety of methods have been used in published studies to record operating time and operating theater time. One of disadvantages of our study is the absence of a mandatory log for all robotic cases, which calls for the documentation of port placement, docking and de-docking of the robot, and console time. We registered the time taken from the insertion of the uterine manipulator until final closure of the abdominal incision for both procedures. As this encompassed the entire operating time, we believe this parameter did not affect the outcome.

According to Lenihan, the learning curve for robotic-assisted surgery depends on setup time, console time, and the number of cases needed to stabilize a surgeon's operating time; about 50 cases are deemed necessary for this purpose [29]. Regardless of individual variables, the total time needed for each procedure remains the point of maximum interest.

We were able to achieve a plateau in the learning after 30 cases. After 30 cases, the surgeon needed 133.74 min for the procedure. Our findings are consistent with a similar retrospective study comprising 45 patients with benign indication [30], and two further retrospective studies in which a significant improvement in operating time was noted after 20 robotic-assisted cases [31,32]. The fact that we were unable to achieve a plateau shortly before 30 cases was probably due to the presence of diverse surgical staff members at the beginning of the operation. The initial setup time in robotic surgery takes longer than the conventional laparoscopic approach, which can largely be overcome by adhering to a consistent and committed team of staff members in the operating room.

The shared decision for the route of the hysterectomy is influenced by various factors, including the indication of hysterectomy, adequate consultation of patients, and the surgeon's level of training. Vaginal hysterectomy is primarily performed in conjunction with surgery to treat prolapse-disorders. The rate of vaginal hysterectomy in the United States decreased from 22% in 2003 to 19% in 2009–2010, which coincides with the introduction of robotic-assisted surgery [19,33].

Despite guidelines supporting the use of minimally invasive hysterectomy procedures, benign gynecological disease is still most commonly managed via laparotomy [19]. Our analysis suggests that, over a 4-year period, robotically assisted hysterectomy was used increasingly often for benign gynecologic disease.

Position statements from various associations of gynecological laparoscopy have not clearly endorsed the role of robotic assistance in laparoscopic hysterectomy. Further data will be needed to determine the most appropriate evidence-based applications of this technology for the treatment of benign disease.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

I. Questionnaire

The table presents the questionnaire sent to the study population.

German speaking community	English speaking community
(1) Zum Zeitpunkt der OP waren Sie: verheiratet☐ in einer festen Beziehung☐ ledig☐ verwitwet☐ ?	(1) What was your relationship status at the time of the operation? Married- in a committed relationship- single- widowed
(2) Wie war Ihr Zustand zum Zeitpunkt der OP? Waren Sie: Noch nicht in den Wechseljahren☐ in den Wechseljahren☐ durch die Wechseljahre durch☐?	(2) What was your hormone status at the time of the operation? Premenopausal Perimenopausal Post menopausal
(3) Wie lange waren Sie krankgeschrieben nach der Gebärmutterentfernung? Tage_____	(3) How long were you on sick leave after hysterectomy? Days: _____
(4) Auf einer Skala von 1-6, wobei analog zum Schulnotensystem, hier 1 = sehr zufrieden/bestmögliche Zufriedenheit und 6 = sehr unzufrieden/überhaupt keine Zufriedenheit, bedeutet: Wie zufrieden sind Sie dann mit dem Behandlungsergebnis der OP insgesamt? Skala: ☺ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ ☹	(4) How satisfied are you with the result of the hospital treatment all in all? On a scale from 1–6, whereby analogous to the German school grading system, here 1 means = very satisfied/best possible satisfaction and 6 means = very dissatisfied/no satisfaction at all: Scale☺ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ ☹
(5) Würden Sie diese Operation unter den gleichen Umständen weiterempfehlen? Ja☐ Nein☐	(5) In the same circumstances, would you recommend this surgery to others? Yes No
(6) Auf einer Skala von 0–10, wobei hier 0 = keine Schmerzen, 10 = stärkste vorstellbare Schmerzen bedeutet, Wie waren die Schmerzen nach der Operation im Abstand nach: 6a) Ca. 1 Woche? Skala: ☺ 0 ☐ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ ☹ 6b) Ca. 4 Wochen? Skala: ☺ 0 ☐ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ ☹	(6) How was the pain after surgery? On a scale of 0–10, 0 means = no pain, 10 means = strongest imaginable pain 6a) After 1 week: Scale: ☺ 0 ☐ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ ☹ 6b) After 4 weeks: Scale ☺ 0 ☐ 1 ☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ ☹
(7) Wie lange haben Sie Schmerzmittel nach der OP eingenommen? In Wochen:_____	(7) How many weeks did you take pain medication after the operation?
(8) Wie schnell nach der OP sind Sie zum Alltag zurückgekehrt? Das heißt.: (8a) Wie viele Tage brauchten Sie Hilfe beim Anziehen, Waschen oder Benutzen der Toilette? (8b) Wie viele Tage waren Sie bei den tagtäglichen Beschäftigungen im Haushalt eingeschränkt? (8c) Wie viele Tage waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen, inklusive Sport, eingeschränkt?	(8) How quickly did you return to everyday life after the operation? Specifically, we wanted to know: (8a) How many days did you need help getting dressed, washing or using the toilet? (8b) How many days were you restricted from daily activities in the household? (8c) How many days were you restricted in your hobbies or other leisure activities, including sports?

(9) Wenn Sie in einer festen Partnerschaft zum Zeitpunkt der OP waren:	(9) If you were in a permanent partnership at the time of the operation:
(9a) Nach wie vielen Tagen/Wochen hatten Sie wieder Geschlechtsverkehr?	(9a) After how many days/weeks did you have sexual intercourse again?
(9b) Wie viele Tage/Wochen waren Sie beim Geschlechtsverkehr, nachdem Sie wieder damit begonnen hatten, eingeschränkt?	(9b) How many days/weeks were you restricted in sexual intercourse after starting again?
(9c) Was war am ehesten der Grund für die Einschränkung beim Geschlechtsverkehr? ☐ Schmerzen ☐ sexuelle Lust ☐ Lubrikation (Feuchte) ☐ Orgasmus ☐Angst	(9c) What was most likely the reason for the restriction in sexual intercourse? pain sexual pleasure lubrication (moisture) orgasm fear
(10) Sind Sie mit dem kosmetischen Ergebnis der Operation zufrieden? Ja☐ Nein☐	(10) Are you satisfied with the cosmetic result of the operation? Yes No
(10a) Wenn nein: Was ist am ehesten die Ursache der Unzufriedenheit? Ort der Narben☐ Anzahl der Narben☐ die Länge der Narben☐ Beschaffenheit der Narben☐ Schmerzhafte/empfindliche Narben☐	(10a) If not: What is most likely cause of the dissatisfaction? Location of scars number of scars length of scars Nature of the scars Painful/sensitive scars

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Management of a Thin Endometrium by Hysteroscopic Instillation of Platelet-Rich Plasma Into The Endomyometrial Junction: A Pilot Study

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Abstract: In patients whose embryo transfer has been previously canceled due to a thin endometrium, the injection of platelet-rich plasma (PRP) guided by hysteroscopy into the endomyometrial junction improves endometrial thickness and vascularity. This may well serve as a novel approach for the management of these patients. In this study, 32 patients aged between 27 and 39 years, suffering from primary or secondary infertility, were selected for hysteroscopic instillation of PRP. This cross-sectional study included a retrospective assessment of the improvement of endometrial thickness (>7 mm) on the commencement of progesterone treatment in 24 of 32 patients (75%) after hysteroscopy-guided injections of PRP into the subendometrial zone. After PRP instillation, the endometrium was 7 mm or thicker in 24 of 32 patients, and all 24 patients underwent frozen embryo transfer. Moreover, 12 of 24 patients who underwent embryo transfer conceived, whereas 10 had a clinical pregnancy with visualization of cardiac activity at 6 weeks and two had a biochemical pregnancy. Our approach of PRP injection into the subendometrial region is consistent with the histologically proven regeneration of the endometrium from the endomyometrial junction. We observed an improvement of endometrial thickness and higher pregnancy rates in cases of previously canceled embryo transfer due to a thin endometrium.

Keywords: platelet-rich plasma (PRP); thin endometrium; hysteroscopy

1. Introduction

The optimal endometrial thickness for embryo transfer is assumed to be about 7 mm or more [1–3]. A thin endometrium has been identified as an important factor in implantation failure [4–6] because it is marked by high blood flow impedance of radial arteries of the uterine vasculature, poor epithelial growth, reduced expression of vascular endothelial growth factor (VEGF), and poor vascular development [7]. Various studies have shown the improvement of endometrial thickness with the use of prolonged estradiol valerate, aspirin, sildenafil citrate, L-arginine, and pentoxifylline, but no consensus has been achieved yet in this regard [8–10]. Intrauterine infusion of granulocyte colony-stimulating factor (G-CSF) is also not effective [11]. Some studies have shown better endometrial thickness (ET) after intrauterine platelet-rich plasma (PRP) [3], which prompted us to use this novel approach in patients who were unresponsive to the aforementioned modalities.

The uterus with its endometrium undergoes cyclical processes of regeneration, differentiation and shedding as part of the menstrual cycle [12]. The endometrium has an enormous ability to regenerate throughout the reproductive life: whether after births, curettage, or in menopausal women

starting hormone replacement therapy, in most cases a proliferation of the endometrium under the influence of estrogen is observed. Stem or progenitor cells seem to be responsible for this regeneration process. The contribution of stem cells to endometrial regeneration was first described in 2004 [13,14]. Both progenitor cells within the endometrium and multipotent cells from bone marrow were shown to contribute to endometrial growth [15]. Evidence for the existence of adult stem and progenitor cells in human and mouse endometrium is becoming visible because functional stem cell assays are being applied to uterine cells and tissues [12]. CD140b+, CD146+, or SUSD2+ endometrial mesenchymal stem cells (eMSCs) and N-cadherin+ endometrial epithelial progenitor cells (eEPs) are just a few examples concerning types of stem/progenitor cells that have been identified [16].

Hysteroscopic instillation of PRP in the subendometrial region is a novel approach for the management of a refractory endometrium. PRP is autologous plasma derived from fresh whole blood enriched with platelets. It is prepared by collecting blood from peripheral veins and contains several growth factors such as VEGF, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and other cytokines that stimulate proliferation and growth [3,17]. In the endometrium, angiogenesis is a critical prerequisite for endometrial growth after menstruation and the achievement of a vascularized receptive endometrium for implantation [18–20]. A number of studies have shown that VEGF is expressed in the human endometrium and regulates vascularization at this site [7]. PRP, owing to its high content of growth factors, contributes to the improvement of endometrial thickness.

2. Materials and Methods

In this study, 32 women aged 27 to 39 years, suffering from primary or secondary infertility, were selected for hysteroscopic instillation of PRP at the Morpheus Bliss Fertility Center, Pune, India. There were three patients with one living child and secondary infertility, five patients with previous history of abortions, and 24 patients with primary infertility. The study was performed over a period of 14 months from July 2018 to September 2019. Day three transfers as well as blastocyst transfers were included. The objective of the study was to evaluate whether PRP injection into the endomyometrial junction, guided by hysteroscopy, improves endometrial thickness and vascularity in cases of previously canceled embryo transfer due to a thin endometrium.

Endometrial and sub-endometrial blood flow was measured with a color doppler in the2D mode on a transvaginal scan using a GE Voluson S6 machine. Endometrial blood flow was detected by intra endometrial or the adjacent subendometrial region within 10 mm of echogenic endometrial borders. The patients where both endometrial and sub endometrial blood flow was detected after the instillation of PRP had an improved blood flow to the endometrium. Previous to the instillation of PRP, no visible endometrial/subendometrial blood flow was detected.

2.1. Inclusion Criteria

1. Patients in whom an embryo transfer had been canceled in previous cycles due to a thin endometrium (<7 mm), despite estrogen supplementation in increasing doses, intrauterine PRP instillation, intrauterine G-CSF, etc.

2. 7 patients in addition had PRP instilled intrauterine but did not show adequate improvement in the endometrial thickness; hence, embryo transfer was cancelled.

3. 13 patients in addition to estrogen supplementation had G-CSF instilled intrauterine but did not show adequate improvement in the endometrial thickness; hence, embryo transfer was cancelled.

4. Patients undergoing frozen embryo transfer cycles.

5. Women with a normal transvaginal ultrasound and no evidence of a clinically significant abnormality in the uterus or adnexa.

6. Negative acid fast bacillus (AFB) culture for genital tuberculosis.

The primary outcome was defined as an endometrial thickness of >7 mm on commencement of progesterone, resulting in an embryo transfer. The secondary outcome was a positive beta-hCG level and clinical proof of pregnancy.

Autologous platelet-rich plasma (A-PRP) is a preparation that contains a high concentration of platelet growth factors, well above normal levels in blood. A-PRP is developed from autologous blood and is therefore inherently safe and free of transmissible diseases, such as HIV or hepatitis. The concentration of platelets in PRP delivers a large number of growth factors in biologically determined ratios, which distinguishes this substance from recombinant growth factor. PRP contains platelet and growth factor in levels ranging from 80% to 98%, and has been extensively used to improve tissue repair and hair growth.

2.2. Methods for PRP Preparation

Eight mL of the patient's blood was taken in a PRP tube (GeoPRP kit -US-FDA approved regenlab PRP Kit). The tube was shaken thoroughly and the contents were centrifuged at 3600 rpm for 6 min. The tube was then shaken upside down 20 times for homogenization, and the supernatant PRP collected with an 18 G needle.

2.3. PRP Injection

All patients were instructed to take oral contraceptive pills (OCPs) once daily for 21 days in a previous cycle. Next, 3.75 mg of leuprolide acetate was administered by the intramuscular route to all patients on day 16 of OCP intake for down-regulation of gonadotropins (Figure 1).

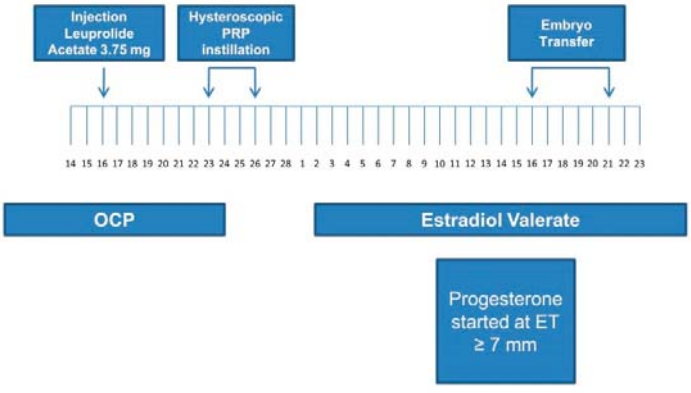

Figure 1. Preparation and procedure of the platelet-rich plasma instillation. OCP: oral contraceptive pills; PRP: platelet-rich plasma; ET: endometrium thickness.

All patients underwent hysteroscopic instillation of PRP in the subendometrial region 7–10 days after the injection of leuprolide (Figure 1).

A total of 4 mL of PRP was injected with an ovum pickup needle into the subendometrial region in all four walls of the cavity (1.0 mL in each wall) under hysteroscopic guidance. Optimum instillation was ensured by keeping the beveled edge of the ovum pickup (OPU) needle facing the cavity in slanting position (Figures 2–4).

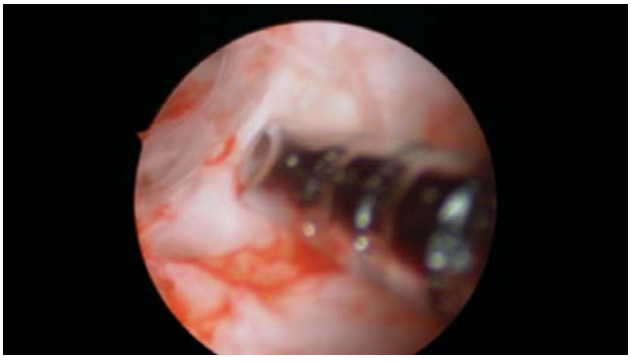

Figure 2. Hysteroscopic instillation of PRP, the beveled edge of the ovum. pick up needle is oriented towards the uterine cavity in order to determine the exact depth of insertion.

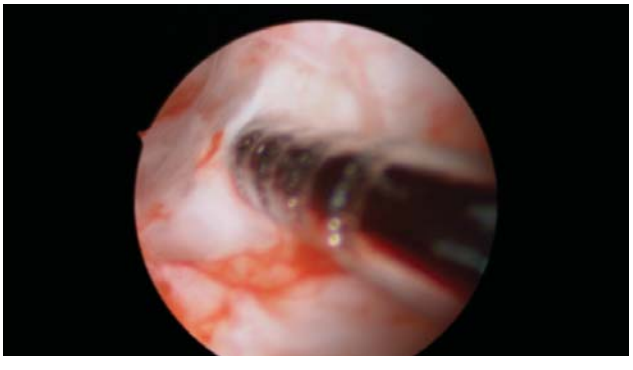

Figure 3. The markings on the ovum pickup needle help to determine the correct depth of insertion.

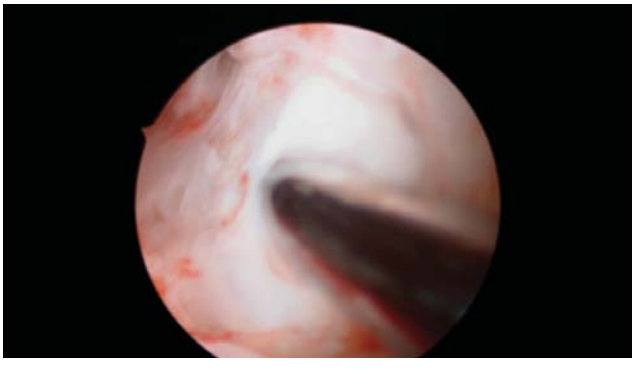

Figure 4. Prepared PRP is pushed into the endomyometrial junction and the needle is withdrawn under vision. No leakage of injected fluid was seen on withdrawal of the needle; PRP was instilled within 20 to 30 min of its preparation.

2.4. Endometrial Preparation and Embryo Transfer

One week after cessation of the OCP, on the second day of menses (withdrawal bleeding) in the embryo transfer cycle, women were given estradiol valerate tablets at a dose of 6 mg; the dose

was progressively increased to 12 mg per day. From day 6 onward, a transvaginal ultrasonography was performed to measure endometrial thickness on alternate days. To assess ET, the same examiner measured the thickest portion in the longitudinal axis of the uterus. Luteal phase support with 400 mg of vaginal progesterone was started when the ET reached the optimum thickness of 7 mm. Frozen-thawed embryo transfer was performed after synchronizing the day of progesterone treatment with the age of the embryo (only day 3 or day 5 embryos were transferred). Both estradiol valerate and progesterone were continued in the same dosage for luteal support. Serum beta-hCG levels were measured two weeks after embryo transfer. A transvaginal sonography was performed two weeks later in patients with positive beta-hCG levels in order to confirm a clinical pregnancy.

3. Results

The instillation of PRP caused no side effects and was well tolerated by all patients. In the subsequent cycle monitored to day 15, ET was 7 mm or thicker in 24 of 32 patients, and 6-7 mm in 4 of 32 patients. Endometrial thickness did not improve in four of 32 patients and remained below 6 mm (Table 1).

Table 1. Endometrial thickness following platelet rich plasma (PRP) administration.

Endometrial Thickness	Number of Patients
≥7 mm (on the day of progesterone start and embryo transfer done)	24 (75%)
6–7 mm (embryo transfer not done)	4 (12.5%)
<6 mm no improvement (embryo transfer not done)	4 (12.5%)

Progesterone was started the day the endometrium achieved a thickness of 7 mm or more. Subendometrial blood flow increased significantly in 28 of 32 patients. The mean increase in ET was 1.5 to 2 mm. Next, 24 patients underwent frozen embryo transfer. In 8 patients (25%), the cycles were canceled because they did not achieve optimal endometrial thickness.

Moreover, 12 patients had day 3 embryos transferred and 12 patients had two blastocysts transferred on day 5. Luteal phase support was given to all 24 patients. Further, of the 12 of 24 patients who underwent embryo transfer conceived, 10 had a clinical pregnancy with visualization of cardiac activity at 6 weeks, and two had a biochemical pregnancy. In 8 of 10 pregnant patients, the pregnancy progressed uneventfully.

Two patients had a missed abortion in the first trimester. Five patients have already delivered and three pregnancies are in progress at the date of this publication (Table 2).

Table 2. Pregnancy outcome in 24 patients who underwent frozen embryo transfer after platelet-rich plasma (PRP) instillation.

Pregnancy Outcome	Number of Patients (24 in Total)
Beta-hCG positive	12 (50%)
Clinical pregnancy	10 (41.66%)
Biochemical pregnancy	2 (8.33%)
Ongoing pregnancy	3 (12.5%)
Live birth	5 (20.83%)
Missed abortion	2 (8.33%)

4. Discussion

The clinical application of platelet-rich plasma (PRP) has increased markedly in the last decade. PRP has been extensively used for hair regeneration and tissue regeneration in cosmetic dermatology and gynecology.

PRP is an autologous blood plasma enriched with four- to five-fold higher levels of platelets than those in circulating blood. PRP stimulates proliferation and regeneration with a large quantity of growth factors and cytokines, including PDGF, TGF, VEGF, EGF, fibroblast growth factor (FGF), insulin-like growth factor I, II (IGF I, II), interleukin 8 (IL-8), and connective tissue growth factor (CTGF) [3].

We analyzed hysteroscopic instillation of PRP in the endomyometrial junction to improve endometrial thickness for embryo transfer in the subsequent cycle. As such, 75% of the patients achieved an endometrial thickness of 7 mm or more, underwent an embryo transfer, and 50% of the patients conceived.

Considering these results, the question arises as to what the possible causes of non-proliferating endometrium might be. Herein, 25% of the patients did not achieve an endometrial thickness of 7 mm or more. Anatomical or structural abnormalities such as Asherman's syndrome, for example, could be the cause of a lack of endometrial proliferation. Intrauterine adhesions with symptoms like hypomenorrhea/amenorrhea, reduced fertility, or abnormal placentation are known under the term Asherman's syndrome. Possible causes might be a lesion of the basal layer of the endometrium (i.e., after curettage), hysteroscopic surgery, or uterine artery embolization [21]. Furthermore, unspecific factors can be discussed, like age, race, nutritional status, and previous infections. Nonetheless, a history of trauma seems to be the determining factor [22].

Another possible cause of the less proliferated endometrium could be the lack of special marker molecules, which are considered characteristic for endometrial receptivity. A German study group [23] analyzed Leukemia inhibitory factor (LIF), vascular endothelial growth factor (VEGF), and β 3 integrin, which are marker molecules for endometrial receptivity. These marker molecules were found to be inadequately expressed or completely absent in the endometrial tissue samples the specific group of subfertile patients with suspected endometrial deficiency [23].

The human endometrium has its own immunosensititvity to sex steroid hormones. There are different endometrial concentrations of estrogen and progesterone receptors throughout the menstrual cycle [24]. The molecular and cellular events mediating these changes are not fully understood. The establishment of normal endometrial receptivity appears to be tightly associated with the down-regulation of epithelial progesterone receptor [24,25]. A histological analysis of endometrial tissue can be done in order evaluate the estrogen receptor concentrations. Low estrogen receptor concentrations seem to be related to low pregnancy rates [26].

Maekawa et al. [27] found an aberrant Th1-pro-inflammatory/Th2-anti-inflammatory balance and increased cytotoxic condition in patients with thin endometrium. Genome-wide mRNA expression analysis was used in order to show the different expression profiles that exist in case of patients with thin endometrium compared to the control group with an endometrium ≥7 mm [27]. An overactivation of the uNK cells and a cytotoxic/Th1 pro-inflammatory environment was found to be present in a thin endometrium, which is associated with implantation failure [27]. Possible limitations of our study are based on previously cited studies. We have not examined our patients more closely for possible causes of thin endometrium and we did not investigate marker molecules for endometrial receptivity, nor did we perform an mRNA expression analysis.

A further point of criticism is that the number of cases with 32 patients is expandable and no subgroup analysis was performed with regard to primary and secondary sterility, habitual miscarriage, and recurrent implantation failure. This should be considered and integrated in further studies.

To further prove the benefit of the application method (instillation vs. infusion of PRP) the following setting would be desirable in a further study: the case group would receive a hysteroscopic instillation of the PRP, while the control group would receive an infusion of the PRP into the uterine cavity.

In our study, there were three patients with one living child and secondary infertility, five patients with previous history of abortions, and 24 patients with primary infertility.

Infertility is defined as failure to achieve clinical pregnancy after at least 12 months of unprotected coitus. Couples who already have a child but waited another 12 months or more for a new pregnancy suffer from secondary infertility also fall under this description.

The causes of primary infertility can be many and varied. Endometriosis, uterine abnormality—such as septa, polyps, and fibroids—chromosomal aberrations, infections, obesity, thrombophilia, or immunological causes are a few examples. An essential difference in the pathomechanism of primary versus secondary infertility is the age of the woman. The age for the first maternity has already shifted significantly backwards in today's society. In this case, a reduced egg cell reserve and a limited quality of the oocytes can be assumed [28].

Previous traumas affecting the endometrium can promote or even cause secondary infertility. Possible reasons might be caesarean section, abrasion, or hysteroscopic surgery. These procedures can impede adequate proliferation of the endometrium and in rare cases cause Asherman's syndrome [21].

Over time, other gynecological conditions that do not cause much discomfort at an earlier age can also become real obstacles when it comes to conception. These include, for example, increased symptoms of endometriosis, fibroids of the uterus, intracavitary polyps, or increasing disorders of ovulation. Other clinical pictures that make a new pregnancy difficult and that increase over the years include rheumatological and degenerative diseases, high blood pressure and diabetes.

Furthermore, male fertility disorders can be the trigger for secondary sterility. In men with advanced age, reduced sperm quality (concerning the quantity and motility of the sperm cells), erection problems, high blood pressure, diabetes, and other impairments can become increasingly apparent [29].

Since the first in vitro fertilization (IVF) attempts in the mid-1970s, a number of assisted reproduction technologies (ART) have been used. These include stimulation protocols, embryo culture/culture medium, and embryonic growth to the blastocyst stage. The human endometrium undergoes significant changes during implantation. Immune cells and their secretions, such as granulocyte colony-stimulating factor (G-CSF) in the luteal phase, play an important role in the process of implantation.

In contrast to the approaches mentioned above, the phenomenon of implantation itself is not fully understood. Little is known about the mother-fetus dialog and the individual steps or possible sources of error in apposition, adhesion, and invasion. This has resulted in limited options for achieving implantation. One of the options is to influence the maternal immune system in order to promote implantation and the continuation of pregnancy. Due to heterogeneous data regarding live birth rates, immunomodulatory therapies, such as intralipid infusion, immunization with partner lymphocytes, or glucocorticoid administration, are not included in the corresponding guidelines [30].

PRP is a relatively new method of enhancing endometrial thickness and achieving higher pregnancy and live birth rates.

Chang et al. published the first trial on the use of PRP in human reproduction technologies in 2015. They showed the efficacy of intrauterine infusion of PRP for endometrial growth in women with a thin endometrium. All five treated patients became pregnant and delivered their infants at term; the fifth patient had an abortion due to an XO fetus [17]. In contrast to our study, Chang et al. infused PRP into the uterine cavity with a catheter, and the embryo was transferred during the same cycle. Endometrial thickness was re-assessed 72 h after infusion. The infusion had to be repeated in four patients due to inadequate endometrial thickness.

A pilot study by Zadehmodarres et al. included 10 patients with a history of inadequate endometrial growth into the study. The patients got infusion of PRP before frozen-thawed embryo transfer. In all patients, endometrial thickness increased after PRP and embryo transfer was done in all of them. Five patients were pregnant. According to this study, it seems that PRP was effective for endometrial growth in patient with thin endometrium [3].

Our study has added a novelty to this and already new method: the hysteroscopically controlled instillation of PRP. This approach has not yet been described in the literature and is therefore an

absolute novelty. The idea is not only to perform an infusion or irrigation but to inject PRP directly into the stem/progenitor cell site into the junctional zone to have even more influence on angiogenetic and growth cells. This method was performed in patients with thin endometrium, who had cycle cancellation due to thin endometrium despite of intrauterine PRP or GCF infusion before.

A study group from Teheran [31] investigated 138 patients with repeated implantation failure in 2016 and 2017. The women failed to conceive after three or more embryo transfers with high-quality embryos. The intrauterine PRP infusion was performed 48 h before blastocyst transfer. A control group received standard treatment, while 97 patients in the study group were given PRP infusions. The biochemical pregnancy rate was higher in the PRP group than in controls (53.06% versus 27.08%, respectively; $p = 0.009$) and the clinical pregnancy rate was also higher in the PRP group than in controls (44.89% versus 16.66%, respectively; $p = 0.003$). The authors concluded that PRP infusions cause higher pregnancy rates in women with repeated implantation failure [31].

In contrast to our study, the above mentioned patients suffered from repeated implantation failure, whose causes were not clearly specified. Implantation failure was not exclusively due to a subliminally proliferated endometrium. Instead of using a catheter, we instilled PRP into the endomyometrial junction under hysteroscopic guidance. Notably, the patients benefited from the treatment in both studies.

The above mentioned study group performed a randomized double-blind controlled trial concerning PRP [32]. In total, 60 patients who had a history of canceled frozen-thawed embryo transfer cycle due to a thin endometrium (<7 mm) were randomly assigned to PRP or a sham-catheter group in a double-blind manner. Intrauterine PRP infusions or a sham-catheter infusion was performed on day 11-12 and was repeated after 48 h, if necessary. All participants needed a second intervention because of inadequate endometrial expansion. After the second intervention, the endometrial thickness was 7.21 ± 0.18 and 5.76 ± 0.97 mm in the PRP group and sham-catheter group, respectively; the difference was significant ($p < 0.001$). Embryo transfer was performed in all patients in the PRP group and just six women in the sham-catheter group. A chemical pregnancy was reported in 12 cases in the PRP group and two cases in the sham-catheter group [32].

Maleki-Hajiagha et al. [33] performed a systematic review and meta-analysis concerning PRP; seven studies encompassing 625 patients (311 cases and 314 controls) were included. The probability of chemical pregnancy, clinical pregnancy, and implantation rates were significantly higher ($p < 0.001$) in women who received PRP compared to controls. The two groups did not differ in regard to miscarriages. Following the intervention, endometrial thickness increased in women who received PRP, but did not increase in the controls. The findings of this systematic review suggest that PRP is an alternative treatment strategy in patients with a thin endometrium and recurrent implantation failure (RIF) [33].

In our pilot study, we examined the new aspect of the injection site for the first time. In contrast to the "simple" infusion of platelet rich plasma into the uterine cavity, we injected the PRP under hysteroscopic view in the endomyometrial junction. Although reported as a safe procedure, it would be interesting to evaluate the long-term consequences. Indeed, the pathogenesis of endometriosis and adenomyosis may involve micro trauma at the junctional zone. It would be the task of the following studies, should the hysteroscopic instillation of PRP be used regularly, to investigate whether there is an association between a higher incidence of adenomyosis after prior PRP infiltration. Adenomyosis is associated with a higher risk of infertility. In this case, it would have to be considered whether the benefit of PRP outweighs the risk of possibly indicated adenomyosis.

The origin and pathogenesis of endometriosis is not fully understood. A possible developmental mechanism for endometriosis might be the dysregulation of endometrial stem cells, maybe in combination with the Sampson theory of retrograde menstruation [34,35]. When progenitor cells are shed at the time of menstruation, they can implant and generate endometrium in ectopic locations, for example, in the small pelvis or in the myometrium. The celomic theory describes that embryonic cells from the Müllerian ducts persist in ectopic locations. At puberty, stimulated by estrogens,

they grow to build up endometriotic lesions [36]. Nyholt et al. [37] described in their meta-analysis five novel loci related to the risk of developing endometriosis. All five are involved in sex steroid pathways. Furthermore, there is evidence that endometriosis is a pelvic inflammatory condition with a peritoneal fluid showing an increased concentration of activated macrophages and cytokines There are novel insights concerning pathogenesis of adenomyosis. Ibrahim et al. [38] described so called pale cells, a cell population found among the epithelial cells of the basal glands at the endomyometrial-junctional-zone. The cells got their name because of the electro-lucent cytoplasm and seem to migrate into the stroma of the basal endometrium and subsequently into the myometrium. Those pale cells have also been observed in the pelvic peritoneal endometriotic lesions, irrespective of the cycle day [38]. Going back to our study, one could consider that microtrauma in the area of the junctional zone to promote the migration of the pale cells and thus the development of adenomyosis. The same research group showed that the presence of myofibroblasts at the junctional zone is microscopic evidence of chronic tissue trauma in patients with adenomyosis. They are of nonmyometrial origin, as they lack desmin immunolabeling [39]. Further studies are necessary to investigate the influence of PRP instillation into the junctional zone on possible microtrauma and thus endometriosis development.

Nevertheless, many of the current studies concerning PRP comprise small numbers of cases and have different study designs. Before PRP can be recommended in clinical routine, it is necessary to perform further large prospective randomized controlled trials (RCTs) of high quality and identify women who would benefit most from PRP [40].

PRP is a new option for the improvement the endometrial thickness in women with a thin endometrium; its use is considered safe because it is derived from the patient's own blood.

Our approach of injecting PRP into the subendometrial region is consistent with the histologically proven regeneration of the endometrium from the endomyometrial junction. Instillation of PRP a few weeks before embryo transfer rather than intrauterine instillation on day 10 or 12 of same cycle ensures the maximum benefit for the patient. In many previous studies, PRP infusion had to be repeated because of no change in endometrial thickness [32,41]

Despite the use of PRP for musculoskeletal injuries, dentistry, and other medical fields including human-assisted reproduction, the method of preparing PRP for clinical use is far from standardized [42]. Furthermore, the limited body of clinical data on the subject is largely derived from non-randomized trials. We need well-designed randomized studies and basic research at the cellular and molecular level to improve our understanding of PRP as well as determine specific clinical situations for its use.

5. Conclusions

The thin endometrium has perplexed ART clinicians worldwide and still is a challenge in terms of treatment. The method of improving endometrial thickness by hysteroscopic instillation of PRP, developed at our center, yielded promising results and has created new options for the use of PRP in infertile women with previously canceled cycles due to a thin endometrium.

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Increased Institutional Surgical Experience in Robot-Assisted Radical Hysterectomy for Early Stage Cervical Cancer Reduces Recurrence Rate: Results from a Nationwide Study

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Abstract: The aim of this study was to evaluate the impact of institutional surgical experience on recurrence following robotic radical hysterectomy (RRH) for early stage cervical cancer. All women in Sweden who underwent an RRH for stage IA2-IB1 cervical cancer at tertiary referral centers from its implementation in December 2005 until June 2017 were identified using a Swedish nationwide register and local hospital registers. Registry data were controlled by a chart review of all women. Recurrence rates and patterns of recurrence were compared between early and late (≤50 vs. >50 procedures) institutional series. Six hundred and thirty-five women were included. Regression analysis identified a lower risk of recurrence with increased experience but without a clear cut off level. Among the 489 women who did not receive adjuvant radio chemotherapy (RC-T), the rate of recurrence was 3.6% in the experienced cohort (>50 procedures) compared to 9.3% in the introductory cohort ($p < 0.05$). This was also seen in tumors < 2 cm regardless of RC-T ($p < 0.05$), whereas no difference in recurrence was seen when analyzing all women receiving RC-T. In conclusion, the rate of recurrence following RRH for early stage cervical cancer decreased with increased institutional surgical experience, in tumors < 2 cm and in women who did not receive adjuvant RC-T.

Keywords: cervical cancer; robotic radical hysterectomy; recurrence rate; learning curve

1. Introduction

Robotic radical hysterectomy (RRH) for early stage cervical cancer was introduced in Sweden in December 2005, gradually replacing open surgery as the primary surgical method. Concurrently, a rapid increase in robotic surgery in women with endometrial cancer occurred. In Sweden, the vast majority of the more than 3000 new cases of gynecological cancers annually are centralized to seven university tertiary centers with subspecialized surgeons. Approximately 550 women with novel cases of cervical cancer are diagnosed annually where approximately 65% of cases allow for primary

surgery [1]. Preoperative evaluation, patient selection, principles for adjuvant radio chemotherapy (RC-T) and follow-up adhere to national guidelines [2].

Recent publications have raised concerns regarding the oncologic safety of RRH [3–5]). The randomized trial by Ramirez et al. (LACC study) and the observational study by Cusimano et al. mainly compared traditional laparoscopic surgery (84% and 89% of the minimally invasive surgery (MIS) groups, respectively) to open surgery, whereas the US register study by Melamed et al., in which 79.8% of MIS was performed robotically, was carried out during a robotic surgery introductory phase (2010–2013) in a low case load per institution setting. In contrast, a nationwide Swedish study including 864 consecutive women (236 ORH and 628 RRH) with cervical cancer operated between 2011 and 2017 and, where the major contributing centers had passed the introductory phase of RRH, did not demonstrate an inferior survival rate for RRH compared to open radical hysterectomy (ORH). Since tumor size and adjuvant treatment had a skewed distribution in the Swedish study, a propensity score model was used, accounting for age, grade, tumor size, lymph vascular space invasion (LVSI), lymph node status, primary treatment, and year of diagnosis and a similar oncologic outcome was demonstrated [6]. A Danish nationwide study of 1125 women did not find an increased risk of recurrence after the adoption of robotic radical hysterectomy [7]. In tumors less than 2 cm where the risk of recurrence is lower, a large amount of material is needed to investigate the recurrence rate. Existing studies have been unable to evaluate this subgroup properly [3–5,8]. Previous studies have shown a reduction in surgical time, blood loss and the rate of postoperative complications with increased surgical experience after 28–50 surgeries [9–13]. Two recent single institution studies, including 165 and 168 RRH, respectively, demonstrated reduced recurrence rates with increased experience [14,15]. The former used a multivariate risk-adjusted cumulative sum analysis and found a learning phase of 61 RRHs whereas the latter divided their experience based on the year of enrollment, which translated into 77 RRHs [14,15].

The primary aim of this nationwide study was to evaluate the effect of the institutional surgical experience of RRH for early stage cervical cancer on recurrence rates and patterns of recurrence. The secondary aims were to investigate the impact of institutional surgical experience on types of recurrences and perioperative complications.

2. Material and Method

All women in Sweden ≥ 18 years with a preoperative stage IA2-IB1 (FIGO 2009) with squamous adenocarcinoma or adenosquamous histology who underwent pelvic lymphadenectomy and an RRH according to Querleu–Morrow classification types B2 or C1 (or similar to the classification at the one clinic performing RRHs before 2008) from the first RRHs performed from December 2005 to June 2017 were included [16,17]. All RRHs were performed without the use of an intrauterine manipulator. Women converted to open surgery were included on an intention to treat basis. The women were identified by, and data retrieved from, the Swedish Quality Register of Gynecologic Cancer (SQRGC) and controlled by a review of local hospital registers to identify any missing women in the national quality register [6]. A full chart review was thereafter performed on all women by three of the authors (L.E, E.W and E.A) to control and harmonize the existing register data according to predefined common criteria regarding demographic information, age, body mass index (BMI) kg/m^2, smoking status, tumor histology, FIGO stage, tumor grade, LVSI, tumor size, lymph node status in the pathology report, adjuvant treatment, all intraoperative and postoperative complications within 30 days, and time and site of recurrences within 24 months (which was the total follow up time in all women). Per institution, operations were chronologically numbered. Tumor size was defined as the largest diameter in a preoperative cone biopsy or hysterectomy specimens, hence representing the minimum size of the tumor. Women with a tumor size > 40 mm at final pathology, positive lymph nodes or women with margins of <5 mm (this included women with parametrial involvement) were recommended adjuvant RC-T. Neither depth invasion, LVSI nor grade were used as separate parameters influencing primary or postoperative treatment. Intraoperative complications (defined as a complications diagnosed

and treated during primary surgery, or directly related to surgery but diagnosed postoperatively) and postoperative complications up to 30 days post-surgery were registered; the latter using the Clavien–Dindo classification [18]. Exclusion criteria were high-risk histology, FIGO 2009 stage <1A2 or >1B1, intraoperative abortion of the RRH in favor of RC-T, an unwillingness to receive recommended adjuvant treatment or loss to follow up within 24 months. All inhabitants in Sweden are assigned a unique personal identification number used for population registration and in health care. Health care for cancer is only provided by public hospitals. Hence, a woman was only lost to follow up if she emigrated abroad.

Preoperative examination included a computer tomography (CT) scan of the abdomen and thorax and pelvic magnetic resonance imaging (MRI). At follow-up, a clinical examination was performed at four to six months intervals. The criteria for offering adjuvant RC-T remained unchanged during the observation time. If a patient presented with symptoms indicating a recurrence, radiological examinations as indicated were performed followed by a biopsy for final diagnosis. Oncological outcome data were registered at 24 months, defined by the date of histological verification for all women. The recurrences were grouped into four categories: locoregional (vaginal vault or local pelvic recurrences), abdominal (port and/or intraabdominal recurrences), lymph nodes/distant (lymph nodes outside the pelvis or other distant recurrences), and multiple (multifocal recurrences).

The possible impact of surgical experience on oncologic outcome might be influenced by whether or not adjuvant RC-T was administered. As a result, the data set was split into two subgroups and analyzed accordingly. RRH was introduced at the first institution in 2005, whereas the sixth institution performed their first RRH in 2014, at which point the primary institution had performed more than 150 RRHs. Considering different baseline surgical and robotic skills, institutional recurrence rate depending on time of introduction was investigated.

The institutional review boards at Lund University (DNR 2008-663), the Karolinska Institute (DNR 2015-2140) and Gothenburg University (DNR 397-18) approved this study.

Statistical Analyses

A logistic regression analysis was used to evaluate the effect of surgical order, center of treatment, the patient's age, tumor size and tumor histology on the probability of recurrence occurring up to 24 months. The results were tested against a null hypothesis of an unimproved recurrence rate over time. As a potential effect of learning likely diminishes over time and eventually has no impact, a logistic regression model was constructed to compensate for such an effect (Appendix A). Both surgical order and center of treatment can be viewed as parameters representing skill. A potentially different baseline surgical and robotic skill between hospitals would likely impact the calibration of the effect of surgical order. For this reason, the logistic regression model was applied for all included hospitals as well as for the three centers of treatment with the earliest implementation and the highest number of performed RRHs (>100). In order to establish a suitable cut off level for comparison of the absolute recurrence rates between early and experienced cohorts, a model was constructed to evaluate any decrease over time in tumors of a median size (Appendix B). For comparison of clinical and recurrence data and potential skewness between early and experienced cohorts, the chi^2 test was used.

For the logistic regression, data were entered into a Microsoft Excel data base, pseudo-anonymized and analyzed using the Python package Statsmodel Discrete Logic (version 0.11.1, Texas, USA) (Appendix C). For the remaining analyses, the SPSS version 12.0 statistical software was used (SPSS, Chicago, IL, USA). A p-value of less than 0.05 was considered significant in all statistical tests.

3. Results

Of the 719 identified women, 60 were excluded due to a high-risk histology (n = 20), FIGO 2009 stage <1A2 or >1B1 (n = 12), intraoperative abortion of the RRH in favor of RC-T (n = 17), an unwillingness to receive recommended adjuvant treatment (n = 6) or loss to follow up (n = 5, due to women who emigrated abroad). RRH was performed at nine institutions during the study period. Three hospitals performed

ten or fewer RRHs, a number which was deemed unsuitable for statistical analysis, and were therefore excluded. The number of RRHs, included per site as well as distribution over time, can be seen in Figure 1.

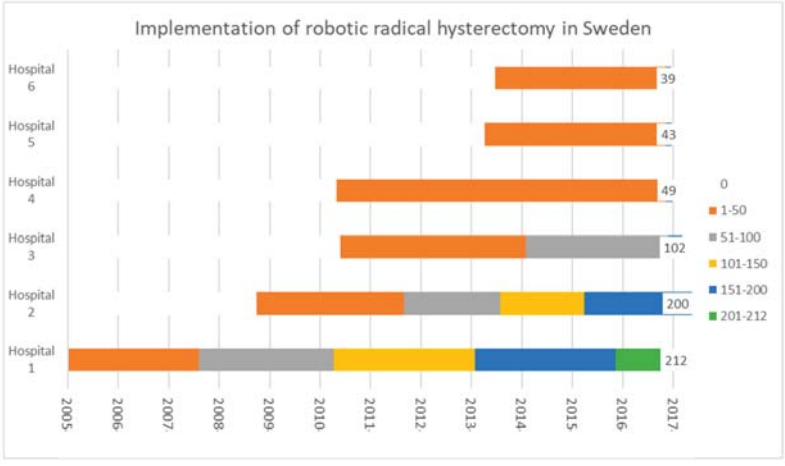

Figure 1. Implementation and number of robotic radical hysterectomies (RRHs) for stage IA2-IB1 (FIGO 2009) squamous, adenocarcinoma or adenosquamous cervical cancer performed per hospital in Sweden from the first RRH in December 2005 until June 2017.

Of the 635 women included in the final analysis, 146 (23%) received adjuvant RC-T due to at least one of the following reasons (lymph node metastases (n = 68, 47%), tumor size > 40 mm at final histology (n = 11, 7.5%) or margins < 5 mm (n = 67, 45.5%). The remaining 489 women received surgery alone with RRH (Figure 2, strobe flow chart). Clinical and demographic data are shown in Table 1. Three hospitals performed > 100 RRHs and three hospitals < 50.

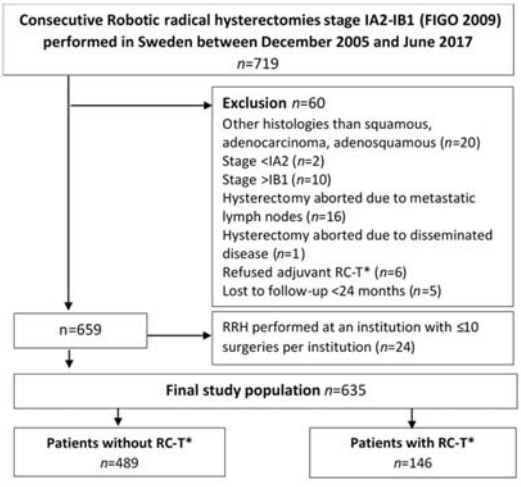

Figure 2. Strobe flow chart for all women in Sweden with stage IA2-IB1 squamous, adenocarcinoma or adenosquamous cervical cancer operated by robotic radical hysterectomy between December 2005 and June 2017 evaluating the impact of surgical experience on the rate of recurrence and postoperative complications. Sub-legend: * Oncologic protocol violations = women unwilling to receive recommended postoperative RC-T.

Table 1. Characteristics of 635 patients with stage IA2-IB1 squamous, adenocarcinoma or adenosquamous cervical cancer operated with robotic radical hysterectomy in Sweden between December 2005 and June 2017 with or without postoperative radio chemotherapy. Introductory and experienced cohort refer to the first 50 surgeries per institution compared to all following robotic radical hysterectomies.

Total (n = 635)		**No Radio Chemotherapy (n = 489)**			**Radio Chemotherapy (n = 146)**		
		Introductory cohort		Experienced cohort	Introductory cohort		Experienced cohort
median (range)/number (%)		≤50 n = 214	p -value	>50 n = 275	≤50 n = 66	p -value	>50 n = 80
Age	42.9 (22.3–86.6)	42.0 (23.8–86.6)	$p = 0.25$ [a]	42.8 (22.3–83.0)	47.3 (25.3–83.2)	$p = 0.77$ [a]	46.1 (24.9–79.9)
BMI [1]	25 (17–59.9)	25.1 (17.6–59.9)	$p = 0.52$ [a]	24.5 (17.0–48.2)	24.7 (19.0–35.0)	$p = 0.98$ [a]	26.1 (17–38.9)
Smoking *	Yes	46 (31.7%)	$p = 0.25$	81 (37.7%)	14 (33.3%)	$p = 0.59$	25 (38.5%)
	No	99 (68.3%)		134 (62.3%)	28 (66.7%)		40 (61.5%)
	Unknown **	69(32.3%)	$p < 0.01$	60 (21.8%)	24 (36.4%)	$p = 0.02$	15 (18.8%)
Tumor size	13 (0.2–62)	11.0 (1.5–60)	$p = 0.43$ [a]	10 (0.2–62.0)	20 (3–48)	$p = 0.08$ [a]	22.5 (2–50)
Figo Stage IA2	71 (11.2%)	26 (12.1%)		43 (15.6%)	0 (0.0%)		2 (2.5%)
Figo Stage IB1	564 (88.8%)	188 (87.9%)	$p = 0.27$ [b]	232 (84.4%)	66 (100.0%)	$p = 0.68$ [b]	78 (97.5%)
Histology							
Squamous	367 (57.8%)	116 (54.2%)		152 (55.3%)	43 (65.2%)		56 (70%)
Adenocarcinoma	233 (36.7%)	83 (38.8%)	$p = 0.24$ [b]	113 (41.1%)	18 (27.2%)	$p = 0.82$ [b]	19 (23.7%)
Adenosquamous	35 (5.5%)	15 (7.0%)		10 (3.6%)	5 (7.6%)		5 (6.3%)
LVSI *	Yes	38 (26.6%)	$p = 0.64$	46 (34.3%)	39 (75.0%)	$p = 0.65$	42 (71.2%)
	No	105 (73.4%)		143 (75.6%)	13 (25.0%)		17 (28.8%)
	Unknown **	71 (33.2%)	$p = 0.65$	86 (31.3%)	14 (21.2%)	$p = 0.69$	21 (26.2%)
Grade *	1 + 2	107 (63.7%)	$p = 0.60$	82 (60.7%)	31(53.4%)	$p = 0.71$	27 (52.9%)
	3	61 (36.3%)		53 (39.3%)	27 (46.6%)		24 (47.1%)
	Unknown **	46 (21.59)	$p = 0.001$	140 (50.8%)	8 (12.1%)	$p = 0.06$	29 (36.3%)
Reason for adjuvant treatment							
Metastatic nodes					33 (50.0%)		35 (43.7%)
Tumor > 40 mm					6 (9.1%)	$p = 0.51$ [b]	5 (6.3%)
Insufficient margins					27 (40.9%)		40 (50.0%)
Recurrence ≤ 24 months	51 (8.0%)	20 (9.3%)	$p = 0.01$ [b]	10 (3.6%)	9(13.6%)	$p = 0.82$ [b]	12(15%)
Recurrence rate ≤ 24 months in tumors < 2 cm	22/431 (5.1%)	11/158 (7.0%)	$p = 0.01$ [b]	4/215 (1.9%)	4/31 (12.9%) [2]	$p = 0.83$ [b]	3/27 (11.1%) [2]
Recurrence rate ≤ 24 months in tumors ≥ 2 cm	29/204(14.2%)	9/56 (16.1%)	$p = 0.33$ [b]	6/60 (10.0%)	5/35 (14.3%) **	$p = 0.74$ [b]	9/53 (17.0%) **
		All patients' tumors < 2 cm with and without RC-T			**All patients' tumors ≥ 2 cm with and without RC-T**		
		Introductory cohort	p-value	Experienced cohort	Introductory cohort	p-value	Experienced cohort
Recurrence rate ≤ 24 months		15/189 (7.9%)	0.02 [b]	7/242 (2.9%)	14/91 (15.4%)	0.67 [b]	15/113 (13.3%)

Sub-legend: * Percentages refer to women with known information. ** Percentages refer to all women within that group. [1] Data unavailable in 17 women. [2] No significant difference in rate of node positive women between the introductory and experienced cohort. [a] Mann-Whitney test. [b] Chi-squared test.

The regression analysis showed a decrease in the rate of recurrence with increased experience in women without RC-T for all six hospitals ($p = 0.03$) and for the three most experienced hospitals ($p = 0.006$). The statistical model using the three hospitals with >100 RRHs showed that the probability of recurrence decreased rapidly until about 50 surgeries, representing a probable inflection point (Appendix B). Therefore, when comparing the absolute recurrence rate in the whole study population, the first 50 cases from each of the six hospitals (introductory cohort) were compared with the remaining > 50 cases from the three most experienced hospitals (experienced cohort).

Of the 489 women with no RC-T, fewer recurrences occurred in the experienced cohort compared to the introductory cohort (3.6% compared with 9.3%, $p = 0.009$). In tumors < 2 cm, this was true both for tumors < 2 cm without RC-T ($n = 373$, 1.9% compared with 7.0%, $p = 0.01$) and tumors < 2cm regardless of adjuvant treatment ($n = 43$, 2.9% compared with 7.9%, $p = 0.02$). Extrapelvic (abdominal, multiple or nodal/distant) recurrences were seen predominantly in the introductory cohort (6 of 214 vs. 2 of 275) but the regression analysis did not verify a significant decline with experience for these few incidents ($p = 0.10$). No difference with experience in overall recurrence or pattern of recurrence was seen in tumors ≥ 2 cm (16.1% vs. 10.0%, $p = 0.33$) or in women who received adjuvant RC-T (Table 1).

Of the 635 women, ten (1.6%) experienced an intraoperative complication and three conversions to laparotomy (0.5%) were necessary due to adhesions ($n = 1$), vessel injury ($n = 1$) and subcutaneous emphysema ($n = 1$). Almost 90% of the postoperatively (<30 days) diagnosed complications were mild or moderate (grade I-II) whereas injury to the ureter ($n = 10$), intraabdominal abscess ($n = 7$), port-hernia ($n = 4$), vesicovaginal fistula ($n = 2$), postoperative bleeding ($n = 1$), vaginal dehiscence ($n = 1$) and compartment syndrome of the legs ($n = 1$) occurred in 4.1%. The rate of postoperatively diagnosed complications (≥grade IIIa) decreased with increased experience (2.5% vs. 6.1%, $p = 0.03$) (Table 2). A significant decrease in complications directly associated with surgery was seen when these postoperatively diagnosed complications, i.e., ureter injury, vesicovaginal fistulas and compartment syndrome were added to the intraoperative complications group ($p = 0.01$). This second categorization was used due to the shortcoming of the Clavien–Dindo classification that does not classify intraoperative complications as a separate entity and where postoperatively discovered intraoperative complications are classified as postoperative.

Table 2. Number and percentage of intraoperative and postoperative complications according to Clavien–Dindo in the introductory and experienced surgical cohort of robotic radical hysterectomy with and without radio chemotherapy in Sweden between December 2005 and June 2017.

***n* (%) Total *n* = 635**	**Total *n* = 635**	**Introductory Cohort ≤50 *n* = 280**	**Experienced Cohort >50 *n* = 355**	***p*-Value**
Postoperative complications Grade I-IIIb	186 (29.3%)	90 (32.1%)	96 (27.0%)	$p = 0.20$ [a]
Postoperative complications Grade ≥ IIIa	26 (4.1%)	17 (6.1%)	9 (2.5%)	$p = 0.03$ [a]
Intra-operatively diagnosed complications	10 (1.6%)	7 (2.5%)	3 (0.8%)	$p = 0.10$ [a]
Intra-operative and surgical postoperative complications [b]	23 (3.6%)	16 (5.7%)	7 (2.0%)	$p = 0.01$ [a]

Sub-legend: [a] Chi-squared test. [b] Combination of complications discovered intraoperatively and surgical complications discovered postoperatively i.e., injury to the ureter, compartment syndrome and vesicovaginal fistula.

4. Discussion

The rate of recurrence following RRH for early stage cervical cancer decreased with increased institutional surgical experience in women who did not receive adjuvant RC-T as well as in women with tumors < 2 cm, regardless of given adjuvant treatment. A similar decrease in recurrence was not seen in women with tumors ≥ 2 cm. In women with tumors ≥ 2 cm or who received adjuvant RC-T, the inherent higher risk of extrapelvic recurrence, the possibility of occult disease at the time of surgery,

and probable prevention of locoregional recurrence following RC-T rather than the surgical technique per se, are probable contributing factors. The study is, however, underpowered for smaller subgroup analyses. But we cannot exclude that increased surgical experiences have less positive impacts on women with larger tumors where no RC-T is administered. For all women having undergone RRH, surgical complications were less frequent in the experienced cohort.

Previous studies have demonstrated a positive effect of increased experience with RRH in regard to surgical time, blood loss, and early postoperative complications, which was also seen in the present study [9–12]. A positive impact on oncological outcome with increased experience has been shown for robotic radical prostatectomy by Galfano et al. and was implied by Chong et al., who investigated RRHs during the learning phase compared to conventional laparoscopic radical hysterectomies performed by experienced surgeons. [19,20]. Two recent single-institution studies investigated the impact of learning curve on oncological outcome following RRHs for early stage cervical cancer and found improved survival rates with increased surgical experience, achieving similar levels of adequate experience to our study [14,15]. Neither of the studies discussed or further clarified which elements associated with increased experience would be expected to have a positive effect on recurrence rates. Rather than discarding RRHs for early stage cervical cancer, the authors similar to our experience, emphasize the necessity of centralized health care combined with a validated learning curriculum to shorten and make the learning process more effective. In addition, taking into account the institutional oncological outcomes when counseling patients is emphasized [14,15]. The results from these two studies and the present nationwide study might explain the discrepancy in the recurrence rate following RRH and open radical hysterectomy (ORH) in the US register study by Melamed et al. and the Swedish study by Alfonzo et al., both national studies including 2461 (978 RRH) and 864 women, respectively [3,6]. The increased rate of recurrence after RRH compared to ORH in the former was probably partly due to a low case load setting, including data from 479 institutions and with 357 institutions sharing a total of 978 RRHs over the studied period (personal communication Dr Melamed) representing an introductory phase of robotic surgery [3,6]. Alfonzo et al. on the other hand found no difference in recurrence rate for RRHs and ORHs performed between 2011 and 2017 when the two major contributing institutions had passed their learning phase [6]. As described in the introduction, confounding factors were compensated for using propensity score analysis. A similar nationwide study from Denmark, where the organization of care is similar to Sweden, also failed to show differences in recurrence in ORH and RRH groups. These studies represent hybrids between prospectively retrieved quality register data and retrospective control of these data. According to a post-hoc 80% power analysis of 236 ORH and 628 RRH included in the Swedish study, a difference in recurrence of up to 5.7% for either group (compared with 9.5% in the LACC study) theoretically may have remained unnoticed. However, we believe it is unlikely that a difference in recurrence in the magnitude of what is demonstrated by the LACC study would have been missed.

In Sweden, the centralization within gynecological cancer surgery, adherence to national guidelines as well as strict requirements/curriculum for achieving a subspecialization in gynecological cancer surgery (at least 4 years at a tertiary unit) ensures conformity. The requirements for tertiary units providing subspecialization and the credentials for subspecialization are defined by the Swedish Society of Obstetrics and Gynaecology. Surgery within gynecologic oncology is, with few exceptions, performed at tertiary referral centers. Within these centers, robotic gynecological cancer surgery, including RRH, is performed by a limited number (1–3 per institution) of surgeons to ensure an adequate case load per surgeon and to further enhance quality, the bedside assistant is usually also an experienced robotic surgeon. Even though the number of RRHs per institution per year, despite centralization, were relatively low (between 7 and 23 in 2017) the six included university hospitals had an annual case load of between 66 and 302 robotic; mainly gynecological cancer procedures (in 2017). It is probable that training by, and exchange of experience with surgeons already experienced in RRH, may affect baseline skills for institutions with a later implementation of RRH. This was implied when comparing early cohorts from the hospitals where RRH was firstly implemented to the two hospitals

with the latest introduction (Figure 1 and Table S1 Supplementary Material). A further indication of interinstitutional exchange of experience was seen in the regression analysis where a stronger significance level was present when comparing the effect of learning for the two hospitals with the latest introduction to all six hospitals.

Overall organization of care, including case load per surgeon of RRH and other robotic procedures, and timing of the study in relation to implementation of a novel technique, must be taken into consideration when comparing a new approach to a well-established surgical method. This is further emphasized by Doo et al. and Sert et al. where the former reported a higher risk of recurrence following RRH compared to ORH during an introductory phase, whereas Sert et al. found no difference in their multicenter study with a higher annual case load per institution [8,21]. Although the ORH group in the LACC trial and ORH group in the trial by Sert et al. were almost identical in terms of inclusion period, proportion of lymph node metastases, adjuvant treatment and follow-up time, there was, for unknown reasons, a substantial discrepancy in the oncologic outcome in favor of the ORH in the LACC study [4,21].

Recent studies have highlighted the importance of evaluating possible factors inherent to robotic and laparoscopic surgery that might influence oncologic safety of the procedure, and potential areas for improvement and learning [4,22,23]. A possible contributing factor as suggested by Ramirez et al. in the LACC trial is the use of an intrauterine manipulator, a device never utilized for RRH in Sweden. Instead a fornix-presenter (a simple tube or cup delineating the fornices) was used. A recent multi-institutional (89 centers) retrospective study (the SUCCOR study, including 291 MIS radical hysterectomies (RHs) of which 63 were robotic) comparing ORH and MIS, found MIS and the use of an intrauterine manipulator to be associated with an increased risk for recurrence. Given the low average institutional number of MIS RHs in general and RRHs in particular, this study may support our conclusion of the importance of experience [24]. Moreover, avoiding tumor contamination of the abdominal cavity during the opening of the vagina and the retrieval of the specimen might be of importance. Köhler et al. recommended an initial closure of the vagina to prevent this exposure [25]. The very low incidence of lymph node metastases in the Köhler study (3%) compared to the present study (10.7%) makes a direct comparison impossible. Although vaginal closure was not applied in this material an increased awareness and preventive measures regarding this possible risk factor might theoretically have influenced our results. Alternatively, a large cone biopsy at upfront surgery to remove an exposed tumor may be applied. Another possible risk factor associated with robotic surgery is overestimation of distance due to magnification. This could lead to a larger proportion of women undergoing RRH having surgical margins close to insufficient. The fixed grip force of the instruments that might crush metastatic lymph nodes if directly grasped and cause an inadvertent tumor spread would only be of importance if the nodes were metastatic. The performance of an adequate sentinel node technique and the extent of the pelvic lymph node dissection, measures to prevent contamination of tumor as well as the surgical margins are possible areas where surgical experience would have a positive impact, which might influence the oncological outcome for the patient. Previous studies on surgical experience in robotic surgery have focused on surgical time and rate of complications and have unsurprisingly shown a decrease with time. [9–12]. The use of CO_2 and pneumoperitoneum have been suggested to have a negative oncologic effect, although neither can explain the reduced recurrence rate with increased experience observed in the study.

In Sweden, RRHs were first implemented in 2005. Later implementations were aided by study visits and proctoring by surgeons from either of the two institutions with the earliest start ensuring a homogenous surgical approach among all centers. RRHs rapidly became the primary approach of choice, initially limited by robot access at some institutions. Laparoscopic RHs were never implemented in Sweden.

Our decision to compare institutional experience rather than individual surgeons' experience was due to the rarity of the procedure and the fact that some surgeons retired or stopped performing RRHs during the 12-year study period. This is a weakness of the study. However, within each institution,

one surgeon performed the procedure from implementation, representing continuity. During 2017, either one of two surgeons at each of the two main contributing centers performed all RRHs. The institutional experience also entails the experience of the whole surgical team, which is necessary for a successful robotic program. Surgeons introduced at a later date likely benefited from the experience of the novel surgeon in terms of surgical time and rate of complications. The present study suggests that this transfers into an oncological benefit. To what extent an increased individual surgical experience, transfer of experience or improvements of team performance affect results remains unclear. This is a potential weakness of our study but also an incentive to evaluate institutional performance rather than individual surgeons' results. The effect of a difference in baseline skill is discussed and compensated for in the statistical analysis.

The heterogeneity of cancer and its inherent characteristics and risk factors as well as the multifactorial aspects of learning and experience does not allow for an exact cut off level when experience with an impact on oncological outcome has been achieved. The level utilized in the present study is within the range previously reported by other authors.

The strengths of the study are the nationwide setting with consecutive procedures with only five women (0.7%) lost to follow up and the quality and conformity of data secured by a chart review using commonly defined criteria for clinical parameters of all women performed by three of the investigators with regular audits. The organization of care with centralization both within gynecological cancer surgery and gynecological oncology allowed for an investigation of the nationwide implementation of RRH as well as a true representation of the rate of recurrence. Utilizing recurrence rate at 24 months ensures the same follow-up for all included women although excludes the recurrences that occur at a later date. Consequently, a weakness of the study is that a direct comparison with similar cohorts with longer follow-up is not possible.

Another potential weakness is that data on LVSI and grade were missing for approximately 1/3 of women. However, the new 2020 WHO histological classification of tumors of the cervix does not include grade for squamous cell carcinomas. Furthermore, the prognostic value of grade is debated when newer classifications are suggested [26]. According to Swedish national guidelines, these parameters do not influence selection for surgery or postoperative RC-T. In the majority of women where these data are available, there is no difference between early and late groups. Furthermore, it is unlikely that the proportions of these parameters were differently distributed throughout the country or over time. Therefore, we do not believe that the lack of data on these parameters in some women affect the interpretation of our results.

In the light of the available evidence, the question arises whether a possible increased risk of recurrence can be accepted even when potentially hazardous parts of an RRH can be compensated for. A more accurate detection of sentinel lymph nodes with robotic surgery might decrease the rate of undetected lymph node metastases and facilitate a structured and safely implemented sentinel lymph node (SLN) concept, thereby minimizing the risk of lower limb lymphedema, a major lifelong side effect in some women [27]. In obese women, MIS in endometrial cancer favors immediate and long-term wound healing and reduces infections [28]. Bowel obstruction and intraabdominal adhesions are less common following MIS, the latter is especially beneficial when adjuvant RC-T is indicated [29–32]. Finally, future technological progress and development including tracers, intraoperative tumor markers and intraoperative imaging will likely be dependent on a minimally invasive platform. Randomized trials investigating the optimal surgical approach for cervical cancer and the future of RRH are currently ongoing [33,34].

Although recent studies have led to a change in practice patterns at many institutions where MIS for cervical cancer has been abandoned in favor of ORH, the results are conflicting. The reduced rate of recurrence and rate of serious postoperative complications, as well as the reduced rate of multiple and intraabdominal recurrences following RRH for early stage cervical cancer with increased surgical experience, must be taken into account when organizing care and counseling the patient prior to surgery. This is supported by a previous Swedish nationwide study as well as two recent publications

investigating the influence of learning curve where similar recurrence rates for RRH and ORH were seen at high-volume centers after the implementation period [6,14,15]. When interpreting available studies and performing future studies on RRH for cervical cancer, the negative impact of novel early adopters and low-volume surgeons on the rate of recurrence and postoperative complications must be considered.

5. Conclusions

The rate of recurrence following RRH for early stage cervical cancer decreased significantly with increased institutional surgical experience in the larger subgroup of women who did not receive adjuvant RC-T as well as in women with tumors <2 cm, regardless of the given adjuvant treatment.

Studies on RRH for cervical cancer, and organization of care, should consider the negative impact of early adopters and low volume surgeons on the rate of recurrence. A multicenter RCT, which started in 2019, comparing ORH with RRH (the RACC study) where bias by early adoption and low case load is minimized, is currently ongoing [33].

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/11/3715/s1, Table S1: Number of robotic surgeries per hospital during the introduction of robot assisted radical hysterectomy (RRH) (≤50 surgeries) and the experienced years (>50 surgeries). Rate of recurrence and tumor size in the cohort without Radio chemotherapy (RC-T) presented per hospital.

Author Contributions: L.E.: conceptualization, methodology, investigation, validation, formal analysis, writing—original draft, writing—review and editing. E.W.: conceptualization, methodology, investigation, validation, writing—review and editing. E.A.: conceptualization, methodology, investigation, validation, writing—review and editing. P.R.: conceptualization, methodology, validation, formal analysis, writing—review and editing. C.L.: conceptualization, methodology, writing—original draft, writing—review and editing. P.D.-K.: conceptualization, methodology, writing—review and editing. H.F.: conceptualization, methodology, writing—review and editing. J.P.: conceptualization, methodology, validation, formal analysis, writing—review and editing and supervision. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Jan Persson, Henrik Falconer and Celine Lönnerfors have received honoraria for lectures and proctoring in robotic surgery, all outside of the presented research. The other authors have no conflicts of interest.

Appendix A

The connection between the probability of recurrence within 24 months and the variables surgical order, hospital, patient age, tumor size and histology are evaluated using logistic regression. Since it is reasonable to believe that the impact of the skill component decreases over time and eventually goes away, the surgical order has been transformed. The resulting model can be seen below.

$$\log\left(\frac{p}{1-p}\right) = \alpha_{size} \cdot size + \alpha_{order}\left(1-\mu^{order}\right) + \sum_{h}^{Hospitals} \alpha_h + \sum_{t}^{Tumor\,types} \alpha_t.$$

Both surgical order and hospital can be viewed as parameters representing skill. The hospitals have performed varied number of surgeries, ranging between 39 and 212. If their baseline skills are different this is likely to impact the calibration of the effect of surgical order. Therefore, it is important to either include both the hospital specific parameters, or to perform the analysis only on hospitals with a matching number of surgeries. Due to the interpretability as well as the repeatability of the

results, the transformation parameter μ = 0:96 was estimated using maximum likelihood prior to performing the standard logistic regression using the python package statsmodels.discrete.discrete model in Logit (version 0.11.1). Since it is reasonable to believe that the impact of surgical order is highest if the patient does not undergo adjuvant treatment, the data set is split in two and the analysis is performed on the group without adjuvant treatment.

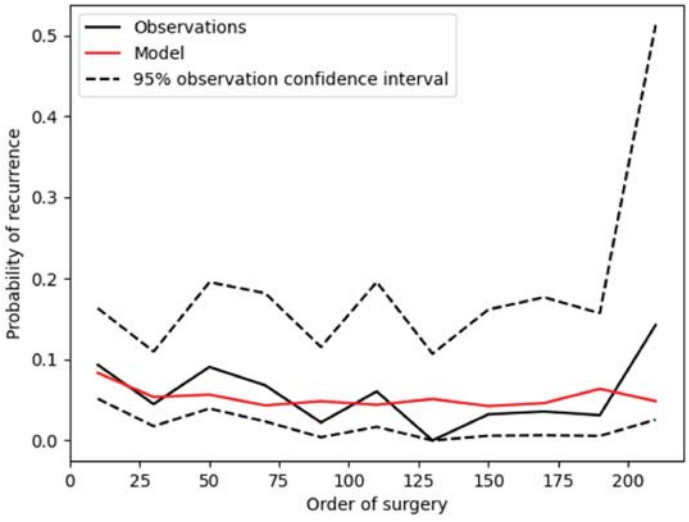

Figure A1. Analysis performed on all hospitals.

Comparing modelled probabilities to the observed fraction of recurrence within 24 months in women without adjuvant radiochemotherapy. The observed fractions were estimated using an average of ten consecutive surgeries. The confidence intervals were calculated using Wilson's method. The steep rise at the end is due to one recurrence in the last ten patients.

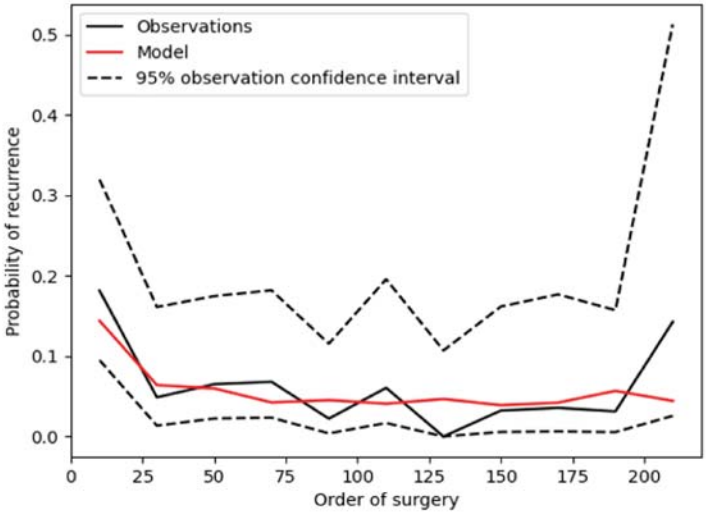

Figure A2. Analysis performed on the three hospitals with the earliest implementation and >100 RRH.

Comparing modelled probabilities to the observed fraction of recurrence within 24 months. The observed fractions were estimated using an average of ten consecutive surgeries. The confidence intervals were calculated using Wilson's method. The steep rise at the end is due to one recurrence in the very last ten patients.

Table A1. Connection between the probability of recurrence within 24 months and the variables tumor size and surgical order.

	p-Value
Tumor size at all hospitals	0.001
Order of surgery at all hospitals	0.028
Tumor size at three largest hospitals	0.006
Order of surgery at three largest hospitals	0.006

Appendix B

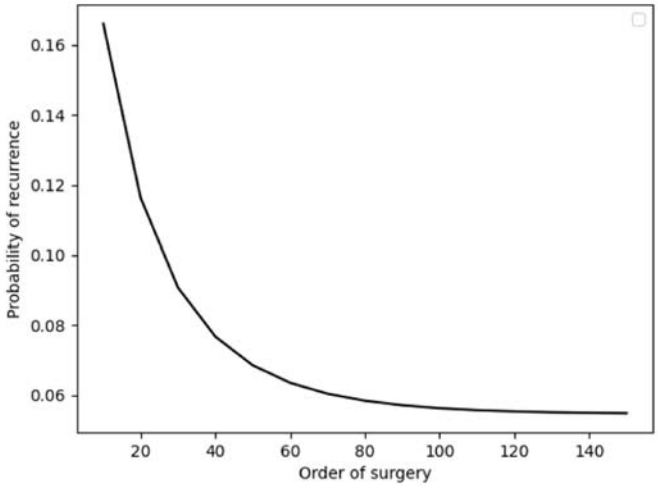

Figure A3. Constructed model showing the probability of recurrence given the order of surgery for a median tumor size of 21 mm (median in sample) for the model using the three hospitals with >100 RRH.

Before 20 and after 80 there is little difference in probability. Therefore, a cut off of 50 procedures was used.

Appendix C

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Review

Systematic Review and Meta-Analysis on Hysterectomy by Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) Compared to Laparoscopic Hysterectomy for Benign Indications

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Abstract: (1) Objective: We aimed to report an update of the systematic review and meta-analysis by Baekelandt et al. (2016). (2) Method: We followed PRISMA guidelines to perform this systematic review. We searched MEDLINE, EMBASE, CENTRAL and additional sources and aimed to retrieve randomised controlled trials (RCTs), controlled clinical trials (CCTs) and prospective/retrospective cohort studies in human subjects that allowed direct comparison of vNOTES to laparoscopy. (3) Results: Our search yielded one RCT and five retrospective cohort trials. Pooled analysis of two subgroups showed that, compared to conventional laparoscopy, vNOTES is equally effective to successfully remove the uterus in individuals meeting the inclusion criteria. vNOTES had significantly lower values for operation time, length of stay and estimated blood loss. There was no significant difference in intra- and postoperative complications, readmission, pain scores at 24 h postoperative and change in hemoglobin (Hb) on day 1 postoperative.

Keywords: hysterectomy; NOTES; laparoscopy; minimally invasive; systematic review; meta-analysis

1. Introduction

Background and Rationale

In natural orifice transluminal endoscopic surgery (NOTES), the natural orifices of the human body are used to access the abdominal cavity to perform surgery. Since the safety of colpotomy is not debated, transvaginal NOTES was the first to be adopted clinically, not only for hysterectomy but also for adnexal and even gastro-intestinal surgery such as cholecystectomy and appendectomy [1]. The proposed benefits of NOTES include reduced postoperative pain, faster postoperative recovery

and improved cosmesis compared to standard laparoscopic approaches using the abdominal wall as access [2]. Hysterectomy via vaginal natural orifice transluminal endoscopic surgery (vNOTES) was first described by Su et al. in 2012 [3]. The route through which hysterectomy for benign disease is performed is determined by many factors including the size of the uterus, accessibility to the uterus, extra uterine disease, patient preference and surgeon preference and training. Current evidence supports vaginal hysterectomy as superior to laparoscopic and abdominal routes due to the shorter operating time and shorter recovery time [4]; however, its clinical application can be restricted by poor visualisation and limited manipulation [5]. These restrictions might be overcome with vNOTES as it combines the advantages of vaginal and endoscopic surgery [6]. An earlier systematic review and meta-analysis by Baekelandt et al. [2] assessed the effectiveness and safety of vNOTES hysterectomy for non-prolapsed uteri and benign gynecological disease compared to the conventional laparoscopic technique. As many publications including a randomised control trial have been published since, we aimed to update this systematic review.

The objectives of this systematic review are to assess the effectiveness and safety of vNOTES hysterectomy for non-prolapsed uteri and benign gynecological disease compared to conventional laparoscopic techniques.

1. Is vNOTES equally effective as the laparoscopic approach for successful removal of the uterus without the need for conversion?
2. Is the operation time for removal of the uterus by vNOTES faster compared to laparoscopy?
3. Is the complication rate of vNOTES hysterectomy different compared to laparoscopy?
4. What is the difference in hospital stay in women treated by vNOTES compared to laparoscopy?
5. What is the readmission rate in women after hysterectomy by vNOTES versus by conventional laparoscopy?
6. What is the difference in postoperative pain between women treated by vNOTES hysterectomy and conventional laparoscopic hysterectomy?
7. Are there differences in women's health, concerning dyspareunia, sexual wellbeing or health-related quality of life after hysterectomy by vNOTES compared to laparoscopy?
8. Are there differences in the financial costs of both techniques?

2. Methods

We conducted this systematic review according to the Cochrane Handbook for Systematic Reviews [7] and reported following PRISMA guidelines [8]. The protocol of this review was registered in PROSPERO under registration number CRD42020198104.

2.1. Eligibility Criteria

We aimed to retrieve randomised controlled trials (RCTs), controlled clinical trials (CCTs) and prospective/retrospective cohort studies in human subjects that allow direct comparison of vNOTES to laparoscopy. All studies that did not allow direct comparison (e.g., case series, case reports, editorials, letters to the editor) were excluded. There was no restriction in timeframe or language, provided that articles could be translated using Google Translate if necessary.

2.2. Population

We included studies in the adult female population, undergoing removal of the uterus for benign gynecological disease. Studies on interventions for genital prolapse or gynecological malignancy were excluded.

2.3. Intervention

vNOTES hysterectomy was the experimental intervention.

2.4. Comparison

Hysterectomy by conventional laparoscopy using the umbilicus was the comparator. This included laparoscopy assisted vaginal hysterectomy (LAVH), total laparoscopic hysterectomy (TLH) using single port (SILS) or multiple port (MP) access. We excluded abdominal and vaginal hysterectomy as comparator.

2.5. Outcome

Primary outcome was the proportion of women successfully treated with the intended approach to perform hysterectomy without conversion to any other technique

Secondary outcomes:

1. Duration of surgery (in minutes).
2. Intra- or postoperative complications using the Clavien–Dindo classification [9,10] and postoperative infection defined by lower abdominal pain with fever (>38°) and suggestive clinical signs or laboratory findings.
3. Length of hospital stay in days.
4. Readmission after discharge.
5. Postoperative pain measured by visual analogue scale (VAS).
6. Women's health reported as incidence and severity of dyspareunia, sexual wellbeing and quality of life (QOL) measured by validated tools.
7. Comparative financial cost.

2.6. Literature Search

We developed a search strategy by combining medical subject headings (MeSH, Emtree) and free text words. The complete search strategy for all databases is presented in Appendix A.

The final literature search was done until 8 October 2020. We searched MEDLINE (PubMed interface), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). Additional sources we searched were ClinicalTrials.gov, the WHO ICTRP search portal, Web of Science, INAHTA, LILACS and Open Grey. The search of the Centre for Reviews and Dissemination (CRD) used in the first review was preplaced by that of INAHTA, as the two other databases in CRD (DARE and NHS EED) have not been updated since 2015 and are hence not relevant for the search strategy of this systematic review.

2.7. Study Selection

Two independent reviewers (SH and NN) screened the titles and abstracts and obtained full text reports of all titles that met the inclusion criteria. After screening the full text records, any disagreement was resolved by a third reviewer (JJAB).

2.8. Data Collection

Two reviewers (SH and NN) extracted data from the eligible studies using standardised data extraction forms. Data were extracted for: study design, study population, in- and exclusion criteria, interventions, comparators and outcomes. We calculated mean values and standard deviation (SD) if these were expressed as median and range for continuous data. The study authors were contacted to resolve uncertainties.

2.9. Risk of Bias Assessment

We aimed to assess the methodological quality of the selected studies by applying the RoB2 tool to assess the risk of bias in randomised trials [11] and the ROBINS-I tool for non-randomised trials [12]. The risk of bias assessment was performed by two reviewers independently (SH and NN) and disagreement was resolved by discussion and when needed by consulting a third review

author (JJAB). We aimed to assess bias across studies for each outcome measure and pool data based on study design.

2.10. Summary Measures

Continuous data were analysed as mean differences (MD) with a 95% confidence interval (CI). We analysed ordinal outcomes as continuous outcomes. Dichotomous data were reported as an odds ratio (OR) with a 95% CI.

2.11. Synthesis of Results

For the meta-analysis, we combined each outcome and calculated the summary effect size using Review Manager 5.4 software (http://training.cochrane.org). We used the Mantel–Haenszel method (M-H) for the fixed effect model for dichotomous data and Inverse Variance (IV) for the fixed effect model for continuous data. Subgroup analysis was done to compare randomised and observational studies. When possible, heterogeneity was tested by the I^2 test. Overall effect was reported as Z-score where p value < 0.05 was considered significant.

3. Results

In total, we retrieved 2504 records. MEDLINE, EMBASE and CENTRAL yielded 1799 records. The additional search described above added another 705 records. After removing duplicates (n = 732) in Endnote X9 (Clarivate Analytics, Philadelphia, PA, USA), 1772 records were uploaded in Rayyan (http://rayyan.qcri.org) and screened by title and abstract. Full text screening for eligibility was done for the remaining 51 records and six records were included in the systematic review (Figure 1).

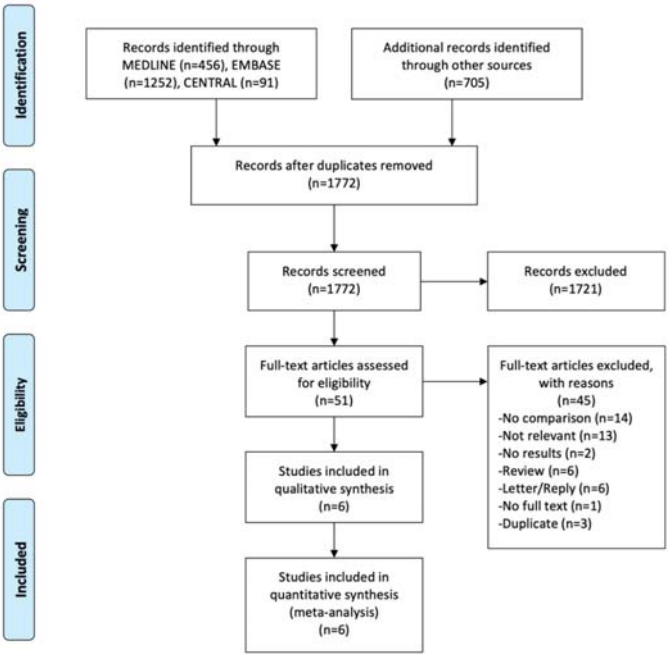

Figure 1. PRISMA flow chart.

3.1. Description of the Studies

We refer to Table 1 and Table S1 for more detailed characteristics of the included studies.

Table 1. Characteristics of the included studies.

Item	Wang 2014	Y S Yang 2014	Kim 2018	Baekelandt 2019	Kaya 2020	C-Y Yang 2020
study design	Retrospective chart analysis (Canadian Task Force Classification II-1)	Retrospective chart analysis (Canadian Task Force Classification II-1)	Retrospective chart analysis (Canadian Task Force Classification II-1)	RCT, non-inferiority trial, single blind	Cross-sectional study (retrospective)	Retrospective chart analysis (Canadian Task Force Classification II-1)
study setting	Single centre tertiary referral hospital	Single centre university affiliated hospital	Single centre university affiliated hospital	Single centre, teaching hospital	Single centre university affiliated hospital	Single centre university affiliated hospital
population	Women undergoing hysterectomy for benign uterine diseases in a non-prolapsed uterus aged 38–69 years Intervention: tVNOTEH (n = 147) Control: LAVH (n = 365)	Women undergoing hysterectomy for benign uterine diseases Intervention: NAVH (n = 16) Control: SP-LAVH (n = 32)	Women undergoing surgery for benign uterine disease, NAVH (n = 40), LAVH (n = 120)	Women 18–70 years old, undergoing hysterectomy for benign disease. vNOTES (n = 35), TLH (n = 35)	Women undergoing hysterectomy (TLH or vNOTES) for various gynaecological indications. vNOTES (n = 30), TLH (n = 69)	All women (n = 183, aged 38–56 years) undergoing TLH or vNOTES during the study period vNOTES (n = 31) and TLH (n = 152)
inclusion criteria	The indications for surgery in these patients included uterine myomas, adenomyosis, severe cervical dysplasia and menometrorrhagia.	Patients with benign uterine diseases documented by results from ultrasound examinations and who fulfilled the inclusion criteria, which included no history of pelvic inflammatory disease or medical illness.	Benign uterine disease, such as uterine myoma, adenomyosis, endometriosis	Age 18–70, benign disease such as symptomatic uterine fibroids, adenomyosis, high-grade cervical dysplasia, treatment-refractory dysfunctional uterine bleeding, atypical endometrial hyperplasia, BRCA-positive women 45 years or older	Various gynaecological indications, such as adnexal masses, uterine fibroids and treatment resistant heavy menstrual bleeding	Patients undergoing hysterectomy who did not have any of the below mentioned exclusion criteria
exclusion criteria	For tVNOTEH: history of abdominal–pelvic surgery with adhesion formation suspected, uterine prolapsed (international continence society classification Stage III or IV), suspected severe endometriosis and complete obliteration of the posterior Douglas pouch noted at pelvic examination. A history of cesarean section and nulliparity were not considered as contraindications for tVNOTEH.	History of pelvic inflammatory disease or medical illness, history of severe adhesions, suspected severe endometriosis, suspicion of gynaecologic malignancy or a fixed uterus and strong pelvic adhesions noted at pelvic examination were excluded.	Diagnosis of malignancy, findings of severe pelvic adhesions or a fixed uterus	History of rectal surgery, suspected rectovaginal endometriosis, suspected malignancy, pelvic inflammatory disease (PID), active lower genital tract infection, virginity, pregnancy	Presence of sacro-uterine nodularities, tubo-ovarian abcesses, endometriosis, pregnancy, history of colorectal surgery, uterine size above the umbilicus, uterine immobility in pelvic examination, suspicion of uterine sarcoma and any other pelvic organ malignancy	Prolapsed uterus, history of previous abdominal surgery, possibility of gynaecological malignancy, severe pelvic adhesions and a fixed uterus as determined by vaginal examination
intervention	tVNOTEH	NAVH	NAVH	vNOTES hysterctomy (VANH) plus 4 superficial non-therapeutic skin incisions identical to those in the control group	vNOTES hysterectomy	vNOTES hysterectomy
comparison	LAVH	SP-LAVH	LAVH	TLH	TLH	TLH

Table 1. *Cont.*

Item	Wang 2014	Y S Yang 2014	Kim 2018	Baekelandt 2019	Kaya 2020	C-Y Yang 2020
outcomes	Operating time, estimated blood loss, postoperative Hb, complication, postoperative stay, requirement of blood transfusion and hospital charges	Operating time estimated blood loss, decrease in hemoglobin on POD1, amount of analgesic drugs used, intra- and postoperative complications and length of postoperative hospital stay.	Operating time, intraoperative/postoperative complications, uterine weight, hemoglobin change between preoperative and postoperative day 1	Primary: removal of the uterus according to the allocated technique Secondary: operation time, proportion of hospital stay <12 h, length of hospital stay, complications, total amount of analgesics used, VAS pain scores in the first week, costs on the hospital bill until 6 weeks postoperative, occurrence and severity of dyspareunia before and 3 and 6 months after surgery, QOL at baseline and 3 and 6 months after surgery	Operating time, change in Hb and Hct, peri- and postoperative complications, length of hospital stay, conversion, VAS score at 6 and 24 h postoperative	Operating time, blood loss, decrease in hemoglobin level POD1, postoperative complication, length of stay, re-admission rate
n (vNOTES)	147	16	40	35	30	20
n (control)	147	32	120	35	30	66
operative time (min)	tVNOTEH 76.7 +/− 25.0 vs. LAVH 98.4 +/− 39.5	NAVH 70.6 +/− 12.8 SP-LAVH 93.2 +/− 21.4	NAVH 75.4 +/− 25.1 vs. LAVH 58.3 +/− 28.2	vNOTES 41 +/− 22 vs. TLH 75 +/− 27	vNOTES 79.56 +/− 32.54 vs. TLH 124 +/− 29.94	vNOTES 129.3 +/− 39.0 vs. TLH 148.1 +/− 60.7
estimated blood loss (EBL) (mL)	191.8 +/− 201.3 vs. 324.6 +/− 242.4	201.8 +/− 127 vs. 228.1 +/− 172	NI	NI	NI	53.5 +/− 74.9 vs. 43.8 +/− 83.7
decrease in Hb (g/L)	NI	1.05 +/− 1.06 vs. 1.42 +/− 1.07	0.975 +/− 0.826 vs. 1.339 +/− 1.057 (corrected after consulting author)	NI	1.1 +/− 0.9 vs. 0.84 +/− 0.93	1.14 +/− 0.6 vs. 1.09 +/− 0.75

NI: no information, tVNOTEH: transvaginal natural orifice transluminal endoscopic hysterectomy, LAVH: laparoscopy-assisted vaginal hysterectomy, NAVH: NOTES-assisted vaginal hysterectomy, SP-LAVH: single port laparoscopy assisted vaginal hysterectomy, TLH: total laparoscopic hysterectomy, LH: laparoscopic hysterectomy, AH: abdominal hysterectomy, POD1: postoperative day 1.

We retrieved one RCT and five observational studies that allowed for direct comparison between vNOTES hysterectomy and conventional laparoscopic hysterectomy.

The HALON trial by Baekelandt et al. [13] was the only published RCT that we could retrieve at the moment of this review, although we found registrations of two planned or ongoing RCTs during our search [14,15]. The HALON trial was conducted at Imelda Hospital in Belgium, from December 2015 to June 2017. The study group consisted of 70 women aged 34–68 years old who were scheduled for hysterectomy for benign disease. Study participants were randomly assigned in a 1:1 fashion to vNOTES with superficial abdominal skin incisions to allow blinding (experimental group) or TLH (control group). All surgical procedures were done by the same surgeon. Primary outcome was hysterectomy by the allocated technique. Secondary outcomes were the number of patients leaving the hospital within 12 h (day care setting), length of hospital stay, occurrence of complications, total use of analgesics, postoperative visual analogue scale (VAS) pain scores, direct health care costs, dyspareunia and quality of life (QoL).

The study by Wang et al. [16] is a retrospective cohort study conducted in 2015 at Chang Gung Memorial Hospital in Linkou, Taiwan. The study group consisted of 147 women aged 38–69 years with different indications scheduled to undergo hysterectomy by vNOTES between April 2011 and October 2013. The comparison group consisted of 365 women receiving LAVH. All surgical procedures were done by the same surgeon. The authors used a propensity score matched analysis: the sample of 147 vNOTES cases was compared with a similar number of LAVH treated women group using a "nearest neighbour" approach. The following outcomes were studied: the operative time, the estimated blood loss, complications, the length of postoperative hospital stay and the hospital charges.

The study by Yun Seok Yang et al. [17] is a retrospective cohort study conducted in 2014 at Eulji University Hospital in Doonsandong Daejeon, South Korea. The study group consisted of 16 women undergoing hysterectomy by vNOTES between July 2012 and June 2013. The comparison group consisted of 32 women undergoing hysterectomy by single port LAVH (SP-LAVH) during the same study period and who were matched by age, body mass index (BMI), parity, number of previous abdominal surgeries and weight of uterus. All surgical procedures were done by the same surgeon. The following outcomes were measured: operative time, estimated blood loss, complications, length of postoperative hospital stay, decrease in hemoglobin on postoperative day one and the total amount of analgesics used.

The study by Kim et al. [18] is a retrospective cohort study conducted in 2017 at Eulji University Hospital in Doonsandong Daejeon, South Korea. The study group consisted of 40 women undergoing vNOTES hysterectomy (in this article referred to as NAVH—natural orifice transluminal endoscopic surgery-assisted vaginal hysterectomy) between July 2012 and September 2015. These subjects were matched in terms of baseline characteristics (age, height, weight, BMI), with 120 patients undergoing conventional 3-port LAVH. The surgical procedures were done by the same team. The following outcomes were measured: operation time, complications, uterine weight, hemoglobin change between preoperative and postoperative day 1.

The retrospective cross-sectional study was conducted by Kaya et al. [19] in 2020 at the University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital in Istanbul, Turkey. During the time period reviewed, between January 2016 and 2019, the study group consisted of 30 patients that underwent vNOTES hysterectomy for various benign reasons. The control group consisted of 69 patients that underwent TLH during the same period. In the control group, 30 records were matched with the study group with a multiple logistic propensity score-matching analysis. All the surgical procedures were performed by the same surgeon. The following outcomes were measured: operating time, length of stay, VAS scores at the 6th and 24th hours, decrease in Hb/Hct and complications.

The study by Chih-Yi Yang et al. [20] is a retrospective study conducted in 2020 at the China Medical University Hospital in Taiwan. The study group consisted of 20 patients that underwent vNOTES hysterectomy for benign, non-prolapse indications between January 2015 and December 2017.

The control group consisted of 66 patients that underwent TLH in the same period. All the surgical procedures were performed by the same surgeon. The following outcomes were measured: operation time, blood loss during surgery, uterine weight, decrease in Hb level on postoperative day 1, postoperative pain scale (VAS), postoperative complications, length of stay and re-admission rate.

3.2. Risk of Bias within Studies

The RoB2 tool [11] was used to assess the risk of bias in the RCT (HALON trial). In this trial, the risk of bias was considered low. The five other included studies were observational studies, based on retrospective chart analysis, assessed for bias with the ROBINS-I tool [12]. The risk of bias was moderate, which can be attributed to the retrospective design of the studies, leading to selection bias and bias on measurement of outcomes and publication bias. A summary of the risk of bias assessment is presented in Table 2.

Table 2. Simplified summary of the risk of bias assessment.

	Baekelandt 2018	Wang 2014	Yang 2014	Kim 2018	Kaya 2020	Yang 2020
Bias due to confounding	low risk	moderate risk	moderate risk	moderate risk	moderate risk	moderate risk
Selection Bias	low risk	moderate risk	moderate risk	moderate risk	moderate risk	moderate risk
Bias in classification of interventions	low risk	low risk	low risk	low risk	low risk	low risk
Bias due to deviations from intended intervention	low risk	low risk	low risk	low risk	low risk	low risk
Bias due to missing data	low risk	low risk	low risk	low risk	low risk	low risk
Bias in measurement of outcomes	low risk	low risk	moderate risk	moderate risk	moderate risk	moderate risk
Bias in selection of reported result	low risk	low risk	low risk	low risk	low risk	low risk
Overall	low risk	moderate risk	moderate risk	moderate risk	moderate risk	moderate risk

3.3. Results of Individual Studies

Details of the individual results can be found in Table 1 and Table S1.

1. Is vNOTES equally effective as the laparoscopic approach for successfully removing the uterus without the need for conversion? The HALON trial [13] is an RCT designed to answer this question as the primary outcome. No conversions were reported. Neither did the studies by Y. S. Yang et al. [17] and Kaya et al. [19]. Kim et al. [18] reported one conversion in the experimental group, but the reason for conversion is not mentioned. The studies by Wang et al. [16] and C-Y. Yang [20] do not explicitly mention conversions in their cohorts.
2. Duration of surgery. Except for the study by Kim et al. [18], all included studies reported a shorter operation time for vNOTES compared to LAVH, TLH or SP-LAVH. This result was significant in each study except for the study by C-Y. Yang [20].
3. Intra- or postoperative complications using the Clavien–Dindo classification [9,10] and postoperative infection defined by lower abdominal pain with fever >38° and suggestive clinical signs or laboratory findings are summarized in Table 3. Clavien–Dindo score is reported in parentheses.

4. Length of stay. Four studies (Wang et al. [16], Y. S. Yang et al. [17], Baekelandt et al. [13] and Kaya et al. [19]) showed a significantly shorter length of hospital stay after vNOTES compared to their control. The other two studies did not report a significant difference.
5. Readmission after discharge. Four studies reported on readmission after discharge. Wang et al. [16] reported one readmission in the control group due to vault hematoma. S. Y. Yang et al. [17] reported no readmissions. Baekelandt et al. [13] reported one readmission in the vNOTES group (suspicion of deep venous thrombosis (DVT) demanding CT angiography) and six in the control group (two for pain, one for cuff infection, one for vault hematoma, one for repair of a vesicovaginal fistula and one for pulmonary embolism with ICU admission). C-Y. Yang et al. [20] reported three readmissions in the control group due to pelvic inflammatory disease (PID). None of these findings was significant in the individual reports.
6. Postoperative pain measured by visual analogue scale (VAS). Four studies reported on postoperative pain scores by VAS. Y.S. Yang et al. [17] reported pain scores at 12 and 24 h postoperative. VAS scores at 12 h were 2 (range 0–6) for vNOTES and 2 (0–6) for LAVH. VAS scores at 24 h were 0 (0–4) for vNOTES and 0.5 (0–8) for LAVH. None of these differences were significant. Baekelandt et al. [13] reported pain scores twice a day in the first week after surgery. Average VAS pain score was consistently and significantly lower in the vNOTES group compared to TLH. We requested and received the VAS scores on postoperative day 1 to use for this meta-analysis. Kaya et al. [19] reported VAS scores at 6 and 24 h postoperative. VAS pain score at 6 h was 6 (range 4–7) for vNOTES and 6 (3–7) for TLH. Scores at 24 h were 2 (2–4) for vNOTES and 2 (0–5) for TLH. Differences were not statistically significant. C-Y. Yang et al. [20] reported significantly lower postoperative pain scores comparing vNOTES to TLH.
7. Incidence and severity of dyspareunia, sexual wellbeing and quality of life (QOL) measured by validated tools. Only Baekelandt et al. [13] report on this outcome. They report no differences between both arms of the RCT for occurrence and severity of pain on sexual intercourse at 3 and 6 months and health related quality of life at 3 and 6 months.
8. Comparative financial cost. Two studies mention financial cost. The study by Wang et al. [16] reported significantly higher hospital charges for vNOTES compared to LAVH: 22,573.3 +/− 5528.8 vs. 17,744.6 +/− 8939.2 New Taiwan Dollar (NTD). They mention that this was driven by the higher cost of disposable devices (wound retractor and vessel sealing device) in spite of a shorter hospital stay for vNOTES. Baekelandt et al. [13] reported no difference in direct health-related cost by measuring the difference in hospital bill up to 6 weeks postoperative. The direct hospital charge for disposable devices is not reflected entirely in the hospital bill described in the latter report, as the Belgian national health insurance automatically covers the cost of disposable devices up to approximately 550 EUR.

Table 3. Summary of complications in the individual studies.

Study	Complications in vNOTES	Complications in Control
Wang 2014	*n* = 147 *intraoperative* 1 bleeding 1 bladder trauma *postoperative* 9 transfusions (II) 2 fever (I) 1 reintervention for bleeding (IIIb)	*n* = 365 *intraoperative* 3 bleeding 1 ureter trauma 1 bowel trauma *postoperative* 61 transfusions (II) 10 fever (I) 4 reinterventions for bleeding (IIIb) 1 vault hematoma (I)

Table 3. *Cont.*

Study	Complications in vNOTES	Complications in Control
Yang 2014	*n* = 16 *intraoperative* 0 *postoperative* 0	*n* = 32 *intraoperative* 0 *postoperative* 0
Kim 2018	*n* = 40 *intraoperative* 0 *postoperative* 1 fever (I)	*n* = 120 *intraoperative* 1 bladder and vagina trauma 1 bowel trauma *postoperative* 2 fever (I) 2 bleeding (II)
Baekelandt 2018	*n* = 35 *intraoperative* 1 bladder trauma *postoperative* 1 suspicion DVT (I) 1 infected hematoma (II) 1 transfusion (II)	*n* = 35 *intraoperative* 0 *postoperative* 2 pain (I) 2 vaginal cuff infection (II) 1 hematoma (I) 4 UTI (II) 1 transfusion (II) 1 ileitis (II) 1 repair vesicovaginal fistula (IIIb) 1 pulmonary embolism (IVa)
Kaya 2020	*n* = 30 *intraoperative* unclear * *postoperative* unclear *	*n* = 30 *intraoperative* unclear * *postoperative* unclear * 1 reintervention for bleeding (IIIb)
Yang 2020	*n* = 20 *intraoperative* NI ** *postoperative* 2 fever (I)	*n* = 66 *intraoperative* NI ** *postoperative* 8 fever (I) 3 PID (II)

* The report mentions bleeding and transfusion but does not state number of events nor in which arm. ** NI: no information.

3.4. Synthesis of Results

Our search for studies allowing a direct comparison between vNOTES hysterectomy and conventional laparoscopic hysterectomy yielded six studies: one RCT and five observational studies. In each study, the interventions in both comparison arms were performed by one surgeon or one team, either during or beyond their learning curve for vNOTES. Although the control groups varied in type of surgery (TLH, LAVH or SP-LAVH) and the technique for the vNOTES approach is not standardised across different studies, we considered it useful to pool the data into a meta-analysis comparing the results of the RCT to those of the observational studies. The pooled results for the different outcomes are described here.

1. Is vNOTES equally effective as the laparoscopic approach for successfully removing the uterus without the need for conversion? Zero or very few conversions were reported in the studies examined for this review. Keeping in mind possible selection bias in the observational studies and case selection applied in all reports reviewed, we consider vNOTES equally effective.

2. Is the operation time (OT) of hysterectomy by vNOTES shorter compared to laparoscopy? The pooled data showed a mean difference in operation time (OT) of 16.73 min, in favour of vNOTES (MD −16.73 (95% CI −21.04 to −12.40), Z = 7.57 ($p < 0.05$)) (Figure 2). We performed a sensitivity analysis on the outlier, the study by Kim et al. [18], which is responsible for the high heterogeneity in this subgroup. They reported a significantly shorter OT for the control group. We believe this to be attributed to the technique of LAVH described in the paper, where the dissection of the ovarian ligaments, round ligaments and broad ligaments was performed by a 45 mm EndoGia® (Covidien, Ireland).
3. Is the complication rate of vNOTES hysterectomy different compared to laparoscopy? The types of complications reported were comparable across studies and comparison arms. Intraoperative complications were of bladder or bowel injury or bleeding in both vNOTES and laparoscopic hysterectomy. The differences were not significant (OR 1.10 (95% CI 0.31 to 3.87)) (Figure 3). Postoperative infection (reported as fever or PID) was less frequent in vNOTES than in controls (OR 0.41 (95% CI 0.17 to 0.99), Z = 1.98 ($p = 0.05$) (Figure S1). Figure 4 shows the fraction of intra- and postoperative infections according to the Clavien–Dindo classification [9,10]. Clavien–Dindo grade I contains cases of fever (without mentioning treatment with antibiotics), pain and hematoma. Grade II contains cases of wound infections, PID and blood transfusion. Grade IIIb contains one case of vesicovaginal fistula repair and cases of reintervention for bleeding. The case in Grade IVa is a case of pulmonary embolism with ICU admission (summary in Table 3). The pooled data for postoperative complication show an OR of 0.38 (95% CI 0.23 to 0.62) in favour of vNOTES. This result was not significant (Figure S2). We additionally pooled data on estimated blood loss (EBL) and decrease in Hb on postoperative day 1 (Figures S3 and S4). EBL was significantly lower in vNOTES (MD −98.87 mL (95% CI −126.67 to −71.07), Z = 6.97 ($p < 0.05$).
4. What is the difference in hospital stay in women treated by vNOTES compared to laparoscopy? Although there was substantial variation in mean hospital stay between studies, hospital stay was shorter for vNOTES in each study. The pooled data showed a mean difference (MD) of 0.58 days (95% CI −0.71 to −0.45) in favour of vNOTES. Z = 8.73 ($p < 0.05$). We performed a sensitivity analysis for the outlier, the study by Kim et al. [18], which is responsible for the high heterogeneity in this subgroup. They report a range of 4–17 days in length of stay for their control group, leading to a higher MD, which was calculated from the reported median (Figure 5).
5. What is the readmission rate in women after hysterectomy by vNOTES versus by conventional laparoscopy? Pooled analysis of the reported readmissions showed a lower rate of readmissions after vNOTES (OR 0.18 (95% CI 0.03 to 1.08)). This difference was not significant (Figure S5).
6. What is the difference in postoperative pain between women treated by vNOTES hysterectomy and conventional laparoscopic hysterectomy? The randomised trial by Baekelandt et al. [13] reports lower pain scores (VAS 0–10) at 24 h postoperative (not significant), which is comparable to the pooled results extracted for three studies (MD −0.09 (95% CI −0.49 to 0.32)). The data from Chin-Yi Yang et al. [20] could not be used for the pooled analysis for this outcome as we were unable to retrieve information on the timepoint of this score after surgery. (Figure 6).
7. Are there differences in women's health after hysterectomy by vNOTES compared to laparoscopy concerning dyspareunia, sexual wellbeing or health-related quality of life? No pooled data were available since only one study reported on this outcome [13].
8. Are there differences in the financial costs of both techniques? The results of the two studies [13,16] reporting this outcome measure are too heterogenous to allow pooling of the data.

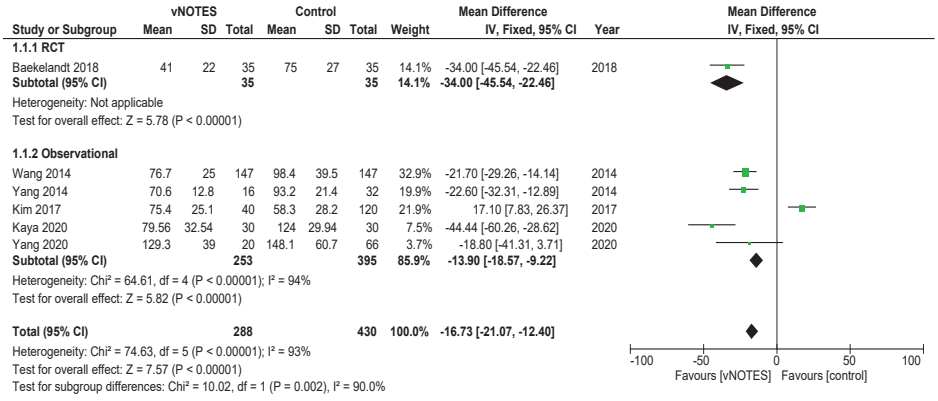

Figure 2. Forest plot of comparison vNOTES versus control, outcome: operation time.

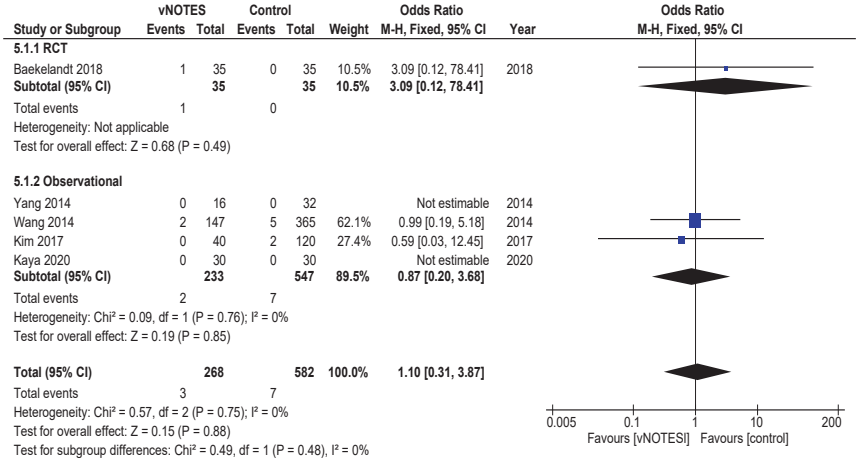

Figure 3. Forest plot of comparison vNOTES versus control, outcome: intraoperative complications.

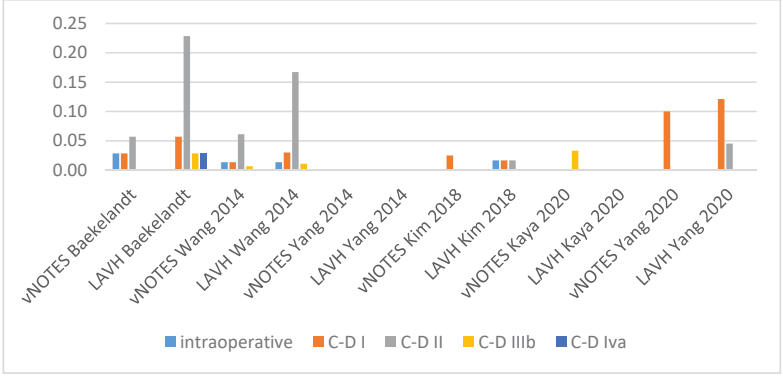

Figure 4. Intra- and postoperative complications (C-D: Clavien–Dindo score).

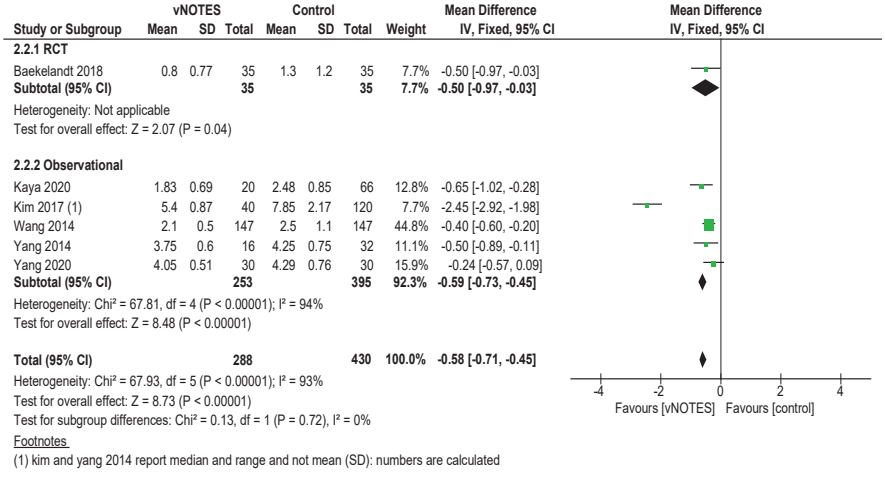

Figure 5. Forest plot of comparison vNOTES versus control, outcome: length of hospital stay.

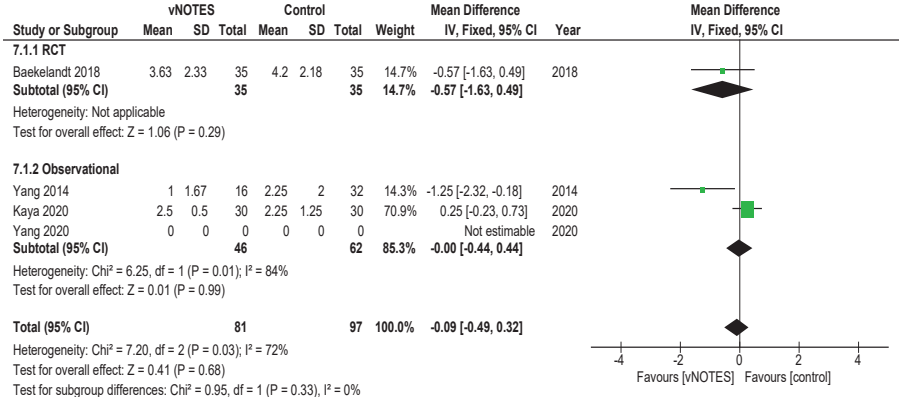

Figure 6. Forest plot of comparison vNOTES versus control, outcome: VAS pain scores Day 1.

4. Discussion

4.1. Summary of Evidence

The pooled results of the reports that we selected show that vNOTES is equally effective as conventional laparoscopy in successfully removing the uterus in individuals meeting the inclusion criteria. vNOTES had significantly lower values for operation time, length of stay and estimated blood loss. There was no significant difference in intra- and postoperative complications, readmission, pain scores at 24 h postoperative and change in hemoglobin (Hb) on day 1 postoperative. We were unable to perform meta-analysis on the outcomes on women's health and comparative cost.

4.2. Limitations

Since our search yielded only six studies, of which only one was an RCT, the strength of evidence is low. The results of the RCT are in line with those of the observational studies. The quality of the observational trials is limited due to the non-random allocation of patients. To reduce the risk for selection bias in the observational studies, two studies [16,19] used matched controls based on baseline characteristics, whereas two other studies [17,18] applied propensity score matching.

Although Chin-Yi Yang et al. [20] did not report any correction for bias, the baseline characteristics in both groups were comparable. All interventions were done by experienced endoscopic surgeons, but for vNOTES, some authors report not being beyond their learning curve. All studies involved a single surgeon or single surgical team, and the included studies are concentrated in predominantly Asian centres. This may limit the generalisability of the results.

5. Author's Conclusions

We aimed to perform a systematic review comparing vNOTES hysterectomy to conventional laparoscopic hysterectomy. Six studies were included in the meta-analysis. The available randomised and observational data show that vNOTES hysterectomy is an effective and safe novel technique for women eligible for endoscopic surgery. Further prospective multicentre randomised trials are needed which are designed to include outcomes on financial cost and women's health. Our search yielded two ongoing trials [14,15]. Although our scope was to select studies on hysterectomy for benign disease, many IDEAL stage 1 studies indicate the use of vNOTES for other gynaecological surgery. These studies report on the use of vNOTES for benign indications (adnexal surgery, myomectomy, prolapse surgery, and so on) and for oncologic indications (borderline ovarian cancer and endometrial cancer). No randomised controlled trials for these indications have been published to date.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/12/3959/s1, Table S1: Characteristics and outcomes of the included studies (supplementary to Table 1); Figure S1: Forest plot of comparison vNOTES versus control, outcome: infections; Figure S2: Forest plot of comparison vNOTES versus control, outcome: postoperative complications; Figure S3: Forest plot of comparison vNOTES versus control, outcome: Estimated blood loss (EBL); Figure S4: Forest plot of comparison vNOTES versus control, outcome: Change in hemoglobin (Hb) preoperative-postoperative day 1; Figure S5: Forest plot of comparison vNOTES versus control, outcome: Readmission after discharge.

Author Contributions: Conceptualisation: S.H., J.D., J.B.; Methodology: J.J.A.B., L.C.; Formal analysis: S.H., N.N.; Investigation: S.H., N.N.; Resources: S.H.; Data curation: S.H.; Writing—original draft preparation: S.H.; Writing—review and editing: S.H., N.N., J.B., S.K., L.C., J.J.A.B., J.D., I.A.; Supervision: J.D., J.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: J.B. (Jan Baekelandt) discloses consultancy for Applied Medical, but this did not interfere with this report.

Appendix A. Complete Search Strategy

Pubmed

("Hysterectomy" [Mesh] OR hysterectom*[tiab]) AND ((VANH[tiab] OR VAMIS[tiab] OR TVNH[tiab] OR ("glove"[tiab] AND "port"[tiab]) OR gloveport[tiab] OR "single port"[tiab] OR "single incision laparoscopic surgery"[tiab] OR SILS[tiab] OR "laparo-endoscopic single site"[tiab] OR "laparoendoscopic single site"[tiab]) OR ("Natural Orifice Endoscopic Surgery"[Mesh] OR NOTES[tiab] OR vNOTES[tiab] OR ("natural"[tiab] AND "orifice"[tiab] AND "endoscop*"[tiab])))

Embase

('hysterectomy'/exp OR 'hysterectom*':ti,ab,kw OR 'uterus amputation':ti,ab,kw OR 'uterus extirpation':ti,ab,kw) AND ((VANH:ti,ab,kw OR VAMIS:ti,ab,kw OR TVNH:ti,ab,kw OR (glove:ti,ab,kw AND port:ti,ab,kw) OR gloveport:ti,ab,kw OR 'single port':ti,ab,kw OR 'single incision laparoscopic surgery':ti,ab,kw OR SILS:ti,ab,kw OR 'laparo-endoscopic single site':ti,ab,kw OR 'laparoendoscopic single site':ti,ab,kw) OR ('natural orifice transluminal endoscopic surgery'/exp OR NOTES:ti,ab,kw OR vNOTES:ti,ab,kw OR (natural:ti,ab,kw AND orifice:ti,ab,kw AND endoscop*:ti,ab,kw)))

Cochrane Central

([mh "Hysterectomy"] OR (hysterectom*):ti,ab,kw) AND ([mh "Natural Orifice Endoscopic Surgery"] OR (VANH OR VAMIS OR TVNH OR ("glove" AND "port") OR gloveport OR "single port" OR "single incision laparoscopic surgery" OR SILS OR "laparo-endoscopic single site" OR "laparoendoscopic single site" OR (Natural AND Orifice AND Endoscop*) OR NOTES OR vNOTES):ti,ab,kw)

Web of Science (All Databases)

(TS = (hysterectom*)) AND (TS = ((Natural AND Orifice AND Endoscop*) OR "NOTES" OR "vNOTES"))

Clinicaltrials.gov

'Other terms': hysterectomy (filter: studies with results)

ICTRP WHO

Hysterectomy (filter: with results)

LILACS

tw:((tw:(hysterectomy)) AND (tw:((tw:(natural)) AND (tw:(orifice))))) AND (db:("IBECS" OR "LILACS" OR "CUMED"))

INAHTA

"hysterectomy"[mh] OR hysterectom* (filter: completed)

Open Grey

Hysterectom*

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Initial Experience with the Safe Implementation of Transanal Total Mesorectal Excision (TaTME) as a Standardized Procedure for Low Rectal Cancer

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Abstract: Introduction: The laparoscopic approach for TME is proven to be non-inferior in oncological outcome compared to open surgery. Anatomical limitations in the male and obese pelvis with resulting pathological shortcomings and high conversion rates were stimuli for alternative approaches. The transanal approach for TME (TaTME) was introduced to overcome these limitations. The aim of this study was to evaluate the outcomes of TaTME for mid and low rectal cancer at our center. Methods: TaTME is a hybrid procedure of simultaneously laparoscopic and transanal mesorectal excision. A retrospective analysis of all consecutive TaTME procedures performed at our center for mid and low rectal cancer between December 2014 and January 2020 was conducted. Results: A total of 157 patients underwent TaTME, with 72.6% receiving neoadjuvant chemoradiation. Mean tumor height was 6.1 $\pm$ 2.3 cm from the anal verge, 72.6% of patients had undergone neoadjuvant chemoradiotherapy, and 34.2% of patients presented with a threatened CRM upon pretherapeutic MRI. Abdominal conversion rate was 5.7% with no conversion for the transanal dissection. Early anastomotic leakage occurred in 7.0% of the patients. Mesorectum specimen was complete in 87.3%, R1 resection rate was 4.5% (involved distal resection margin) and in 7.6%, the CRM was positive. The three-year local recurrence rate of 58 patients with a follow-up $\geq$ 36 months was 3.4%. Overall survival was 92.0% after 12 months, and 82.2% after 36 months. Conclusion: TaTME can be performed safely with acceptable long-term oncological outcome. Low rectal cancer can be well addressed by TaTME, which is an appropriate alternative with low conversion, local recurrence, adequate mesorectal quality and CRM positivity rates.

Keywords: rectal cancer; mesorectal; transanal; laparoscopic; local recurrence; survival; conversion rate

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1. Introduction

Colorectal cancer is the third-most frequent cancer worldwide, with an incidence of up to 10.2% in Western population [1]. Low anterior rectal resection following the principles of total mesorectal excision (TME) is still the gold standard of surgical treatment for mid and low rectal cancer [2]. The quality of the TME specimen, as well as involved circumferential resection margin (CRM), have shown to be predictive for local recurrence and cancer-free survival [3–5].

Laparoscopic surgery in rectal cancer has proven beneficial regarding postoperative pain, blood loss, and wound infections, as well as recovery time [6,7]. Mid- and long-term

oncological outcome of laparoscopic surgery is similar to open resection, with a 3-year locoregional recurrence rate of 5% each [8]. Nevertheless, high positive CRM (17.2%) and conversion rates of up to 16.0% in experienced centers are reported for laparoscopic surgery [8,9].

Transanal total mesorectal excision (TaTME) was introduced for mid and lower rectal cancer and is proposed to allow a precise mesorectal dissection through better visualization in anatomically limited pelvis (male, narrow, obese). The "bottom-up" approach has been proposed to improve TME quality (88.5% complete TME) with low local recurrence rates in specialized centers in the mid-term follow-up [10–14].

Despite these promising results, Norwegian and Dutch authors recently reported early TaTME experiences with an unacceptably high local recurrence rate of almost 10% within two years and consequently critically appraised the implementation of TaTME in low-volume centers without stringent proctorship in the early implementation phase. Additionally, these results prompted a national moratorium for TaTME in Norway, blaming technical failures for the often multifocal devastating recurrences [15].

Without doubt, it has turned out that the transrectal approach harbors specific challenges, which need to be addressed properly. Interestingly, the common practice of performing an abdomino-perineal excision for low rectal cancers has somehow mitigated the prevailing lack of anatomical specification of the fascial layers around the pelvic floor, and the transanal dissection very close to tumors adjacent to the sphincter apparatus with the aim of performing a continence preserving resection unmasked these limitations. Further, the new technique may also have resulted in hampered oncological prudence for very low or advanced cancers, due to the aim of performing a sphincter preserving operation in all technically feasible cases.

Recently, however, several high-volume centers as well as international registry data contradicted the Norwegian experience, highlighting the importance of a structured training for safe implementation and indication of this challenging new technique [10,16].

The aim of the present study is to report our single-center experience of implementation of TaTME for mid and low rectal cancer, including all learning curve cases and evaluate the merit of this procedure in the management of rectal cancer.

2. Methods

2.1. Study Design

This study was a retrospective analysis of all consecutive patients undergoing TaTME in our center as recorded in the prospectively maintained international TaTME registry from December 2014 to January 2020. The LOREC® TaTME registry is a database collecting clinical and histopathological data of patients undergoing surgery with transanal assistance for benign and malignant diseases described as TaTME. All consecutive patients treated at our institution had been included prospectively in this database. All patients provided written informed consent for being treated with the new technique of TaTME, as well as for the Charité IRB-approved (Reg.-No. 711/16) data collection within the international registry and retrospective data analysis.

Patients data were entered in pseudonymized form by the clinical team including the following information:

- Patient data: sex, date of birth;
- Pre-operative information: tumor staging (CT/MRI), previous treatments (e.g., neoadjuvant treatment);
- Surgery specific data;
- Post-operative course;
- Long-term follow-up data (Complications—Clavien–Dindo; readmissions);
- Histopathological and oncological outcomes.

2.2. Surgical Technique

Patients were placed in the lithotomy position and prepped the usual way for rectal cancer surgery. Care was taken to ensure comfortable positioning of the legs in bootstraps and extensive padding within a vacuum mattress to enable firm immobility within the steep Trendelenburg position during surgery. Whenever possible, a two-team approach with an abdominal and a transanal team was used. When two teams worked together, the pneumoperitoneum was established first to prevent retroperitoneal air cushioning due to the sub-peritoneal air inflation during TaTME. Both the abdominal and the transanal team worked with a pressure of 14mmHg.

2.3. Abdominal Procedure

The abdominal cavity was entered through an umbilical access and, usually, a multi-port approach was used. As the specimen was always extracted through the abdominal wall, the retrieval site was either the umbilicus, or—if performed—the ileostomy site in the right lower quadrant. First, the inferior mesenteric vein (IMV) was identified and mobilized from medial to lateral, with care taken to preserve the anterior layer of the renal fat capsule and not to mobilize the pancreatic tail. Next, the inferior mesenteric artery (IMA) was identified and mobilized. The mesocolic plane was identified from medial to lateral preserving the fascia of Told covering the left ureter. The IMV was clipped close to the inferior margin of the pancreas, and the left colic flexure was completely mobilized. The IMA was double-clipped and transected close to its origin from the aorta (high-tie), and care was taken to mobilize the surrounding lymphatic tissue without damage to the hypogastric nerve fibers. The greater omentum was dissected from the transverse mesocolon and the lesser sac entered starting from the level of the falciform ligament. The left colic flexure was taken down. To ensure maximum mobility of the colon, the left-sided transverse mesocolon was completely mobilized, and transected close to the pancreas from lateral to medial close to the first left-sided branches of the middle colic vessels. The TME planes were completed in a circular fashion. Anteriorly, the peritoneum was only incised at the lowest point of the cul-de-sac, and the circular dissection pursued down to the level of S3.

2.4. Transanal Phase

2.4.1. Prepping of the Transanal Access

After sterile prepping, a LoneStar (CooperSurgical, Trumbull, CT, USA) retractor was put in place and the anal sphincter carefully dilated. If the tumor was located more than 2–3cm above the dentate line, the transanal port (GelPoint Path, Applied Medical) was introduced, and two wet swaps placed inside the rectum below the tumor. The transanal insufflation using the AirSeal System (CONMED, Utica, NY, USA) was initiated. The first step was a safe purse string suture using a monofilament 2–0 suture below the swap to tightly close the rectum with the tumor. The insufflation was terminated, the port opened and the purse string suture closed tightly. Next, the distal rectal stump was rinsed with iodine-saline solution. Following re-insufflation of the rectal stump, the rectum was transected using the monopolar cautery hook, and the TaTME procedure started.

In cases of lower tumors, the anal canal was dilated and a conventional anal canal retractor introduced. After positioning of a swap inside the rectum to avoid any spilling, and making sure to maintain at least a 1cm distal margin to the tumor, the rectum was cut with monopolar energy and, simultaneously, the purse string suture was set, making sure to completely evert the tumor bearing inner part of the rectum and firmly close the purse string. A second purse-string suture was set if first was insufficient. In case of very low rectal cancers (iuxtasphinteric), frozen sections from the resection surface or the external part of the rectum were performed to ensure tumor-free distal and circumferential margins (R0). After that, the transanal port was put in place and the space rinsed with iodine/saline solution. During the whole procedure, any compromise to the tightness of the purse string was immediately corrected by a second purse string sutures.

2.4.2. Transanal Resection

Following transection of the rectum, the levator muscle was identified at the dorsal circumference covered by the endopelvic fascia. Following the transsection layer to the anterior aspect, the rectum was completely mobilized and the caudad beginning of the mesorectal plane identified. Care was taken to leave the deep pelvic fascia covering the levator muscle, and to spare the fibrous tissue dorsal to the urethra on the ventral side. In a screwed circumferential way, the dissection was driven cranially to the abdominal and transanal rendezvous. Transanal preparation was performed using the monopolar hook and applying the traction-countertraction principle to expose the mesorectal dissection planes. Following the rendezvous (typically first on the ventral 12 o'clock position, then on the dorsal 6 o'clock position), the lateral transection was performed in collaboration between the abdominal and the transanal team.

The specimen was harvested through the abdominal wall, and depending transection level, either a transanal stapled or a hand-sewn transanal side-end coloanal anastomosis was performed. Hand-sewn anastomoses were performed with interrupted sutures (3–0 absorbable polyfilament thread) in side-to-end or end-to-end fashion. Stapled anastomoses were performed using a 29 or 33mm circular stapler in side-to-end or end-to-end fashion.

All patients were transanally drained for 48 h, and a transabdominal drain was placed in the pelvis for 48 h.

2.5. Patients

The potential indication for a TaTME approach was given if a TME for mid/low rectal cancer (at or below 12cm from the anal verge (AV)) was indicated by our multidisciplinary tumor board. While early in the experience, all TME-patients were evaluated for a transanal approach, we later switched to an anatomy driven approach, allocating patients low rectal cancer (<6cm from the AV), and patients with a bulky tumor or a narrow and/or deep pelvis to a TaTME procedure.

Both male and female patients were included. Patients were included independent of their T stage (mrT1-T4) and 65.8% of the study population were diagnosed preoperatively with positive lymph nodes (mrN+). Thoraco-abdominal computed tomography (CT) and MRI-scan of the lower abdomen and pelvis were routinely performed preoperatively to stage rectal cancer patients.

Tumor recurrence up to 180 days after diagnosis were defined as synchronous cancer occurrence, and, therefore, listed as preoperative M+ stage.

2.6. Statistical analysis

Data were reported as mean +/− standard deviation or total numbers (%). Intergroup comparisons were conducted using the Chi-2 test for dichotomous variables, and the student t-test for parametric numeric, or the Mann–Whitney U test for non-parametric numeric variables. Normal distribution was determined using the Kolmogorov–Smirnov test. Survival analyses were conducted using the Kaplan–Meier method and the log-rank test. For all analysis, a p-value of equal or below 0.05 was considered statistically significant.

3. Results

Between December 2014 and January 2020, 157 consecutive patients with mid or low rectal cancer underwent combined procedure (laparoscopic and transanal) for TME at our institution. A total of 317 patients underwent surgical treatment for rectal cancer between 2014 and 2020, in 157 (49.5%) patients TaTME was performed. A total of three patients (1.9%) had metastatic disease at time of initial diagnosis (synchronous liver metastasis). A total of seven (4.5%) patients were staged with T4 in the pre-treatment MRI. Involvement of the mesorectal fascia of less than 1mm was suspected in 54 (34.2%) patients. The preoperative patient characteristics are listed in Table 1.

Table 1. Patient characteristics (n = 157).

Age (y); mean ± SD	60.6 ± 12.4
Sex; *n* (%)	
Male	117 (74.5)
Female	40 (25.5)
BMI (kg/m^2); mean ± SD	26.2 ± 5.0
ASA classification; *n* (%)	
ASA 1	14 (8.9)
ASA 2	104 (66.2)
ASA 3	35 (22.3)
ASA 4	4 (2.5)
Tumor height AV (cm); mean ± SD	6.1 ± 2.3
Tumor height AV; *n* (%)	
>6cm	64 (40.8)
≤6cm	93 (59.2)
Neoadjuvant treatment; *n* (%)	
Yes	114 (72.6)
No	43 (27.4)
Preoperative T stage; *n* (%)	
mrT0	1 (0.6)
mrT1	5 (3.2)
mrT2	36 (22.9)
mrT3	100 (63.6)
mrT4	7 (4.5)
mrTx	8 (5.1)
Preoperative N stage; *n* (%)	
mrN-	42 (26.8)
mrN+	104 (66.3)
mrNx	11 (7.0)
Preoperative M stage; *n* (%)	
M0	137 (87.3)
M1	20 (12.7)
Preoperative mrCRM+ *; *n* (%)	54 (34.2)

ASA, American Society of Anesthesiologists; AV, Anal verge; BMI, Body mass index; CRM, Circumferential resection margin; mrTNM, TNM stage on preoperative MRI; SD, Standard deviation; * Positive CRM on MRI is defined as the distance of tumor or malignant lymph node to the mesorectal fascia of ≤1 mm.

The mean tumor height was 6.1 cm and 59.2% of the tumors were located at 6 cm or below from the AV. Neoadjuvant treatment had been performed in 72.6% of the patients.

3.1. Intraoperative Data

Intraoperative data are displayed in Table 2. In total, 85.4% of all surgeries were performed in a simultaneous two team-approach (i.e., at least the rendezvous procedures between abdominal and transanal part were done simultaneously). Laparoscopic abdominal dissection was performed in 98.1%. The abdominal conversion rate was 5.7%. All conversions were due to medical reasons (morbid obesity, CO_2 retention, adhesions) for the abdominal part, no conversion was necessary for the transanal dissection. Mean anastomotic distance from the AV was 3.5cm. The majority of the anastomoses were stapled and, in seven patients, TaTME was primarily performed as low Hartmann procedure without anastomosis. In 86%, a defunctioning loop ileostomy was created and, in 10.2%, no stoma was created. A total of 3.8% of the patients were resected without reconstruction with creation of a terminal colostomy. No urinary tract (ureter/urethra) injury occurred.

Table 2. Intraoperative data (n = 157).

Operative time (min); mean ± SD	306.6 ± 108.5
Two-team approach; *n* (%)	134 (85.4)
Abdominal dissection; *n* (%)	
Open	3 (1.9)
Laparoscopic	154 (98.1)
Conversion; *n* (%)	
Abdominal	9 (5.7)
Perineal	0 (0.0)
Defunctioning stoma; *n* (%)	
None	16 (10.2)
Ileostomy	135 (86.0)
Colostomy	6 (3.8)
Anastomotic technique; *n* (%)	
None	7 (4.5)
Hand-sewn	54 (34.4)
Stapled (circular)	96 (61.1)
Anastomotic distance from AV (cm); mean ± SD	3.5 ± 1.5
Urinary tract trauma; *n* (%)	0 (0.0)
Pursestring failure; *n* (%)	10 (6.4)

AV, Anal verge; SD, Standard deviation.

3.2. Postoperative Outcome

Postoperative outcomes are listed in Table 3. In-hospital and 30-day overall complication rate was 31.2%. A total of twenty-one patients (13.4%) required a re-operation. In total, four patients were re-operated due to ischemia of the colon with preservation of the anastomosis in one patient and permanent deviation in three patients. A total of two patients were operated due to small bowel obstruction; one due to an internal herniation, the other due to stenosis at the ileostomy site, resulting in early stoma closure with healed colorectal anastomosis.

In 11 patients (7.0%), an early anastomotic leakage (defined as occurring within 30 days postoperatively) was observed. Four anastomoses successfully healed under endoluminal VAC therapy (36.4%) and seven patients (63.6%) required re-operation, five of them after initial endoluminal VAC therapy for damage control. A total of three patients (27.3% of patients with leakage and 1.9% of the overall study population) were discharged with a permanent colostomy. In total, ten of eleven (90.9%) patients with anastomotic leakage underwent TaTME with planned defunctioning stoma.

Neither disease-free survival (Figure 1) nor overall survival (Figure 2) were shown to be influenced statistically significantly by occurrence of anastomotic leakage (p = 0.958 and p = 0.750, respectively). A total of three patients (1.9%) died within 30 days: One patient died on postoperative day four in the course septic multiple organ failure after reoperation for colonic ischemia. One patient died on postoperative day eight due to a myocardial infarction. The third patient died 15 days post-operation with an ischemic brain damage after cardiogenic shock and resuscitation due to cardiac comorbidities.

Table 3. Postoperative Outcome (n = 157).

Complications; n (%)	49 (31.2)
Anastomotic leak	11 (7.0)
Colon ischemia	5 (3.2)
Compartment syndrome	1 (0.6)
Haemorrhage	2 (1.3)
Internal hernia	1 (0.6)
Obstruction	2 (1.3)
Perforation	1 (0.6)
Stoma complication	5 (3.2)
Wound breakdown	14 (8.9)
Cardiovascular complication	3 (1.9)
DVT	1 (0.6)
PE	2 (1.3)
Pulmonary complication	4 (2.5)
Renal Failure	7 (4.5)
Urinary tract infection	3 (1.9)
Others	3 (1.9)
Re-operation	21 (13.4)
Early anastomotic leak *; n (%)	11 (7.0)
Endoscopic therapy	9 (81.8)
Re-operation	7 (63.6)
Definitive stoma after leakage	3 (27.3)
Length of stay (days); mean ±SD	11.4 ± 9.2
Surgical morbidity (Clavien–Dindo III-V) **; n (%)	30 (19.1)
Postoperative death	3 (1.9)

AV, Anal verge; SD, Standard deviation; * Early anastomotic leak is defined as the overall anastomotic failure within the first 30 postoperative days. ** Surgical morbidity (Clavien–Dindo III-V) is defined as the overall morbidity/mortality within the first 30 postoperative days.

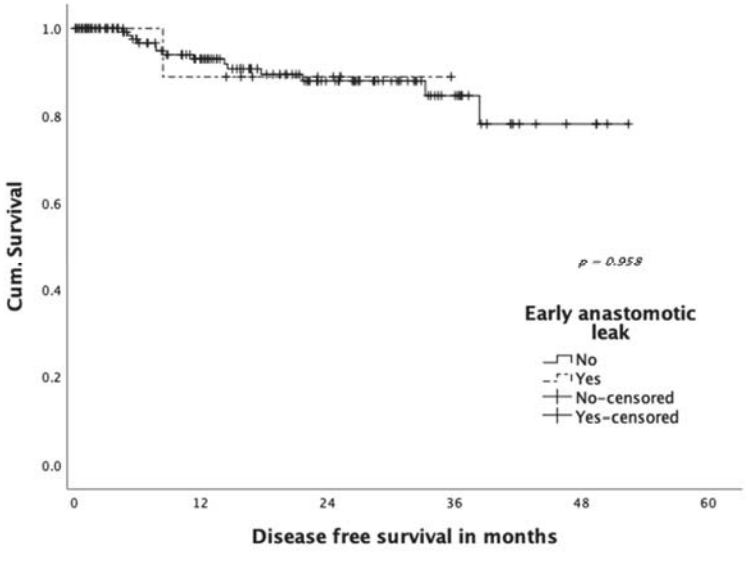

Figure 1. Disease-free survival according to early anastomotic leakage.

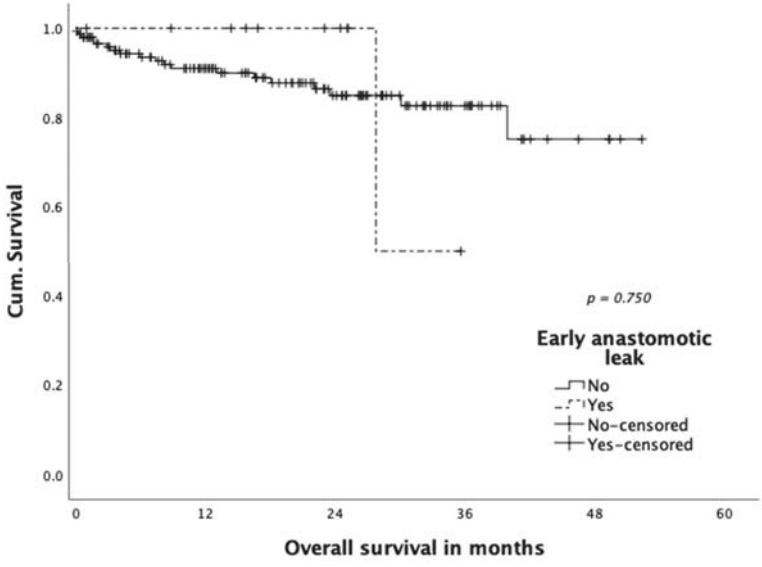

Figure 2. Overall survival according to early anastomotic leakage.

Regarding the learning curve, we divided our patient cohort into four equal groups according to case number (e.g., 1: n = 1–40, 2: n = 41–80, etc.) and analysed overall and severe complication rates as well as leakage rates (Figure 3). Over time, we recognized a decrease in complications and anastomotic leak rates, which, however, did not reach statistical significance. The data point to a flat and long learning curve due to the challenging technique.

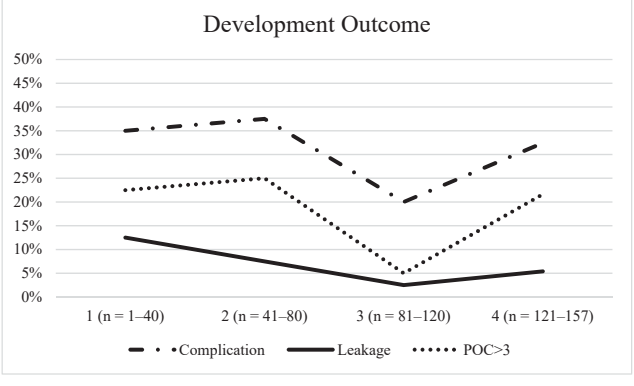

Figure 3. Development Outcome.

3.3. Histopathological Outcome

Mean CRM was 14.5 mm and, in 7.6%, the CRM was positive (Table 4). Positive marginal status did not differ between patients with low rectal tumors (<6cm) (7.6%) and tumors >6cm from anal verge (7.7%). Complete pathological response (pCR) following chemoradiation was detected in 19.3% (ypT0), with a mean number of harvested lymph nodes of 16.2. In 87.3% of the specimens, mesorectal quality was reported as complete (Mercury grade 1) and R1 resection rate was 4.5% (involved distal resection margin).

Table 4. Histopathological outcome (n = 157).

Tumor size (mm); mean ± SD	27.5 ± 17.4
Distal margin (mm); mean ± SD	21.0 ± 22.0
Circumferential margin (mm); mean ± SD	14.5 ± 11.4
Positive circumferential margin *; *n* (%)	12 (7.6)
Positive circumferential margin; *n* (%) Tumor height from AV >6cm, (n = 65) Tumor height from AV ≤6cm, (n = 92)	 5 (7.7) 7 (7.6)
No. lymph nodes harvested; mean ± SD	16.2 ± 6.3
pTMNT; *n* (%) T0 T1 T2 T3 T4 Tx	 26 (16.6) 17 (10.8) 55 (35.0) 52 (33.1) 6 (3.8) 1 (0.6)
pTMNN; *n* (%) N0 N1 N2	 112 (71.3) 30 (19.1) 15 (9.6)
Quality of mesorectal specimen (Mercury grade); *n* (%) I (complete) II (nearly complete) III (incomplete) Missing	 137 (87.3) 12 (7.6) 3 (1.9) 5 (3.2)
Resection margin R1; *n* (%)	7 (4.5)

AV, Anal verge; SD, Standard deviation; * Positive circumferential margin is defined as the distance of tumor or malignant lymph node to the mesorectal fascia of ≤1 mm.

3.4. Oncological Outcome

The oncological outcome is shown in Table 5.

Table 5. Oncological outcome (n = 157).

Follow-up (mo); mean ± SD (range)	19.5 ± 13.5 (0.1–52.3)
Local recurrence, *n* (%) Local recurrence only Simultaneous local/systemic recurrence Tumor recurrence (systemic), *n* (%) Death, *n* (%) Cancer Not cancer related 30-day mortality Unknown	6 (3.8) 3 (1.9) 3 (1.9) 13 (8.3) 22 (14.0) 10 (45.5) 4 (18.2) 3 (13.6) 5 (22.7)
3-year follow up * (n = 58) Local recurrence, *n* (%) Local recurrence only Simultaneous local/systemic recurrence Tumor recurrence (systemic), *n* (%) Death, *n* (%) Cancer Not cancer related 30-day mortalityUnknown	 2 (3.4) 0 (0.0) 2 (3.4) 7 (12.1) 12 (20.3) 7 (58.3) 2 (16.7) 1 (8.3)2 (16.7)

SD, Standard deviation; * Patients with a complete 3-year follow-up.

Figure 4 shows an overall disease-free survival after 12 months of 92.2%, and 85.2% after 36 months, respectively. After a mean follow-up of 19.5 months, we recorded a local recurrence rate of 3.2% in our patients, with an actual three-year local recurrence rate of 3.4% in 58 patients with a follow-up exceeding 36 months.

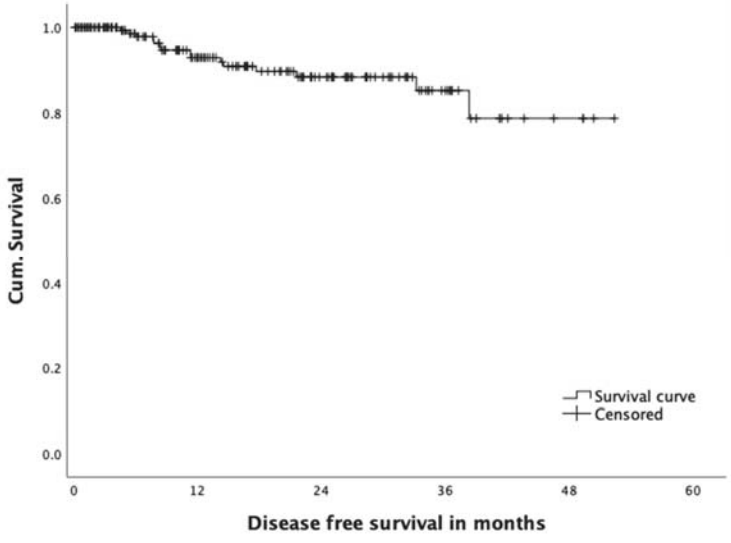

Figure 4. Overall disease free survival.

Three patients (1.9%) were diagnosed with simultaneous local and systemic recurrence and further three patients (1.9%) with only local recurrence in the follow-up. A total of thirteen (8.3%) patients developed distant metastatic disease. Mean time to the occurrence of local and systemic recurrence did not differ significantly (14.2 vs. 13.9 months). Tumor recurrence significantly impacted overall patient survival (local and systemic) and is displayed in Figure 5 (36-month survival rate 41.1% in patients with tumor recurrence versus 89.3% without recurrence ($p = 0.001$)). The impact of local recurrence versus systemic recurrence was compared separately in Figure 6, with a significantly reduced overall survival in patients with both local as well as systemic tumor recurrence ($p = 0.002$).

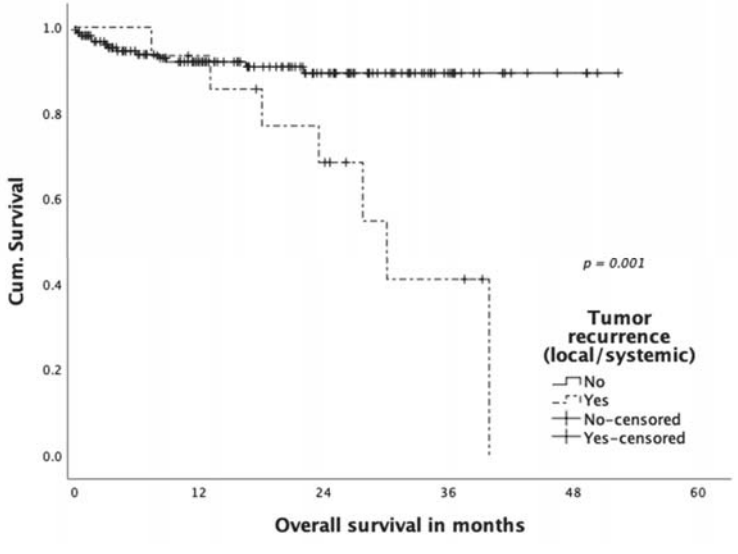

Figure 5. Overall survival according to tumor recurrence.

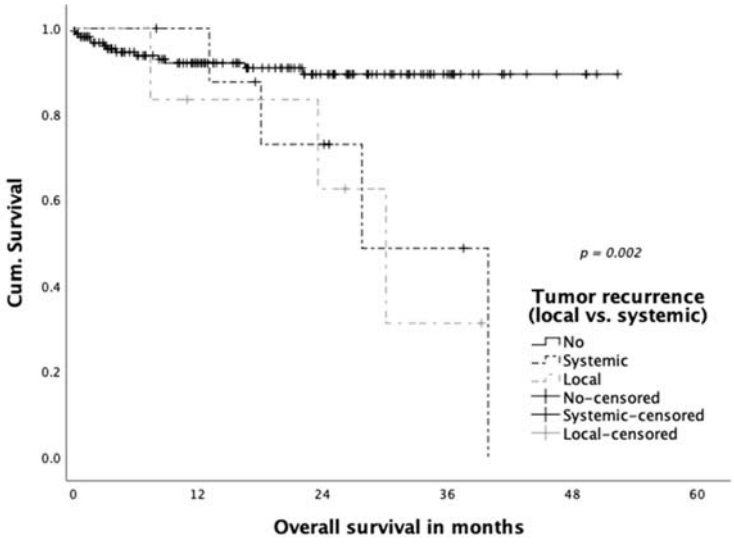

Figure 6. Overall survival according to site of tumor recurrence (local/systemic).

A total of fourteen percent of the patients died within the observational period. A total of 6.3% of the deaths were cancer related, 2.5% were not cancer related, three patients (1.9%) died postoperatively (30-day mortality) and, in 3.2%, cause of death could not be determined. Overall survival is shown in Figure 7. Overall survival was 92.0% after 12 months and 82.2% after 36 months.

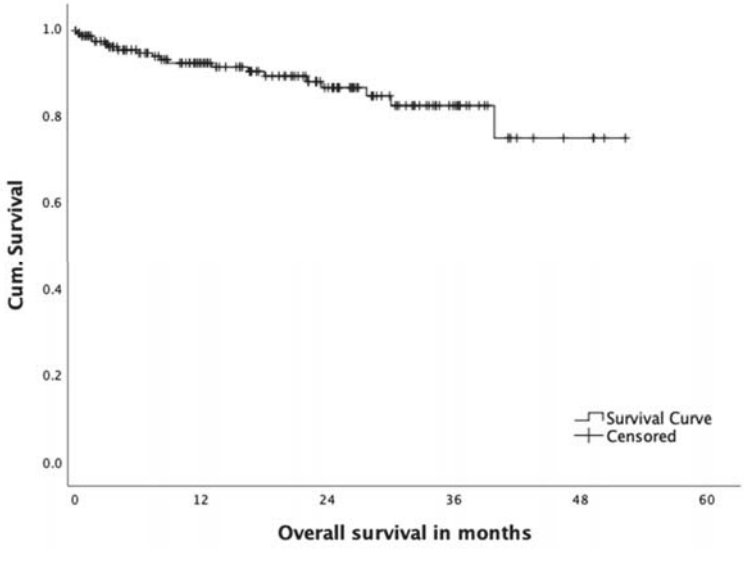

Figure 7. Overall survival.

4. Discussion

The concept of a transanal approach to rectal cancer treatment was first developed from a NOTES perspective, using the anus as an access route [17]. This concept did not flourish in terms of reducing the abdominal access trauma; however, it improved the

dissection of the lower third of the rectum close to the pelvic floor by direct visualization of the structures and the ability to access the supralevatoric rectum through a direct, straight access. The concept was evaluated with interest, as laparoscopic rectal surgery is equal to open surgery [7], but even in highly proficient centers, conversion rates, especially in low rectal cancer patients, are constantly reported to be around 15% [8]. Furthermore, the rates of "technical" excision of the sphincter in patients, who could have received a continence-preserving procedure are ill documented, but may range up to one out of four patients with low rectal cancer. Therefore, irrespective of other technical developments such as improvements in surgical instruments or robotic systems in transabdominal colorectal surgery, the access from below and the possibility of not having to exceed the tumor in the rectum in order to reach the projected anastomotic region is appealing. It is able to work under constant direct control of the margins directly on the pelvic floor and the sphincter complex. This defines the merits and potential benefits of such an access. This is not only relevant for the correct oncologic treatment of low rectal tumors, and the chance to prevent a definitive colostomy, but also to potentially better preserve nerval function and, thus, maintain quality of life in this patient cohort. According to our own data derived from the first 50 TaTME cases, LARS Score after 12 months was 27 (minor LARS; $n = 39$). 24 months after surgery a median LARS score of 14 (no LARS; $n = 34$) was assessed, highlighting a significant reduction ($p < 0.001$) due to pelvic floor exercise and transanal irrigation. However, only scarce prospective data about non-inferiority pelvic floor function and quality of life of TaTME patients in comparison to a conventional abdominal approach are available so far [18–20].

Furthermore, in 6.4%, a purse string failure was recognized intraoperatively and a second purse string was set immediately. This shortcoming and technical failure was reported in the TaTME community and recommendations for a second purse string suture was highlighted in the COLOR III study protocol amendment [21]. Regarding the oncological outcome, we did not detect any local recurrences in patients with purse string failure in our study group.

Surgical and oncological outcome of TaTME for low and mid rectal cancer was demonstrated to be equal compared to conventional TME (laparoscopic and open) in a meta-analysis of observational and matched-paired cohort studies [14]. However, data from randomized controlled trials (COLOR III and ETAP-GRECCAR 11 trials) are still missing to correctly answer this question of non-inferiority [21,22]. Significant difference was reported in the conversion rate to the open approach between TaTME and laparoscopic TME (1.4% vs. 8.8%; OR 0.17; 95% CI 0.1–0.29, $p < 0.00001$) [14], which was nil in our cohort.

Simillis et al. could not demonstrate any significant difference in local recurrence rate, disease-free survival and overall survival in the 5-year-follow-up in a network meta-analysis including all TME techniques (open, $n = 2350$; lapTME, $n = 3276$; robotic, $n = 561$; TaTME, $n = 50$) [23].

Significant superiority of TaTME, however, was shown in the rate of negative CRM, which was confirmed by Hajibandeh et al. (OR 0.67; 95% CI 0.45–0.98, $p = 0.04$) [14].

The published data reflect the TaTME pioneering centers' experience, also including cases from the beginning of the learning curve. A selection bias, however, with inclusion of cases with accumulation of risk factors for inappropriate TME cannot be disclaimed. Those were exclusively excluded in comparing studies like COLOR II [8,10,13,16,24–26].

Respecting this, local recurrence rates like those in our own series (3.2% at 3-year follow-up) after overcoming the learning curve are remarkable and comparable with 2–3-year follow-up data of the laparoscopic arms in the ACOSOG Z6051 trial (4.5%) and the COLOR II trial (5%) [8,27].

Worrying data from Norway and the Netherlands regarding multifocal local recurrences in the short-term follow-up (7.4 and 10%) significantly higher than those from national and international controls (2.4 and 1.8%) resulted in critical appraisals facing results of experienced high-volume centers with regard to center and selection bias and questioning inclusion of learning curve cases [25]. We think that our series of consecu-

tive patients undergoing TME for mid and low rectal cancer clearly demonstrates the flat learning curve of the transanal approach even in experienced hands and a distinguished minimally-invasive institution. Additionally, we have entered all patient data into the international TaTME registry [28] for transparency and ongoing quality control.

The transanal approach inevitably results in a very low anastomosis within less than 2cm of the dentate line and, therefore, in our opinion, is not suitable as a "one-fits all" approach to mid and low rectal cancer surgery. However, in this series, it has proven to be a very versatile approach to the pelvic floor and allowed for safe dissection of this area in all patients, as documented by our 0% conversion rate for the transanal part of the procedure. Therefore, irrespective of the minimally invasive technique used for the abdominal phase of the operation, we think the technique has earned its merits for every situation, when the superior approach is limited or compromised by anatomical or tumor-related specific findings. With regard to the published problems of tumor-spread through the direct preparation, it needs to be reiterated that (1) a complete seal of the tumor site from the subperitoneal dissection plane, where the insufflation device (AirSeal®) results in a constant circulatory flow, and (2) no alteration of the oncologic understanding of proper resection margins, as they were implemented in rectal surgery decades ago, are absolutely key to performing a safe TaTME and strictly need to be adhered to. Unfortunately, as in many innovative techniques, the transanal approach for rectal cancer surgery is also threatened to be compromised by a too-quick distribution and too-loose indication by the surgical community.

Consequently, colorectal societies in many countries have raised concerns about structured training curricula due to the complexity of TaTME and fostered proctorship for the first own TaTME cases [25,29,30] to encounter technical pitfalls of the transanal approach (e.g., urethral injury or unfavourable oncological results due to technical failures like insufficient purse-string sutures). In those centers continuing the TaTME programme beyond 45 cases, local recurrence rates leveled off below 4% comparable to the rate we have observed in our series of >150 cases. In our center, the first 100 cases of TaTME were performed by the same team of leading surgeons (F.A. and M.B.) to sustain quality after having overcome the flat learning curve.

International recommendations aim at a minimum of 25 annual cancer resections by TaTME following the indications for benign or malignant rectal resection where there is anticipated technical difficulty in pelvic dissection; ideally reaching >40 annual resections involving the rectum for benign and/or malignant disease [31]. The high-volume of rectal cancer cases is therefore decisive since potential training TaTME cases are vanishing if indications for TaTME are restricted (e.g., not including high rectal cancer, T4 or sphincter involving or early rectal cancer).

TaTME is, therefore, reserved for sub-specialized colorectal institutions and should be selectively applied for patients with mid and low rectal cancer. After completion of a structured training programme, TaTME is a helpful alternative in cases where supraanal or intersphincteric resection are planned and, thus, performed by colorectal specialists, including cases where conversion and salvage strategies (APE) are discussed.

5. Conclusions

Hybrid laparoscopic and TaTME is technically challenging with additional staff requirement especially when performed synchronously. TaTME shows a flat learning curve; however, it is proposed as a relevant alternative not only in mid rectal cancer but especially in low rectal cancer cases with anatomical limitations. In our study cohort, we observed low conversion rates— respectively, none in the transanal part as well as a low local recurrence rates.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Charité Universitätsmedizin Berlin (protocol code 711/16 and date of approval 22 Nov 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Due to the principals of this research, participants of this study did not agree that their data is shared publicly, so supporting data is not available. For further information please contact the corresponding authors (L.D.; F.A.).

Conflicts of Interest: F.A. and M.B. received educational grants and honorarium for TaTME training courses and invited talks from Applied Medical, Storz and Olympus.

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Hydroceles of the Canal of Nuck in Adults—Diagnostic, Treatment and Results of a Rare Condition in Females

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Abstract: Nuck's hydroceles, which develop in a protruding part of the parietal peritoneum into the female inguinal canal, are rare abnormalities and a cause of inguinal swelling, mostly resulting in pain. They appear when this evagination of the parietal peritoneum into the inguinal canal fails to obliterate. Our review of the literature on this topic included several case reports and two case series that presented cases of Nuck hydroceles which underwent surgical therapy. We present six consecutive cases of symptomatic hydroceles of Nuck's canal from September 2016 to January 2020 at the Department of Surgery of Charité Berlin. Several of these patients had a long history of pain and consecutive consultations to outpatient clinics without diagnosis. These patients underwent laparoscopic or conventional excision and if needed simultaneous hernioplasty in our institution. Ultrasonography and/or Magnetic Resonance Imaging were used to display the cystic lesion in the inguinal area, providing the diagnosis of Nuck's hydrocele. This finding was confirmed intraoperatively and by histopathological review. Ultrasound and magnetic resonance imaging (MRI) captures, intraoperative pictures and video of minimal invasive treatment are provided. Nuck's hydroceles should be included in the differential diagnosis of an inguinal swelling. We recommend an open approach to external Type 1 Nuck´s hydroceles and a laparoscopic approach to intra-abdominal Type 2 Nuck hydroceles. Complex hydroceles like Type 3 have to be evaluated individually, as they are challenging and the surgical outcome is dependent on the surgeon's skills. If inguinal channel has been widened by the presence of a Nuck's hydrocele, a mesh plasty, as performed in hernia surgery, should be considered.

Keywords: cysts of the canal of Nuck; Nuck hydrocele; hydrocelectomy; TAPP; Lichtenstein

1. Introduction

The canal of Nuck was first described by the Dutch anatomist Anton Nuck in 1691. As the female fetus develops, the ligamentum rotundum of the uterus descends down to the ipsilateral labia majora, extending through the inguinal canal. Along with the round ligament, a peritoneal evagination also descends, which is known as the canal of Nuck. The homologous structure in men is called the processus vaginalis [1].

More precise embryologically, the processus vaginalis—in women named canal of Nuck—becomes clinically apparent within the 12th week of gestation. Normally it obliterates from the seventh month

of gestation to one year of age. Persistently open canals of Nuck present most often in girls before the age of five [1–4]. The Nuck hydrocele corresponds to the male hydrocele testis [4]. Nuck's hydroceles or inguinal hernias occur in 9–11% of infants born prematurely, as the obliteration of the processus vaginalis begins during pregnancy [5].

Classification divides the Nuck hydroceles into three types [6]:

- Type 1: there is no communication between hydrocele and peritoneal cavity. It mostly appears as an encysted mass without hernia defect in children. Examples for this type are the intra-abdominal protruding forms. In adults, we assume the fascia transversalis along with the ligamentum rotundum is thinned out because of the hydrocele, mimicking a direct hernia [6].
- Type 2: the hydrocele communicates with the peritoneal cavity, thus mostly resulting in an indirect hernia [6].
- Type 3: or combined type has an encysted part that does not communicate with the peritoneal cavity and another that does. Its appearance resembles an hourglass and commonly causes a hernia [6].

To have a successful clinical outcome after surgery, complete excision of the hydrocele is recommended [7]. Following that, if a hernia defect is identified it requires repair by hernioplasty. There are about 134 publications on PubMed covering this topic, but only few case series and even fewer that compare the different surgical therapy options with each other. Especially, hydrocele of the canal of Nuck in adults have been reported only in single case presentations. To our knowledge, no case series with a cohort of adult females with Nuck's hydrocele has been published so far.

In our case series, we present six patients aged 29 to 44 with hydrocele of the canal of Nuck. Four of them received a Transabdominal Preperitoneal Patch Plasty (TAPP), one had an open hernia repair using the Lichtenstein method and another one an open hydrocelectomy along with a fascial suture, because there was no defect of the abdominal wall. We aim to share our experience on this rare condition and demonstrate that both types of hernioplasty can be performed for repairing a hernia caused by a Nuck hydrocele according to localization. Furthermore, we reviewed the case reports and case series published so far and compared their results and conclusions.

2. Methods

From 2016 to 2020, six cases of Nuck's hydroceles presented to our Department of Surgery at Charité Universitätsmedizin Berlin. We retrospectively analyzed the collected data in all of these cases with regard to patient demographics, presenting symptoms, diagnostic workup, operative procedures and postoperative course.

The literature search was conducted with PubMed and Google Scholar using the following keywords: "nuck", "nuck's hydrocele", "surgery", "nuck hernia" and "canal of nuck". In addition, we cross-checked reference lists from eligible publications and relevant review articles to identify additional studies. The inclusion criteria contained case reports or case series, with the main diagnosis of a "nuck's hydrocele" or "nuck cyst" and included a surgical therapy. Exclusion criteria for case reports was the absence of any surgical therapy.

Surgical procedure: both conventional and laparoscopic approaches were used for exploration.

Laparoscopic hydrocelectomy and TAPP:

Open access methods were used to place a laparoscopic trocar into the umbilicus for carbon dioxide (CO_2) pneumoperitoneum. The peritoneum was opened above the spina iliaca anterior superior which then revealed a hydrocele of the canal of Nuck and an indirect hernia. The hydroceles were excised laparoscopically and a TAPP with a 10 × 15 cm polypropylene mesh placed over the hernia and glued with 1ml of fibrin before suturing the peritoneal flap.

Open hydrocelectomy and Lichtenstein:

After skin incision the external oblique aponeurosis is opened in the direction of the fibers. Preparation of the structures up to the cyst roof. Exposure of the Nuck's hydrocele. Excision and high ligation of the hydrocele. Restoration of the anatomical structures and placement of a 12 × 6 cm polypropylene mesh. If the abdominal wall is intact, only a fascial suture was performed. Layer-appropriate closure and insertion of a drainage.

3. Results/Case Series Presentation

3.1. Case 1

A 29-year-old female presented in September 2016 with right-sided painful swelling in her inguinal region for one week. Both pain and size were increasing since she first noticed the swelling. There was no fever, no vomiting, no bowel or bladder dysfunction. On examination the swelling was painful and a manual reduction was not possible. There was no peristaltic activity or signs of inflammation.

Ultrasonography showed a well-defined, 3 × 2 cm fluid-filled mass with discreet increase in size during Valsalva maneuver and there was a viewable connection to the inguinal canal.

The patient decided to proceed with elective exploration, hydrocelectomy of the type 2 and TAPP hernioplasty. The early postoperative period was uneventful and the patient was discharged home two days after surgery in satisfactory condition. On routine follow up, an inguinal seroma of 3.9 × 0.8 cm occurred three weeks postoperatively which was self-absorbed as it had disappeared in the subsequent follow-up under conservative therapy. The patient has remained asymptomatic on follow up lasting 6 months.

3.2. Case 2

A 29-year-old female presented to a gynecological ambulance in 2014 with an unclear right-sided inguinal mass. She first noticed it because of pain after doing sports and visited a hospital. A small seroma measuring 3.47 × 1.15 cm in the right groin region extending towards the vulva was found by ultrasound (Figure 1). At that time, it had not been deemed as requiring puncture. Two years later, in June 2016, she noticed that the swelling was growing in size and presented again. The magnetic resonance imaging (MRI) finding in T2 weighted imaging of a 11.1 × 3.4 cm hyperintense mass without wall-enhancement of the contrast agent (Gadovist) now resembled a cyst rather than a seroma. It was punctured and 40 mL of serous liquid was aspirated. The results of the examination revealed mesothelial cells and lymphocytes matching the findings of a lymphocele with a connection to the abdominal cavity. Taking into account the location of the cyst the diagnosis of a Nuck's hydrocele was made. The patient was referred to our clinic five months later, in November 2016, and underwent exploration, hydrocelectomy of the type 2 and TAPP (Figure 2 and Video S1) hernioplasty.

The histopathological examination showed a mesothelium-coated cyst wall with chronic macrophage-rich inflammation and was consistent with those of a Nuck hydrocele. The patient was discharged two days after surgery and her follow up remains uneventful 6 months postoperatively.

The demonstrated image and video material in Figure 1 (preoperative sonography) and Figure 2 (intraoperative laparoscopic images and video) originates from this case.

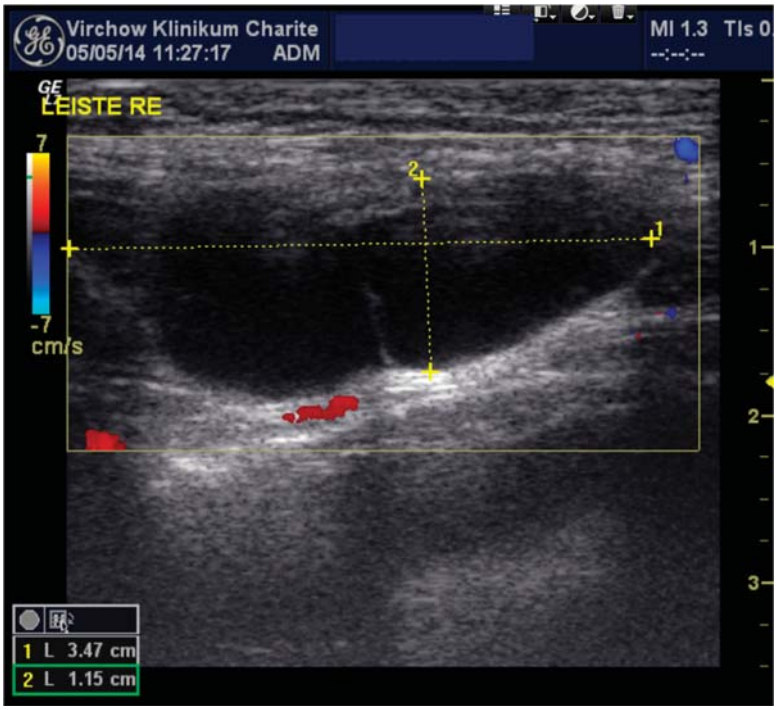

Figure 1. Sonographic imaging of the right inguinal area: anechoic elongated fluid structure 3.47 × 1.15 cm.

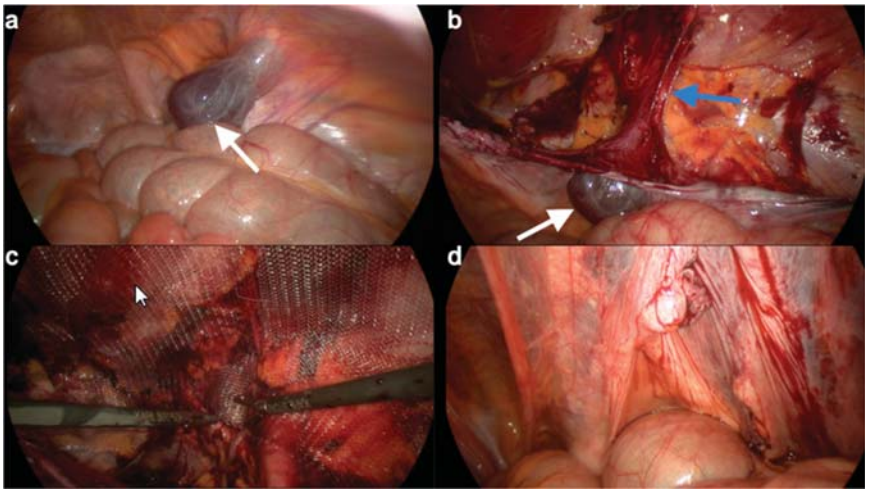

Figure 2. Laparoscopic procedures for hydrocelectomy and TAPP. (**a**) In the laparoscopic view, a type 2 hydrocele of the canal of Nuck (white arrow) (**b**) Approach to the inguinal canal and dissection of the hydrocele (white arrow) attached to the round ligament (below blue arrow). (**c**) Placement of the polypropylene mesh. (**d**) Sutured peritoneum.

3.3. Case 3

A 44-year-old female with multiple sclerosis was referred by her general practitioner to our general surgery department in July 2016 with a known cystic structure in the left inguinal region. The swelling was painful to touch and had increased in size over the last 2 months. Ultrasonography revealed a 3 × 4 cm liquid mass, with non-echoic content and without septations.

We performed a laparoscopic excision of the type 2 hydrocele and a left sided inguinal hernioplasty by TAPP. The histopathological examination showed peritonealized soft tissue with marks of chronic inflammation. Based on the intraoperative and histopathological picture the findings were compatible with a hydrocele of the canal of Nuck. The early postoperative period was uneventful and the patient was discharged home the next day in good clinical condition. On follow up an inguinal hemato-seroma measuring 7 × 4 cm occurred 8 days postoperatively which was self-absorbed. No other complications occurred during a 12-month follow-up.

3.4. Case 4

A 35-year-old patient presented in February 2018 with a right-sided inguinal mass that first appeared two years prior. The protruding mass was causing a very unpleasant feeling of pressure to the patient. An MRI was performed at an external radiological institute showed a liquid mass at inguinal area. The most probable diagnosis to that point was a lymphocele. Then the patient was referred to our clinic for further examination. After interdisciplinary discussion of the external MR imaging by radiologists and surgeons of our institution, a type 1 cyst in the canal of Nuck was diagnosed [6].

The patient decided to proceed with elective surgical therapy. The cyst was excised and a right-sided Lichtenstein hernioplasty was performed to cover the hernia defect. The histopathological examination revealed a peritoneal inclusion cyst matching a cyst in the canal of Nuck. The patient was discharged home in stable condition two days after surgery. The patient was asymptomatic in our 6-month follow-up routine.

3.5. Case 5

A 41-year-old female was referred to our emergency department in April 2018 for a suspected incarcerated hernia. She complained about pain in the inguinal area. There was no fever, no vomiting, no bowel or bladder dysfunction. Her blood count levels and urinalysis were normal. An irreducible mass containing anechoic fluid was found by ultrasound.

We proceeded with emergency surgical therapy. Laparoscopy revealed an hourglass-shaped Type 3 hydrocele inside the canal of Nuck. A TAPP hernia repair was performed due to widening of the ingunal channel by the hydrocele. The early postoperative period was uneventful and the patient was discharged home two days after surgery in satisfactory condition. The patient remains asymptomatic in our routine follow-up lasting 6 months.

3.6. Case 6

A 34-year-old patient with recurrent groin pain since 2012. Several outpatient consultations passed without a clear diagnosis. She the presented herself at gynecological outpatient department of our hospital in January 2020. In the MRI (T1/T2-weighted with contrast agent) showed a hypointense and hyperintense cystic structure, respectively, without septation of the left groin of 5.6 × 3.7 cm size. A clinically inapparent cyst on the contralateral side was also found (Figure 3). The puncture of the unclear symptomatic cyst revealed histpathologically undefined cell formations.

The patient then presented herself at our surgical outpatient clinic for further examination. We re-evaluated the case and diagnosed a Nuck's hydrocele on both sides. Intraoperatively, a left-sided Type 2 hydrocele was seen, which could be confirmed by the histopathological finding of a mesothelial covered cystic lesion. The early postoperative period was uneventful and the patient was discharged home the day after surgery in satisfactory condition. Thus far, the patient remains asymptomatic in

our routine follow-up. Surgical treatment of the asymptomatic right-sided cyst will also be performed in the course of time in case of discomfort.

The demonstrated image material in Figures 3 and 4 originates from this case.

A chart of the cases is shown in Table 1.

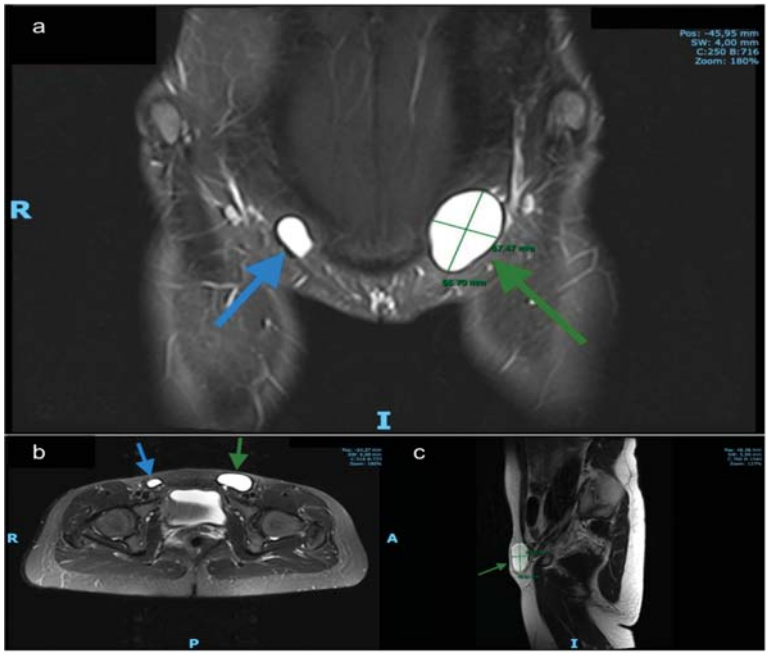

Figure 3. MRI findings. (**a**) Coronal T2-weighted. (**b**) axial T2-weighted and (**c**) sagittal MR images demonstrate a left inguinal hyperintense cystic structure without septation and a smaller (asymptomatic) on the right side. Green arrows: left hydrocele, blue arrows: right hydrocele.

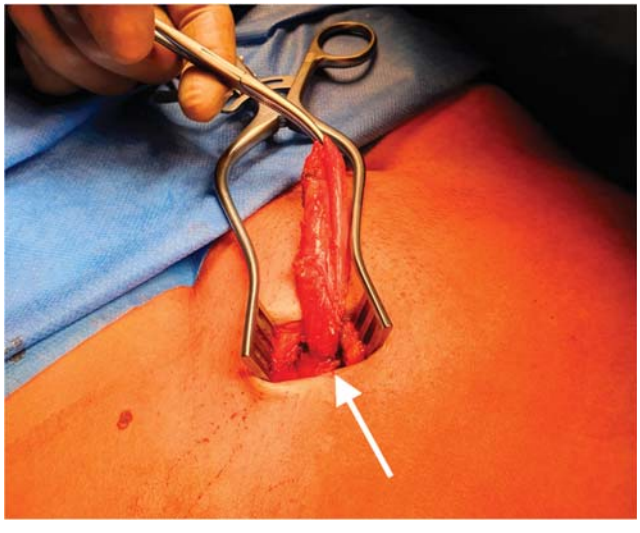

Figure 4. Intraoperative picture of a hydrocele of the canal of Nuck. The round ligament (white arrow).

Table 1. Chart with patients treated in our institution due to a cyst of the canal of Nuck.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	29	29	44	35	41	34
Symptoms/Reason of Presentation	Inguinal pain	Asymptomatic inguinal swelling	Inguinal pain and swelling	Inguinal pain and swelling	Inguinal pain and swelling	Inguinal pain and swelling
Diagnostic Study	Ultrasound	Ultrasound	Ultrasound	Ultrasound and magnetic resonance imaging (MRI)	Ultrasound	MRI
Elective/Emergent	Elective	Elective	Elective	Elective	Emergent	Elective
Procedure	Hydrocelectomy and TAPP hernioplasty	Hydrocelectomy and TAPP hernioplasty	Hydrocelectomy and TAPP hernioplasty	Hydrocelectomy and Lichtenstein hernia repair	Hydrocelectomy and TAPP hernioplasty	Open hydrocelectomy and fascial suture
Operating Time (min)	52 min	62 min	62 min	49 min	65 min	27 min
Type of Nuck hydrocele	type 2	type 2	type 2	type 1	type 3	type 2
Postoperative-Hospital Stay (days)	2	2	2	2	2	1
Complication	inguinal seroma	none	inguinal hemato-seroma	none	none	none
Recurrence	no	no	no	no	no	no
Follow up Period (months)	1, 3 and 6	1, 4 and 6	6	6	3 and 6	1 and 6

3.7. Review of the Literature

The selected studies included ten case reports and two retrospective case series. Overall, 39 cases of Nuck Hydroceles have been described in those publications. All patients presented with inguinal swelling. Two patients underwent emergency surgery (5%). The diagnosis was made by Ultrasound (33 patients—85%), Ultrasound and MRI (3 patients—8%), one case with CT and MRI (2.6%) and one case only by clinical examination (2.6%). Of all patients, 26 (67%) underwent laparoscopic hydrocelectomy and high ligation, one patient was treated by laparoscopic TAPP repair (2.6%) and another with laparoscopic total extraperitoneal (TEP) repair (2.6%). Nine patients underwent conventional surgery (23%) and a mesh was implanted in a further three patients (8%). Four patients showed a hernia (10%)—a subdivision in two groups (children and adults) resulted in no case of hernia defects in children but four adults (67% in the adult group). All patients had an uneventful follow-up and showed no recurrence.

An overview of the articles that were included in this review of the literature is shown in Table 2.

Table 2. Comparison of the literature referring to Nuck hydroceles with surgical treatment.

	Year of Publication	Children/Adult	Type of Publication	Diagnostic Study	Elective/Emergent	Procedure	Presence of Hernia	Hospital Stay	Follow-Up	Author's Conclusion
Kim et al. [8]	2016	adult	Single case report	CT and magnetic resonance imaging (MRI)	elective	Open Hydrocelectomy with high ligation	unknown	unknown	unknown	Inclusion in differential diagnosis of inguinal swelling.
Janssen et al. [4]	2011	child	Single case report	none	elective	Open Hydrocelectomy with high ligation	unknown	unknown	uneventful, no recurrence	Inclusion in differential diagnosis of inguinal swelling.
Qureshi et al. [9]	2013	adult	Single case report	Ultrasound	elective	Laparoscopic hydrocelectomy and hernia repair with mesh	yes	unknown	uneventful, no recurrence	-
Lombardo et al. [10]	2017	adult	Single case report	Ultrasound and MRI	elective	Open hydrocelectomy and hernia repair with mesh	yes	unknown	uneventful, no recurrence	-
Topal et al. [11]	2018	adult	Single case report	Ultrasound and MRI	elective	Open hydrocelectomy and hernia repair with mesh	yes	1 day	unknown	Inclusion in differential diagnosis of inguinal swelling.
Mandhan et al. [12]	2013	child	Single case report	Ultrasound	emergent	Open Hydrocelectomy with high ligation	no	unknown	uneventful, no recurrence	Inclusion in differential diagnosis of inguinal swelling. Surgery is mandatory for final diagnosis an treatment.
Matsumoto et al. [13]	2014	adult	Single case report	Ultrasound and MRI	elective	Hydrocelectomy and hernia repair with mesh (TEP)	yes	3 days	unknown	TEP approach with its advantage of a shorter recovery period could be useful
Sarkar et al. [14]	2014	child	Single case report	Ultrasound	emergent	Open Hydrocelectomy with high ligation	no	unknown	uneventful, no recurrence	Inclusion in differential diagnosis for inguinal swelling. U/S and MRI preoperatively. Surgery is the treatment of choice.
Lucas et al. [15]	2019	adult	Single case report	Ultrasound	elective	Open Hydrocelectomy with high ligation	no	unknown	uneventful, no recurrence	Inclusion in differential diagnosis of inguinal swelling.
Lee et al. [7]	2018	children	Case series (26 patients)	not enough information	not enough information	Laparoscopic hydrocelectomy with high ligation	none	on average 7.5 h	uneventful, no recurrence	Lap. Hydrocelectomy with high ligation is an effective method for treating Nuck´s hydroceles in pediatric patients
Caviezel et al. [16]	2009	adult	Case report	MRI	elective	Open Hydrocelectomy	no	unknown	uneventful, no recurrence	Inclusion in differential diagnosis of inguinal swelling, Ultrasound for a first evaluation and MRI for precise information
Papparella et al. [17]	2018	Children	Case series (353 patients, of whom 3 had a Nuck hydrocele)	Ultrasound	elective	Open Hydrocelectomy with high ligation	no	unknown	uneventful, no recurrence	Surgery with high ligation is considered as therapy of choice for Nuck's hydroceles

4. Discussion

The hydrocele of the canal of Nuck in the context of an inguinal swelling is a rare finding and as such it has to be named correctly in terms of terminology after a reliable diagnosis is made. Publications from the nineteenth century show that such cases were often misinterpreted and thus diagnosed and treated as an ordinary inguinal or femoral hernia [18]. For many years, this entity was only presented in individual case reports. The very few case series initially dealt only with the diagnosis and not with the surgical therapy [6,19]. The entity of Nuck's hydrocele in adults has been covered only by single case reports. No case series regarding adult females with this inguinal pathology has been published.

A variety of masses can be found in the female inguinal region. In summary, the differential diagnosis includes hernia, lymphadenopathy, abscess, Bartholin's cyst, neurofibroma, sarcoma, liposarcoma, Burkitt lymphoma and posttraumatic/postoperative hematoma [20]. Patients with endometriosis in the canal of Nuck have also been reported [21,22]. Similar findings are conceivable for the canal of Nuck, with single hydroceles or in combination with hernias being the most common one [23].

Furthermore, it is reported that pathologies in the canal of Nuck could be more frequent than previously assumed and should play a more important role in the differential diagnosis of groin pain [1]. The most prevalent conclusion of the studies we reviewed was that Nuck's should be included in the differential diagnosis of inguinal swelling.

Symptoms can be acute or chronic and infections of the hydroceles are also possible [12–14]. Although the majority of published cases did not require emergency surgery, the few cases that did should not be underestimated and left behind [15,24]. Ultrasonography can be the initial imaging because of its low cost and its wide availability and magnetic resonance imaging (MRI) could be used for complex cases and further investigation [1,25–28]. The sonographic findings mostly show a mass with an elongated morphology, that contains anechoic fluid in the sense of a well-defined unechoic lesion [29]. In the case of a hernia, it may contain omental fat, ovary, fallopian tube, the uterus, parts of the bowel or the urinary bladder [1,23,30]. To differentiate an encysted hydrocele from a hernia, a Valsalva maneuver could be helpful, because it would sometimes change the appearance of a hernia but leave an encysted hydrocele unimpaired [28,31]. As mentioned before, ambiguous sonographic findings can be further investigated with MRI, especially when a herniation is suspected [1]. Our experience with the presented cases showed that the sonographic findings remain undiagnosed if the examiner is not familiar with the possibility of the presence of a Nuck's hydrocele. The radiological findings have to be confirmed intraoperatively and by the histopathological report.

The hydrocelectomy would be the first surgical step followed by the hernioplasty in case of a hernia. TAPP and Lichtenstein are equivalent and can be used as therapy without any noteworthy limitations [9,10,13]. Most likely, the results of a comparison between the two methods will be similar to those found in the meta-analysis by Scheuermann et al. in inguinal hernia in males, showing that TAPP is associated with less chronic inguinal pain in comparison with Lichtenstein repair [32]. In addition, the TEP approach is an alternative that could also be useful [13]. A comparison between TAPP and TEP will most likely show comparable outcomes for the two techniques with advantages on the TAPP side regarding operation time and conversion rates [33–35]. Furthermore, it is an accepted opinion that, when using the TEP technique, it is more difficult to identify anatomic landmarks compared to the TAPP technique and, therefore, this method is not suitable for exploration [34]. Sonographically guided aspiration of the cyst could be used to temporarily alleviate patient discomfort, especially in elderly patients, who probably would not circumvent a surgery [36].

5. Conclusions

We can report that all our patients have benefited from the treatment in terms of their symptoms and, so far, we report no recurrence of the hydroceles. The maximum postoperative hospital stay was two days and the follow-up six months postoperatively has been uncomplicated. We are now sensitized by the experiences we have made in our clinic, mostly through random findings, and

we believe that our case series could be used as a benchmark for further studies with larger case series and possibly register data. Therefore, although being rather rare, Nuck's hydroceles should be included in the differential diagnosis of inguinal swelling. Taking the classification into consideration, we recommend a conventional approach for the encysted, external type 1 and a laparoscopic approach for the intra-abdominal type 2 Nuck's hydroceles. Type 3 has to be evaluated individually as it is challenging and the surgical outcome is depending on the surgeon's skills. A fascial augmentation with mesh, as performed in inguinal hernia surgery, should be considered if inguinal channel has been widened or fascial fibers are damaged by the presence of a Nuck hydrocele.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/12/4026/s1, Video S1: TAPP repair of Nuck´s hydrocele

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Review

Impact of Surgical Management of Endometrioma on AMH Levels and Pregnancy Rates: A Review of Recent Literature

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Abstract: Ovarian endometrioma are found in up to 40% of women with endometriosis and 50% of infertile women. The best surgical approach for endometrioma and its impact on pregnancy rates is still controversial. Therefore, we conducted a literature review on surgical management of ovarian endometrioma and its impact on pregnancy rates and ovarian reserve, assessed by anti-Müllerian hormone (AMH) serum levels. Ovarian cystectomy is the preferred technique, as it is associated with lower recurrence and higher spontaneous pregnancy rate. However, ablative approaches and combined techniques are becoming more popular as ovarian reserve is less affected and there are slightly higher pregnancy rates. Preoperative AMH level might be useful to predict the occurrence of pregnancy. In conclusion, AMH should be included in the preoperative evaluation of reproductive aged women with endometriosis. The surgical options for ovarian endometrioma should be individualized. The endometrioma ablation procedure seems to be the most promising treatment.

Keywords: endometriosis; endometrioma surgery; ovarian reserve; anti-Müllerian hormone; spontaneous pregnancy

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1. Introduction

Endometriosis is an inflammatory condition characterized by the presence of endometrial-like tissue outside the uterus. It affects mostly women of reproductive age and approximately 30–50% of women with endometriosis may present infertility [1].

Between 17% and 44% of endometriosis patients have endometriotic ovarian cysts (endometrioma), which are bilateral in about 19–28% of cases [2,3]. The aetiopathogenesis of endometrioma is still uncertain and several hypotheses have emerged. Hughesdon [4] and Brosens et al. [5] demonstrated the formation of a pseudocyst by invagination of the ovarian cortex following the bleeding of a superficial endometriotic implant and the accumulation of menstrual debris. According to Nezhat et al. [6], endometrioma results from the transformation of a functional cyst. More recently, Donnez et al. [7] confirmed the involvement of metaplasia of invaginated coelomic epithelium in the origin of endometrioma.

Recommendations on the different surgical options available for ovarian endometrioma have recently been published by the working group of the European Society for Gynaecological Endoscopy (ESGE), the European Society of Human Reproduction and

Embryology (ESHRE) and the World Endometriosis Society (WES) [8]. In summary, the available approaches for conservative surgical treatment of ovarian endometrioma are cystectomy, ablation or a combined technique.

Laparoscopic ovarian cystectomy is performed by the stripping technique, in which the drained endometrioma and ovarian cortex are pulled apart and haemostasis is applied on the ovarian cyst bed [9]. Traction and counter-traction must be performed using appropriate instruments with low to moderate force to avoid excessive bleeding.

In the ablative approach, endometrioma is fenestrated, drained and washed out and the cyst wall is then destroyed with an energy source, such as a CO_2 laser, bipolar coagulation or plasma energy [9]. Care must be taken to ablate the entire surface of the cyst wall in order to reduce the risk of residual ovarian endometrioma. The entire depth of the cyst capsule must not be ablated as endometriotic tissue is present only superficially, with a mean depth of 0.6 mm [10].

In cases of large ovarian endometrioma, a three-step approach could be suggested, requiring a first laparoscopy for draining the cyst, followed by 3 months of gonadotropin-releasing hormone (GnRH) agonist therapy [7,11]. At the end of the medical treatment, a second laparoscopy is performed in order to ablate the reduced ovarian endometrioma [7,8].

In order to avoid two laparoscopic procedures, Donnez et al. [11] described a combined technique in which 80–90% of the endometrioma is excised according to the cystectomy technique, and a CO_2 laser is then used to vaporize the remaining 10–20% of the endometrioma close to the ovarian hilus. Indeed, in this region of the ovary, dissection is usually more difficult and is associated with a higher risk of bleeding which needs coagulation close to the ovarian vessels.

Surgical treatment of endometrioma improves patients' symptoms, such as pain, but the most appropriate approach for reproductive outcomes is still controversial, according to the Royal College of Obstetricians and Gynaecologists (RCOG) [12]. The guidelines from the ESHRE and a Cochrane review state that ovarian cystectomy is the preferred technique in terms of recurrence and spontaneous pregnancy rate after surgery [13,14]. In infertile women with stage I/II endometriosis according to the revised American Fertility Society (rAFS) classification of the American Society for Reproductive Medicine (ASRM), ESHRE recommends performing an operative laparoscopy rather than only a diagnostic laparoscopy [13]. On the other hand, ASRM proposed that in the initial stages and in women under than 35 years, expectant management or superovulation/intrauterine insemination can be considered as first-line therapy [15]. For stage III–IV disease, both societies agree with the benefit of surgical therapy [13,15]. However, the safety of this option has been questioned as it may cause ovarian damage, with a negative effect on ovarian reserve.

Ovarian reserve is defined as the functional potential of the ovary and reflects the number and quality of the follicles in the ovaries at any given time. Anti-Müllerian hormone (AMH) is a reliable marker of ovarian reserve [16]. AMH is a glycoprotein secreted by granulosa cells of primary, pre-antral and antral follicles, but it is not produced by primordial follicles. After the AMH peak at 24 years old, it gradually decreases to become undetectable at menopause [17,18].

The risk of postsurgical ovarian failure has reopened the debate between excision and ablation [19]. The deleterious effects of the presence of endometriosis in the ovarian reserve itself as well as the risk of affecting the ovarian reserve by the surgical procedures are taken into account when deciding whether or not to operate on patients who want a pregnancy [20–23]. Therefore, in many centres, patients are directly referred to in vitro fertilization (IVF) instead of offering them an appropriate surgical procedure associated with the possibility of getting pregnant spontaneously. Therefore, as endometriosis is mainly found in women of reproductive age, the impact of endometrioma and its treatment on ovarian function must be evaluated in order to maintain the best chances of pregnancy.

The aim of this review was to evaluate the effect of surgical management of endometrioma on ovarian reserve, assessed by serum AMH concentration, and on pregnancy rates, through a review of the literature.

2. Methods

The literature search was done using the PubMed and Cochrane search engines. The keywords used were "endometrioma", "surgery", "ovarian reserve", "AMH", "anti-Müllerian hormone" and "spontaneous pregnancy". This research was limited to English and French language publications, focusing on the last 5 years (2015–2019). The studies were selected based on the abstract. This research was supplemented by the bibliography of experts and the references cited in the documents reviewed. Clinical cases and comments were excluded.

3. Results

3.1. AMH after Surgery for Endometrioma

3.1.1. AMH and Ovarian Cystectomy

A recent systematic review and meta-analysis confirmed previous studies and systematic reviews reporting consistent evidence of a negative impact of excision of endometrioma on ovarian reserve [3,21,22]. In the late postoperative period (9 to 12 months), a 39.5% and 57% reduction in postoperative circulating AMH was observed in patients with unilateral (1.65 ng/mL, 95% confidence interval (CI) 1.15 to 2.15) and bilateral endometriomas (2.03 ng/mL, 95% CI 1.47 to 2.58), respectively [3].

Celik et al. showed that cystectomy leads to a significant and progressive decrease (61%) in serum AMH levels in a prospective study with 65 patients comparing AMH measured preoperatively (1.78 ± 1.71 ng/mL), at 6 weeks (1.32 ± 1.29 ng/mL) and 6 months after surgery (0.72 ± 0.79 ng/mL) [24]. Alborzi et al., in a prospective study with 193 patients, observed the same trend within 9 months of follow-up (baseline AMH = 3.86 ± 3.58 ng/mL; 9 months after surgery = 1.77 ± 1.76 ng/mL) [25].

Subsequent studies assessing AMH levels up to 1 year after surgery revealed that this decrease would be only temporary and could recover [26–30]. Vignali et al., in a prospective study with 22 patients undergoing laparoscopic cystectomy for endometrioma, verified that the mean 1-year postoperative AMH levels were not statistically different from the mean values prior to surgery [26]. Sugita et al. also performed a prospective study including 39 patients and observed that 50% had higher AMH levels 1 year after surgery than 1 month after surgery (20 vs. 19 patients). The comparison of these two groups (increase vs. decrease in AMH levels at 1-year follow-up), showed a significant difference in the number of follicles in specimens due to removal of ovarian cortex during surgery [27]. A larger prospective study with 171 patients performed by Wang et al. showed that, 12 months after surgery, AMH levels were no different from the preoperative assessment in small cysts (≤7 cm), unilateral cysts and stage III endometriosis [28]. Kostrzewa et al. also performed a 1-year follow-up and observed a significant decrease in AMH levels 3 months after cystectomy (4.89 ± 3.66 vs. 3.45 ± 3.37 ng/mL, $p < 0.001$), but no further fall in the 1-year assessment (3-months = 3.45 ± 3.37 vs. 1-year = 3.43 ± 3.62 ng/mL, $p > 0.05$) [29]. The same result was achieved by Kovačević et al. in a prospective study that enrolled 54 patients (37 with unilateral endometrioma and 17 with bilateral) [30].

In a prospective cohort study with 59 patients with endometrioma and 16 with other benign cysts, the comparison of the postoperative decline in serum AMH revealed a higher and significant decrease in the group with endometrioma (baseline = 4.3 ± 0.4 vs. 3 months after surgery = 2.8 ± 0.2 ng/mL, $p < 0.001$) [31]. The same result was achieved by Taniguchi et al. in a study that enrolled 40 women with endometrioma and 16 with benign ovarian tumours. The postoperative decline rate of AMH levels had statistically significant differences at 6 months after surgery when patients with endometrioma were compared with those with other ovarian cysts (0.63 (0.26–0.69) vs. 0.24 (–0.86–0.32), $p < 0.05$). However, in the evaluation performed 1 year after surgery, that reduction did not remain significant (0.46 (0.14–0.73) vs. 0.21 (–0.52–0.78), $p = 0.34$) [32]. Kostrzewa et al. also compared a group of patients with endometrioma ($n = 35$) with a group with other benign ovarian tumours ($n = 35$). The decline in serum AMH levels in the first 3 months following surgery was 3 times higher following laparoscopic cystectomy of endometrioma (45.39% vs. 14.87%;

$p = 0.021$) [29]. The same result was observed when comparing laparoscopic cystectomy in patients with endometrioma and dermoid cysts [33].

The reduction in AMH level after surgery is higher in bilateral endometrioma [3,24,26–28,34]. Additionally, it is inversely correlated with the diameter of the cyst, with a clear decrease when the cyst is greater than 5 cm. Nevertheless, this decline is not associated with the follicular loss evaluated by histology [24,28,35].

Kim et al. reported that the decrease in AMH levels was also dependent on the stages of endometriosis, with stages III and IV having a significantly greater decrease in AMH from the pre- to postoperative period in comparison with lower stages [28,31]. However, they showed that the decline was independent of multiplicity, bilaterality and GnRH agonist use [31]. In addition, the postsurgical reduction in patients over 35 years old was greater, highlighting the negative effect of age on ovarian function [32].

In a prospective controlled study, Muzii et al. observed that surgery for recurrent endometriomas is more harmful to ovarian reserve, even though they only used antral follicle count (AFC) and ovarian volume [36].

Recently, in a prospective study with 124 patients, Zhou et al. verified that a decrease in AMH levels after surgery happened in both patients with high (>2 ng/mL) and low ($\leq$2 ng/mL) preoperative AMH levels (4.51 $\pm$ 1.20 vs. 3.04 $\pm$ 0.90 ng/mL, $p < 0.001$; 0.89 $\pm$ 0.36 vs. 0.51 $\pm$ 0.27 ng/mL, $p < 0.001$, respectively) [37].

The presurgical identification of patients with decreased ovarian reserve and the risk of poor postoperative ovarian response can be predicted using preoperative measurements of serum AMH. Ozaki et al. proposed that 2.1 ng/mL was the best cut-off value of preoperative AMH for predicting diminished ovarian reserve (DOR) at 3 and 6 months in patients undergoing unilateral cystectomy. In cases of bilateral ovarian surgery, the optimal cut-off points were 3.0 ng/mL to predict DOR 3 months after surgery and 3.5 ng/mL to predict DOR 6 months after surgery [34].

After complete excision of the cyst capsule, final hemostasis must be guaranteed [8]. The traditional hemostatic technique is bipolar coagulation, but it might be used with caution to avoid excessive compromise of ovarian reserve [8,38]. A recent systematic review and meta-analysis comparing this approach with suture, ultrasonic energy and intra-ovarian hemostatic sealants showed a lower impact in postoperative AMH levels with the use of suturing [39]. The same result was achieved in a previous meta-analysis comparing just bipolar coagulation vs. suture [40]. In this field, there are two ongoing randomized clinical trials comparing ovarian function after laparoscopic cystectomy for endometrioma complemented with hemostatic approaches, the results of which are highly anticipated [41,42]. Dual-wavelength laser systems (DWLS) are a new instrument that have been described for hemostasis and that seem not to determine a significant reduction of ovarian reserve [43].

3.1.2. AMH and Endometrioma Ablation

Roman et al. conducted a prospective study [44] analysing serum AMH levels at 3 time points (before surgery, 3 months after surgery and >6 months after surgery) in 22 patients with unilateral endometrioma $\geq$30 mm without any history of previous surgery who underwent ablation with vaporization using plasma energy. This resulted in a post-operative drop in the AMH level, followed by a gradual re-increase. There was usually no return to preoperative AMH values, but the difference no longer reached statistical significance >6 months after surgery.

A more recent study by Stochino-Loi et al. [45] gathering 180 patients with stage III and IV endometriosis and intention of pregnancy compared AMH evolution after plasma energy vaporization according to preoperative AMH levels $\geq$ or <2 ng/mL. Plasma energy ablation caused a temporary decrease in AMH level in both groups.

3.1.3. Comparison of AMH after Ovarian Cystectomy and Endometrioma Vaporization

Saito et al. [46] performed a prospective study comparing AMH levels after cystectomy or endometrioma vaporization with bipolar current forceps in unilateral and bilateral endometrioma. They demonstrated that both methods decrease the ovarian reserve, especially in cases of severe endometriosis or over the age of 38. However, the postoperative decline in AMH was higher after cystectomy than vaporization and was statistically significant for bilateral endometrioma. In patients submitted to bilateral cystectomy, AMH levels declined from 3.1 ± 1.7 ng/mL at preoperative staging to 0.5 ± 0.5 ng/mL at 1 month after surgery, 0.8 ± 0.7 ng/mL at 6 months and 0.8 ± 0.7 ng/mL at 1 year. For bilateral vaporization, preoperative AMH levels were 2.7 ± 1.8 ng/mL and decreased to 0.8 ± 0.6 ng/mL at 1 month after surgery, 1.2 ± 1.3 ng/mL at 6 months and 1.3 ± 1.5 ng/mL at 1 year [46].

The multicentre randomized clinical trial of Candiani et al. [47] compared changes in AMH and antral follicle count (AFC) after cystectomy or CO_2 laser vaporization in 60 patients with endometrioma larger than 3 cm. Three months after surgery, they observed a significant decrease in serum AMH in the subjects treated with cystectomy (from 2.6 ± 1.4 to 1.8 ± 0.8 ng/mL; 95% CI: −1.3 to −0.2; $p = 0.012$), while no significant reduction was evident in the group treated with CO_2 laser vaporization (from 2.3 ± 1.1 to 1.9 ± 0.9 ng/mL; 95% CI: −1 to −0.2; $p = 0.09$).

A retrospective study with prospective recording of data performed by the same group showed that postoperative recurrence rates were comparable between patients that underwent CO_2 fiber laser vaporization or cystectomy [48]. During a 3-year follow-up, no difference was observed in recurrence of ovarian endometriosis (cystectomy group = 6.3% vs. vaporization group = 4.9%, $p = 0.74$) and of endometriosis-related pain (cystectomy group = 7.8% vs. vaporization group = 9.8%, $p = 0.67$).

For large endometriomas (>5 cm), a prospective randomized study performed by Giampaolino et al. revealed that the decrease of AMH levels assessed 3 months after surgery was greater following excisional surgery than ablative treatment (−24.1 ± 9.3% vs −14.8 ± 6.7%, $p = 0.011$) [49].

3.1.4. AMH and the Combined Technique

The combined approach, using excision of 80–90% of the cyst and ablation of the rest, has been proven not to be deleterious to the ovary through comparison of the ovarian volume and AFC. AMH serum levels were not analysed in this study published by Donnez et al. [11].

Tsolakidis et al. [50] performed a prospective randomized clinical trial comparing AMH levels before and 6 months after laparoscopic cystectomy for endometrioma or the three-step procedure. They found that AMH is less diminished after the three-step procedure (from 4.5 ± 0.4 to 3.99 ± 0.6 ng/mL, $p > 0.05$) compared with cystectomy of endometrioma (from 3.9 ± 0.4 to 2.9 ± 0.2 ng/mL; $p = 0.026$). This is explained by the fact that vaporization avoids ovarian tissue ablation and excessive thermal damage.

3.2. Pregnancy Rate after Surgery for Endometrioma

The role of surgery to improve the pregnancy rate in infertile women with endometriosis is controversial.

In a retrospective study with 43 infertile women with surgically proven endometriosis and no other factors, Lee et al. reported that the spontaneous conception rate was 41.9% during the first year after laparoscopic surgery, which involved the destruction or removal of all visible endometriotic implants and the lysis of adhesions [51].

For endometrioma, surgery seems to improve the success rates of fertility treatment by between 20% and 60% [9,52–54]. A recent meta-analysis compared pregnancy rates based on four different treatments for endometrioma in infertile women: surgery (excisional and/or ablative) + assisted reproductive technology (ART), surgery + spontaneous pregnancy, aspiration ± sclerotherapy + ART and only ART. There was no difference among groups. However, the success rate of surgery was higher (43.8%, confidence interval (CI): 22.5–66.4), while the success rate of only ART was the lowest (32%, CI: 15.0–52.0) [55].

3.2.1. Pregnancy Rate and Ovarian Cystectomy

In a meta-analysis by Vercellini et al., the chance of pregnancy after laparoscopic excision of endometriomas ranged from 30% to 67%, with an overall weighted mean of about 50% [56]. Zhou et al. recently conducted a prospective study with 124 patients that was consistent with these results, with a total spontaneous pregnancy rate of 50.49% within 24 months after excisional surgery [37]. Taniguchi et al. also reported a cumulative pregnancy rate of 50% after cystectomy for ovarian endometrioma [32].

Women with higher AMH levels had a significantly higher cumulative pregnancy rate after surgery for endometrioma [37,54,57]. Ozaki et al. compared patients according to preoperative ovarian reserve and observed that the rate of spontaneous pregnancy was greater in patients with AMH $\geq$ 1.1 ng/mL (59.2% vs. 14.3%, $p = 0.04$) [34]. According to Dong et al., the best cut-off point of the preoperative AMH for postoperative spontaneous pregnancy is > 3.68 ng/mL (Hazard ratio (HR): 2.383; 95% CI, 1.093–5.197) [57]. A very similar value was proposed by Zhou et al. (3.545 ng/mL; sensitivity 80.39%; specificity 69.23%) [37]. Thus, preoperative AMH level might be a useful marker to predict the occurrence of natural pregnancy and could be offered as part of patient assessment [37].

Studies comparing AMH level after cystectomy between patients who became pregnant and those who did not showed a higher AMH level 1 year after surgery in the group of pregnant women [32,58].

When the likelihood of spontaneous pregnancy after laparoscopic cystectomy of endometriomas was compared with other benign ovarian cysts, it was observed that it is more than 3 times higher in the group of patients with other benign tumours (HR 3.57; $p = 0.03$) [29].

3.2.2. Pregnancy Rate and Endometrioma Ablation

A retrospective pilot study by Roman et al. [59] evaluated recurrence and pregnancy rates in 55 patients with endometrioma treated by ablation using plasma energy. Recurrence (10.9%) and pregnancy rates (67%, spontaneously in 59%) are encouraging and are comparable to the reported results after endometrioma cystectomy. A more recent study by the same group enrolled 22 patients with unilateral endometrioma $\geq$30 mm and no history of previous surgery who underwent ablation with vaporization using plasma energy. The overall pregnancy rate during postoperative follow-up reached 73% [44].

Stochino-Loi et al. [45] performed a retrospective comparative study with 180 patients with stage III and IV endometriosis and pregnancy intention. They observed that the probability of postoperative pregnancy was comparable between women with low and normal AMH levels (AMH levels < 2 ng/mL = 73.9% and AMH levels $\geq$ 2 ng/mL = 74.6%); most of them got pregnant spontaneously (58.8% and 54%, respectively).

Motte et al. [60] conducted a retrospective case control study in which plasma energy ablative therapy demonstrated a higher implantation, pregnancy and delivery rates per IVF cycle, albeit with a lower number of oocytes retrieved. Thus, plasma energy has been suggested as a more favourable ablative technique for endometrioma management.

3.2.3. Comparison of Pregnancy Rate after Ovarian Cystectomy and Endometrioma Vaporization

A Cochrane review by Hart et al. published in 2008 showed a beneficial effect of excisional surgery over drainage or ablation of endometrioma when considering achievement of spontaneous pregnancy in subfertile women (odds ratio (OR) 5.21, CI 2.04–13.29) [14]. However, there were only two studies that addressed this issue, so publication bias cannot be excluded.

3.2.4. Pregnancy Rate and the Combined Technique

In a descriptive and prospective study, Donnez et al. reported a pregnancy rate of 41% at a mean follow-up of 8.3 months after the combined approach for endometrioma [11].

4. Discussion

The benefit of endometrioma excision for pain management is consensual, but surgical excision for the sole purpose of improving reproductive outcomes is controversial [9]. Ovarian involvement with endometriosis might have a negative impact on ovarian reserve [23,26,32]. That fact, alongside the risk of postsurgical ovarian failure, has reopened the debate between excision and ablation [19].

The reduction of ovarian reserve after surgery for endometrioma is inevitable, regardless of the technique. Both excisional and ablative approaches lead to a postsurgical decrease of up to 60% in AMH levels. However, studies comparing the two techniques show a higher and significant decrease after cystectomy [46,47].

The decline in ovarian reserve after ovarian surgery is multifactorial. Healthy ovarian tissue may be unintentionally removed during ovarian cystectomy due to the absence of a clear histologic cleavage plane, which can result in loss of follicles. This justifies the theory that ovarian reserve is better preserved by ablation than by cystectomy. However, other proposed mechanisms for the ovarian reserve decline include thermal damage caused by bipolar coagulation, ovarian vascular injury and postoperative inflammatory response [19,24,28,61]. Therefore, bipolar electrocoagulation should be kept to a minimum, especially for patients with reproductive goals [61]. With the use of a CO_2 laser, the glandular epithelium and the underlying stroma [11,47] are destroyed without reaching the fibrous capsule surrounding the endometrioma or healthy neighbouring ovarian cortex. The CO_2 laser would provide better control of the depth of vaporization, remaining superficial compared to bipolar electrocoagulation [47,50]. This is an advantage as it would not be necessary to destroy the entire fibrous capsule by vaporization, as only 1.0–1.5 mm of the inner lining would be sufficient [62]. The CO_2 laser as well as plasma energy are techniques for sparing ovarian tissue with a shallower thermal diffusion [50,59]. Their low thermal energy avoids excessive ischaemic damage while providing high precision and optimal coagulation, reducing the need for electrocoagulation or suturing [19,50]. Thus, CO_2 technology may be used to treat endometrioma with minimal damage to the adjacent healthy ovarian tissue and it might be an alternative treatment in women with a desire for pregnancy.

Excision of the ovarian cortex could be involved in the reduction of ovarian reserve just after surgery, but a continuous decrease could be attributed to other factors, such as vascular compromise by excessive coagulation or adhesiolysis as well as postsurgical inflammation [24,26,27,44].

The number of studies that have evaluated changes in ovarian reserve after cystectomy over a period longer than 6 months is limited, but it seems that the decrease in AMH following surgery for endometrioma is temporary and can be recovered. This can be explained by surgery-related reversible mechanisms related to ovarian vasculature and inflammation-mediated injuries. After ovarian injury, compensatory mechanisms may include the recruitment and growth of primordial follicles and the excessive activation of granulosa cells [28]. This leads to rearrangements of the cohort of follicles, including follicles producing AMH, which can explain the "recovery" in the ovarian reserve. The delay in this recovery is explained by the approximate 180-day duration of folliculogenesis from the primordial follicles to the pre-ovulatory follicles [27]. A similar pattern of AMH recovery has been reported in young women after chemotherapy, in which a complete restoration of AMH levels was observed [26,63]. However, some studies showed that ovarian reserve cannot be fully restored in all patients after surgery for endometrioma, indicating some elements of permanent damage. Since the literature on the late postoperative period is scarce, recovery of the ovarian reserve should be interpreted with caution [3]. Furthermore, factors like AMH decline with age and endometriosis must be considered [23,64].

Bilaterality, size of endometrioma, stage of endometriosis and patient's age are independent factors that should be also considered when planning a surgery in patients who are interested in preserving their fertility [3,30]. Bilateral endometriomas, stage III/IV endometriosis and patients over the age of 35 have a higher impact on postsurgical AMH

levels. For large cysts, a proportional loss of healthy ovarian tissue with the diameter of the cyst can explain the higher decrease of AMH levels [35,65]. Additionally, for endometriomas with more than 5 cm, ablative treatment seems to have low impact in postoperative AMH levels than excisional surgery [49]. For recurrent endometrioma, a second surgery is associated with higher loss of ovarian tissue and is more harmful to the ovarian reserve [36]. Indications for surgery for recurrent endometrioma should thus be considered with caution and excisional surgery must be avoided [36]. Medical treatment may be the first option, but when surgery may still be indicated, an ablative approach can be considered, as recurrence rates are similar [48].

All of these factors will allow clinicians to select therapies to prevent further decline of ovarian reserve, especially for infertile patients with ovarian endometrioma [34]. Therefore, surgery should be performed when mandatory, such as pain refractory to medical therapy, pain associated with otherwise unexplained infertility and in the case of non-reassuring features of the cyst on preoperative ultrasound [66]. Individual reproductive plans and oocyte or ovarian tissue cryopreservation should be discussed with patients before surgery. Ideally, surgery can be postponed until the reproductive project is complete [3].

The decline of AMH levels after surgery is higher in patients with ovarian endometrioma than in those with other benign tumours [29,31–33]. This is in line with the impact per se of endometriosis in ovarian reserve and the fact that it is also present when surgery is performed by a specialised surgeon [26,32,66]. The likelihood of spontaneous pregnancy after surgery is also lower in patients with endometrioma [29].

According to the ESHRE guideline, there is evidence to suggest that ovarian cystectomy via stripping is the preferable surgical technique for management of endometrioma, compared with other excisional/ablative techniques in terms of the pregnancy rate [13,14]. However, studies carried out later show a higher overall pregnancy rate after the ablative approach than the excisional (67–73% vs. 30–67%) [44,59]. This fact is in line with the lowest impact on AMH levels.

Favourable preoperative ovarian reserve and its postoperative maintenance together may be implicated in postsurgical pregnancy after surgery for endometrioma [34,37]. The potential risk of postsurgical poor ovarian response could be predicted by using optimal cut-off points of presurgical AMH levels (2.1 ng/mL of unilateral endometrioma; 3 and 3.5 ng/mL for bilateral endometrioma at 3 and 6 months after surgery, respectively) [34]. The cut-off value to predict spontaneous pregnancy rates after endometrioma cystectomy is approximately 3.5 ng/mL, with higher AMH levels associated with a higher pregnancy rate [37,54,57]. Thus, after cystectomy, better ovarian reserve with optimal rearrangement of the follicle cohort may be related to subsequent pregnancy [58]. In patients at risk, alternative management of cystectomy should be foreseen. However, AMH is a quantitative but not qualitative surrogate for oocytes [34].

In patients with stage III and IV endometriosis submitted to ablative surgery, the probability of pregnancy and the risk of decreasing ovarian reserve is similar in patients with high and low preoperative AMH levels [45]. Therefore, a young patient suffering from severe endometriosis with a decreased ovarian reserve and a preoperative AMH level below normal could benefit from surgical management. This surgery could restore the capacity of spontaneous pregnancy in this population and may be an alternative to ART [45].

This review highlights the importance of preoperative evaluation of AMH in the therapeutic planning of patients with endometrioma and in the selection of the surgical technique. Based on this value, it is possible to offer more detailed preoperative counselling regarding the pregnancy rate after surgery and the risk of decreased ovarian reserve, assessed through AMH values. Recent studies suggest that the ablative approach, namely, with the use of a CO_2 laser, seems to be the most interesting surgical technique, with the least impact on postoperative AMH levels and better pregnancy rates. However, this review has some limitations as more studies, namely, randomized clinical trials, are needed to draw definitive conclusions. Additionally, more studies assessing live birth rate rather

than pregnancy rate are needed, as live birth rate was recently defined as a core outcome set for endometriosis [67].

5. Conclusions

In conclusion, measurement of AMH should be included in the evaluation of reproductive-age women with endometriosis. The indication of surgery for an ovarian endometrioma should be thoroughly discussed with the patient, with particular emphasis on the issue of possible damage to the ovarian reserve. The review of the literature demonstrates that the endometrioma ablation procedure, even if performed in patients with a decreased ovarian reserve, is beneficial in terms of pregnancy.

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Prospective International Multicenter Pelvic Floor Study: Short-Term Follow-Up and Clinical Findings for Combined Pectopexy and Native Tissue Repair

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Abstract: Efforts to use traditional native tissue strategies and reduce the use of meshes have been made in several countries. Combining native tissue repair with sufficient mesh applied apical repair might provide a means of effective treatment. The study group did perform and publish a randomized trial focusing on the combination of traditional native tissue repair with pectopexy or sacrocolpopexy and observed no severe or hitherto unknown risks for patients (Noé G.K. J Endourol 2015;29(2):210–215). The short-term follow-up of this international multicenter study carried out now is presented in this article. Material and Methods: Eleven clinics and 13 surgeons in four European counties participated in the trial. In order to ensure a standardized approach and obtain comparable data, all surgeons were obliged to follow a standardized approach for pectopexy, focusing on the area of fixation and the use of a prefabricated mesh (PVDF PRP 3 × 15 Dynamesh). The mesh was solely used for apical repair. All other clinically relevant defects were treated with native tissue repair. Colposuspension or TVT were used for the treatment of incontinence. Data were collected independently for 14 months on a secured server; 501 surgeries were registered and evaluated. Two hundred and sixty-four patients out of 479 (55.1%) returned for the physical examination and interview after 12–18 months. Main Outcome and Results: The mean duration of follow-up was 15 months. The overall success of apical repair was rated positively by 96.9%, and the satisfaction score was rated positively by 95.5%. A positive general recommendation was expressed by 95.1% of patients. Pelvic pressure was reduced in 95.2%, pain in 98.0%, and urgency in 86.0% of patients. No major complications, mesh exposure, or mesh complication occurred during the follow-up period. Conclusion: In clinical routine, pectopexy and concomitant surgery, mainly using native tissue approaches, resulted in high satisfaction rates and favorable clinical findings.

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The procedure may also be recommended for use by general urogynecological practitioners with experience in laparoscopy.

Keywords: prolapse; pelvic floor; laparoscopy; native tissue; pectopexy

1. Introduction

Due to controversies about the use of meshes, native tissue repair in pelvic surgery has currently rebecome the matter of choice in several countries. Native tissue repair was considered to be insufficient for a long period of time. However, several publications have shown that, from a clinical perspective, it provides better outcomes than meshes in the long term. In fact, the patients' symptoms are improved to a much greater extent compared to the assessment of the sheer anatomical results [1–3]. Various vaginal or abdominal techniques (Manchester; sacrospinous fixation; high uterosacral fixation etc.) have been suggested for the restoration of apical support. To date, we lack validated data about the adequacy of these approaches. Sacral colpopexy with mesh is a frequently used technique in laparoscopy and has been evaluated in several studies. Due to the disadvantages of the approach (see below), our group devised the procedure of laparoscopic pectopexy in 2007 [4].

The so-called gold standard of laparoscopic sacral colpopexy (LSC) is based on several decades of extensive experience. The introduction of alloplastic material to fill the gap between the vagina and the sacrum accelerated the acceptance of the technique [5]. Extensive data have been reported from single-center studies, but a prospective multicenter trial comparing access and quality has not been published so far [6–8].

LSC commonly employs a y-shaped mesh deeply covering the total posterior length of the vagina and the anterior wall next to the bladder neck [9,10]. Comparison with published data is rendered difficult by the manifold approaches currently in use. Therefore, our group did focus on the use of mesh material only for apical support and did repair other defects with native tissue strategies [11].

Using pectopexy as apical support in combination with native tissue may reduce the risk of defecation disorders, which occur frequently after LSC. Additionally, mesh-related problems such as exposure at the vaginal wall were reduced [12].

De novo defecation disorders are anticipated in 17–34% of cases after LSC [9,13–17]. Slow intestinal transit, chronic flatulence, pain during defecation, and mild to severe constipation are the main symptoms reported in the literature. Published data on pectopexy have indicated the benefits of offering a standardized alternative option to LSC with the potential of reducing the risk of defecation disorders and bowel constriction by the mesh material, especially in obese patients [12]. The combination of native tissue repair and sufficient apical support leads to a low rate of de novo stress urinary incontinence (SUI) (4.5–7%) as well as minimal use of mesh material [3,12].

The present multicenter trial was performed to evaluate the effectiveness of the approach in general use by trained surgeons and determine the results of native tissue repair combined with apical mesh support in different hospitals and by different surgeons.

2. Materials and Methods

The study was initiated at 11 hospitals with 13 surgeons in four European counties. In order to ensure a standardized approach and obtain comparable data, all centers were instructed to use a prefabricated mesh (Dynamesh PRP 3 × 15) (approximately 25 cm^2). In pectopexy, the mesh for apical support is fixed bilaterally at the pectineal ligament and anchored by sutures close to the crossing psoas muscle. This provides a fixation point at the level of the first sacral vertebra. Placement of the tape does not interfere with organs, vessels or nerves, and the defined fixation point ensures correct anatomical positioning

of the vaginal axis. Owing to its position, the tape does not disturb the rectum or the hypogastric plexus. The diameter of the lower pelvis is not reduced by the technique.

Surgeons were trained by experts from the center at which the technique was developed, and data were collected on a secure server at the University of Wuerzburg. Every needed to have performed a minimum of 20 procedures before entering the study. All of the surgeons had private access to the server and could collect their data independently.

All patients who required surgical treatment (conservative treatment was either insufficient or was not accepted by the patient) were included in the study, except those with contraindications for laparoscopy. In accordance with common practice at the majority of the hospitals, the Baden-Walker classification (grades 1 to 4) was used to describe the defects. A distinction was made between apical defects, cystocele midline—cystocele lateral defects, and posterior defects. A modified version of the ICIQ-VS (International Consultation on Incontinence Questionnaire—Vaginal Symptoms) questionnaire was used to assess clinical complaints. The group did focus on complaints such as pelvic pressure, SUI, urgency, stool bulking/constipation, pain, and sexual impairment. Table 1 shows the rating of the complaints. Obstetric data and the patients' histories of previous surgery, especially hysterectomy and cesarean section, were registered. Stress urinary incontinence (SUI) was stratified from grade 1 to 3, according to Stamey's definition.

Table 1. Measurement of symptoms by the questionnaire based on International Consultation on Incontinence Questionnaire—Vaginal Symptoms (ICIQ-VS).

	Measurement	
Complaints	**Positive**	**Negative**
Pelvic pressure	Daily or regularly	Rare or no pressure
SUI	Stratification by Steamy	No SUI
Urgency	Positive answer and bothersome for the patient	No nycturia or frequency, no urge feeling
Stool bulking	Feeling of pressure in the lower rectum	No rectal problems
Constipation	Need for laxatives, slow transit	Normal defecation
Pain	Pain in the pelvis	No pain

Concomitant surgeries, whether by the vaginal or laparoscopic approach, total operating times, and the time used for pectopexy, were registered. Intraoperative complications and postoperative data such as the duration of hospital stays, early—and late-onset infection (14 days after surgery), and wound infection were recorded in the database.

A total of 501 patients were registered in 14 months. Surgical data were analyzed and have been published recently [11]. Telephone interviews were not included in the evaluation. IBM SPSS statistics and Sigma plot Statistics (Systat Software, Inc., D-40699 Erkrath, Germany) were used for statistical evaluation.

3. Results

After the scheduled 14 months of data collection, 501 patients were registered on the server. Surgical and early complications have been reported in a previous publication [11]. Follow-up was performed 12–18 months after surgery (mean, 15 $\pm$ 2 months). A large number of patients, especially those at the main center, had to travel long distances (>100 km) or had difficulties arranging their transport, which had a negative impact on evaluation rates. Two hospitals, which had contributed two and 20 patients each, did not participate in the follow-up. More than 93% of the patients answered the follow-up inquiry. More than half of the patients who could not arrange to come answered the questionnaire, the others responded positively by phone. Only 7% did not react. Two hundred and sixty-four of 479 patients (55.1%) underwent a physical examination and were followed up with the questionnaire used prior to surgery. A distinction was made between de novo and persistent complaints and defects.

The distribution of concomitant surgeries in the examined group was similar to that in the entire study group. Table 2 shows the total and relative numbers for all surgical

approaches in the entire group compared to the examined group. The distribution of defects was similar in both groups (Table 3). Table 4 shows primary symptoms preoperatively and during follow-up.

Table 2. Concomitant surgeries in the entire trial group and the physical examined follow-up group.

Study Group Total/Follow-Up Approach	Frequency Entire Group	Percentage	Frequency in Follow-Up (Examined) Group	Percentage
Pectopexy	501	100	264	100
Laparoscopic cystocele repair	173	34.5	83	31.5
Laparoscopic posterior repair	132	26.3	58	22.0
Vaginal anterior repair	68	13.6	50	18.9
Vaginal posterior repair	59	11.8	41	15.5
Laparoscopic lateral repair	115	22,9	50	18,9
Burch colposuspension	64	12.8	34	12.9
Vaginal tape	2	0.4	2	0.76
LSH	313	62.5	175	66.3
TLH	5	1.0	2	0.76

Table 3. Distribution of defects in the total study group compared to the examination group.

Defect	Total Group	Examination Group
Apex grade 2	57%	52%
Apex grade 3 and 4	37%	39%
Cystocele grade 2 and 3	60%	59%
Posterior grade 2	12%	11%
Posterior grade 3	13%	14%

Table 4. Impact of surgery on complaints in the follow-up group before and after surgery.

	Pre-Surgery	Follow-Up	De Novo	Persistent
Pelvic pressure	86.7% (229)	9.8% (26)	5.7% (15)	4.1% (11)
Pain	18.9% (50)	2.7% (7)	2.3% (6)	0.4% (1)
Urgency	51.7% (136)	11.4% (30)	4.2% (11)	14% (19)
Sexual impairment	15.9% (42)	3.4% (9)	2.7% (6)	7.1% (3)
Stool bulking/	11.2% (28)	3.2% (8)	0.4% (1)	25.0% (7)

3.1. Pelvic Pressure

Only 4.1% of patients with a preoperative sensation of pelvic pressure reported no significant change after surgery (chi-square $p < 0.001$), while 5.7% reported de novo pressure due to relapse or de novo changes. Previous symptoms were reduced in 95.9% of patients.

3.2. Urgency

50% of the patients included in the study reported urgency before surgery, whereas 86% of this group had no urgency after surgery (chi-square $p < 0.001$). De novo urgency was registered in 4.2% of patients. 25% (34) had an additional loss of urine prior to surgery. One (9%) of the patients with de novo urgency also had a first-degree loss of urine. In the group with urgency persistence, 3 (16%) women with persistent grade 1 incontinence were registered.

3.3. Sexual Impairment

Sexual impairment was considered relevant by 16.8% of the total cohort (15.9% of the follow-up group). Only 7.14% of patients complained of persistence after surgery.

3.4. SUI

Twenty-four percent of the patients reported SUI before surgery. SUI was rated: grade 1 by 25%, grade 2 by 66%, and grade 3 by 9% of patients. Of those who underwent

additional surgery (colposuspension n = 43), 72.1% of patients were dry, and 93% were improved; 7% reported persistence of previous symptoms after surgery. Thirteen patients did not receive any treatment for incontinence; 53.4% were dry after prolapse surgery; and 30.8% reported persistence of their previous incontinence. Only two cases (0.8%) of de-novo incontinence were identified in the whole cohort.

3.5. Stool Bulking and Constipation

Preoperatively, 11.2% of patients experienced stool bulking or constipation. We noted persistence in 25.0%, and one patient with de novo symptoms.

Since a slight degree of under-correction of level I. (between grade 0–1) was agreed upon in order to avoid the side effects of over-correction, grade 1 was considered to indicate cure of presurgical stages 2 and above. Cure was registered in 94.3% of patients, while 96.6% were either cured or improved.

3.6. Level II

Out of 35 untreated grade 1 cystoceles, 15 (42%) persisted while two (6%) deteriorated (Grad 2). 133 patients with a grade 2 or higher midline defect received an additional native tissue repair. 121 (91%) showed cure or improvement, while 12 persisted or worsened.

99 patients with clinically relevant posterior defects were treated with additional native tissue repair. In this group, 94 (95%) showed an improvement or cure.

When asked "Would you recommend the treatment to a relative?" the question was answered positively by 95.1% of patients. The mean rating on an analogue satisfaction scale from 1–10 was 8.7. Overall, 90.2% of patients gave a rating between 7 and 10. The reasons for not recommending the treatment were pelvic pressure (persistent or de novo) (eight cases), de novo pain (two cases), and de novo sexual impairment (three cases, two of which involved persistent incontinence).

3.7. Complications

Three lymphatic seromas at the lateral suspension site were treated by laparoscopy. One TVT was placed after 7 months because of incontinence. Two re-interventions were performed by the laparoscopic approach because of early level 1 recurrence. One patient with urinary retention received medical treatment. One de novo enterocele and one de novo cystocele were operated on during the follow-up period. No mesh exposure or mesh complication was observed during follow-up.

4. Discussion

4.1. Main Findings

Previous publications have indicated that pectopexy is safe and can be incorporated in clinical routine [11,12]. Since controversies concerning meshes may also affect abdominal techniques with the extended use of meshes (deep anterior or posterior mesh placement), Our group collected data on reduced mesh use adding to the effectiveness of pectopexy. In this study, 15 cm of PVDF tape (Dynamesh PRP 3 × 15) were used solely for apical support (approximately 25 cm^2). In a computer simulation, Bhattarai et al. showed that bilateral fixation in pectopexy permits better physiological positioning of the bladder and vaginal cuff than unilateral sacral colpopexy during the Valsalva maneuver [18].

The anchor point of pectopexy lies 1–2 cm above the natural apex and does not allow for correction of a cystocele or a posterior defect by pulling the vagina cranially. Therefore, in this study, our group did combine apical support with concomitant repair, depending on individual defects and disorders (Table 2). Notably, no additional mesh was used for cystocele, rectocele, or enterocele repair.

The results were compared with those of LSC, mainly performed with deep mesh fixation [9,10,19]. The comparison was rendered difficult by inconsistent results and the absence of prospective multicenter trials. Therefore, the group did compare its findings mainly with reports from single-center studies, which comprised small sample sizes and

patients who did not undergo physical examination. The majority of published studies have been focused on anatomical changes or outcomes; clinical findings were given less importance.

The cure rate in this study for level 1 was 94.3%, while 96.6% of patients were either cured or improved. This is a confirmation of previous data [12]. Similar rates have been reported for LSC (94–100%) [10,20–22].

The primary symptom was pelvic pressure and bulging, which occurred in 86.7% (n = 229). Persistence of this symptom was noted in 4.1% of patients. Symptoms were reduced in 95.2% ($p \leq 0.001$ for the chi square test). De novo symptoms, mainly due to de novo pelvic floor defects, were reported by 5.7% of patients. Liedel et al., who studied 277 patients, noted reduced symptoms in 82.7% (p = 0.00001) after vaginal pelvic floor surgery [23]. In retrospective data, Bojahr et al. noted a reduction of symptoms in 90.7% of patients after LSC [24].

This study did register a reduction of pain in 98% of patients, whereas Liedel et al. observed the same in 53.1%, and Bojahr et al. in 44% of patients. These diverse outcomes may have been due to different interpretations of the sensation of pain.

Of the follow-up group, 51.7% (136) of patients complained of urgency and frequency before surgery. This symptom was reduced in 86% of patients during follow-up; 4.2% complained of de novo urgency. Several studies have focused on urgency and prolapse. Whilst Malanowska et al. reported a reduction of symptoms in 76% and a de novo rate of 2.6% of patients for the lateral suspension technique, Illiano noted a reduction of symptoms in 73.6% of patients after LSC and Rexhepi et al. observed a reduction in 67% of patients who were treated with bilateral LSC. Compared to published success rates for pectopexy, we achieved excellent results [25–27].

The measurement of sexual impairment was one of the most problematic issues. Pelvic floor defects are associated with a combination of anatomical obstacles and psychological embarrassment. Prolapse problems could not be distinguished easily from interpersonal incompatibility in sexual relationships. The data are quite heterogeneous. Our group did observe different outcomes in its studies; 15.9% of the follow-up cohort complained of sexual impairment before surgery. The reduction registered in 92.9% of patients was surprisingly high, but a de novo problem occurred in 2.7%. Half of the latter patients would not recommend the procedure because of their de novo sexual impairment.

This study measured a reduction of stool bulking and constipation in 75% of patients ($p < 0.001$). Whilst studies addressing vaginal repair have reported a reduction of symptoms in 66% of patients after vaginal repair, most LSC studies mention an increased rate during follow-up [16,17,23,24,28,29]. As LSC is known to be associated with bowel symptoms, vaginal repair, as well as pectopexy, appear to significantly improve this complaint. The results support previous findings from our first randomized trial [12].

De novo incontinence occurred in 0.8% of cases, and 56 patients had relevant incontinence before surgery. A total of 43 patients were treated simultaneously with colposuspension, whereas 13 did not receive additional treatment. Improvement was registered in 93% of the first group, but only 53.4% of the second group (p = 0.003; Fisher's exact test). High incontinence rates (5–40%) have been reported after LSC. Some authors recommend adding Burch colposuspension to the surgical strategy. However, this topic remains controversial [20,24,30–32]. Our findings support simultaneous treatment in a multiple compartment setting.

There are some long-term studies on sacropexy or hysterosacropexy available which report a high level of safety in the procedures. The latter technique enables an exposure rate of only 0.4% with a median observation of 46 months (multicenter questionnaire study). Nightingale and Phillips examined 93 of 112 patients over 9 years of age (mean 6 years follow-up) and reported only one mesh complication (bowel obstruction). We did not find any mesh complication yet and hope to publish a long term follow up soon [33,34].

4.2. Strengths and Limitations

The multicenter setting provided a large cohort of patients who could be studied prospectively at a large number of international centers. Clinically relevant anatomical, functional, and subjective findings are reported here. Due to the heterogeneity of clinical practices in four countries and 11 centers, and to ensure the comparability of data, we used a standardized questionnaire designed for the study in addition to routine data collection. This limits the comparability of the present investigation with other publications based on questionnaires provided by the International Urogynecology Association (IUGA) or International Continence Society (ICS). An international trial entails the inclusion of different experiences and diverse traditions. We could standardize the technique for pectopexy and laparoscopic cystocele and rectocele repair, but the vaginal approaches were based on local experience. The effect of these differences on the collected data could not be measured.

4.3. Interpretation

A positive recommendation rate of 95.1% and a mean satisfaction rate of 8.7 (from 1 to 10) expressed the high degree of clinical acceptance by the patients. Figure 1 shows the distribution of the rating scale for the entire treatment. The negative recommendations resulted from de novo sexual impairment (3), de novo defects, and relapse. Complications such as infections or seroma were widely accepted.

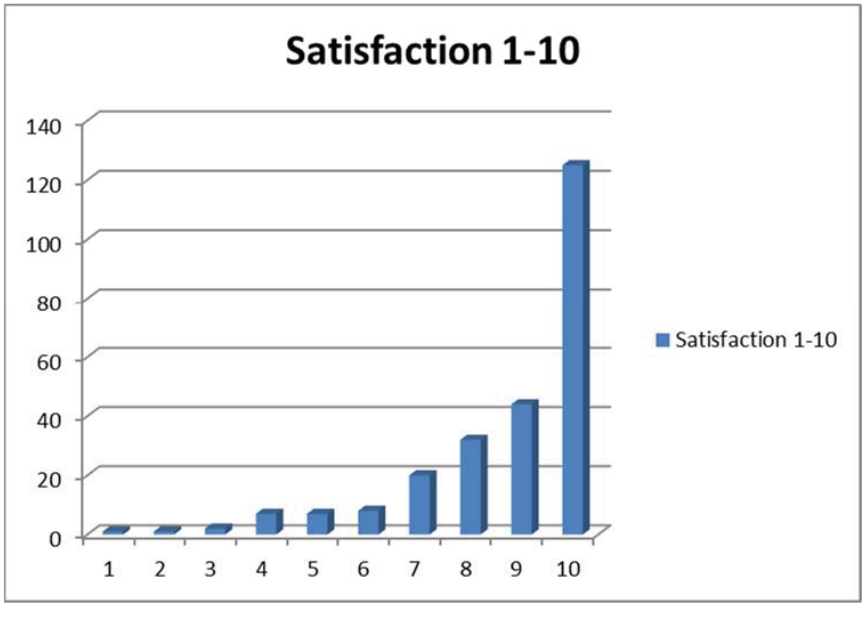

Figure 1. Rating scale for patients' satisfaction with their treatment.

5. Conclusions

Pectopexy combining apical support with a prefabricated PVDF tape and native tissue repair for level 2 and 3 defects yielded favorable clinical outcomes and a low re-intervention rate after a mean follow-up period of 15 months. A prospective international multicenter study provides valid results because of the large sample size and the standardized procedures performed by independent surgeons. Given the favorable results and the low rates of side effects, the approach may be recommended as an alternative to LSC for experienced

surgeons. It provides the option of reducing mesh use by combining adequate apical support with native tissue repair. The long-term follow-up should permit the identification of those patients who require additional mesh for level 2 and 3 treatment.

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Review

Genital Prolapse Surgery: What Options Do We Have in the Age of Mesh Issues?

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Abstract: Here, we describe the current laparoscopic procedures for prolapse surgery and report data based on the application of these procedures. We also evaluate current approaches in vaginal prolapse surgery. Debates concerning the use of meshes have seriously affected vaginal surgery and threaten to influence reconstructive laparoscopic surgery as well. We describe the option of using autologous tissue in combination with the laparoscopic approach. Study data and problematic issues concerning the existing techniques are highlighted, and future options addressed.

Keywords: pelvic floor repair; laparoscopic repair; vaginal repair; mesh use; native tissue

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1. Introduction

Vaginal prolapse is and remains a problem for a large number of women around the world. After a prolonged period of slow development, prolapse surgery progressed significantly towards the end of the 1990s. For a long time, native tissue repair dominated the surgical procedure. These techniques are advantageous as they do not require any foreign material to be implanted. A number of techniques were introduced, but were not investigated in multicenter studies. The influence of alloplastic material in the lower pelvis, its side effects, and complications were clearly underestimated. In the last two decades, mesh materials have been used to an increasing extent in pelvic floor surgery, and have almost triggered a crisis. In the last few years, we have learned more about material characteristics and behavior in tissue. As patients with weakened connective tissue cannot permanently be reconstructed, meshes are very helpful. Surgeons' lack of experience, too little training, too little knowledge about the material properties, and incorrect indication were certainly very decisive for the mesh problem.

After the withdrawal of numerous mesh products from the market and negative media campaigns in many countries, the use of synthetic fabrics declined significantly [1]. This had a major impact on vaginal reconstructive surgery. Traditional methods such as colporraphy, the Manchester-Fothergill procedure, and sacrospinous fixation re-emerged as important approaches. Various mesh products were developed for the latter procedure, and were marketed along with clever fixation techniques. Once mesh surgery began its triumphant advance at the end of the 1990s, we were confronted with the problem of meager study data on traditional procedures that meet the current requirements.

In some countries, the use of meshes in sacropexy is viewed critically by government agencies. The technique is still recognized as the "gold standard" in prolapse surgery [2–4], but the extensive use of deep mesh placement is associated with greater mesh exposure and shrinkage [5]. Degradation of the material is followed by its spread within the body. Current study data indicate that these materials cause local effects on muscle, as well as fatigue syndrome [6,7]. The mesh problem in vaginal surgery has encouraged the use of native tissue and laparoscopic procedures. In the last decade, lateral suspension [8] and pectopexy [9] were introduced as alternatives to sacrocolpopexy for laparoscopic

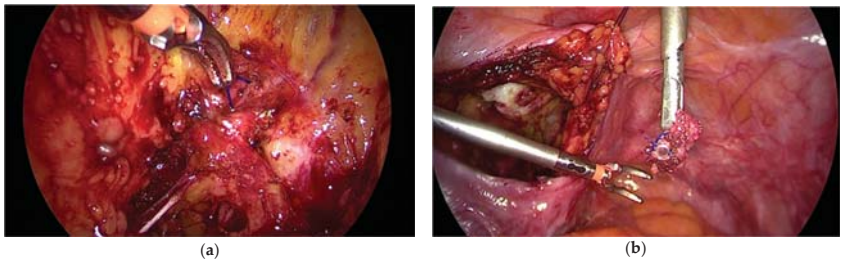
pelvic floor repair. Apart from laparoscopy, traditional vaginal procedures based on mesh materials or sewing applicators were developed further.

2. Vaginal Pelvic Floor Surgery

Vaginal surgery is more ambiguous than laparoscopic surgery. Regulations and practices concerning the use of meshes differ from one country to the other. All of the existing methods of vaginal mesh application are used in Germany. The indications for their use have become more stringent, but meshes are not subject to any official restrictions, although governed by a variety of regulations. The use of meshes is entirely prohibited in some countries. In others, their use is permitted in clinical studies or at selected centers. In yet other countries, it is common practice to use self-tailored meshes.

Although a number of single-center studies revealed the superiority of mesh surgery, the so-called PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials) trial showed no benefits [10]. The above-mentioned study data have been interpreted diversely. An objective presentation is almost impossible at the present time. However, research efforts are still being focused on enhancing the safety of meshes in vaginal surgery. One of the many debated issues is whether the quantity of mesh or the combination of different alloplastic tissues (such as the combined use of incontinence tapes and prolapse meshes) is a crucial determinant of success [11,12]. The second debated issue is geographical centralization of pelvic floor surgery in order to achieve better outcomes. Many studies suggest strong evidence of a close connection between surgical expertise and complication rates [13]. A large number of publications in the last decade have addressed this issue in nearly every field of surgery. The vast majority of investigations identified a clear link between success rates, complications, the number of performed interventions, and the surgeon's expertise.

The use of meshes is nearly impossible or very limited in some countries. Traditional methods are experiencing a renaissance in these regions. For several decades, the sacrospinous ligament was used for apical fixation. Vaginal mesh surgery developed in the 1990s and current alternative methods are also based on fixation to this ligament. A Cocrane analysis in 2013 examined randomized trials that compared vaginal (especially sacrospinous fixation) and sacrocolpopexy (SC). The review disclosed the superiority of SC, but also highlighted the significantly longer operating times and the longer learning curve for SC [14]. Mesh surgery has replaced sacrospinous fixation to a significant extent. The technology of mesh fixation has been revived. It is either performed using the traditional method, or with the aid of suture devices for fixing the threads [15]. To improve the outcome, surgeons use narrow meshes instead of sutures. The meshes are fixed with sutures or anchors. Analogous to suture techniques, the anchors are placed in the ligament, close to the pudendal nerve, and are sutured at this site. All of these techniques are not performed under direct vision, and therefore require great skill. Anchors placed close to a nerve or at the wrong site may cause severe pain (Figure 1).



(**a**) (**b**)

Figure 1. (**a**) Anchor placed in the lateral pelvic fascia instead of the sacrispinous ligament (**b**) (removed anchor on the right photograph).

A rather limited body of data derived from single-center studies is available at the present time [16,17]. These studies report excellent outcomes in combination with traditional colporrhaphy. However, the majority of the published reports are short-term evaluations and do not provide data on mesh-related complications due to fibrosis or mechanical stress. The same is true of traditional methods such as the Manchester-Fothergill technique or high utero-sacral fixation. Our literature search yielded a handful of small studies and case reports. Randomized or prospective studies do not exist. The procedure of culdoplasty, frequently associated with the name McCall, is used to prevent prolapse after hysterectomy. Schiavi et al. compared two suturing techniques for culdoplasty, and noted the preventive value of both techniques. A suspension suture was performed in all patients. The study did not include a control group and provided no analysis of the general risks of a pelvic floor defect. Nevertheless, the authors conclude that the method is effective [18]. We lack any real evidence of the effectiveness of these procedures. To circumvent the use of meshes, therapy approaches based on preventive suspension have been presented at several medical conventions.

Data concerning the use of meshes in vaginal surgery are very diverse. Mesh techniques should be investigated in prospective multicenter studies in order to separate the wheat from the chaff, and to provide surgeons and patients with reliable, unequivocal data. A number of skilled surgeons use a large portfolio of techniques and are able to treat their patients effectively with low complication rates. Meshes have been used very effectively in vaginal surgery. As prolapse is a very common problem, we need effective and resilient surgical techniques with a low risk profile.

3. Laparoscopic Sacral Colpopexy (LSC)

This approach was first published in 1920. However, it was not until the 1960s that artificial tissue was used to bridge the distance to the sacrum. The technique is performed by placing a Y-shaped mesh posteriorly and anteriorly to the vaginal wall. The conjunction is sutured to the apical structure (cervix and vault), and the distal part of the mesh is anchored to the promontory or sacrum. It has been common practice to place the mesh as low as possible [19]. This approach is justified in terms of correct anatomical location.

The need for deep mesh placement is a debated issue. Many investigations on laparoscopic sacropexy have been performed with deep mesh implantation [20]. We lack sufficient data to provide a conclusive answer to the debated issues highlighted above. A few studies have reported on the combined use of SCP and the vaginal approach. Kaser et al. described the advantages of LCP combined with vaginal posterior colporrhaphy. In a follow-up investigation of 258 patients, the laparoscopic procedure was used in 196 patients and open laparotomy in 62 [21]. Banerjee et al. published a cohort study of patients who were treated with vaginal native tissue repair (anterior and posterior colporrhaphy), laparoscopic lateral repair, and LCP (n = 246). The mesh was placed between the apex and the longitudinal ligament, at the level of the first sacral vertebra [22]. After a mean period of 28 months, the re-intervention rate was 7.8%:4.8% due to de novo stress urinary incontinence (SUI) and 3% due to pelvic floor defects.

Bojahr et al. published a retrospective analysis of 301 patients treated with sacral colpopexy. In 96% of the cases, LSC was performed exclusively without deep mesh fixation or additional surgery. Approximately 4% of patients underwent vaginal colporrhaphy. Recurrent symptoms were noted in 24.7% of patients at 24.5 months after surgery [23]. This may indicate that apical fixation alone is not effective. Mesh exposure in LSC (1–5%) has been reported in many publications (1–5%) [5,24]. Computer-based models showed that straight fixation causes extensive shear forces on the pelvic fascia in LSC, and may be inferior to bilateral fixation. Further investigations on fixation techniques and mesh material will be needed to reduce the use of meshes in LSC. Other risk factors such as osteomyelitis of the promontory and frequent defecation disorders have led to the development of new strategies, as mentioned above [25,26].

Indication: In most cases, LSC is used to correct all existing defects simultaneously. In cases of cystocele, the thinned tissue of the vagina is pulled cranially. The resulting shear forces may cause tissue defects. Compensating a cystocele by pulling it cranially may result in organ displacement. This could be one explanation for the high rates of de novo SUI after LSC.

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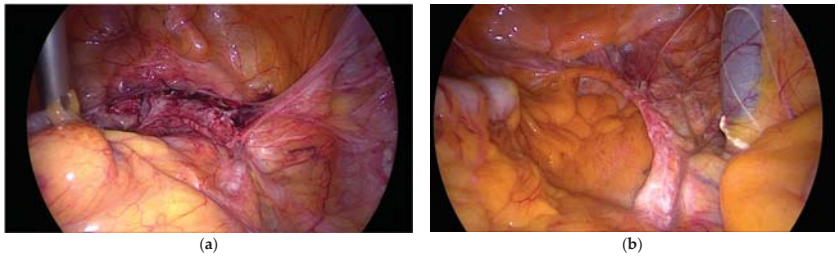


(a) (b)

Figure 2. (**a**) Laparoscopic sacral colpopexy (LSC) 10 years after surgery and (**b**) 12 years after surgery, both fixed to the longitudinal ligament on SV2 (Sacral Vertebra 2).

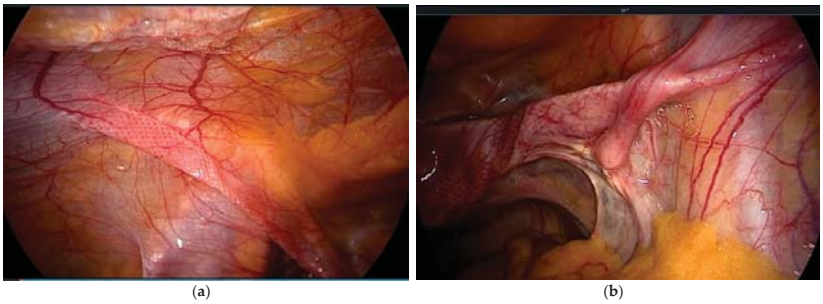
4. Lateral Suspension (LS)

LS was introduced by Dubuisson in 2002. Operating times for LSC have been reported to range from 90 to 300 min. Using tackers at the promontory and dispensing with fixation at the second sacral vertebra have simplified the technique. However, the use of tackers is associated with osteomyelitis [26]. The latter is a rare condition but may develop into a real threat for the patient. Aberrant vessels or scars may hinder access to the sacrum or promontory.

The difficulties of tackers and sutures caused Dubuisson to use long mesh tapes similar to TVT (tension-free vaginal tape). A trocar is placed bilaterally at the level of the umbilicus (current modification), and graspers are introduced behind the peritoneum. The latter is undermined with the grasper in the direction of the apex. The mesh itself is fixed with absorbable tackers to the vagina and the apex. The prefabricated mesh consists of two cranial arms approximately 20 cm long and 1.5 cm wide, which are moved out extraperitoneally. The length of the arms is supposed to provide enough resistance to hold the apex without the use of sutures or tackers at the promontory [27].

Indication: (All in one repair for apical and combined prolapse). The technique is used in a similar manner as LSC, with anterior and posterior exposure. Two options are available: either the mesh is placed on the anterior vaginal wall alone, or is used by the surgeon to cover the vagina anteriorly and posteriorly. A handful of single-center studies have been published on the technique, but a randomized or multicenter trial is lacking. The large body of data from the developing center are based on hospital records and telephone interviews [28]. Patients who reported for follow-up investigations were examined physically. One year after surgery, 21.6% of patients complained of persistent prolapse symptoms. De novo incontinence was noted in 5.2%, and mesh-related complications occurred in 4.2%. The authors reported a reintervention rate of 7.3% due to symptoms of pelvic organ prolapse (POP). The long-term follow-up by telephone encompassed 51.3% of the patients, of whom 87.8% reported improvement of their symptoms after surgery.

The results of the studies reveal that the technology is producing satisfactory results. In view of the fact that the existing data are derived solely from individual centers, a multicenter study or a randomized trial would be welcome. LS is based on extensive mesh use (Figure 3). Yet, we lack data about potential long-term complications of the fibrosed arms, which cross vessels and nerves. This is a clear disadvantage in view of the perennial discussion on the use of meshes in pelvic floor surgery. The main advantage is the simplicity of the technique, which enables even less experienced laparoscopists to perform a POP correction.



(a) (b)

Figure 3. (**a**) Mesh arms extraperitoneal on the left; (**b**) crossing vessels and the psoas muscle on the right side.

5. Laparoscopic Pectopexy (LP)

Scientists who reported on LP in 2010 started to develop the technique in 2007 [9]. They had extensive experience in the use of LSC using the suture technique and placing the mesh on SV2 (Sacral vertebra 2). In obese patients, the distance between the mesh and the sigmoid colon is usually small because of fatty tissue. Moreover, patients frequently have a history of diverticulosis or diverticulitis. Defecation disorder rates ranging from 7% to 20% have been reported in connection with LSC [26,29]. These problems led to the development of the bilateral suspension technique using the pectineal (Cooper's) ligament (Figure 4). The procedure was performed earlier in India through laparotomy, using the medial portion of the ligament [30]. To avoid lifting the apex towards the abdominal wall, the developer used the most cranial part of the ligament. A 15-cm PVDF (Polyvinylidenfluorid) tape was used to fix the apex bilaterally to the pectineal ligament using a suturing technique.

Indication: The technique was introduced as an apical suspension procedure with accompanying surgery to treat level-2 and level-3 defects. The so-called defect-oriented strategy enabled the surgeon to get by with little use of meshes [31].

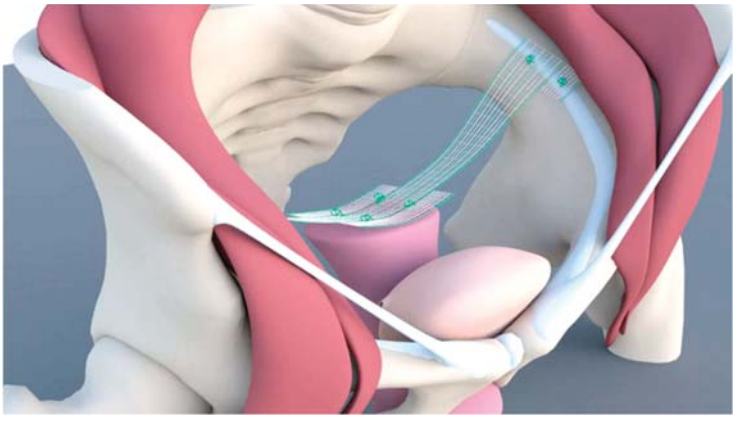


Figure 4. Mesh placement in pectopexy.

After a first pilot study, a randomized investigation was conducted to determine potential new risks and outcomes compared with LSC. The surgical data revealed no significant differences between the two techniques, although operating times were clearly shorter for the pectopexy approach [32]. After a mean follow-up period of 21 months, a significant difference was noted with regard to defecation disorders. Moreover, significantly fewer de novo lateral defects were observed in the pectopexy arm. The overall success rate

for apical support was 97.5%, and the recommendation rate 95% [33]. After the randomized trial, an international multicenter study was conducted at eleven centers in four European countries. The purpose of the study was to evaluate the safety of the technique. The data revealed a low risk for patients, and equivalent operating times as that for LSC [34]. The follow-up data also showed very satisfactory results, especially with regard to the stringent use of mesh material (see further original research).

6. Uterus Preservation

Indications for hysterectomy as part of prolapse surgery have changed frequently, as noted in a German study spanning the period from 1960 to 1985. Only 24.3% of the interventions were combined with hysterectomy between 1960 and 1963, while 97.7% of the interventions were combined with hysterectomy between 1978 and 1985 [35]. The overall risk profile of the intervention changed. The indications were mainly for the prevention of cancer and birth control. Hysterectomy offered no advantages in terms of long-term success. On the contrary, De Lancy emphasized the integrity of paracervical structures for the prevention of cystocele and rectocele in as early as 1992 [36]. The disadvantages of uterine preservation have not been reported so far.

In 2013, Kerbly et al. investigated reasons for hysterectomy as reported by patients; 213 women were interviewed at several centers. Only 20% of women desired a hysterectomy, while 36% were clearly opposed to it. A fifth of them would have accepted a poorer outcome, while 44% were unable to commit themselves [37]. Current reasons to preserve the uterus include the desire to have children and the desire to preserve the physical integrity of the body. Both vaginal and laparoscopic techniques are available today. While the study data for vaginal techniques (especially vaginal meshes) are still limited, sacropexy is an established procedure.

In 2013, the data of 507 women were examined retrospectively over 10 years [38]. Notable features of the study were a low complication rate of 1.8% and no mesh exposure. The hysteropexy could not be completed in 17 patients (3.4%) and 93.8% of the patients said their prolapse was “very much” or “much” better—of these women, 2.8% required repeated apical surgery.

7. Native Tissue Repair

Native-tissue repair, especially vaginal colporrhaphy, has long been equated with a poor outcome. According to the PROSPECT trial [10], the use of native tissue was not inferior to meshes in vaginal surgery. Barber et al. were able to show that a clinical symptom-oriented assessment of success in contrast to a strictly anatomical evaluation (pelvic organ prolapse quantification (POP-Q)) yielded very good long-term success rates for native tissue reconstruction [39]. Thus, adequate apical fixation in combination with native tissue repair reduces the use of foreign materials. These data clearly confirmed the effectiveness of native tissue repair. The limited use of meshes may also reduce complications and re-intervention rates.

8. Laparoscopic Native Tissue Repair

Vaginal surgery is frequently combined with the laparoscopic approach. However, in view of the variety of surgical instruments used, it would be advisable to perform native tissue repair using the laparoscopic approach. As the surgeon uses laparoscopic surgery alone, only laparoscopic instruments are required. This saves time, reduces sterilization costs, and economizes on the use of disposable instruments. Lateral repair has been known for many years, but laparoscopic treatment of anterior midline defects and posterior defects was first reported in 2018 [40,41]. The access routes for the two procedures are comparable to ventral and dorsal dissection of the vagina in sacrocolopexy, especially when placing a so-called Y-shaped mesh. In the presence of a cystocele, the tissue is usually dilated and thin. When using the vaginal approach, the vaginal mucosa must be opened and detached from the fasica in order to reach the defect. When using the laparoscopic approach, the

tissue is not separated but rather compressed as a whole by sutures. Puncturing the fascia five to seven times in small increments creates a densely pleated effect when knotting. This reduces expansion and causes a significant thickening of tissue. The second effect is also useful when placing a Y-mesh to create more tissue between the mucosa and the mesh material. In addition to reducing the risk of erosion, it prevents the displacement of organs due to tension.

Native tissue repair enables the surgeon to restore the natural width and length of the vagina before the apex is adjusted in an anatomical position with minimal tension. It is not necessary to compensate a cystocele or rectocele by pulling it cranially. Similar effects can be achieved by making adjustments initially through the vaginal route. As described above, the advantage of the laparoscopic approach is that the entire tissue is retained and no vaginal scars develop. The preliminary results of the techniques have been very encouraging, but need to be substantiated in larger numbers of patients [40]. With regards exposure, the enhancement of tissue prior to the application of a mesh in LSC would also reduce risks to a significant extent.

9. Robotic Surgery in Urogynecology

Robotic surgery has gained significant importance in the USA. It is also being used more often in Europe and will continue to gain popularity because of new and cost-effective procedures. The remote control of the surgical instruments enables the surgeon to work without getting tired. The variety of instrumentation is very helpful to get free access to the operating field. This allows the surgeon to move safely in the working area. For several reasons, it takes time for experienced laparoscopists to perceive the advantages of robotic-assisted surgery. In addition to the laborious and time consuming procedure of docking, a number surgical steps must be modified to the new setting. On the other hand, the advantages of robotic surgery are more easily experienced by low-volume surgeons or beginners. The complexity of suturing and knotting is offset by the extensive degrees of freedom in using instruments. Less experienced surgeons are able to perform complex procedures with the aid of robotic-assisted surgery.

The main obstacle to the implementation of the technology is its cost. Robotics could be very helpful, especially in complex suturing techniques such as those used for native tissue repair. The various alternatives of robotic SC are a part of the standard repertoire at many centers. Single center studies as well as comparative studies and reviews are available in the published literature [42,43]. Robotic SC is considered equivalent to laparoscopic SP in terms of clinical and anatomical results. Generally speaking, the costs and operating times are significantly higher than those for laparoscopy. However, the time factor is of secondary importance for specialized surgeons. The positive results are comparable to the laparoscopy, and the complication rates are also equivalent. Exposure rates are similar to LSC, albeit low [24]. Robotics may be able to shorten learning times and enable more surgeons to offer minimally invasive surgery in urogynecology. Endoscopic autologous tissue reconstruction might serve as a new field for robotics.

Dealing with mesh complications and the need to remove mesh materials can be challenging. Precision and working in very small steps are essential. The support provided by robotics can be very helpful to ensure a safe approach [44].

10. Conclusions

The parameters that are available for the indication and the assessment of the therapeutic success (age, body mass index (BMI), general health status, sexual activity, wishes of the patient, and fears of long-term effects) require a good surgical portfolio to meet the different demands or to meet necessities. A careful diagnosis and indication are the basis for a low complication rate.

The partly serious side effects of vaginal mesh surgery have created a precarious situation in urogynecology. The use of meshes is highly restricted and even prohibited in some countries. This is a major disadvantage for patients, as meshes are required at

least for the fixation of the apex. Study data indicate that patients with severely weakened connective tissue will also need tissue reinforcement with mesh materials in the future. We still use techniques that were introduced a long time ago and have never been evaluated by current standards. The existing techniques have been adapted, in part, to the skills of individual surgeons. Lateral suspension is certainly the easiest technique to perform, but also yields the most unfavorable results. Furthermore, lateral suspension has not been investigated in a randomized study or on a multicenter basis.

A large body of single-center data exist for LSC, but the implementation of the technology is very heterogeneous and therefore not comparable. LSC in particular is carried out in a wide variety of ways. Deep mesh implantation both anterior and posterior, meshes in short form, prefabricated or self-tailored meshes, the use of various sutures, and variable fixing points complicate the assessments. Hysteropexy is also performed using the Oxford technique (mesh collar), sometimes as a simple cervical fixation or as an extended posterior mesh plastic. Prospective multicenter studies are completely lacking. A major problem is the frequent and extensive use of meshes, which leads to exposure problems and reinterventions. Pectopexy is comparatively new, but offers a database extending from pilot studies to randomized studies and multicenter trials. The combination of native tissue repair and laparoscopic apex fixation permits the effective treatment of pelvic floor defects with a low risk of alloplastic materials remaining in the body. More collaborative research is needed to improve its safety for women.

Risks must be minimized in the treatment of benign disease. Training and centralization are also crucial. The ongoing improvement of treatment through competent research and standardized techniques is pursued in all surgical specialties. Independent research and development will serve as a shield against statutory restrictions. Registers should be used to optimize training and ensure consistent quality control. We need a variety of options to deal with the peculiarities of patients and the skills of surgeons. A one-fits-all strategy is not desirable. Simplifications should not be achieved at the expense of quality. Urogynecology does not belong in the hands of low-volume surgeons. Importantly, clinics should consider the entire spectrum of conservative treatment options before surgery.

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Review

Advances and Trends in Pediatric Minimally Invasive Surgery

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Abstract: As many meta-analyses comparing pediatric minimally invasive to open surgery can be found in the literature, the aim of this review is to summarize the current state of minimally invasive pediatric surgery and specifically focus on the trends and developments which we expect in the upcoming years. Print and electronic databases were systematically searched for specific keywords, and cross-link searches with references found in the literature were added. Full-text articles were obtained, and eligibility criteria were applied independently. Pediatric minimally invasive surgery is a wide field, ranging from minimally invasive fetal surgery over microlaparoscopy in newborns to robotic surgery in adolescents. New techniques and devices, like natural orifice transluminal endoscopic surgery (NOTES), single-incision and endoscopic surgery, as well as the artificial uterus as a backup for surgery in preterm fetuses, all contribute to the development of less invasive procedures for children. In spite of all promising technical developments which will definitely change the way pediatric surgeons will perform minimally invasive procedures in the upcoming years, one must bear in mind that only hard data of prospective randomized controlled and double-blind trials can validate whether these techniques and devices really improve the surgical outcome of our patients.

Keywords: pediatric surgery; minimally invasive surgery; fetal surgery; single-incision surgery; surgical techniques; surgical devices; open surgery; endoscopy; endoscopic surgery

1. Introduction

Minimally invasive pediatric surgery has developed rapidly in the last 30 years extending from fetuses to 17 year old overweight adolescents. As many meta analyses and analyses of meta analyses comparing minimally invasive surgery to open procedures can be found in the recent literature, this review focuses on the current trends and advances which already have or may have an impact on pediatric minimally invasive surgery [1,2].

2. Materials and Methods

The techniques and development of minimally invasive pediatric surgery are reported descriptively. Print and electronic databases including Index Medicus, MEDLINE®/PubMed, EMBASE®, Cochrane Register (CENTRAL) and www.clinicaltrials.gov using the keywords or medical subject headings (MeSH) "laparoscopy," "thoracoscopy", "minimally invasive surgery",

"single incision laparoscopic surgery" "robotic surgery" and "pediatric surgery" were systematically searched. Latest entry was set to November 2020 and the search was not restricted to specific languages. We then conducted a cross-link search with references found in the literature. Full-text articles were obtained for potentially eligible publications and quality and eligibility criteria applied independently. Potential disagreements regarding the quality of studies and inclusions/exclusions were resolved by discussion. Articles were translated if needed and appropriate.

3. Review

3.1. Milestones of Pediatric Minimally Invasive Surgery

Minimally invasive surgery (MIS) evolved rapidly during the last 30 years, starting in adult general and gynecologic surgery. The first MIS appendectomy was performed by Kurt Semm, a gynecologist, which gained much attraction and dispute by the general surgical community [3]. The first laparoscopic cholecystectomies were performed in 1985 in Germany by Erich Mühe and in 1987 in France in a shared gynecology and general surgery practice by Phillipe Mouret [4,5]. Thereafter, especially laparoscopic cholecystectomy became the new minimally invasive standard of surgical care, although hard long term data were not yet available.

With the advent of electronic videoscopes, small instruments and insufflators feasible for children, MIS was also gaining ground in pediatric surgery (Figure 1).

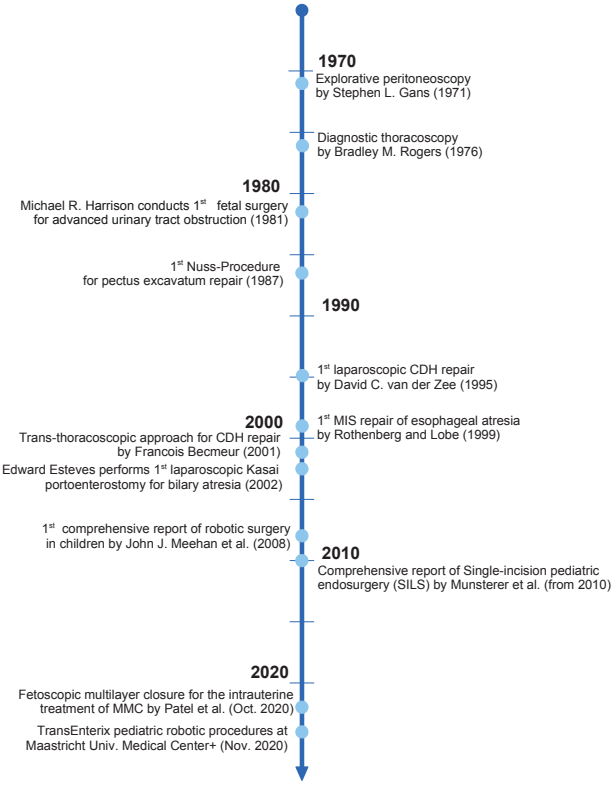

Figure 1. Timeline of the milestones of minimally invasive surgery.

Earlier, explorative laparoscopy (then called peritoneoscopy and performed by direct vision through the laparoscope) was performed in children as early as in 1971 by Gans for exploration of the abdomen through and small series of explorative peritoneoscopy were reported in by Carnevale for abdominal trauma in 1977 [6,7]. In 1976 Rodgers reported thoracoscopy for diagnostic reasons in children [8].

Concerning pediatric procedures, consecutively the first repair of a congenital diaphragmatic hernia (CDH) [9], the trans-thoracic approach to CDH [10], the first MIS repair of esophageal atresia [11], the Nuss repair of pectus excavatum [12], laparoscopic choledochal cyst excision [13] and the minimally invasive Kasai procedure were reported [14]. With the availability of robotic surgery in the early 2000s, some centers established robotic pediatric surgery programs [15]. As MIS advanced into the new millennium, new techniques as single incision laparoscopic surgery (SILS) were developed: Muensterer reported the first single incision procedures in infants in 2010 and his colleague Hansen a large series of 224 cases in 2011 [16,17].

3.2. Technical Developments of Pediatric Laparoscopy

The successful progress minimally invasive pediatric endoscopic surgery has experienced in the last 20 to 30 years has been fundamentally due to the incessant achievement of highly sophisticated technological equipment and thus the continuous development of instruments designed specifically for these surgical techniques. Equipment and instruments are designed to allow safe access to the child's small anatomic cavity, maintain a good working space and perform maneuvers with the same or even better safety and efficacy as in open procedures.

While 10 mm-diameter rigid videoscopes and 5 mm-diameter instruments have been of use very commonly for decades, technical advances led to a widespread introduction of even smaller equipment more feasible in pediatric patients. Today there is a large choice of 3 mm diameter instruments by several companies such as Karl Storz (Tuttlingen, Germany), Wolff (Knittlingen, Germany) or Aesculap (Braun, Tuttlingen, Germany). Handling of tissues is very delicate and scarring is very satisfactory. More recently, microlaparoscopy with 2 mm diameter instruments has been introduced into pediatric surgery [18]. Although their use has its limitations due to fragility, the tendency for bending and difficulty in grasping there are selected and distinctive indications these instruments are applied for. Successful reports of thoracoscopic congenital diaphragmatic hernia repair in newborns, hiatoplasty with repair of an upside-down-stomach, laparoscopically assisted pull-through for Hirschsprung's disease and laparoscopic transperitoneal pyeloplasty also suggest the further consideration of microlaparoscopy for advanced procedures in children [19].

The latter has also been accomplished by the introduction of smaller and distinguished devices for safe and meticulous hemostasis. More recently developed 5-mm-clips and -staplers and also advanced energy source devices, such as the LigaSure™ or the EnSeal® have proved to be imminently helpful in minimally invasive pediatric surgery [20–22].

With the use of new-generation videoscopes and cameras that allow three-dimensional procedures together with a high-definition video format, such as the 4 mm Karl Storz IMAGE1 S™ 3D, vision in small and challenging spaces has improved immensely and therefore augmented the safety of the procedures (Figure 2) [23].

Figure 2. IMAGE1 STM D3-LINK Module with TIPCAM®1 STM 3D, 10 and 4 mm diameter, available with 0° and 30° optic. The 4 mm 3D optic combines three dimensional vision with a small diameter access especially in infants. Taken from: https://www.karlstorz.com [23].

3.3. Natural Orifice Transluminal Endoscopic Surgery (NOTES)

NOTES promises to avoid the access through the abdominal cavity by introducing flexible or rigid instruments and optics through natural orifices as the stomach, vagina or rectum. By perforating these organs the instruments can be passed into the abdominal cavity for various surgical procedures. NOTES appears to offer no visible scars and promises lesser pain and thus faster recovery—including the inherent risk of elective viscerotomy and closure at the end of the procedure.

The first pure NOTES transvaginal cholecystectomy was performed by Tsin at Mount Sinai Hospital of New York in 2003 [24]. Since then, several pure NOTES procedures have been reported, as transvaginal nephrectomy or transvaginal appendectomy [25–27].

Pure NOTES is technically challenging, due to instrument clashing, suboptimal exposure and inline placement of the instruments compared to triangulation in laparoscopic surgery [28]. Hybrid NOTES, with an additional port through the umbilicus, appeared to increase instrumentation and safety, as the entry through the vagina or stomach can be visually controlled. Several reports found hybrid NOTES to be applicable in general surgery, as for cholecystectomy and appendectomy and several technical reports on instrumentation for NOTES can be found (Figures 3 and 4) [29,30].

Figure 3. The ANUBIS project from Karl Storz for NOTES endoluminal and transluminal procedures [31].

Figure 4. The ENDOSAMURAI by Olympus is a platform with two arms fitted to the tip of an endoscope that includes forceps channels in addition to the endoscope itself and its two arms. (**a**) The platform and (**b**) closeup of the tip of the instrument. Image taken from Kume, 2016 [28].

Bulian reported a prospective, randomized, nonblinded, single-center trial comparing hybrid NOTES to laparoscopy with 3mm instruments: Comparable in terms of safety, NOTES appeared to cause less pain, increase satisfaction with the esthetic result and improved postoperative quality of life in the short term [32,33]. A current meta-analysis concluded, that transvaginal NOTES cholecystectomy, adnexectomy, and appendectomy appears safe and truly minimally invasive [34].

NOTES has, to the best of our knowledge, been reported only once in the pediatric population: Lamas-Pinheiro reported a hybrid natural orifice transluminal endoscopic surgery approach for laparoscopic Duhamel procedure in three cases. The 12 mm port for the endoscopic stapler was introduced through the rectum instead of inserting it transabdominally (Figure 5) [35].

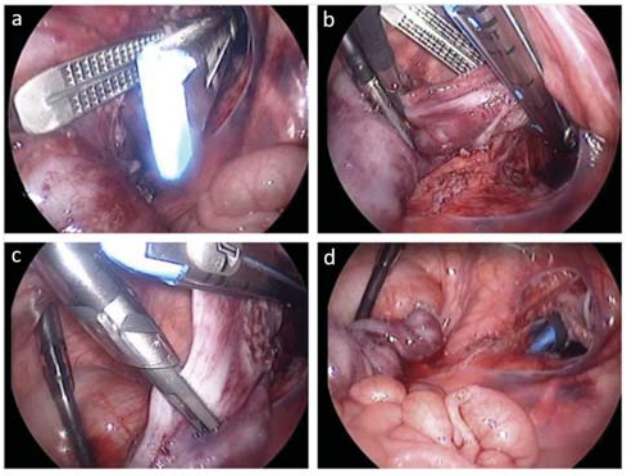

Figure 5. Laparoscopic Duhamel procedure assisted by transrectal NOTES. Three 5 mm transabdominal trocars were combined with a 12 mm transrectal trocar. (**a**) Introduction of the endoscopic stapler, (**b**) adjusting the stapler, (**c**) stapling of the colon, (**d**) situs after transection of the colon. Figure taken from Lamas-Pinheiro 2012 [34].

Nevertheless, transgastric endoscopic drainage of pancreatic pseudocysts after blunt abdominal trauma and pancreatitis is common in children and counts, technically, into the armamentarium of NOTES. Drainage can be achieved by placing a stent or leaving the gastric incision open to the pseudocyst for drainage and secondary healing [36,37]. Therefore, one can postulate that NOTES is already in clinical application in pediatric minimally invasive surgery.

3.4. Single Incision Laparoscopic and Thoracoscopic Surgery

As previously stated technology and innovation continue to advance the field of pediatric MIS thus creating space for the establishment of single-incision laparoscopic surgery (SILS) and uniportal video assisted thoracoscopic surgery (VATS). Applications have been previously described using this approach for various general, urologic, thoracic and pediatric surgical procedures. For example, there are reports of successful surgical treatment of acute appendicitis, gastroesophageal reflux, ureteropelvic junction stenosis, and pleural empyema [38–41].

Despite a lack of literature promoting this surgical approach across the pediatric population there are a few randomized studies that support single-incision techniques for appendectomy in both feasibility and safety compared to conventional laparoscopic surgery [42,43].

As some disadvantages have been generally attributed to laparoscopic procedures, such as higher costs [44], longer operative time [45], and more demanding surgical skills and equipment [46], transumbilical laparoscopic-assisted appendectomy (TULAA) has emerged as a variation from the standard laparoscopic appendectomy [47]. It combines the advantages of laparoscopy and open surgery, with global visualization of the abdominal cavity and minimal invasion with lower costs and instrumental requirements [48–51].

Based on those available data, single incision laparoscopic or laparoscopic assisted surgery has for many pediatric surgeons emerged as the first choice for the mode of minimally invasive access in many different procedures. Conversion to classical three port laparoscopic or thoracic surgery can be easily performed when procedures were started through a single incision. Therefore, the single incision procedure is a versatile technique in children, providing a safe, effective, and the least invasive treatment for different diseases [52].

3.5. Endoscopic Pediatric Surgery

With the development of endoscopy, more pathologies become addressable by newly designed devices. For achalasia, Heller's myotomy has been the standard of care [53]. Per-oral endoscopic myotomy (POEM), a modern treatment for achalasia, has only recently emerged as an option for pediatric patients. Wood reported in her study on 21 pediatric cases POEM to be a viable and safe treatment for pediatric patients with achalasia [54].

Appendicitis is the most common abdominal emergency for surgery in childhood. Appendectomy can be performed by the open approach, classical three port laparoscopic or single port procedures. A new technique is endoscopic retrograde appendicitis therapy (ERAT). It consists of five steps, which are all performed endoscopically after insertion of the colonoscope into the cecum and identification of the appendiceal orifice: endoscopic appendiceal intubation, appendiceal decompression, retrograde appendicography, stent drainage and cleansing of the appendiceal lumen. First described by Liu in 2016, Kang et al. reported in November 2020 their series of 36 children treated with ERAT in a randomized prospective trial. They concluded that ERAT appears to provide a new alternative to surgical appendectomy for uncomplicated appendicitis in children [55,56].

3.6. Robotic Pediatric Surgery

In pediatric surgery, many procedures are restricted by the limited working space of the small abdominal and thoracic cavity, encumbering even 3-mm instrument and multi-port procedures. A further development of the minimally invasive technique is robot or computer-assisted surgery, in which the instruments inserted into the body are remotely controlled by the surgeon, who is placed at a console next to the patient or even far more remote.

Due to the magnification of the operative field, application of 3D technology and thus spatial vision, improved ergonomics for the surgeon and a greater range of motion of the robotic instruments compared to conventional laparoscopic instruments, robotic assisted minimally invasive surgery appears to be beneficial over conventional minimal invasive surgery, especially in complex reconstructive procedures [57–61].

Currently, there are two systems commercially available and certified for robotic surgery in children: the DaVinci (Intuitive Surgical, since 2001) and Senhance (Transenterix, since 2020) robotic system.

The DaVinci robotic system includes a control unit for the surgeon and a patient side cart with four remotely controlled arms. To each arm, a camera with 3D Vision, different surgical instruments and energy or stapling devices for vessel sealing and dissection can be attached. The diameter of the instruments is 8 mm and their tip is bendable with seven degrees of freedom analogous to the human wrist ("endowrist"). Smaller diameter instruments (5 mm) are available too, but due to their angulation of the tentacle-like continuum tool shafts rather than the articulated wrist joints that characterize standard 8-mm instruments, the smaller 5-mm instruments have less dexterity than the standard 8-mm instruments in spatially constrained operative fields (Figure 6) [62].

Figure 6. Comparison of the DaVinci 8 mm (**a**) and 5 mm diameter instruments (**b**). Due to their tentacle-like continuum tool shafts, the smaller diameter instruments need more operative space than the 8 mm instruments and are therefore not suitable in smaller cavities, such as infants. Figure taken from Marcus 2015 [62].

Thakre examined the feasibility of the DaVinci robotic surgery in small cavities and reported that surgical drills could only be performed in cubes with edges of 70 mm length or greater [63]. This impairment in small cavities is a major limitation of the DaVinci surgical system in small cavities, such as in newborns and infants [64,65]. Although sporadic reports exist on robotic infant surgery, the DaVinci is mainly used in older children [15].

The second robotic system commercially available and certified for application in children larger than 10 kg of body weight is the Senhance (Transenterix). This system consists of a control unit for the surgeon and three to four separate carts, each with one arm for either camera or instruments. The instruments resemble classic 5 mm diameter laparoscopic instruments. In contrast to the DaVinci system, the instruments are not articulating, except an 8 mm diameter articulating needle driver, but offer haptic force—feedback. Additionally, a complete range of 3 mm diameter instruments is also available. As smaller diameter instruments can be placed more closely together and do not need a long insertional depth, it may be hypothesized that robotic surgery might be feasible in small cavities with this system, in contrast to the DaVinci (Figure 7).

Figure 7. Robotic assisted (Senhance, Transenterix) cholecystoenterostomy in a 5 kg piglet with 3 mm and 5 mm instruments. The size of the instruments compared to the gallbladder and intestine demonstrates the small size of the cavity in which it is being operated.

Due to its relatively new emergence on the market, not much data can be found on potential feasibility of the Senhance in small cavities: It was demonstrated in inanimate models, that even in small volumes of 90 mL (edges of 2.9 cm × 6.3 cm × 4.9 cm boxes) intracorporal suturing and manipulation appears feasible with this system [66]. Currently, the first pediatric robotic procedures have been performed in the Department of Pediatric Surgery at the Maastricht University Medical Center+ [67].

Also being counted as robots are automated suturing robots, like the KidsArm, an image-guided pediatric surgical robot, to automate anastomosis, which has been reported in 2013 or the STAR reported by Leonard in 2014, both awaiting wider examination by pediatric surgeons [68,69].

3.7. Fetal Surgery

Fetal surgery is pediatric surgery and pediatric surgery is fetal surgery: Since congenital conditions and malformations are often leading to serious consequences on fetal and eventually children's development the field of fetal surgery has grown to be of major interest for pediatric surgeons from the early 1980s, with Michael Harrison being the most prominent innovator in this field [70,71].

Today, prenatal diagnostics allow for a high rate of fetal anomaly detection from a very early gestational age. This allows for an early-stage multidisciplinary approach for fetal therapy, joining the expertise of various specialists. The surgeon necessarily must rely on neonatologists, anesthesiologists, radiologists and obstetrician—gynecologists among many others, to contribute to the successful treatment of the fetus.

Improvement in pathophysiological knowledge and the development of therapeutic tools led to advancement in fetal surgery and set in motion changes in treatment approaches from open procedures to fetoscopic techniques for many conditions of the unborn child [72].

With selective fetoscopic laser photocoagulation a Diode or Nd:YAG Laser is used to treat twin twin transfusion syndrome (TTTS) successfully and evidentially ameliorates the double-twin survival rate [73].

Fetoscopic endoluminal tracheal occlusion (FETO) by fetal endotracheal balloon placement for isolated severe congenital diaphragmatic hernia (CDH) improves neonatal survival significantly [74], while being subject to ongoing investigation in an international randomized trial called The Tracheal Occlusion To Accelerate Lung (TOTAL) growth trial (www.totaltrial.eu) for severe and moderate pulmonary hypoplasia [75].

Fetal cystoscopy is used to treat lower urinary tract obstructions in most cases due to posterior urethral valves, for which Ruano et al. found a significant improvement in survival at 6 months after intervention and an advantage of fetal cystoscopy for renal function [76].

While fetoscopic myelomeningocele (MMC) repair-techniques showed disadvantages especially in safe closure of the MMC defect comparable to open repair [77], Patel et al. just recently presented a promising fetoscopic multilayer closure with dural patch repair using a standardized, 3-port, carbon dioxide insufflation technique for the intrauterine treatment of MMC [78]. Furthermore, fetoscopic bimanual surgery is associated with a higher risk of premature rupture of membranes—caused by chorioamniotic separation when compared to open surgery as the uterotomy is stapled and the membranes are fixed to the uterine wall in contrast to the fetoscopic ports which are inserted by puncture. Michael A. Belfort developed a hybrid open/fetoscopic method to lower the risk of preterm rupture of amniotic membranes anchoring them to the uterine wall without opening the uterus by hysterotomy and thus pushed fetoscopy and fetoscopic bimanual surgery to another limit [79–81].

Altogether, fetoscopy is effective for treating several fetal anomalies at present. In the future continuous refinement of the techniques and technologic advances will allow the use of fetoscopy more extensively and aid entry to treatment for other pathologies, such as in utero gastroschisis repair, for carefully selected fetuses [72,82–84].

3.8. Outlook: The Future of Pediatric Minimally Invasive Surgery

Technical development is unstoppable, new and smaller instruments, devices and systems are emerging on an ever growing market of miniaturizing and digitizing surgery [85]. Some devices only exist in the heads and minds of pediatric surgeons, others have already found their way into preclinical or even clinical evaluation:

3.8.1. Magnetic Anastomosing Devices

In surgery, one of the most critical parts is forming a new connection between hollow organs, vasculature or nerve fibers, called anastomoses. Classically, those connections were sutured by hand which takes a relevant amount of operating room time and every surgeon knows the dreaded feeling when suspecting his or her anastomosis to become insufficient, which implies possible severe consequences for the patient. With the development of anastomosing devices for intestinal anastomoses, called intestinal staplers, the time to perform an anastomosis could drastically be reduced and also standardized, as every type of stapler works the same [86]. Although some staplers can be applied endoluminally, they still need a laparotomy or laparoscopy for visual control and firing. A pure endoscopic application might be the use of magnets—a device that could automatically and consistently produce an optimal anastomosis, reduce morbidity and save considerable operative time and resources. Two magnets are specifically used to perform an anastomosis by compressing the according intestinal wall between each other: the tissue between the becomes ischemic and sloughs while the outer rim

heals, thus establishing the anastomosis. Once the anastomosis is complete, the two magnets would be automatically transported through the intestine by peristalsis [87,88].

Different types of magnets and techniques have been examined in experimental and human settings, especially for esophageal atresia or esophageal strictures [89–92].

Research culminated in the development of an FDA cleared device for endoscopic magnetic anastomosis in infants with esophageal atresia (Figure 8) [93–95].

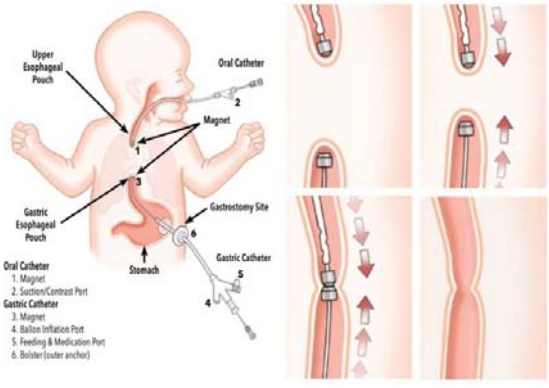

Figure 8. FDA-approved device for magnetic compression anastomosis in infants with long gap esophageal atresia. Magnamosis established by the Flourish™ device. It consists of two catheters, each holding a magnet at its tip. The magnets placed at each end of the esophagus attract each other, causing the ends of the esophagus to stretch toward each other and eventually creating an anastomosis with the open passage of the esophagus. Figure taken from Morrow 2017 and www.cookmedical.com [93,96].

3.8.2. Articulating Laparoscopic Instruments and Devices for Single-Incision Laparoscopic Surgery

One disadvantage of classical laparoscopic surgery is the straight instruments. Therefore, the success of the procedure depends on whether the surgeon is able to place the instruments in a certain angle which allows him access to all areas of the operative field but also sufficient angulation of the instruments to each other, especially for suturing and knot tying in reconstructive procedures. One advantage of robotic surgery is the application of angled or wristed instruments, which give the surgeon up to seven degrees of bendable or rotational freedom, just like having his or her hands with the articulating wrist inside of the patient. By many surgeons, these wristed or articulating instruments are deemed as one major benefit of robotic surgery.

In the last years, articulating instruments also became available for laparoscopic surgery. The FlexDex device is a laparoscopic needle driver with the same degrees of wristed angulation as offered in the DaVinci robotic system [97–99]. It has been clinically evaluated in children and appears to improve reconstructive procedures without the costs as for a robot (Figure 9) [100].

Figure 9. The FlexDex laparoscopic needle driver offers wristed instrumentation similar to DaVinci robotic instruments without the costs of the robot, but still more expensive than conventional laparoscopic instruments. Image taken from https://flexdex.com [99].

Several other articulating laparoscopic instruments, or prototypes of, have been either FDA approved, evaluated in dry lab trainer or live animal models with ambiguous results towards feasibility and learning curve: The Radius Surgical System (Tübingen Scientific) was evaluated in experimental and clinical settings and appeared to improve intracorporal maneuverability [101,102]. The Artisential Laparoscopic System (Livsmed) is FDA approved and offers a wide range of articulating instruments as well as energy devices [103,104]. The Hand-X electronic articulating needle driver (Human Extensions, Netanya, Israel) received FDA approval in 2018 and offers a 5 mm diameter wristed electronically driven instrument [105]. The SymphonX Surgical Platform (Fortimedix Surgical B.V.) received FDA approval on 26 August 2016. According to the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), "it provides a path of entry for laparoscopic instruments and camera through a single site and allows for triangulation similar to standard laparoscopy. The device fits through a standard 15-mm trocar and has 4 channels, enabling a surgeon to use two 5-mm instruments, a 5-mm camera and a 3-mm device. The device does not require inversion or hand crossing to achieve triangulation" [106]. It was also recently evaluated during human application in adult general surgery [107,108].

The Spider Surgical system (Single Port Instrument Delivery Extended Reach, Transenterix, Durham, NC, USA) is a platform similar to the SymphonX for single port procedures. It has been evaluated in different human general surgical, gynecologic and urological procedures and appeared feasible and safe [109–112].

Several other articulating instruments as well as prototypes have been described and examined during the last ten years of development, which was mainly driven by the push of Intuitive's DaVinci endowrist and robotic surgery [103,104,113–118].

Another approach is followed by Microsure (Eindhoven, The Netherlands), which developed the MUSA, a robot for open microsurgical procedures such as vessel or nerve anastomosis. This system has recently been evaluated in human gynecological surgery and appears to confer the feasibility of connecting vessels with a diameter between 0.3 and 0.8 mm for the reconstruction of lymphatic flow and vascularized tissue transplantation [119–121].

All those abovementioned devices promise an improvement in the surgical care of pediatric patients, nevertheless, none of those has yet been systematically evaluated for its probable application in pediatric surgery.

3.8.3. New Robots for Children

Until this review, two robotic systems are commercially available for application in children. Both exhibit specific advantages and disadvantages as described above. With more emerging robotic systems appearing on the market in the upcoming years, the anticipation of pediatric surgeons increases, for a system that offers full intracorporal maneuverability with fully wristed instruments that are less than 5 mm in diameter and therefore applicable in children as small as newborns and infants.

The Dexter (Distalmotion, Lausanne, Switzerland) offers fully wristed 8 mm robotically instruments remotely controlled from a console similar to the Da Vinci system. This system consists of the robotic instruments only, without a camera and optical console, therefore being cheaper than the Da Vinci and because of its reduced size fitting into the setting of classical laparoscopic surgery enabling the surgeon to instantly switch to the laparoscopic robotically assisted part of the procedure. With its 8 mm diameter instruments its application in pediatric surgery in small children has to be critically evaluated [122].

Verb Surgical (Santa Clara, CA, USA), a cooperation of Google and Johnson & Johnson appears to develop a robotic system that will be integrated in a more comprehensive pre- and postoperative setting with enhanced medical data science [123]. Whether this system will be applicable in children, has to be evaluated.

Avatera (avateramedical, Leipzig, Germany) is a robot conceptually similar to Intuitive's system but offers 5 mm diameter fully wristed seven degrees of freedom instruments with less angulation than the 5 mm instruments of the Da Vinci. Whether this will be an advantage in small cavities, such as in small children and infants, will have to be critically evaluated [124].

CMR Surgical (Cambridge, UK) developed the Versius robotic system, which has already been clinically applied and evaluated in general surgical, urological and gynecological procedures [125–130]. With its 5 mm diameter fully wristed instruments its application in pediatric surgery appears promising. Any preclinical or clinical evaluation of its feasibility in children and small infants is pending.

In conclusion, there are many more robotic surgical systems either already in the market or emerging in the upcoming years. Whether they will be feasible, safe and therefore applicable in pediatric surgical procedures has to be critically evaluated. Pediatric surgeons should be encouraged to participate in this process in order to give their future patients probable access to this rapidly evolving technology.

3.8.4. Deployable Minirobots

Another development of robotic surgery is the idea of deployable minirobots which can be inserted into the abdominal or thoracic cavity and perform surgical tasks by remote control. Therefore, multiple minirobots can be deployed by just one small incision, further reducing the operative trauma, and may provide task assistance without the constraints of the entry incision.

Although a concept more appearing as science fiction, some groundbreaking work has already been reported: Forgione was able to deploy a remotely controlled instrument with lighting, camera or graspers, assisting in cholecystectomies in an animal model [131]. Shah reported a multiarmed dexterous miniature in vivo robot with stereovision, graspers and cautery (University of Nebraska AB1 Robot) presented by Lehman in 2008 [132]. This robot was successfully applied for assisting various surgical procedures in animal models. In the future, deployable and remotely controllable surgical devices will allow us to perform procedures with fewer incisions that we cannot do today with conventional minimally invasive techniques. Therefore, the future of true minimally invasive surgery has not arisen yet.

3.8.5. Hybrid Procedures

The concept of providing endoscopic assistance for open or laparoscopic surgical procedures is not new, but has not found its way into clinical application in pediatric surgery, although some pioneering and groundbreaking work has already been presented. Laparoscopic endoscopic cooperative surgery (LECS) has been evaluated and held to be a feasible technique for surgery in the upper gastrointestinal tract [133,134]. The case of a 17 year old pediatric patient with non-exposed endoscopic wall-inversion surgery for a gastrointestinal stromal tumor was reported by Matsumoto [135].

In pediatric surgery, the modern approach to an anorectal malformation without a fistula is the posterior sagittal anorectoplasty, as described by Alberto Pena [136]. Although accepted by the pediatric surgeons, the operation consists of surgically splitting the remains of the anal sphincter

muscle complex to identify the rectum. A new approach was suggested by Muensterer, the endoscopic assisted posterior anorectoplasty (ePARP) [137]. ePARP is a combination of endoscopic identification of the lower rectal pouch, endoscopic assisted transperineal puncture and dilation of the new rectal tract and then a modified pull through of the rectal mucosa with rectoperineal anastomosis forming the neoanus. Although not commonly performed yet, this endoscopic assisted surgical approach may offer less trauma to the anal sphincter complex than the current surgical approach.

3.8.6. Robots, SILS and NOTES, the Ideal Combination?

With the technical advancement of robotics, namely smaller diameter and wristed instruments, the combination of single incision surgery or NOTES with robotics appears to open a new era of robotically assisted single port or NOTES procedures, which were not able with the until then available laparoscopic instruments [138].

The SPORT platform (Titan Medical) is a single port robotic system providing bimanual instruments, a camera and light access all through one incision [139]. This system is still under development but has been evaluated in a porcine model.

A similar approach is followed by Intuitive with the SP platform, which offers bimanual wristed instruments, lighting and camera through on incision with a diameter of 2.5 cm [140].

Both systems require incisions of at least 2.5 cm length and therefore appear not suitable in small children and infants, although any preclinical testing is pending.

3.8.7. Artificial Intelligence and Augmented Reality in Pediatric Surgery

Augmented reality (AR) and artificial intelligence (AI) have already grown into our daily lives, as we are used to playing AR games on our mobile phones and AI assists in facial recognition for serious or fun applications [141]. It is therefore just a matter of time, when AR and AI will be implemented into minimally invasive surgical procedures [142]. Three dimensional computer assisted laparoscopy or robotic surgery is an excellent platform for combining data from medical imaging, such as preoperative CT scans or intraoperative ultrasound, with the actual surgical field displayed to the surgeon in terms of augmented reality thereby displaying subsurface structures not visible to conventional laparoscopy [143,144]. Recordings from thousands of procedures, for example cholecystectomies, can be analyzed by AI and will give a real time feedback to the operating surgeon, of where to find the delicate structures not to be damaged. AR and AI have been evaluated in many fields of surgery, any application in pediatric surgery is not yet established [145].

3.8.8. The Artificial Womb

At first sight, the development of an artificial womb does not imply minimally invasive pediatric surgery [146]. However, many congenital malformations, such as myelomeningocele, congenital diaphragmatic hernia, gastroschisis, sacrococcygeal teratoma or congenital pulmonary malformations often affect the fetus prenatally and severely, leading to either hydrops fetalis with imminent fetal demise or irreparable damage of organs at birth. Any fetal surgical intervention leads to a massive trauma, not only the fetus, but also the uterine environment and mother, often resulting in preterm labor with the effect of adding neonatal prematurity to the malformation. With the advent of an artificial uterus, a whole new perspective opens up of early fetal intervention for specific malformations: The fetus can be transferred into an artificial uterus, removing the mother and maternal uterus from damage and preterm labor and therefore the fetus from probable prematurity. The fetus can much easier be operated on in specifically designed artificial environments and then let to be grown inside this artificial uterus until term. Although not applicable in humans yet, animal studies show very promising results. We deem—"extra-uterine intra artificial-uterine fetal surgery"—to be the natural evolution of this approach and the next logical step in the minimally invasive surgical management of congenital malformations.

3.9. In the End: Hard Data on Minimally Invasive Surgery

Patient, parental and caregiver bias is the most relevant factor in surgical research as most outcome parameters depend on patient self-awareness and caregivers' perceptions as well as their expectations on the surgical technique used. As the term "minimally invasive surgery" implies, they expect MIS to be truly minimally invasive and therefore mobilize themselves and start oral diets earlier or perceive pain less painful, because they have been told to be operated on by minimally invasive procedures. Therefore, any study aiming to generate hard data on minimally invasive surgery has to be randomized, prospective and, most important, double blinded, at least during the short term of the hospital stay.

Looking at those studies, some can be found examining the effect of minimally invasive surgery with remarkable results.

For appendectomy, prospective randomized double blind trials in adults found no significant advantage of the laparoscopic compared to the open procedure for the postoperative course, complications, pain or lost workdays. Operating room costs and time were increased and the hospital stay was not shortened. Only quality of life scores at 2 weeks were in favor of the laparoscopic procedure [147–150]. An umbrella review of meta analyses reported a lower rate of surgical site infections but higher rate of intra-abdominal abscess formation in laparoscopic compared to open appendectomy [151]. Similar results were found in a meta-analysis of randomized controlled trials in children [152–154].

For Weber-Ramstedt pyloromyotomy in hypertrophic pyloric stenosis, one prospective randomized multicenter double blinded trial can be found. It reported a significantly faster time to full enteral feedings for the laparoscopic procedure (23.9 versus 18.5 h) and earlier hospital discharge (43.8 versus 33.6 h) although the time to first enteral feedings was not different between the two groups [155]. The overall complication rate was not different but the rate of intraoperative mucosal perforation and incomplete pyloromyotomy, the most relevant complications of the procedure, appeared higher in the laparoscopic group. Unfortunately, this report does not describe the method of blinding the patient's mother, therefore leaving room for interpretation and thus limiting the study. Similar results to this interpretation, no decrease of the incidence of postoperative vomiting, a similar complication rate and risk of inadequate pyloromyotomy were reported by a prospective randomized but nonblinded trials [156,157].

Data of meta-analyses were presented for several other pediatric surgical conditions in a recent report [2]. Although relying on nonblinded trials, the authors concluded that the advantages of minimally invasive surgery (mainly time to enteral feedings and hospital stay) seem to outnumber the disadvantages, such as procedure specific complications.

Most analyses focus on soft outcome parameters of minimally invasive surgery, such as time to enteral feedings, time to full mobilization, duration of hospital stay, cosmetics of the wounds and quality of life, which often result in favor of minimally invasive surgery, partially because of the abovementioned bias [2]. Solid outcome parameters, such as intraoperative and postoperative complication rates as well as long term sequelae of the procedures are often just as reported as byproducts. This changes, when it comes to comparing minimally invasive with open surgery in surgical oncology. Due to the lack of hard data and mostly relying on non-randomized prospective or retrospective analyses, the feasibility and oncological safety of minimally invasive procedures are not proven in many fields of surgery, including pediatric surgery. In 2018, the reports of Ramirez and Melamed, published in the New England of Surgery, changed the way many gynecologists approach early-stage cervical cancer, as they were able to demonstrate that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival and overall survival than open abdominal radical hysterectomy [158,159].

Hard data, such as prospective randomized and double-blind studies, are lacking in pediatric surgical oncology. It is therefore of utmost importance that radical resection and oncological safety should never be jeopardized against soft outcome parameters of minimally invasive surgery.

4. Conclusions

Minimally invasive pediatric surgery is just evolving. Remotely controlled, through natural orifices deployed mini robots or single incision robotic assisted surgery with microinstruments of less than 3 mm diameter, augmented reality in combination with three dimensional stereoscopic view or ex utero in artificial utero fetal surgery all promise to increase the surgical benefit and reduce the surgical trauma of our patients.

However, when it comes down to hard data, as reported in randomized prospective double blinded trials, the so often proclaimed advantages of minimally invasive surgery in children become less evident. Thus, patient and parental counseling must always include all surgical and non-surgical options and—when medically justifiable—include their personal opinion into the decision process. Furthermore, all pediatric surgeons should strive to generate much more hard data on minimally invasive surgery by conducting or participating in randomized controlled double blinded trials.

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Didactic Benefits of Surgery on Body Donors during Live Surgery Events in Minimally Invasive Surgery

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Abstract: Background: Live surgery events serve as a valuable tool for surgical education, but also raise ethical concerns about patient safety and professional performance. In the present study, we evaluate the technical feasibility and didactic benefits of live surgery on body donors compared to real patients. Methods: A live surgery session performed on a body donor's cadaver embalmed in ethanol–glycerol–lysoformin was integrated into the live surgery program presented at a major gynecological convention of minimally invasive surgery. Surgical procedures carried out in real patients were paralleled in the body donor, including the dissection and illustration of surgically relevant anatomical landmarks. A standardized questionnaire was filled by the participants (n = 208) to evaluate the appropriateness, effectiveness, and benefits of this novel concept. Results: The live surgery event was appreciated as a useful educational tool. With regard to the use of body donors, authenticity was rated high (85.5%), and the overall value of body donors for surgical education and training was rated very high (95.0%). The didactic benefit of simultaneous operations performed on body donors and real patients was considered particularly useful (95.5%), whereas complete replacement of real patients by body donors was not favored (14.5%). Conclusions: The study demonstrated both the technical feasibility and didactic benefits of performing minimally invasive surgery in body donors as part of live surgery events. This novel concept has the potential to enhance anatomical knowledge, providing insights into complex surgical procedures, and may serve to overcome yet unresolved ethical concerns related to live surgery events.

Keywords: body donors; laparoscopy; minimally invasive surgery; surgical education; clinical anatomy; live surgery events

1. Introduction

Learning gross human anatomy by means of systematic dissection of body donors has always been a fundamental element of medical education [1]. Anatomy is usually taught at the beginning of medical school, in dissection courses on body donors conventionally fixed in formaldehyde solutions [2]. Knowledge of human anatomy is the basis of any medical intervention. However, manipulation within the human body and the refinement of skills are usually achieved on real patients.

In view of the increasingly limited human and financial resources, as well as higher ethical standards in modern medicine, surgical education must necessarily encompass new training concepts [3,4]. Rapid advancements in medical and digital technology, especially minimally invasive surgery, have resulted in a wide range of training and educational opportunities, such as virtual reality training devices or interactive video learning platforms [5–8]. In view of these new options, the traditional concept of acquiring knowledge of surgical anatomy on vulnerable patients entrusted to our care appears to be debatable, at least from the ethical point of view [9,10].

Surgical training courses using human body donors are becoming increasingly important in curricular and postgraduate education [11–13]. Novel fixation techniques have been developed recently in order to meet this increased demand [14]. One of these techniques is ethanol–glycerol–lysoformin fixation, which is relatively simple and cost effective, and provides realistic tissue and organ properties [15]. We established the suitability of this method for minimally invasive surgical procedures, and demonstrated its didactic benefits for the acquisition and refinement of surgical skills [16,17].

Live surgery events serve as a useful additional platform for training and learning surgery as well as clinical anatomy [18]. In fact, live surgery events constitute a core element of surgical conventions [19]. Leading experts in their respective fields demonstrate live surgeries, which frequently include novel surgical techniques and devices applied on real patients [20]. Typically, the attendees are able to communicate with the surgeons during video transmission [18]. A large number of surgeons are introduced to new surgical techniques and the relevant clinical anatomy is demonstrated on a single patient [19,21]. Furthermore, live surgery events offer the opportunity to learn from experts as a role model in real life, as well as handle surgical complications and manage difficult cases appropriately [22,23]. Such events are especially attractive in minimally invasive surgery because the perspective of the operating surgeon is directly transmitted to the attendees in the auditorium, who then participate virtually in the operation [20].

However, live surgery events are controversial because of medical and ethical concerns [19,24]. In fact, live surgery is known to be associated with prolonged operating and anesthesia times, lower rates of therapeutic success, and delayed time to intervention [25,26]. These disadvantages may not be acceptable under the supreme medical ethics of doing no harm [19]. Some professional associations have issued recommendations for the improvement of these concerns and offered congress organizers suitable guidelines to overcome these problems [22,27].

Based on these considerations, in the present study we evaluated a live surgery event supplemented by minimally invasive surgical procedures performed on a body donor, along with practical demonstrations of surgical anatomy. The rationale for implementing this novel module into a conventional live surgery session was to assess the didactic quality and benefits perceived by the attendees, and the potential reduction in risks associated with live surgery on real patients.

2. Materials and Methods

2.1. Format of the Live Surgery Event

The format of the 23rd Annual Meeting of the Gynecological Endoscopy Working Group (AGE) (2018, Hamburg/Germany) included a live surgery session on real patients from two hospitals in Hamburg (Agaplesion Diakonieklinikum Hamburg, Frauenklinik an der Elbe) paralleled by laparoscopic operations on a body donor, transmitted from the operating room in the institute of anatomy at Kiel University (Kiel/Germany). All transmissions were carried out by a professional

broadcast team (TV-Studio Leonberg, Gerlingen/Germany) and presented on several large-sized HD monitors placed throughout the entire congress hall to allow optimal visibility from all seats (Figure 1A). The surgeries were transmitted simultaneously from the hospitals and the institute of anatomy, but only one source was presented to the auditorium at a time. Communication between surgeons and the auditorium was coordinated by the chairmen (BH, SB, LM, BB, ES, NM), who commented on the surgical procedures and passed questions from the auditorium to the operating surgeons.

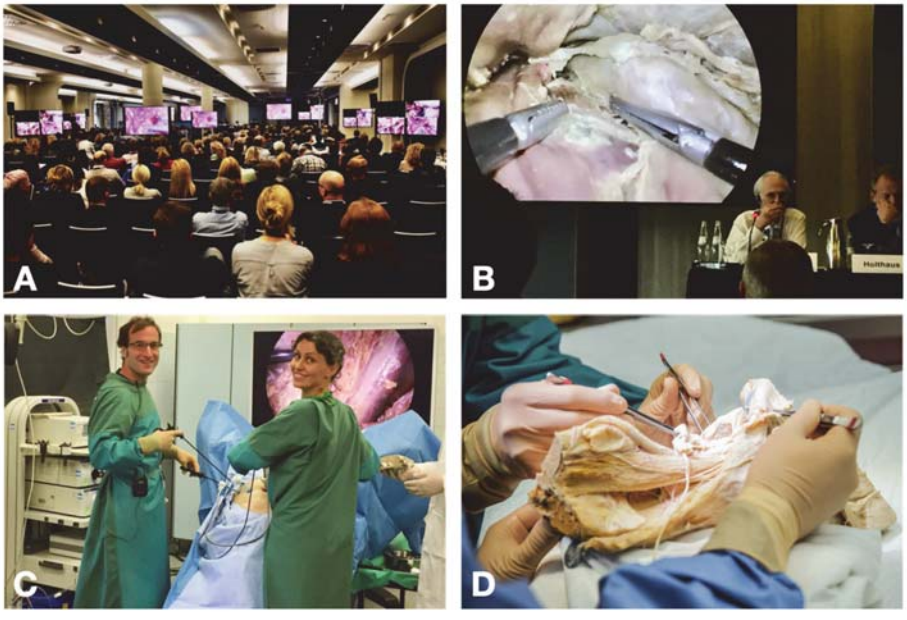

Figure 1. Set-up of the live surgery event. (**A**): Conference room equipped with several HD monitors for transmission of the live surgery event. (**B**): Transmission of laparoscopic procedures performed on a body donor from the attendees' perspective. (**C**): Technical setting for live surgery performed on a body donor. (**D**): Demonstration of relevant anatomical structures on a formalin-fixed pre-dissected anatomical specimen (hemipelvis).

2.2. Laparoscopy on Real Patients

Patients with benign (deep infiltrating endometriosis, uterine fibroids, genital prolapse) and malignant (endometrial and cervical cancer) gynecological diseases were selected for live laparoscopic surgery. All of the operations were performed by a surgeon from the presenting hospitals in cooperation with an invited faculty surgeon who was given adequate time to study the cases. All patients were informed previously about the specific conditions of the live surgery event, had given their written consent, and could meet their respective surgeons the day before the operation. Participation was absolutely voluntary and devoid of any financial advantage. The operations were performed in accordance with current medical knowledge, by surgeons (AH and others) experienced in live surgery events and with the highest certification levels of the AGE.

2.3. Laparoscopy on Body Donor

The body of a female body donor (77 years, 59 kg) was obtained from the body donation program of the institute of anatomy at Kiel University. Prior to her death, the donor had given her written consent to the use of her body for educational and research purposes. Advanced stages of arteriosclerosis and previous abdominal surgery were excluded to allow efficient perfusion fixation and optimal

conditions for laparoscopic surgery. Exploratory laparoscopy was performed before the live surgery event to confirm the presence of the uterus and adnexa, and exclude severe adhesions or other major pathologies. The detailed fixation procedure has been reported previously [16]. Briefly, the body donor was perfused with a fixative solution (70% ethanol, 30% glycerin, 0.3% lysoformin) administered at a ratio of 0.3 l/kg body weight via the femoral artery. Perfusion was carried out by alternating cycles of injections (30 min) and breaks (20 min) over a period of about 24 h. The fixed body donor was draped in cloths moistened with a watery solution supplemented with 1% thymol, placed in a sealed plastic bag, and stored at 4 °C until use.

Laparoscopic surgery was performed in an operating room at the institute of anatomy by two experienced surgeons (IA, GP) and accompanied by a clinical anatomist (TW). The body donor was safely mounted on a mobile operating table to allow optimal positioning. The laparoscopic equipment included an endoscopy system, CO_2 insufflation, a rinsing device, and standard laparoscopic instruments (Figure 1B,C). The aims of laparoscopic procedures carried out on the body donor were twofold. The first of these was that the key steps of live surgery performed on real patients were to be paralleled on the body donor, but with more time taken to focus on anatomical structures and landmarks related to the surgical procedures. Moreover, alternative surgical approaches and modified techniques were demonstrated; for obvious reasons, these could not be shown in the live surgery sessions. Second, special emphasis was given to the dissection of those anatomical regions with structures exposed to the risk of injury, such as the autonomic nerve plexus in the para-aortic and presacral region, the obturator nerve in the obturator fossa, the genitofemoral nerve passing along the psoas muscle and external iliac vessels towards the groin region, or the course of the ureter from the pararectal region throughout the parametrial space towards the bladder. In addition, anatomical structures rarely seen during conventional laparoscopic procedures were explicitly exposed and discussed, such as the ventral roots of the spinal nerves L5-S4, the retrorectal space, branches of the posterior division of the internal iliac vessels, and lumbar vessels.

2.4. Demonstration of Pre-Dissected Anatomical Specimens

The same team (TW, IA, GP) demonstrated selected pre-dissected formalin-fixed specimens to highlight those anatomical structures which could not be entirely dissected during the laparoscopic procedures, but were considered relevant for live surgeries (Figure 1D). The interactive demonstration included the pelvic fascial system, pelvic floor muscles and ligaments, the pelvic and para-aortic lymphatic drainage system, and the inferior hypogastric plexus with terminal branches.

2.5. Evaluation

After the live surgery event, all participants were invited to evaluate the session on a questionnaire (Table 1). The evaluation focused on two major aspects: (1) the benefits of live surgery events for surgical education, prevention of complications, learning new surgical techniques, and improving personal surgical skills; (2) the value of live surgery on a body donor for surgical training, the authenticity of the body donor, the benefit of simultaneous surgery on real patients and body donors, and the potential for body donors to replace real patients at live surgery events.

Table 1. Questionnaire: items and results.

	N	Mean (SD)%	Min./ Max.	Median (IQR)%
1. How do you rate the benefit of live surgery on real patients for surgical training and further education?	206	88.6 ± 19.7	0/100	98.0 (86.5–100)
2. How do you rate the benefit of live surgery on real patients to avoid complications in your own patients?	205	79.6 ± 25.5	0/100	95.0 (79.0–100)
3. How do you rate the benefit of live surgery on real patients for learning innovative surgical techniques?	206	85.6 ± 20.7	0/100	91.0 (66.5–100)
4. How do you rate the benefit of live surgery on real patients for improving your own surgical skills?	206	79.1 ± 24.0	0/100	87.5 (65.0–100)
5. How do you rate the benefit of live surgery on the body donor for surgical training and further education?	204	84.4 ± 21.2	0/100	95.0 (75.0–100)
6. How do you rate the authenticity of the body donor?	202	78.9 ± 22.6	0/100	85.5 (65.5–100)
7. How do you rate the educational value of simultaneous surgery on body donors and real patients?	206	82.8 ± 24.2	0/100	95.5 (74.5–100)
8. Could the body donor replace the real patient in live surgery events?	202	23.3 ± 25.7	0/100	14.5 (0–39.0)

The questionnaire was approved by a statistician and a medical ethics specialist. The answers were recorded on a continuous visual analog scale (VAS) and expressed in percentages (0: very low; 100: very high). The questionnaire recorded age, gender, professional qualification, type of medical care institution, AGE membership, the level (MIC I–III) of skills in minimally invasive surgery according to the AGE criteria (certification criteria are listed on the AGE website [28]), and the number of live surgery events attended in the past. Finally, free optional text fields were provided for appreciation and criticism. The study was approved by the ethics committee of the Medical Faculty of Kiel University (approval number D 453/18).

2.6. Statistical Analysis

The IBM SPSS Statistics 23 program was used for statistical analysis. Quantitative variables were presented descriptively as means and standard deviations, minimum, maximum, quartiles and interquartile ranges (IQR), and tested for normality with the Kolmogorov–Smirnov test. VAS scores were assessed as follows: <20, very low; 20 to <40, low; 40 to <60, moderate; 60 to <80, high; 80 to 100, very high. A correlation analysis was performed to determine the influence of age and the number of live surgery events attended in the past. When significant deviations from normal distribution were found, we used the Spearman-rho test for correlation analysis. The correlation coefficient (r) was evaluated as follows: $r \leq 0.2$, no correlation; $0.2 < r \leq 0.5$, weak to moderate correlation; $0.5 < r \leq 0.8$, strong correlation; $0.8 < r \leq 1.0$, very strong correlation. Tests were performed bilaterally and the level of significance was set to 5% ($p < 0.05$). The Mann–Whitney U-test was used for subgroup analysis of nonparametric data, or the Kruskal–Wallis test for more than two subgroups. Tests were performed bilaterally and the level of significance was set to 5% ($p < 0.05$).

3. Results

3.1. Demographic Data

A total of 487 participants had registered for the live-surgery event day at the AGE congress. 208 participants (50.5% female, 47.6% male) completed the questionnaire after the live surgery session. As the exact number of participants who attended the live surgery event was not recorded, the return rate could not be determined. Assuming that all registered attendees participated in the live surgery session, the response rate would be 42.7%. The majority of the participants were members of the AGE (86%), and nearly a half of them (49%) had an MIC II or MIC III certificate. Most participants were specialists in obstetrics and gynecology (90%). Of these, 40 (19.2%) were clinical directors and 44 were senior consultants (21.2%). Most physicians worked in primary and secondary care medical institutions (41%), followed by quaternary (26%) and tertiary care units (25%). The participants had attended an average number of eight live surgery events in the past (Table 2).

Table 2. Description of participants.

Total Number	208 (100%)
Age (median)	45 years (range, 25–78 years)
Number of previously attended live surgery events (median)	8 (range: 0–100)
Gender	
Female	105 (50.5%)
Male	99 (47.6%)
AGE membership	
Yes	178 (86%)
No	25 (14%)
AGE certification	
MIC I	57 (28.2%)
MIC II	83 (41.1%)
MIC III	16 (7.9%)
no certification	47 (22.6%)
Professional experience	
Resident	11 (5.3%)
Specialist	24 (11.5%)
Consultant	81 (38.9%)
Senior consultant	44 (21.2%)
Clinical director	40 (19.2%)
Medical care unit	
Primary and secondary care	82 (41.0%)
Tertiary care	50 (25.0%)
Quaternary care	52 (26.0%)
Private medical office with a surgical unit	15 (7.5%)

3.2. Value of Live Surgery Events Performed on Real Patients

The value of live surgery events for surgical education and training was rated "very high" by most participants (median 98.0%, IQR 86.5–100%, n = 206). A similar high rating was given to the acquisition of innovative surgical techniques (median 95.0%, IQR 79.0–100%, n = 206). When asked to rate the benefits of avoiding complications in their own patients, the attendees' responses ranged from "very low" to "very high", but most attendees rated the benefits "very high" (median 91.0%, IQR 66.5–100%, n = 205). Finally, the value of improving their own surgical skills was rated "very high" by most participants (median 95.0%, IQR 65.0–100%, n = 206). The results are shown in Figure 2A and Table 1.

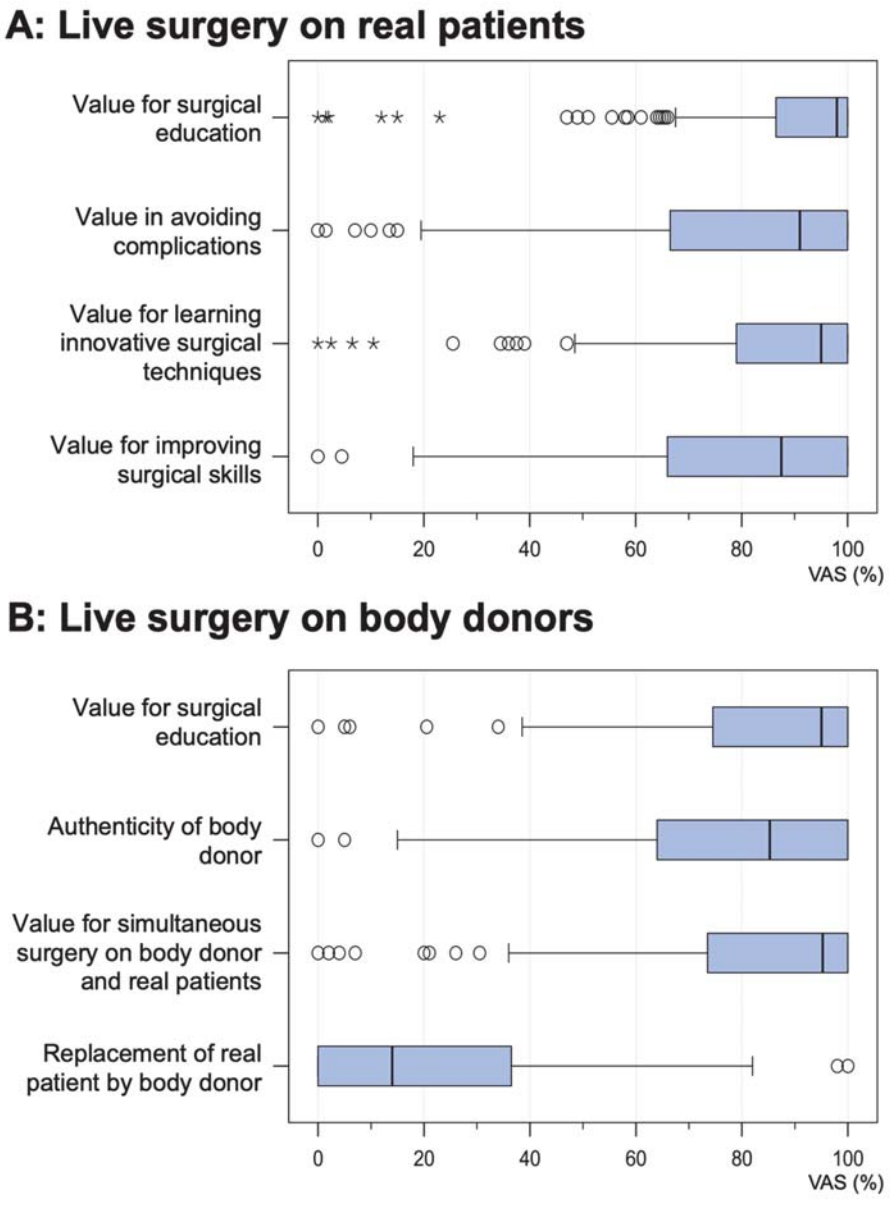

Figure 2. Evaluation (boxplots) of live surgery performed on (**A**) real patients and (**B**) a body donor. The answers were recorded on a continuous visual analog scale (VAS).

3.3. Value of Live Surgery Events Performed on Body Donors

The value of live surgery events for surgical education and training was rated "very high" by most participants (median 95.0%, IQR 75.0–100%, n = 204). Similar ratings were given when the attendees were asked about the value of simultaneous live surgery performed on real patients and body donors (median 95.5%, IQR 74.5–100%, n = 206). Most attendees rated the authenticity of the body donors as "high" or "very high" (median 85.5%, IQR 65.5–100%, n = 202). In contrast, the option of replacing real

patients with body donors at live surgery events was rated "very low" by most participants (median 14.5%, IQR 0–39.0%, $n = 202$). The results are shown in Figure 2B and Table 1.

3.4. Integration of Body Donors and Pre-Dissected Anatomical Specimens into Live Surgery Events

The overall feedback of the attendees in the form of free-text comments was very positive. Both the demonstration of key surgical steps in the body donor related to the live surgeries and the illustration of relevant anatomical structures in pre-dissected specimens were highly appreciated. The didactic benefit was confirmed by repeated suggestions to spend more time on demonstrations of anatomical landmarks, and to switch more frequently between the real patient and the body donor during the live transmission. A representative selection of comments is shown in Table 3.

Table 3. Praise and criticism of live surgery performed on body donors.

What Did You Like?	What Did You Not Like?	What Should Be Done Differently?
"Parallel surgical steps on body donor and patient." "Detailed presentation and explanation of the anatomical structures." "Simultaneous laparoscopy on both real patients and the body donor during the live surgery session was the highlight of the congress."	"Too little time allocated to anatomical dissection and laparoscopy on the body donor." "The start of the anatomical presentation was too early, as many participants were not present yet." "Suboptimal transmission on video screens."	"More transmissions from the anatomy operating room." "More time to combine anatomical demonstration with live surgery." "The videos, especially from the anatomy lab, should be made available to the participants." "Better scheduling of the anatomy block, so that more aspects can be shown." "Switch more frequently between live surgery and the anatomy lab."

3.5. Subgroup Analysis of the Evaluation

Subgroup analyses were performed to assess whether the responses depended on specific characteristics of the participants. However, neither age, gender, professional qualification, type of medical care facility, MIC levels, nor the number of previously attended live surgery events had a significant influence on the response pattern. The only significant difference was registered with regard to AGE membership: when asked about the potential of body donors to replace real patients at live surgery events, the approval rate was significantly higher among non-members ($p < 0.005$) (median 38.5%, IQR 13.5–54.5%) than among members (median 13%, IQR 0–35%) (Figure 3).

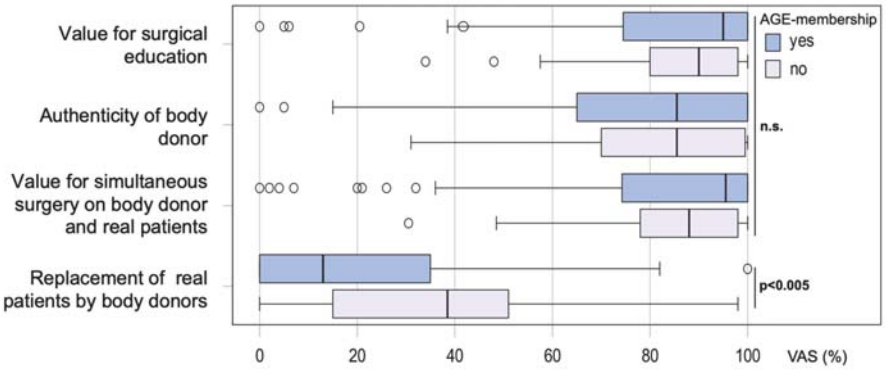

Figure 3. Value of live surgery performed on body donors: comparative subgroup analysis of AGE members and non-members. The answers were recorded on a continuous visual analog scale (VAS).

4. Discussion

Knowledge of clinical anatomy is the basis of successful surgery and the acquisition and development of new surgical techniques [29–32]. The attendance of live surgery events is an established means of learning anatomy as well as novel surgical techniques in nearly all surgical disciplines [20]. However, the demonstration of surgical procedures in real patients at live surgery events is subject to critical discussion from an ethical point of view [21,33]. Several studies have shown a potentially negative impact on the outcome of patients who have undergone live surgery, which is opposed to the no-harm principle of medicine [24–26,34]. These critical issues may be overcome by the use of body donors at live surgery events for the illustration of surgical techniques as well as the demonstration of related anatomical features.

Body donors embalmed in ethanol–glycerol–lysoformin were shown to be particularly suitable for surgical training and education [15–17,35]. Based on these previous encouraging experiences, laparoscopy performed on body donors was integrated into the live surgery session at the largest German surgical working group in gynecology (AGE) in order to evaluate the authenticity of this educational approach, its value for surgical training, and its didactic benefits. Analysis of the feedback showed that each of these aspects was highly appreciated by the participants. However, most attendees could not conceive the complete replacement of live surgery on real patients by body donor surgery. To the best of our knowledge, the current study is the first to address the concept of integrating surgical procedures on body donors into live surgery events.

The benefit of live surgery events for surgical training has been repeatedly and critically discussed [21,23,36]. However, we observed a high degree of approval for this training concept. The benefits in regard to the three primary training goals (avoidance of complications, innovative gain, improvement in own skills) was especially emphasized by the participants, and is most likely generated by the unique concept of live surgery [19]. The presentation of surgical procedures and complex situations by experts makes their knowledge and skills available to a large audience [19,21,37], and the techniques can be widely adopted in daily patient care [20]. Therefore, the live surgery event is likely to exert a sustainable effect on the quality of surgery for the attendees as well as their patients.

These undoubted advantages are counteracted by the potential health risks experienced by individual patients undergoing surgery at live surgery events [23]. Although live surgery has not been associated with additional risks due to a potentially higher complication rate, we do have evidence of health risks due to prolonged surgery and anesthesia time, a potential delay of treatment, and sometimes lower success rates of treatment [21,24–26,34]. These observations are supported by an anonymous assessment of guest surgeons at live surgery events, who questioned the indication for surgery or would even have chosen a different surgical procedure in one half of the cases [38]. Notably, the majority of surgeons involved in the survey would not make themselves available for live surgery as a patient and reported a high level of anxiety in performing a surgical procedure as a guest surgeon in a foreign clinic. On the other hand, the expectations of the audience may induce a greater willingness on the part of the surgeon to take more risks during the transmitted surgical procedure [38]. Moreover, informing the patient correctly about the risks associated with live surgery is a critical issue and will have to be addressed in the future [39]. These aspects illustrate the conflict between medical benefits for general public health and the potential harm to the individual patient arising from live surgery events [22]. However, we lack extensive data on the complications and risks of live surgery events [21]. Further studies will be needed to evaluate pending issues in the interest of patients, as well as provide solutions to the ethical dilemma.

One step towards solving this problem could be the integration of surgical interventions performed on body donors into live surgery events. The additional educational benefit of this concept was clearly revealed in the present study. Simultaneous surgery performed on real patients and body donors was especially appreciated by the participants. The quality and authenticity of the body donors were also considered very realistic, thus confirming previous data about the suitability of ethanol–glycerol–lysoformin fixation for this purpose [16,17]. Moreover, the use of body donors makes

it possible to demonstrate the patient's relevant anatomy beyond the limits observed in real patients. Thus, topographic relationships between the susceptible anatomical structures can be displayed and explained, and will help to avoid or handle complications encountered in real patients. The attendees' enthusiasm for the additional option of anatomical demonstrations supports the didactic value of this concept.

The combined approach may reduce the time of surgery and anesthesia in live surgery, as all anatomical issues, alternative surgical procedures and technical variations can be presented without stress and time pressure in body donors. In addition, the combined use of both body donors and real patients allows one to focus on a broader spectrum of surgical procedures, and at the same time will reduce the number of live surgeries, as several interventions can also be illustrated in body donors. Finally, the synergistic effects of both approaches may optimize the use of existing resources and enhance appreciation of the patient's willingness to make himself/herself available for medical training.

The question arises as to whether the real-patient scenario at live surgery events can be replaced completely by body donors. Our survey showed a clearly defensive attitude on the part of most participants, suggesting that a complete renunciation of the real patient might cause an unacceptable loss of educational and sustainable quality. However, the survey refers to a special setting, focused exclusively on laparoscopic gynecological operations. The statement may not be directly transferrable to other surgical disciplines. Furthermore, selected operations could possibly be performed equally well on body donors and real patients. We conclude that the primary value of surgical interventions on body donors is that it complements traditional live surgery by providing additional anatomical training concepts in terms of "where do I operate?", whereas live surgery on real patients is intended to teach surgical steps and techniques in terms of "how do I operate?" In this respect, the different evaluation of AGE members and non-members is an interesting aspect. While the negative attitude of AGE members was more pronounced than that of non-members, no difference was registered with regard to other sociodemographic factors. The lower level of habituation and adherence to traditions among non-members could be one explanation for this phenomenon.

In summary, the study demonstrated the technical feasibility and educational potential of surgical interventions performed on body donors at live surgery events in minimally invasive surgery. The feedback of the participants proves that the demonstration of surgically relevant anatomical landmarks as permitted by the use of body donors was of considerable benefit in clinical routine. The attendees' positive appraisal favors the integration of this concept as a complementary module in live surgery events, and could potentially resolve the associated ethical concerns. We hope that this "proof-of-principle" may contribute to future discussions concerning the modification of live surgery events in terms of combining surgery on real patients with interventions on body donors.

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Video Feedback and Video Modeling in Teaching Laparoscopic Surgery: A Visionary Concept from Kiel

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Abstract: Learning curves for endoscopic surgery are long and flat. Various techniques and methods are now available for surgical endoscopic training, such as pelvitrainers, virtual trainers, and body donor surgery. Video modeling and video feedback are commonly used in professional training. We report, for the first time, the application of video modeling and video feedback for endoscopic training in gynecology. The purpose is to present an innovative method of training. Attendees (residents and specialists) of minimally invasive surgery courses were asked to perform specific tasks, which were video recorded in a multimodular concept. Feedback was given later by an expert at a joint meeting. The attendees were asked to fill a questionnaire in order to assess video feedback given by the expert. The advantages of video feedback and video modeling for the development of surgical skills were given a high rating (median 84%, interquartile ranges (IQR) 72.5–97.5%, n = 37). The question as to whether the attendees would recommend such training was also answered very positively (median 100%, IQR 89.5–100%, n = 37). We noted a clear difference between subjective perception and objective feedback (58%, IQR 40.5–76%, n = 37). Video feedback and video modeling are easy to implement in surgical training setups, and help trainees at all levels of education.

Keywords: video feedback; video modeling; laparoscopy; gynecology; surgical training; pelvitrainer

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1. Introduction

Endoscopic surgery is available in all developed countries and is widely accepted in all surgical specialties. Its rapid growth and acceptance is seen even in developing countries. The acquisition of skills needed for endoscopic surgery involves a long learning curve. Training programs for laparoscopic surgery are required to fulfil the challenge of imparting a variety of surgical skills [1,2]. Laparoscopic surgery calls for refined psychomotor skills, which differ from those required for conventional surgery [3]. The challenges of laparoscopic surgery include the fact that a two-dimensional image is extrapolated to a three-dimensional working area, the fulcrum effect, specialized coordination of hands and eyes, depth perception, and a different type of tactile feedback. These skills can only be acquired and developed outside the operating room [4]. Thus, the surgeon completes the learning curve in an outsourced setting [5,6].

The traditional concept of teaching open surgery in the operating room [7] has now shifted to training schools for teaching and learning minimal access surgery [8,9]. It leads to superior improvement in knowledge and technical performance in the operating room, compared with conventional residency training [10].

A variety of options are available for acquiring skills in laparoscopic surgery, such as watching video films of operations, surgery on body donors and animals, practicing on laparoscopic trainers (pelvitrainers), and virtual reality simulators. Virtual trainers are the only devices that provide direct feedback and an evaluation of the surgeon's

exercises in laparoscopic training. Minimally invasive surgery requires the interaction of various components. Critical factors, in addition to the previously mentioned and known challenges, include weight distribution, body position, handling, and skilled static and pivotal movements. This, in turn, necessitates modular training on an individual basis.

Feedback is a crucial aspect of any method of training. The aim of feedback is to achieve a positive and constructive improvement in the acquisition of a particular skill. However, feedback about simple observations and achievements are very subjective and unable to meet the demands of fairness and objectivity [11]. A meta-analysis of 33 published empirical studies confirmed the effectiveness of video-supported feedback on the interaction skills of professionals in a variety of professions [12]. According to Hazen et al., simply pointing out mistakes is not enough to improve the skills of athletes [13]. Watching oneself highlights the positive aspects of one's performance in addition to enhancing the learner's motivation and the success of learning [14]. Learners are able to view their pre-existing repertoire of skills. An additional advantage of observational or model learning is that complex modes of behavior, including a large number of behavior patterns, can be acquired more easily and rapidly [15]. Video enhancement was used as an evidence based and reliable tool for the in-training assessment of residents non-technical performance in the operation room [16].

A skill that appears easy at first glance is difficult when performed. However, training the mind is propagated as a means of achieving anything the mind desires. Psychological training of the mind is also important for the refinement of motor functions.

Training on pelvitrainers with subsequent feedback based on video recordings, in conjunction with a comparison of an expert's skills, was shown to be a promising additional means of learning. In 1963, video feedback was used for the first time in communication training [17]. Watt reported a significant improvement of speech as a result of video feedback [18]. Kurtz et al. described video feedback as a gold standard in communication training [19]. The method spread rapidly and successfully to other areas such as first-aid training, sports medicine for primary injury prophylaxis, and parent training programs [20–23]. The benefits of video feedback are very evident in sports. It has been used for the improvement of skills in martial arts, basketball, soccer, swimming, and tennis [24–26]. The addition of a film showing an expert performing the skill is the principle of video modeling [27]. Video feedback and video modeling show the participants their mistakes as well as their correct execution of the skill. Technical options permit visual recording of a task, freezing a particular image in time, and replaying it several times. Like sports, laparoscopic surgery requires a high level of psychomotor skills.

Based on the concept of using video feedback in endoscopic training, in the present pilot study we analyze the feasibility of video feedback and video modeling in a preexisting endoscopic training setup. The impact of such training on the trainees' skills, and the target group that benefits most from additional video feedback and video modeling are also addressed.

2. Experimental Section

2.1. Participants and Training Setup

We collected data from persons who attended a minimally invasive surgery training program for beginners and advanced surgeons at the Kiel School of Gynecological Endoscopy (department of obstetrics and gynecology, University Hospital Schleswig-Holstein, Campus Kiel, Germany) between November 2019 and July 2020. The courses were certified by the German Society of Gynecological Endoscopy (AGE). None of the participants were students, residents, or consultants at the University Hospital Schleswig-Holstein, Campus Kiel. The participants were told that their tasks would be filmed for evaluation of their performance, and appropriate feedback would be given by experts. All participants consented to the procedure.

The attendees trained on a Realsimulator 2.0 (Endodevelop, Saarbrücken, Saarland, Germany) based on the female physique from the Pelvic School of Saarbrücken, and a

SZABO-BERCI-SACKIER pelvitrainer from Karl Storz Company (KARL STORZ GmbH and Co. KG in Tuttlingen, Baden-Württemberg, Germany). The endoscopy system was provided by Karl Storz Company. The attendees used instruments from Karl Storz Company, consisting of the Clickline series (Manhes, Metzenbaum scissors) and two Koh needle holders.

The workplace was equipped with a camera (Panasonic LUMIX Gh5 with a fixed focal length lens Panasonic Summilux 1:1.4/25 (Panasonic, Osaka, Japan)) installed on a tripod, which captured the handling and posture of the surgeon as well as the camera assistant (Figure 1, Video S1).

Figure 1. Setup of video feedback.

The use of instruments was recorded precisely by a camera (Panasonic LUMIX G81 with Panasonic G Vario 1:3.5-5.6/12-60), which filmed alternately from above and in front of the participants (Figure 2). Additional lighting permitted the acquisition of high-quality video recordings. The endoscopic camera recorded the task being performed. All three cameras yielded high definition images. The three video recordings were synchronized and configured as a split screen to compare posture and instrument use with intracorporeal work, and compare it with the expert's recordings. A filmmaker experienced in the use of video feedback in professional sports (such as surfing) accompanied the three- to four-day training courses, provided the necessary equipment, and created a personalized video clip for each participant.

Figure 2. Four camera perspectives: posture (**A**), posture and instruments (**B**,**C**), and the surgical site (**D**).

The recordings were collected on a data storage device and processed with a video editing program (Adobe Premiere Pro cc, (Adobe, San Jose, CA, USA)). Table 1 provides a precise list of the equipment, video cutting and special software, and their costs.

2.2. Task Performance

The participants trained in twos on the pelvitrainer—alternately, as a surgeon and as a camera assistant. At the beginning of the endoscopic work, all participants were instructed in the execution of the exercises and the use of instruments. A task list, an instructional video performed by one of the experts, and oral instruction were given to each one. Any questions or ambiguities during the work were clarified by an expert. Suggestions for improvement and additions were offered. The time taken for each exercise was measured until the exercise was evidently completed. Two tasks were performed during the video feedback. Based on previous studies [28], we selected tasks from all surgical fields with respect to hand-eye coordination, posture, ergonomics, instrument handling, depth perception, and precision.

On the first day of the training program, each attendee of the course performed a resection task. A mark was made on a latex glove. The glove was fixed to a cork board with tacks. This, in turn, was fixed to the floor of the SZABO-BERCI-SACKIER pelvitrainer with Velcro. The marked figure had to be excised precisely. Cutting was only permitted in the upper layer of the glove. The time taken to complete the task was measured.

On the second day, all attendees made a suture and performed an intracorporeal knot on the vaginal vault, which is regarded as a complex task in laparoscopic surgery. An artificial vagina was fixed in an artificial pelvic model of the pelvic trainer aligned to the female physique. Two needle holders and a circular needle with a thread shortened to 15 cm were used. The time taken by each participant to perform one surgical knot was measured.

2.3. Video Feedback and Video Modeling

The video feedback assessment was given individually to each participant with all participants present at one place. Thus, each participant could also learn from the evaluation of other participants by two experienced endoscopic surgeons (Figure 3, Video S1: Video feedback and video modeling clip). The experts were two senior clinicians (I.A. and G.P.) with more than 15 years of experience in the field of minimally invasive surgery. They both perform approximately 800 surgeries per year. Each attendee received a 7- to 10-min video feedback on the two exercises by both the experts together. Recordings from the operating room, such as resection of a part of the peritoneum or closure of the vaginal vault, were used to compare the skills of the participants performing the above mentioned exercises (Figure 4A,B). The software named Coach's Eye permits the user to play the video frame by frame in slow motion. In addition to verbal feedback, the experts could make visual corrections by manual input on the iPad. This was useful to point out improper posture or unsuitable handling of the instruments, and their improvement through visualization. The video, including vocal and visual feedback, was displayed on a screen and recorded. The feedback given by the experts was oriented to the OSATS score (Objective Structured

Assessment of Technical Skills) [29]. At the end of the feedback, all attendees were asked to complete a modified self-formulated questionnaire based on questions already used in a previous study done by our group and approved by a statistician [30].

Table 1. List of equipment used.

	Equipment
Settings	Camera (Panasonic, Osaka, Japan) Panasonic LUMIX GH5 with a fixed focal length lens Panasonic Summilux 1:1.4/25 Panasonic LUMIX G81 with Panasonic G Vario 1:3.5-5.6/12-60
	Memory card 2× 64 GB SanDisk Extreme PRO 95 MB/s
	Tripod Manfrotto 055PROB
	Light (optional) LED light Yongnuo Digital YN600L with tripod (Yongnuo, Shenzhen, Guangdong province, People's Republic of China)
	Laptop MacBook Pro 2015 (Apple Inc., Cupertino, California, USA)
	Staff Filmmaker and training supervisor
Endoscopic system	Karl Storz NDS wide-view HD 26-in monitor with LED backlight (16:10) IMAGE 1 HUBTM HD (so that the camera could display in HD) Camera (H3-z Image 1 HD Camera Head with the HOPKINS Straight Forward telescope 0°).
Instruments	Karl Storz Clickline (KARL STORZ GmbH and Co. KG, Tuttlingen, Baden-Württemberg, Germany) Koh needle holder KARL STORZ GmbH and Co. KG, Tuttlingen, Baden-Württemberg, Germany)
Pelvitrainer	Pelvitrainer 2.0 Realsimulator (Endodevelop, Saarbrücken, Saarland, Germany) SZABO-BERCI-SACKIER pelvitrainer (KARL STORZ GmbH and Co. KG, Tuttlingen, Baden-Württemberg, Germany)
Software used	Adobe Premiere Pro CC (Adobe, San Jose, California, USA)
Video feedback	iPad air A1475
	Software: Coach's Eye (Tech Smith Corp, Okemos, Michigan, USA)
	Smart board: Smart UX60 (SMART Technologies inc., Calgary, Alberta, Canada)

Figure 3. Setting of the video feedback assessment.

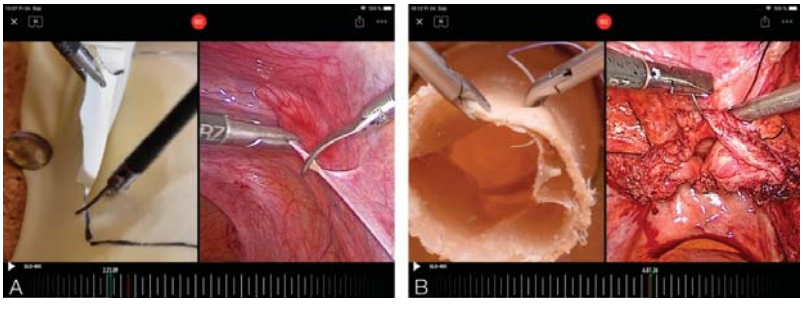

Figure 4. Video modeling of the resection task (**A**); video modeling of the vaginal vault closure task (**B**).

The attendees' basic assessment of the course, the practical success of learning, and sociodemographic data were recorded in a standardized questionnaire. The attendees were asked to provide their self-assessment after the video feedback. They were also asked whether the course had been of any benefit, whether they would recommend it as a new training concept, and how it relates to the subjective improvement of posture and the overall task. The attendees had to answer the questions on a visual analog scale (VAS) of 10 cm. The answers were expressed in percentages (0—not useful to 100—very useful).

2.4. Statistics

All answers to the items in the questionnaire were tabulated in a Microsoft© Excel database (Microsoft Corp., Redmond, WA, USA). The IBM SPSS Statistics 23 program (IBM, Armonk, NY, USA) was used for statistical analysis. Quantitative variables were presented descriptively as means and standard deviations, minimum, maximum, quartiles and, interquartile ranges (IQR), and tested for normality with the Kolmogorov–Smirnov test. VAS scores were evaluated as follows: <20—very low; 20 to <40—low; 40 to <60—moderate; 60 to <80—high; and 80 to 100—very high. A correlation analysis was performed to determine the influence of age and the number of live surgery events attended in the past. When significant deviations from normal distribution were found, we used Spearman's rho test for the correlation analysis. The correlation coefficient (r) was evaluated as follows: $r \leq 0.2$—no correlation; $0.2 < r \leq 0.5$—weak to moderate correlation; $0.5 < r \leq 0.8$—strong correlation; and $0.8 < r \leq 1.0$—very strong correlation. Tests were performed bilaterally

and the level of significance was set to 5% ($p < 0.05$). The Mann–Whitney U test was used for subgroup analysis of nonparametric data, or the Kruskal–Wallis test for more than two subgroups. Tests were performed bilaterally and the level of significance was set to 5% ($p < 0.05$).

3. Results

Thirty-seven persons participated in the study, of which 26 were female and 11 male. Twenty-six were resident doctors and 11 were specialists. Twenty-six persons had attended a minimally invasive surgery course in the past. Table 2 shows descriptive statistics regarding age (median: 33 years and range: 25–56 years) and the number of years of professional experience (median: 4 years and range: 0–40 years). The attendees had a median of 3.8 years of work experience, but the duration of their experience in minimally invasive surgery was only two years. In the self-assessment, the median value for experience as a surgeon in minimally invasive surgery was 10%, and the interquartile range was 3–40%.

Table 2. Sociodemographic data and laparoscopic experience.

	n	Mean	Standard Deviation	Minimum	Maximum	Percentile		
						25.	50. (Median)	75.
Age (years)	35	34.5	7.1	25	56	30.0	33.0	35.0
Professional experience (years)	36	6.89	8.1	0.0	40.0	3.0	3.8	10.0
Total number of laparoscopic procedures as surgeon	37	103.6	340.5	0	2000	2.5	10.0	50.0

The median agreement of the attendees regarding the value of the training was "very high" (80–100%) (Figure 5A). The median value was used because the attendees differed vastly in terms of age, surgical experience, and other variables. Further details are shown in Figure 5B. The median rating for the value for the surgical curriculum was 84% (IQR 72.5–97.5%, $n = 37$). The attendees said they would recommend a training course of this nature (median 100%, IQR 89.5–100%, $n = 37$). Similar ratings was given to the question as to whether the exercise improved their posture (median 96%, IQR 80–100%, $n = 37$). Concurrence of the attendees' self-assessment with the expert's assessment was expressed as follows: median 58%, IQR 40.5–76%, $n = 37$ (Figure 5B).

We also analyzed the attendees' level of training, divided into residents and specialists.

The median agreement of the attendees with regard to the value of the training course for the development of surgical skills was 95% among residents (IQR 80–100%, $n = 26$) and 83% among specialists (IQR 69.75–90%, $n = 11$). Both, residents and specialists would recommend such training to others (median 99%, IQR 96–100%, $n = 11$; median 100%, IQR 83.75–100%, $n = 11$). Improvement of posture by video feedback was given a median rating of 98% (IQR 81–100%, $n = 26$) and 95.5% (IQR 76.75–100%, $n = 11$) by resident doctors and specialists, respectively. Concurrence of the attendees' subjective feedback with the experts' objective feedback was 56% (IQR 27–100%, $n = 26$) and 60.5% (IQR 42.50–71%, $n = 11$) for residents and specialists, respectively. None of the four variables differed significantly between the two groups (U test, $p \geq 0.05$) (Figures 6 and 7A–D).

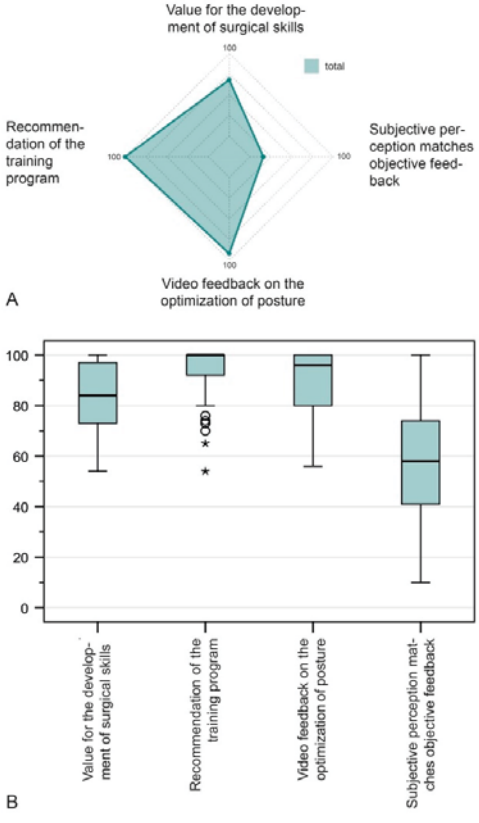

Figure 5. Evaluation of the course by all participants on the radar plot, with regard to four questions plotted on the x-axis. For better illustration, only the medians 50 to 100 are shown (**A**). The box plots show the evaluation of all participants. Circles and stars represent outliers; the black horizontal line within the box plot is the median (**B**).

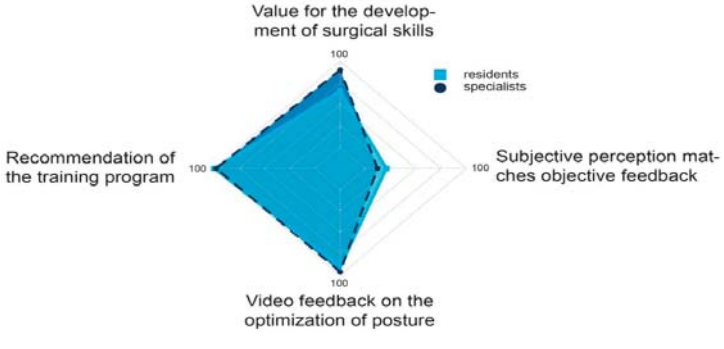

Figure 6. Median ratings of residents and specialists with regard to four questions plotted on the x-axis. For better illustration, only the medians 50 to 100 are shown.

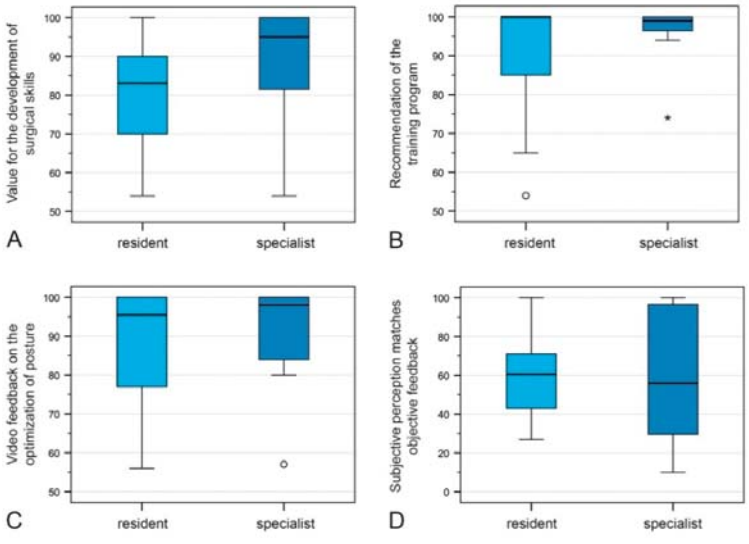

Figure 7. Residents' and specialists' assessment of the value of the training course for the development of surgical skills (**A**), whether they would recommend video feedback training (**B**), whether video feedback helps to optimize their posture (**C**), and whether the attendee's subjective assessment concurs with the expert's objective assessment (**D**). Circles and stars represent outliers; the black horizontal line within the box plot is the median.

We also performed a subgroup analysis of the number of laparoscopic interventions and the four variables. The value of video feedback for the development of surgical skills and the recommendation of such training were insignificantly correlated with the number of performed laparoscopic surgeries (Spearman's correlation coefficients were 0.189 and 0.147, respectively). The number of performed laparoscopic surgeries was not correlated with the value of the course for the improvement of posture; Spearman's rank correlation coefficient was −0.014). Concurrence of the attendees' subjective feedback with the experts' objective feedback was also insignificantly correlated with the number of laparoscopic surgeries (Spearman's rank correlation coefficient 0.166) (Figure 8A–D).

Based on the answers to the open questions, the most frequently cited advantage of attending the video feedback course was that the attendees' strengths and weaknesses were clarified and rendered objective. Comments on hand position and posture were greatly appreciated. One attendee was initially apprehensive of video feedback and less apprehensive afterwards.

Some of the negative comments concerning video feedback and video modeling were that the attendees felt they worked under pressure due to the impending assessment, and had a sensation of being watched. One attendee admitted to fear of others' reactions and stated that all of the person's mistakes were probably not corrected. A representative selection of comments is shown in Table 3.

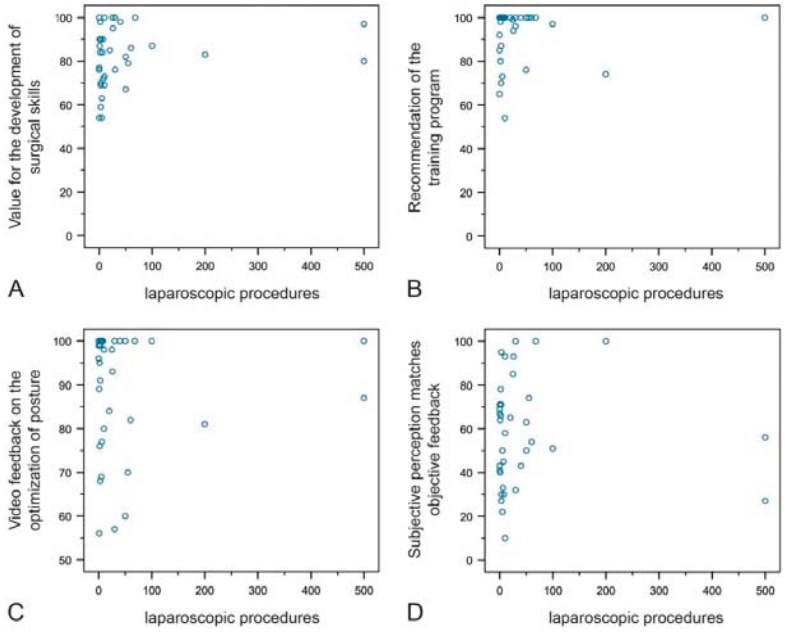

Figure 8. Correlation of the number of laparoscopic interventions and the value of the course for the development of surgical skills (**A**), the recommendation of video feedback training (**B**), the benefit of video feedback for posture (**C**), and whether the attendees' subjective assessment is equivalent to the experts' objective feedback (**D**). One attendee who had performed 2000 procedures was not listed.

Table 3. Comments given by participants to the open questions in the questionnaire.

What Did You Like?	What Did You Not Like?	What Should Be Done Differently?
"It improves self-awareness / self-assessment."		
"Constructive criticism from experienced surgeons."	"You are under pressure to complete the task as quickly as possible."	
"Seeing the expert's demonstration and listening to the explanation help to improve my skills."	"Under pressure, one tries to perform the task quickly and pays less attention to quality."	"Incorporation of breaks in the feedback."
"Seeing yourself from different perspectives improves handling and posture."	"Not all mistakes were corrected."	"Re-evaluation of the performed task after video feedback."
"Learning from others´ mistakes helps to improve oneself."	"Fear of reactions from other participants."	
"There was enough time for the video feedback."		

4. Discussion

We evaluated an innovative teaching concept in minimally invasive surgery. The positive effect of video feedback and video modeling on surgical training was independent of the attendees' sociodemographic characteristics or their level of experience. The attendees' subjective feedback varied considerably from that of video feedback with expert

advice. It enabled us to visualize individual steps of the procedure, register the trainees' mistakes, and correct these. This, we believe, is an important and hitherto neglected step in endoscopic training.

We adapted the concept of video feedback used in sports. Psychomotor skills result from the relationship between physical motion and cognition. In any sport, coordinated physical movements are needed to achieve a desired goal. Such coordination arises from cognition. Like sports, minimally invasive surgery requires psychomotor skills for good surgical performance. Video feedback and modeling are aimed toward psychomotor skills such as posture, weight distribution, body position, handling, and the surgeon's static and pivotal movements.

Video feedback has been used fruitfully in sports. Oñate et al. investigated various feedback concepts based on kinetic analysis for jumping and landing exercises in basketball. The exercises were performed by 51 recreational athletes to improve their performance and prevent injury to the anterior cruciate ligament. The use of self-assessment and video-taped feedback rated by an expert were most valuable for the improvement of landing skills [23]. Gymnastics is a complex sport which requires several body movements and postures. At the University of South Florida, scientists investigated the effect of combined video feedback and video modeling by an expert in four gymnastics students. After performing a specific exercise, the students watched the video of an expert doing the exercise and their own recording of the exercise with feedback—all of the students improved their skill as a result of the intervention [27]. Feedback on posture was given, albeit without any sports science expertise. The purpose was to train awareness of body posture. Such awareness enhances a person's awareness of his/her actions at the operating table as well.

Video feedback has been used for surgical training and has yielded various results. Farquharson et al. clearly showed the improvement of surgical skills by video feedback among undergraduate students [29]. Forty-eight persons were divided into two groups: group 1 received video feedback and group 2 received verbal feedback. Both groups performed the suture and knot technique. The OSATS (Objective Structured Assessment of Technical Skills) score in group 1 was significantly higher after video feedback (the mean score for the first performance was 12.33, and the mean score for the second performance 14.02; $p = 0.002$); the difference was statistically significant compared to group 2 ($p < 0.001$). Backstein et al. performed a quantitative and qualitative evaluation of the benefit of repeated video feedback among 26 first-year surgical residents. The control group received only expert advice and the experimental group received video feedback with expert advice. The MOSAT score (mini objective structured assessment of technical skills) was used for the evaluation. A score of 31.46 in the experimental group versus 29.75 in controls revealed no significant benefit in the former group [31]. Nesbitt compared the views of undergraduate medical students on standard lecture feedback, unsupervised video feedback, and supervised video feedback after the students had tied a reef knot with the aid of an instrument. As in our study, the students strongly recommended individual video feedback (IVF) over standard lecture feedback (SLF) and unsupervised video feedback (UVF)—the difference was significant (IVF vs. SLF, $p = 0.001$). The students also considered group feedback useful [32], as did our course attendees. Analogous to Nesbitt's study and ours, residents rated the assessment positively in Backstein's qualitative evaluation of video feedback. Residents commented on the fine-tuning of a particular task, the benefit of being able to visualize their errors, and believed that visualization would help in further stages once the basic task had been learned. Two residents in this study reported inconsistencies in the expert's feedback during review of the video tapes from one week to the next. This is indicative of a learning curve for experts when using videotape to instruct students [31].

We used video feedback with the demonstration of an expert´s video to compare the recording of the attendee's performance with that of the experts. The concept of video modeling proved to be advantageous in sports and music. Caliendo et al. made music band and choral students listen to and analyze professional recordings of music, and give a critique of their own videotaped performance. The comparison of pre- and post-test results

showed an increase in music achievement scores from 79.6% to 90.2% for band students, and from 74.5% to 87.7% for choral students. In our study, one attendee commented on the positive value of being shown the expert video: it helped to fill in gaps in her performance [27,33].

The assignment of tasks for feedback and evaluation should be aligned to the attendee's level of education. Farooq et al. evaluated the benefit of video feedback in laparoscopic pig gallbladder dissections among 16 medical students and first-year residents of surgery, and found it no better than traditional verbal feedback [34]. The reason was possibly the fact that surgical novices were given a complex task rather than a task aligned to their level of surgical training. Although the time given for the video review was twenty minutes, the attendees were unable to comprehend their mistakes without expert advice.

We selected one simple and one complex exercise in order to accommodate residents and specialists.

Singh et al. found video feedback to be beneficial in laparoscopic training, and the authors used five laparoscopic trials with 30 min of video watching in between them [35]. This investigation clearly showed that the attendees must be given adequate time to view the video. Tasks must be performed repeatedly to achieve improvement. Feedback was given to the group for two hours—each participant was evaluated personally for seven to ten minutes. The time frame was considered sufficient by the participants.

Since a person's perception of his/her performance will be different after having viewed the same on a video, the change of perception will indicate the magnitude of improvement in a task. In our study, the attendee's perception of the task differed markedly after the attendee had watched the video recording along with expert advice. The difference in perception was nearly 40% in both groups. The median assessment of residents (60.5%) and specialists (56%) were similar after watching the video.

Kardash et al. evaluated 26 medical students who were taught laryngoscopy with video feedback. Video feedback changed the students' perception of their performance [36]. Objective video feedback with expert advice had a profound impact on the trainee's personal perception of his/her task and provided significant scope for improvement.

Time and money may be notable issues in any type of additional training. In Nesbitt et al.'s study, students answered open questions in a questionnaire and remarked that a medical school lacks time and financial resources for individualized video feedback [32]. Abbott et al., who used personal video feedback to enhance learning the skill of laparoscopic knot tying, also concluded that video feedback is time consuming and probably costly as well [7]. However, individualized video feedback is feasible in a small setup as endoscopic training courses. Our sequential training course is effective and could possibly reduce the overall duration of training. It also saves time and reduces workload for teachers. The additional cost of video recording, the equipment, and the technical staff might increase the cost of these courses. Nevertheless, the incorporation of this type of a course is justified in view of its added benefit in training surgery students [37].

One limitation of the present study is that it only included the candidate's subjective evaluation of his or her performance after the feedback. Furthermore, giving feedback in groups may come with a certain psychological affect. To counteract this assessment only by zooming on handling or by blurring of faces or using specific identification number can be done. Controlled studies with objective evaluations will be needed to confirm the benefits registered in this pilot study. Secondly, the study lacked a control group. Thirdly, despite the fact that we observed no negative effects, the sustainability of the effects described here will have to be checked empirically. Dynamic developments in video and information technology, such as virtual training and artificial intelligence suggest that high-quality tools will be available in the future. These will meet the requirements of minimally invasive teaching and support the learning process.

5. Conclusions

Video feedback and video modeling have been shown to produce effective results in a variety of applications from communication training to sports. We conclude that it is a promising and sophisticated tool for surgical training as well. Video feedback and video modeling give teachers a lucid view of the tasks performed by trainees. Aspects of the task which may have been missed in ordinary verbal feedback are seen more clearly in video feedback. It helps the trainee to register his/her mistakes and gives the trainee a better perspective of the task.

The combined use of video feedback and video modeling is a promising tool to improve the execution of complex skills in laparoscopic surgery, perform precise body motions, and assume the appropriate position for a task. Another aspect worthy of investigation is the expert's learning curve in giving video feedback.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/1/163/s1, Video S1: Video feedback and video modeling clip.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data privacy protection.

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Review

Neuropelveology: An Emerging Discipline for the Management of Pelvic Neuropathies and Bladder Dysfunctions through to Spinal Cord Injury, Anti-Ageing and the Mars Mission

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Abstract: Neuropelveology is a new specialty in medicine that has yet to prove itself but the need for it is obvious. This specialty includes the diagnosis and treatment of pathologies and dysfunctions of the pelvic nerves. It encompasses knowledge that is for the most part already known but scattered throughout various other specialties; neuropelveology gathers all this knowledge together. Since the establishment of the International Society of Neuropelveology, this discipline is experiencing an ever-growing interest. In this manuscript, the author gives an overview of the different aspects of neuropelveology from the management of pelvic neuropathic pain to pelvic nerves stimulation for the control of pelvic organ dysfunctions and loss of functions in people with spinal cord injuries. The latter therapeutic option opens up new treatments but also widens preventive horizons not only in the field of curative medicine (osteoporosis and cardio-vascular diseases) but also in preventive medicine and anti-ageing, all the way to future applications in the "Mars mission" project.

Keywords: neuropelveology; LION procedure; genital nerves stimulation; chronic pelvic pain

1. Introduction

In the 1990s, laparoscopy was introduced in the surgical treatment of pelvic cancers and deep endometriosis. The challenge then was to perform at least as well as in radically open surgery. The introduction of video-endoscopy allowed for perfect vision and a considerable improvement in the ergonomics of the laparoscopic surgeon, which was necessary for more complicated and longer procedures. Laparoscopic pelvic surgery has thus become an extensive and radical surgery with the consequence of the appearance of postoperative pain too often unexplained and neglected as well as often irreversible functional morbidities. Patients who presented to neurourologists and neurologists did not find much help, only neuroleptic treatments but without any effort to research or treat the cause of the symptoms. The term "minimally invasive surgery" thus became more and more paradoxical. The only possibility to reduce this morbidity seemed to be the in-depth study of the surgical anatomy of the pelvic nerves and their sparing as successfully as possible during interventions. However, although topographical anatomy is extensively described in anatomy textbooks, the operative functional anatomy of the pelvic nerves was, on the contrary, almost completely non-existent.

Incidences of pelvic nerves pathologies are widely underestimated because of a lack of awareness that such lesions may exist, a lack of diagnosis and acceptance and a lack of declaration and reporting of such lesions. The most probable reasons for the omission of the pelvic nerves in medicine are the complexity of the pelvic nerve system, the difficulties of etiologic diagnosis and—probably the overriding reason—the limitations of access to the pelvic nerves for neurophysiological explorations

and neurosurgical treatments. Neurosurgical procedure techniques are well established in nerve lesions of the upper limbs but pelvic retroperitoneal areas and surgeries to the pelvic nerves are still unusual for neurosurgeons. Few open-surgical approaches to the sacral plexus have been described by neurosurgeons for the treatment for traumatic pelvic plexopathies but these approaches are laborious and invasive, offer only limited access to the different pelvic areas and expose patients to the risk of severe vascular complications. Techniques of nerve neuromodulation to control pelvic pain syndromes and dysfunctions are for the same reasons limited to spinal cord and sacral nerves roots stimulation that considerably restrict their indications and effectiveness.

The use of the endoscope in combination with neurofunctional surgical procedures to the pelvic nerves proved to be a decisive advantage in this development [1–4] and in fact it was the beginning of a new medical specialty, neuropelveology [5–7]. This specialty combines the knowledge required for a proper neurological diagnosis, which is essential for an adapted treatment for intractable pelvic neuropathies. The concept of neuropelveology, the first medical practice that focused on the pathologies of the pelvic nervous system, was introduced more than twenty years ago by Possover. Since then, neuropelveology has established itself as a specialty in its own right, promulgated by the creation of the International Society of Neuropelveology in 2014.

Neuropelveology presents three consecutive aspects; the diagnostic stage followed by the therapeutic stage and the post-therapeutic follow-up of the patient. It covers four major areas:

The diagnosis and treatment of pelvic neuropathic pain with particular new techniques of laparoscopic pelvic nerves decompression and neurolysis.

1. The treatment of pelvic organ dysfunctions, in particular the stimulation of the genital nerves (genital nerves stimulation (GNS) therapy).
2. The technique of laparoscopic implantation of neuroprothesis to the pelvic nerves (LION procedure) for the recovery of the loss of functions in people with spinal cord injuries.
3. The stimulation of the pelvic autonomic nervous system for the prevention and/or treatment of general medical conditions such as osteoporosis, some cardio-vascular disease or control of sarcopenia (process of ageing).

The diagnostic stage uses its own instruments and an anamnesis covering many aspects from gynecology, urology, orthopedics, pelvic vessel pathology and psychology of the chronic patient and parapleology. The clinical examination combines the examination of the pelvic organs and their functions, the neurological examination of the musculoskeletal system with a neuropelveological examination and the palpation of the pelvic nerves by the vaginal or rectal route [8]. As somatic, neuropathic pain is more specific, a neuropelveological workup typically allows for specific diagnosis of the lesion site in the pelvic nerves.

Neuropelveolgy encompasses various medical treatments and surgery of the pelvic nerves. The latter includes neurosurgical techniques ranging from decompression, neurolysis, reconstruction and even nerve resection (e.g., sciatic nerve endometriosis) to pelvic neurofunctional surgery.

2. Neuropelveology for the Management of Chronic Neuropathic Pelvic Pain

Chronic pelvic pain (CPP) is a common condition involving multiple, organ-specific medical specialties, each with its own approach to diagnosis and treatment. Its management requires a knowledge of the interplay between pelvic organ functions and neurofunctional pelvic anatomy and also of the neurological and psychological aspects. However, no current specialty field takes this approach into account. Neuropelveology is an emerging discipline focusing on the pathologies of the pelvic nervous system on a cross-disciplinary basis [7].

The neuropelveological approach to pelvic neuropathies is primarily diagnostic with the application of neurological principles and an absolute knowledge of the pelvic neurofunctional anatomy. Patient history is the key with a focus not simply on the pain location but also on pain

history, irradiation, aggravating factors, vegetative and somatic symptoms. The first step is to evaluate whether the pain is visceral or somatic (Table 1).

Table 1. Visceral Versus Somatic Pain: Symptoms (out of: Possover M. Neuropelveology—latest developments in Pelvic Neurofunctional Surgery—ISBN: 97895244533-0-8, 2015:26).

Visceral Pain	Somatic Pain
Pain Quality: Vague; Poorly Localized in The Entire Lower Abdomen with Radiation Into The Lower Back; Dull in Nature.	Pain Quality: Allodynia; Similar to An Electrical Shock. Very Specific Location; Precise and Clear Pain Description; Lack of Vegetative Symptoms.
+Vegetative Symptoms: Malaise/Oppression/Syncope, Fatigue, Irritability, Pupil Dilation, Salivation Inhibition, Tachycardia, Nausea/Vomiting, Pallor, Diaphoresis, Anxiety.	+Caudal Radiation to The Corresponding Dermatome(S)
	+Pelvic Motor Dysfunction: Pelvic Organ Dysfunctions, Sexual Dysfunction, Locomotion Dysfunction

Visceral pain by the lesion of the hypogastric plexuses is recognized due to the diffuse nature of pelveo-abdominal pain, irradiations proximal to the lower back and multiple vegetative symptoms including malaise, oppression, syncope, irritability, nausea, vomiting and fatigue. The clinical examination focuses on specific clinical details for vegetative disorders such as pupil dilation, salivation inhibition and tachycardia. In somatic pain, it is essential to adopt a neurological way of thinking since the location of the pain and the location of the etiology is mostly different. Somatic pain is located superficially at the skin and is described as allodynia or an electrical shock with a very specific location, caudal irradiations to the genito-anal areas or to the lower extremities (dermatomes) and lack of vegetative symptoms. The neuropelveological workup scheme follows these six steps:

(1) Determination of the nerve pathways involved in the relay of pain information to the brain.
(2) Determination of the location of the neurological irritation/injury (troncular vs. radicular vs. spinal vs. cerebral location).
(3) Determination of the type of nerve(s) lesion: irritation vs. injury (neurogenic neuropathy).
(4) Neurological confirmation of the suspected diagnosis by clinical examination with in particular the transvaginal or transrectal palpation of the pelvic somatic nerves with the reproduction of the trigger pain and Tinel's sign (eventually with selective anesthetic nerve(s) blockade).
(5) Determination of a potential etiology based on patient history and diagnostic imaging.
(6) Corresponding etiology-adapted therapy.

It is absolutely crucial to understand which nerves are involved in the pain and then to assess whether it is a nerve irritation secondary to compression or whether it is an axonal nerve lesion. In the first instance, the neuropelveological treatment is based on the laparoscopic exploration/decompression; in the second, on the neuromodulation of the affected nerves.

The intervention in the area of the pelvic somatic nerves, which is covered by large vessels and a dense network of lymph nodes, has hitherto been hindered by the lack of minimally invasive surgical methods. However, developments in video-endoscopy enable the exploration of the retroperitoneal pelvic space with access to the lumbosacral plexus and possibilities for nerve decompression and neurolysis. The most frequent aetiologies treated in neuropelveology are:

- Sacral radiculopathy by vascular or fibrotic entrapment [9–11].
- Compression of the sacral plexus by hypertrophy or atypical insertion of the piriform muscle.
- Deep infiltrating endometriosis of the sacral plexus and the sciatic nerve [9,12].
- Tumor of the sacral plexus (Figure 1) [13,14] and post-surgical pelvic neuropathies [15,16].

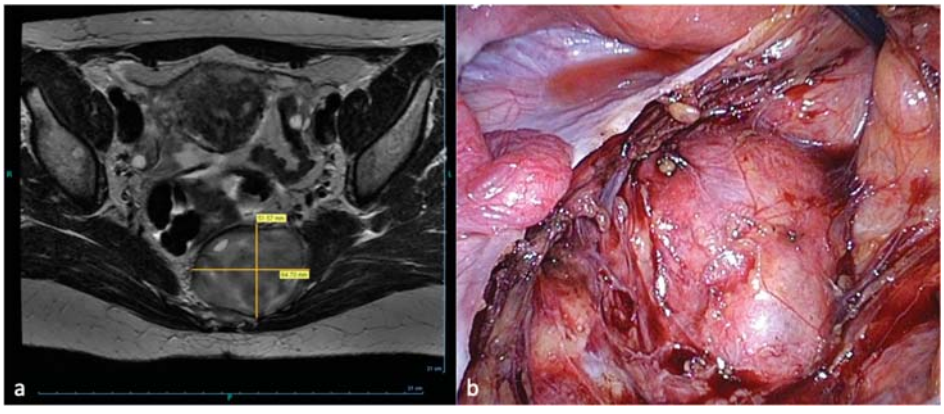

Figure 1. Laparoscopic resection of a sacral plexus schwannoma left. (**a**) MRI-presacral schwannoma (**b**) Corresponding intraoperative findings.

This endoscopic approach further allows in the case of an axonal lesion for the laparoscopic implantation of neuroprosthesis (LION procedure) where electrodes are selectively placed in contact with the injured pelvic nerves for the possible control of neuropathic pain [17].

Post-therapy patient follow-up for pain management is essential. In nerve neuromodulation, the stimulation parameters must be calibrated at regular intervals. After laparoscopic nerve decompression, neuropathic pain first significantly increases while improvement usually does not set in until eight months after the operation. The follow-up of these patients is essential in order to adjust the medical treatment and to treat the pain-memory as successfully as possible. The latter, however, is much more difficult to direct.

3. Genital Nerves Stimulation (GNS) Therapy

Various sites have been used for the implantation of electrodes to the pelvic nerves to treat pelvic organ dysfunctions. Sacral nerve stimulation was the first technique for pelvic nerves stimulation that typically involves the electrical stimulation of the nerve via a dorsal transformational technique of implantation. Sacral nerve stimulation (SNS) and pudendal nerve stimulation evolved as a widely used treatment for an overactive bladder (OAB) but does not completely resolve symptoms in the majority of patients. Both techniques are still unusual for most gynecologists so that the field of pelvic nerve stimulation is still extremely restricted in gynecology. There is definitively a need for a more suitable alternative for neuromodulative treatments; methods that cannot only be reserved for experts in this field but for all gynecologists dealing in daily practice with patients suffering from functional disorders of the bladder. This is why the LION procedure of the sacral plexus [18,19] and then the pudendal LION procedure were developed [20]. However, both techniques of implantation remain too complex for the generalist gynecologist trained in surgery but not in neuropelveological procedures. The stimulation of the dorsal nerve of the penis/clitoris (DNP) emerges then as a very attractive alternative that might result in great outcomes for treating urinary and fecal disorders [21]. DNP is extremely interesting because its stimulation effectively increases bladder capacity, inhibits involuntary detrusor contractions and overactive bladder symptoms [22,23] and may even control idiopathic fecal incontinence [24].

Genital nerves stimulation (GNS) is the surgical procedure developed for the stimulation of the DNP, an implantation technique adapted to the most classical surgical approach in gynecology, the vaginal approach. The procedure consists of two phases: a preoperative non-surgical test-phase and a second phase involving the surgical implantation of the neuroprothesis. In contrast to the classical technique of stimulation, the GNS-test-phase is the only one which does not require any

interventional procedure. Due to the fact that the genital nerves are located just a few millimeters below the skin's surface, test-stimulation can be obtained using skin surface electrodes (Figure 2).

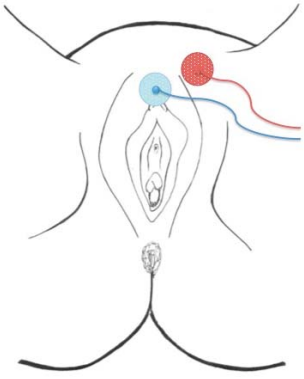

Figure 2. Position of the skin surface electrodes for the test-phase.

The effect of the stimulation can be tested by the patient in their daily, family and professional environment or alternatively at the practice under urodynamic testing or, if required, other electrophysiological testing.

After confirmation of the effectiveness of GNS, implantation of the permanent neuroprothesis can be scheduled. The procedure is performed either under general or spinal anesthesia or using only local anesthesia with IV sedation as in the classical tension-free vaginal tape procedure (TVT). The first step of the procedure consists of the introduction of a hollow curve needle applicator (Curve Applicator® NeuroGyn AG, Baar, Switzerland) with a spear from below, behind the pubic bone according to the classical tension-free vaginal tape (TVT) procedure: A sagittal incision of about 2 mm in length is made approximately 1 cm below the external urethral meatus. The curve needle driver is inserted into the incision. The tip is oriented at an angle of 5–10° from the midline towards the symphysis. The inserter tip is approximately in the 11 o'clock position (1 o'clock on the right side). The curve needle driver is advanced, contacting the inferior edge of the pubic ramus, until it transfixes the urogenital diaphragm, enters into the retropubic space and comes out through the skin in the suprapubic area (Figure 3a–c).

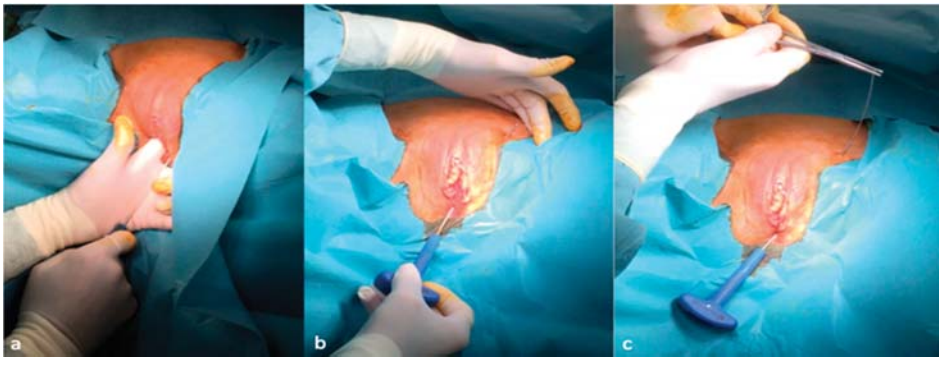

Figure 3. Introduction of the curve applicator from below and behind the pubic bone (**a**,**b**) and the removal of the spear of the curve driver needle (**c**).

The passage of the applicator behind and in direct contact with the dorsal aspect of the pubic bone is controlled with two fingers inserted into the vagina. A cystoscopy is performed to make sure the bladder and urethra are intact. The spear of the curve driver needle is removed. A quadripolar lead electrode with an electrode distance of 60 mm is introduced retrograde into the shaft of the curve needle driver; by the retraction of the curve needle driver, the electrode lead is left in position with the stimulation's poles coming out through the vulvar incision (Figure 4a,b).

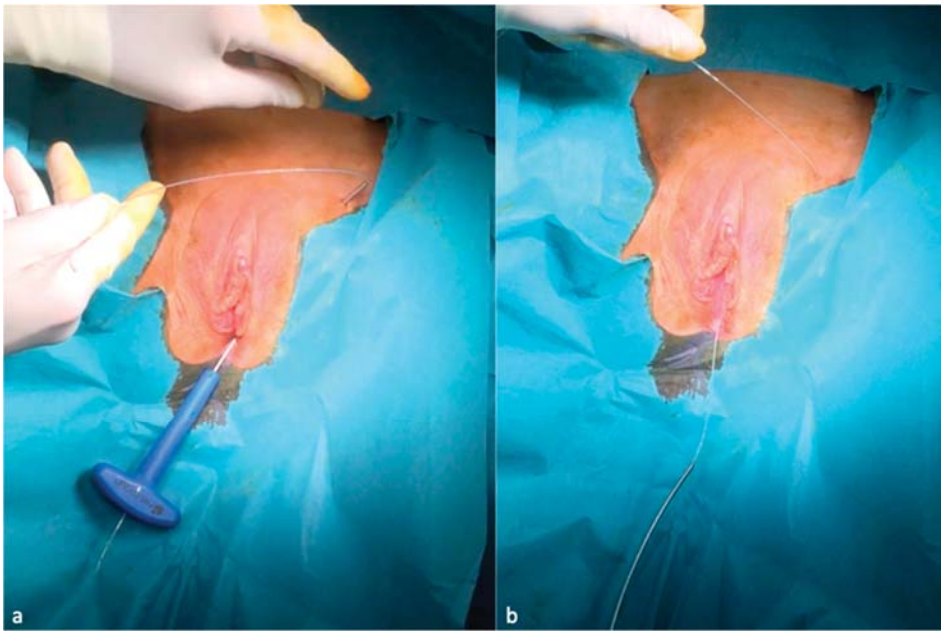

Figure 4. Introduction retrograde of the lead electrode (**a**) and the removal of the curve driver needle from below (**b**).

Through a second median supravulvar incision, the applicator with the spear is introduced from top to bottom so that it is as deep as possible (ventral to the pubic bone but as close as possible to it in order to assure the deep location of the cable electrode) and emerges through the first vulvar incision. After removing the spear, the electrode cable is inserted retrograde into the applicator again (Figure 5a–c).

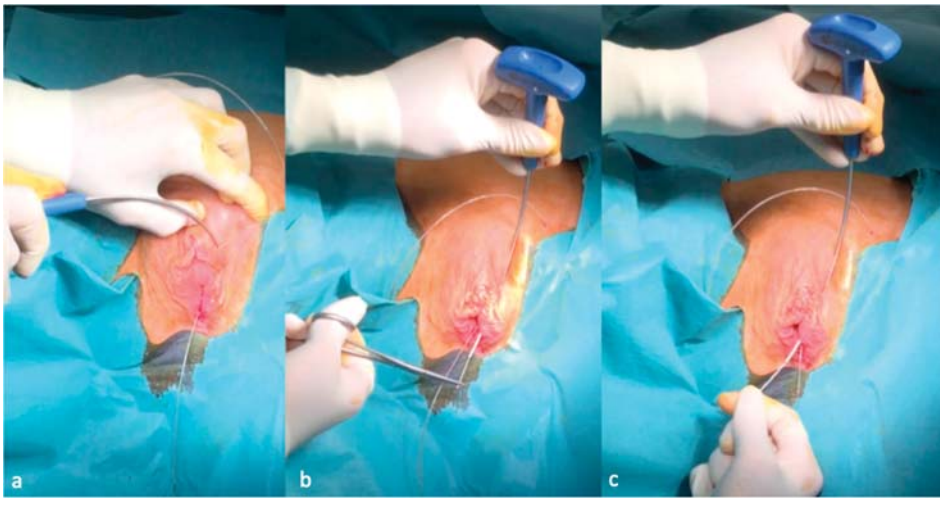

Figure 5. Second introduction of the curve applicator from above down to the first vaginal incision (**a**), removal again of the spear (**b**) and retrograde introduction once again of the lead electrode (**c**). After removing the applicator, the electrode is in place (Figure 6).

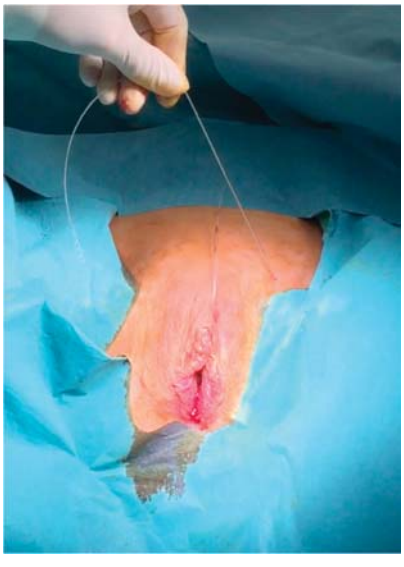

Figure 6. Retropubic passage of the lead electrode.

To use the hollow needle driver for the retrograde introduction of the lead electrode enables the optimal placement of the lead electrode to the genital nerves without the need for any dissection, which, in turn, reduces considerably the risk of bleeding and nerve injury. The introduction of the curve needle driver from below belongs to standard urogynecology (TVT) procedure. As the (dorsal Nerve of The Penis/Clitoris) DNP perforates the perineal membrane laterally to the external urethral meatus at an average distance of 2.7 cm (2.4–3.0 cm) and then runs along the bulbous spongy muscle for a distance of 1.9 cm (1.8–2.2 cm) before penetrating the pillars of the clitoris (Figure 7), the second passage of the lead electrode in front of the pubis ensures direct contact of the electrode to the DNP [25].

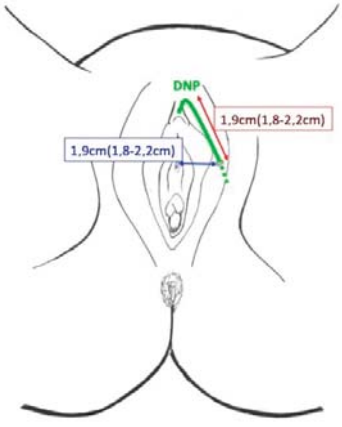

Figure 7. Dorsal nerve of the penis/clitoris (DNP) pathway at the vulva.

The last step is then the connection of the lead electrode to the generator, which is finally fixed behind the pubic bone through a suprapubic mini-laparotomy. The fixation of the generator behind the pubic bone protects from external traumas and dislocation.

No X-ray screening, neurophysiological monitoring or stimulation with (Electromyography) EMG electrodes are mandatory during the procedure for a proper implantation. Due to the fact that the presented procedure does not need two surgical procedures for both the test and the final implantation but only one for the final implantation, the presented protocol allows a considerable cost reduction in comparison with the usual procedures for sacral or pudendal nerves stimulation.

4. LION Procedures

The endoscopic approach allows in case of axonal lesion or dysfunction of the nerves the selective laparoscopic implantation of neuroprothesis (LION procedure) for electrical stimulation of the nerves (Figure 8).

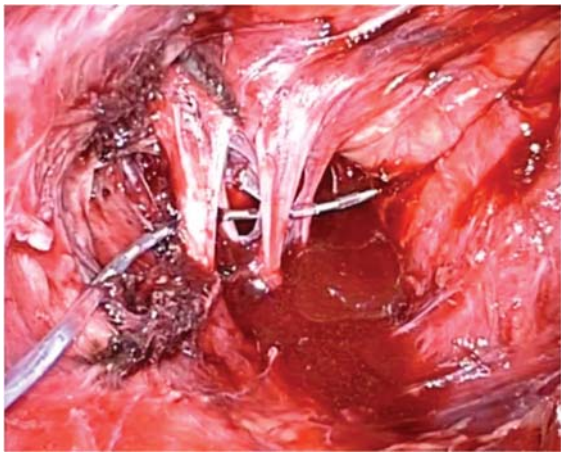

Figure 8. Sacral nerves laparoscopic implantation of neuroprothesis (LION) procedure.

This procedure has been used for the treatment of nerve damage and pelvic organ dysfunctions as reported previously but probably the most impressive indication of this technique is the implantation in people with spinal cord injuries for the recovery of some walking functions [26]. In 2006, we performed the first LION procedure in a paraplegic patient for the control of the bladder function [27]. This intervention consisted of a laparoscopic implantation of a fine wire in direct contact with the endopelvic portion of the nerves for electrical stimulation [28]. Laparoscopic exposure of the endopelvic portion of both the sciatic and of the pudendal nerves was obtained by passing laterally to the external iliac vessels through the lumbosacral space and the gentle detachment of the inter-iliac lymph-fat-tissue from the pelvic sidewall to avoid lymphocele. Multiple channel electrodes enabled the stimulation of both nerves with only one lead electrode. Exposure of the femoral nerves was also obtained by the transperitoneal approach behind the major psoas muscle. The four lead electrodes were not fixed to the nerves (Figure 9) while the cables formed loops in the retroperitoneal space to avoid dislocation and were finally passed through the pelvic wall and connected to a rechargeable pulse generator implanted subcutaneously into the anterior abdominal wall.

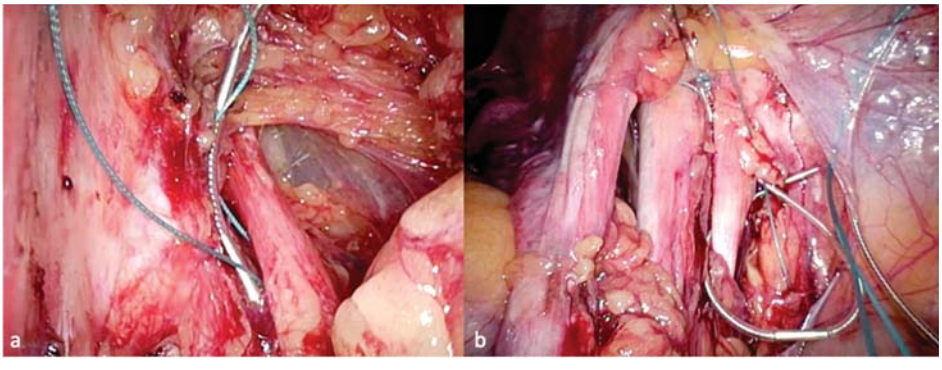

Figure 9. Placement of the lead electrodes to the left sciatic nerve (**a**) and the right femoral nerve (**b**).

Video: LION procedure in SCI (Supplementary Video S1)

The crucial discovery we made with the LION procedure in people with SCI was undoubtedly the fact that some patients experienced enough recovery of supra-spinal control for some leg movement or even standing and walking [26,29]. In the most recent study of 29 patients with SCI 10 years after a LION procedure, 20 of them (71.4%) were able to demonstrate an electrically assisted, voluntary extension of the knee [30] (Figure 10).

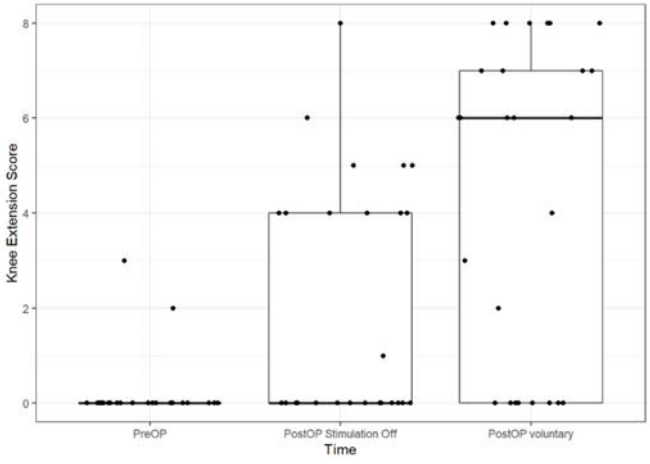

Figure 10. Boxplots of Knee Extension Score pre- and post-op. The line in the box shows the median, the lower and upper hinges correspond to the first and third quartiles and the upper/lower whisker extends from the hinge to the largest/smallest value no further than 1.5 IQR from the hinge (where IQR is the inter-quartile range). Dots show individual data points. PreOP-preoperative, PostOP-postoperative.

26 patients could get to their feet when the pacemaker was switched on (92.8%). Five patients could walk <10 m (17.85%) at the bar (Figure 11). Nineteen patients (AIS A: $n = 8$; AIS B: $n = 9$; AIS C: $n = 2$) could walk >10 m (67.8%); eight of them only at the bar (28.5%) and eleven of them with the aid of crutches/walker and without braces (40%).

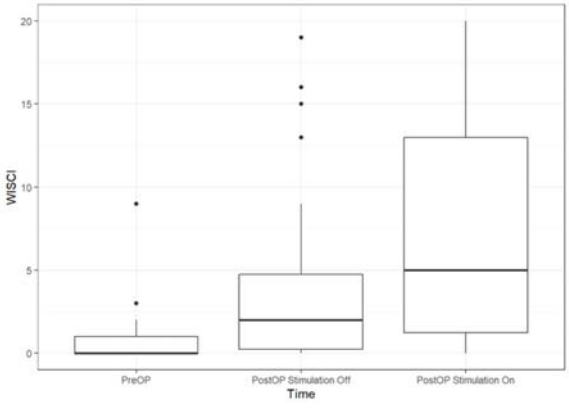

Figure 11. Boxplots of WISCI (Walking index for spinal cord injury) pre-operatively and at the 11/2018 follow-up. The line in the box shows the median, the lower and upper hinges correspond to the first and third quartiles and the upper/lower whisker extends from the hinge to the largest/smallest value no further than 1.5 IQR from the hinge (where IQR is the inter-quartile range).

The precise mechanism at work in people with SCI to recover walking functions after the LION procedure is still unknown. There is increasing evidence to suggest that neuromagnetic/electrical modulation promotes neuroregeneration and neural repair by affecting signaling in the nervous system but our findings suggest that the information signals to the brain might use not only anatomical nerve pathways but also functional pathways activated by a continuous low frequency stimulation of the low-motor neurons below the spinal cord lesion.

Beyond the psychological impact and the gaining of some autonomy, the benefits of locomotion include improvement of contractures, prevention of deep venous thrombosis and oedema and amelioration of spasticity [31]. Standing up in combination with gluteal muscle training (gluteal pads effect) protects patients from decubitus lesions, especially in the buttock [32]. Continuous low frequency stimulation of the implanted nerves outside periods of training may be advantageous for the reduction of spasticity [33] and the regulation of bone density [34,35]. Nerve stimulation has been reported in the treatment of arthritis of the legs [36] but also in vivo studies involving animal models have revealed that electric stimulation of wound healing processes results in more collagen deposition [37], enhanced angiogenesis [38], greater wound tensile strength [39] and a faster wound contraction rate [40]. In addition to these direct cellular actions, electrical stimulation has been shown to improve tissue perfusion and reduce oedema formation that results in a significant increase in transcutaneous oxygen pressures [41]. Therefore, the LION procedure to the pelvic nerves is potentially useful in the rehabilitation of people with spinal cord injuries by reducing the risks of complications.

The LION procedure to the pelvic somatic nerves has been further reported for treating urinary dysfunctions and improving locomotion in multiple sclerosis patients [42].

5. Future Visions in Neuropelveology: The "in-Body-ENS"

The development of new technologies to assist paraplegics with their common problems associated with inertia when confined to a wheelchair may find revolutionary applications in preventive medicine and even in the world of space missions in the future. The LION procedure enables a continuous and passive electrical nerve stimulation (ENS) without the need for an external stimulation system, while the neuroprothesis is located within the body: the in-Body-ENS. This capability of continuous in-body electrical nerve stimulation may open the door to a whole new area of humanity in which implanted electronics may help the human body to a better performance and a longer life. The process of ageing, also called sarcopenia, is characterized by muscle atrophy along with a reduction in muscle tissue quality characterized by such factors as the replacement of muscle fibers with fat and the degeneration of the neuromuscular junction leading to a progressive loss of muscle function and frailty. Prevention of the aging process mainly focuses on the control and treatment of such a muscle atrophy. Several therapies have been proposed for preventing the aging process such as mental activity, muscle training and high-protein diet. A crucial factor in this is sustaining a high individual strength capacity: The elderly need strength training more and more as they grow older to stay mobile for their everyday activities. The crucial factor in maintaining strength capacity is an increase in muscle mass. As continuous passive stimulation of the pelvic somatic nerves enables muscle training and may reduce the process of muscle atrophy, the in-Body-ENS may become an option in the future for slowing down the aging process by preserving body muscle mass. This technique may be appropriate in elderly people who are not capable of active muscle training because of pain, motoric limitations or subcortical pathologies but also in people confined to bed for long periods of time (prophylaxis of decubitus).

As sympathetic trunks travel downward outside the spinal cord and first anastomose to the sacral plexus, which build the sciatic nerve, continuous low frequency/low energy sciatic nerve stimulation (passive in-body- (Functional Electrical Stimulation) FES) permits neuromodulation of the sympathetic nervous system of the lower extremities and of the bottom. Due to the fact that there is further evidence of the role of the sympathetic innervation of bone tissue and of its role in the regulation of bone remodeling in humans, sympathetic nerve stimulation obtained by stimulation of the pelvic somatic nerves might also open new techniques for the prevention of osteoporosis not only in people with SCI as demonstrated in our study but also in elderly people [34,35].

In addition to this, the in-body-ENS may also find revolutionary applications in the world of space missions. Space is a dangerous, unfriendly place that requires daily exercise to keep muscles and bones from deteriorating. Calf muscle biopsies before flight and after a six month mission on the International Space Station show that even when crew members did aerobic exercise for five hours a

week and resistance exercise three to six days per week, muscle volume and peak power both still deteriorated significantly. The in-body-ENS, by contrast, may allow muscle mass to be maintained even whilst the astronaut is at rest and provides an extremely effective and timesaving strength training program. During space flight, crew members also lose bone density; the calcium that is released ends up in the urine, which contributes to an increased calcium-stone forming potential. If the stone completely blocks the tube draining the kidney, the kidney could cease to function with catastrophic even life-threatening consequences for the astronaut. Due to the excruciating pain, affected astronauts could become incapacitated and missions may have to be aborted. Due to the fact that stimulation of pelvic sympathetic nerves may reduce this process of osteoporosis, as shown in our paraplegic study, in-Body-ENS may present a potential prophylactic for kidney stone formation in microgravity.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/10/3285/s1, Video S1: LION procedure in SCI.

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Review

Augmented Realities, Artificial Intelligence, and Machine Learning: Clinical Implications and How Technology Is Shaping the Future of Medicine

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Abstract: Technology has been integrated into every facet of human life, and whether it is completely advantageous remains unknown, but one thing is for sure; we are dependent on technology. Medical advances from the integration of artificial intelligence, machine learning, and augmented realities are widespread and have helped countless patients. Much of the advanced technology utilized by medical providers today has been borrowed and extrapolated from other industries. There remains no great collaboration between providers and engineers, which may be why medicine is only in its infancy of innovation with regards to advanced technologic integration. The purpose of this narrative review is to highlight the different technologies currently being utilized in a variety of medical specialties. Furthermore, we hope that by bringing attention to one shortcoming of the medical community, we may inspire future innovators to seek collaboration outside of the purely medical community for the betterment of all patients seeking care.

Keywords: surgery; artificial intelligence; machine learning; augmented reality

1. The Future of Medicine

In nearly all aspects of healthcare, virtual reality (VR), augmented reality (AR), artificial intelligence (AI), and machine learning (ML) are becoming more commonplace. Although this technology impacts all healthcare disciplines, its significance is paramount for surgical disciplines. The decision to undergo surgery, whether elective or emergent, causes intense emotion. Patients place immense trust in their surgeon, essentially placing their own life in another's hands. As surgeons, operating on patients should never be taken for granted and we should continue to seek improvements and ways to provide safer care.

An important aspect to recognize is the huge mountain to climb in actually implementing safer care for patients. This safer care comes with the evolution of newer surgical techniques and technology. This evolution is paralleled in all other industries in the world due to the fast advancement of technology

and AI. The evolution, specifically in healthcare, is much easier said than done. A massive learning curve presents that requires most current and future physicians to understand, implement, and analyze the results of this technology. What does that mean for physicians? The presence of specialized training for these new technologies must emerge quickly in order for the healthcare field to keep up with the growth of data available. Providing patients with more effective and safer practices is a consequence of this.

Change in surgery is fear-provoking; it is unknown and unpredictable. When laparoscopy was first introduced, it was thought to be a technological "trend" that would not survive the test of time. Now laparoscopy is considered the safer method whenever feasible for patients. Similarly, robotics is under scrutiny. However, all would agree, including critics, that the robotic surgical console provides surgeons with a level of technical ergonomics (7 degrees of freedom) that is absent from conventional laparoscopy [1]. Other factors are also greatly enhanced by robotic surgery, such as precision, flexibility of movement, and completion time. These improvements exist in robotics because of the advancement of different technologies including AR and AI.

2. Virtual and Augmented Reality in Medicine

VR consists of creating a simulation of a given scenario, as opposed to the alteration of an actual reality. Daily, this can be used in video games, design planning, and even simulated roller coaster rides. In healthcare, VR could include a cadaver to help learn anatomical structures and any preoperative imaging to help plan a procedure. VR training curriculums were created in order to allow both training and practicing surgeons to a safer operating room (OR) experience for their patients [2]. VR can also be incorporated into a surgeon's preoperative planning, utilized in unison with AI algorithms, to help virtually map a procedure [3]. VR is not limited to the OR; VR is being incorporated into occupational therapy to help stroke patients recover [4]. VR-based rehab is a proven tool that creates specific scenarios for patients, allowing them to have targeted treatments for their particular recovery level and deficits [4].

From the ever-growing increase in medical complexity, there was born a need for technology to go beyond mere simulated reality. Augmented reality (AR) was the answer to this problem. With AR there is no created scenario; instead, an actual event is being altered in real time, which has significantly enhanced robotic surgery. AR can work in parallel with a telemanipulation system in order to optimize the visual field of the operating surgeon. AR is currently being utilized to overlay key anatomic landmarks during live surgery to optimize patient safety [5]. For example, the preoperative imaging studies of a patient can be superimposed on to the surgical field and highlight structures using markers. Figure 1 shows how AR was used to overlay a preoperative CT image in an extremely accurate fashion on a patient's lower leg. Specifically, the HoloLens was used.

This technology allows the surgeon to have increased accuracy during the operation. Targeted guided surgery (TGS) involves a planned approach to a given procedure based on preoperative images. Once the surgery has begun, TGS implements real-time guidance imagery, using AR, that is shown on the endoscope using the predetermined plan [6]. In robotic surgery, the operator has a lack of tactile feedback. AR can partially fill this gap in feedback by enhancing the visual field of the surgeon. For example, the use of AR in real time can help the surgeon visualize how much cancerous tissue remains in the area of interest [7]. The application of AR in robotic surgery goes beyond detecting cancerous tissue, as seen above, and will continue to advance in order to provide the operator with an optimal visual field. The advances made in VR and AR have allowed for even more complex tasks to be handled by machines. Both technologies are currently used by telemanipulation systems in minimally invasive surgeries. Patient risk of post procedure complications has been reduced with the use of these visual technologies and robotic surgery. One surgeon performed robotic-assisted laparoscopic radical prostatectomy (RALP) on 200 patients over the course of 5 years. Over time, the necessity for blood transfusions and the presence of major complications were recorded in response to the procedure and were shown to be significantly less, and sometimes close to 0%, in patients [8]. These results can

provide a great vision into the potential future reduction in major complications in procedures for patients. Figure 1 provides a simple demonstration of the use of AR in surgery through the use of the HoloLens [9].

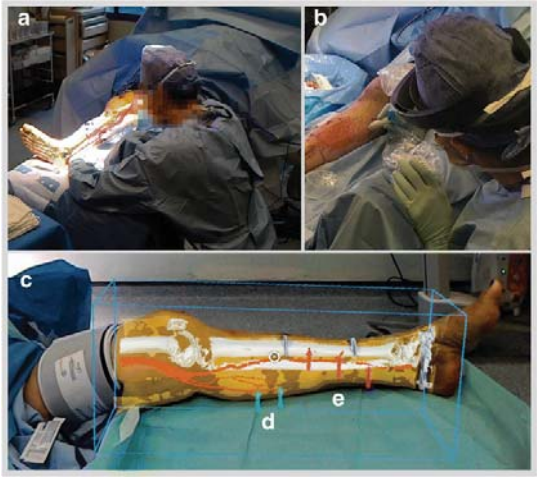

Figure 1. Use of HoloLens augmented reality (AR) goggles during operation in order to increase the accuracy of incision during a lower limb procedure. (**a**): remote view of AR through HoloLens. (**b**): Confirmation of perforator vein location. (**c**): Bound box overlay with (**d**) arrows pointing at medial sural veins and (**e**) arrows pointing at posterior tibial perforators.

3. Artificial Intelligence, Machine Learning, and Deep Learning

With the ever-growing supply of healthcare data, AI algorithms have aided in data organization, synthesis, and analysis [10]. Tasks that would take hundreds of person-hours to complete can be done almost instantaneously by machines with minimal deficiencies, mistakes, or bias. AI has likely had the most profound impact in healthcare by revolutionizing the electronic health record (EHR). AI is now able to expand differential diagnoses, recognize early warning signs of patient morbidity or mortality, and identify abnormalities in imaging studies or images [11,12]. Once an algorithm has recognized a pathologic condition through training, newly generated images based on a cache of previously learned images are applied to educating and testing [9]. AI is utilized to enhance learning for trainees and medical students [12]. This enhancement comes from providing more "realistic" OR situations and even creates previously unseen imaging for the students to assess. AI can also remove the risk of a student making a mistake in their first surgical experience by preparing them with real-time OR situations using AI (in a combination of VR).

Under the umbrella of AI exists machine learning (ML), which consists of teaching a given dataset as a curriculum to a machine. With that dataset programmed into the machine's neural network, new tasks can then be completed through the integration of the learned system into a new task [13]. The new task is first separated into its component parts and then the learned algorithm is applied as a linear regression until each individual component is solved. This differs from deep learning (DL), which is considered a sub-category of ML. Within DL, a computerized neural network is taught multiple datasets and a layered regression model is applied to a given task using these multiple datasets. To help imagine the regression model created by DL, think of the normal linear regression model, $y = mx + b$. There is only one variable considered here. Adding one or two or even three more variables would still be fairly simple. However, imagine a layered regression model including thousands if not hundreds of thousands of variables. This makes the DL neural network a very complex but useful tool. The standalone difference between ML and DL is that with DL,

the machine completes a complex decision-making algorithm and there is not a traceable path as to how the machine reached its conclusion [14]. For example, deep learning is needed for complex tasks such as a fully autonomous surgery. However, in order to have a fully autonomous surgery, normal machine learning algorithms are needed in unison with deep learning algorithms to function efficiently. Figure 2 below provides simple definitions for the different types of AI and also compares the processing steps and types of learning used to teach the ML algorithms. [15].

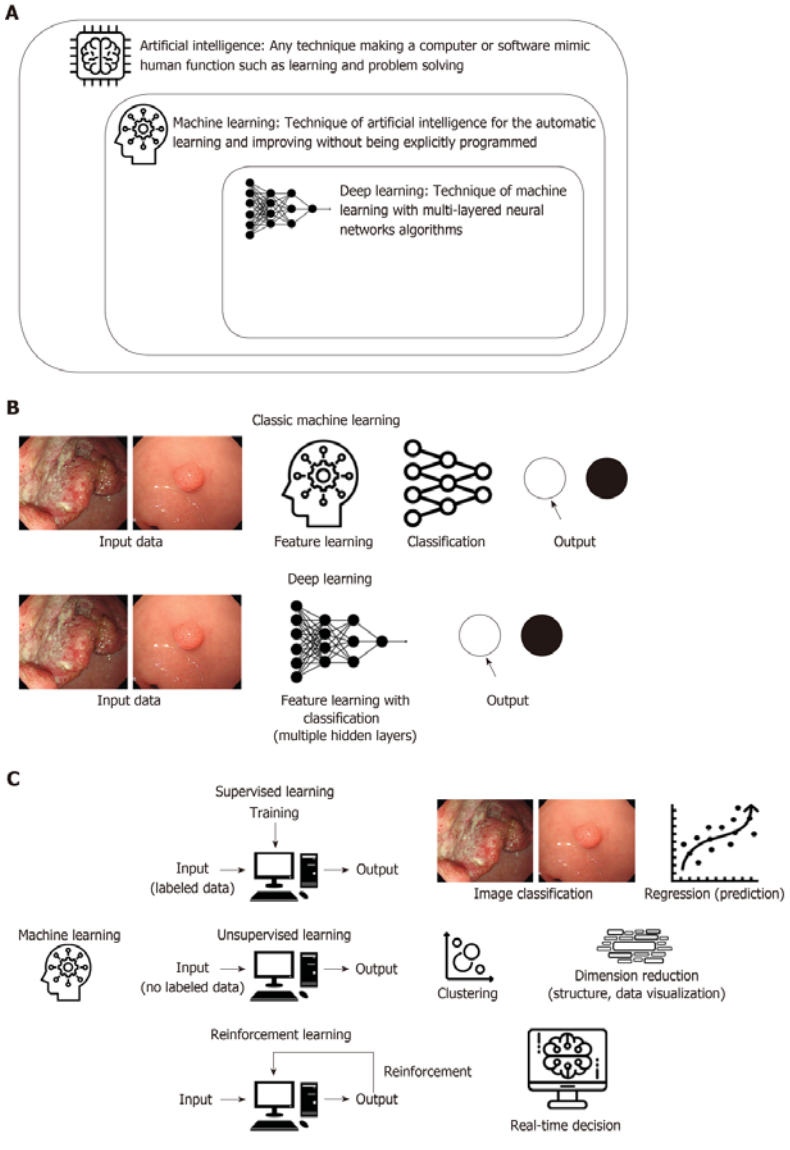

Figure 2. Representation of the processing methods of different types of artificial intelligence (AI). (**A**): Defining AI, ML and DL. (**B**): Difference in how ML and DL algorithms process information (**C**): Demonstrating the different types of learning.

4. Current Limitations of Artificial Intelligence in Surgery

Unfortunately, despite these newly developed neural networks allowing machines to complete complex tasks, the environments in which they function are static. When any change is introduced into the system outside of what has been learned, the neural network is not efficient at adapting. There are currently too many unknowns and potential changes that occur during surgery that it would not be safe nor effective to have a completely automated surgery.

To combat this issue, outlier detection algorithms are used in order to recognize an unknown or a problem that the algorithm cannot accomplish. That unknown is then taught to the algorithm so that the next time it is seen, the algorithm knows how to react. This process is crucial to reach a fully autonomous surgery algorithm. The algorithm must go through many surgical scenarios over and over again in order to constantly decrease the number of outliers. Unfortunately, there will never be a way to eliminate all the outliers and the algorithm will always have to be slightly altered in order to navigate challenges.

Additionally, there are numerous shortcomings with the hardware (physical pieces) of the current neural networks. However, even if the right hardware existed, there currently are too many restrictions on gathering patient data to allow the neural networks to properly learn. The ability of a neural network to learn is largely dependent on the amount of data points the system is given. In other areas of neural networking, like autonomous vehicles, datasets are widely available and easily gathered. The issue in medicine stems from the patient–physician relationship. Large datasets have not yet been created out of concern for breach of confidentiality, which exists between a single patient and provider [16]. In order for us to move towards autonomous surgery, we need our robotic surgical algorithms to first be able to learn. This requires access to a vast amount of real patient data that would allow the algorithm to have enough surgical information to implement certain techniques (after series of training and testing). In simple terms, the more access to patient data, imaging, real-time OR data, and even virtual OR data we have, the more algorithms can be taught. Without easy access to this data, the algorithm will be restricted in its ability to perform more complex tasks in healthcare.

5. Where We Are

We are not far from the first automated procedure. Already in orthopedics, robotic surgical systems are being used to cut bone with unparalleled precision [17]. Additionally, automated machines have proven to effectively suture as well as, or better than, surgeons with up to 5 years of training [13]. Fully autonomous procedures can be done today on fixed anatomical structures such as the eye and bone. However, the challenge comes when attempting a soft tissue surgery with constant moving structures. A bone is set in place and will experience very little movement during a procedure. On the other hand, the small intestines can be easily manipulated and could change position which makes the use of autonomous surgery tougher. Even if this position change is 2 mm, this could drastically jeopardize the task execution by the machine. In these cases, markers may need to be implemented on the soft tissue structures in order for the algorithm and machine to constantly track the structure(s).

Cost is the ongoing issue facing healthcare facilities in implementing any technological advancement with regard to automated procedures. Challenges surgeons have faced for many years such as fatigue, burnout, and tremor can all be decreased with this advancement, which would be beneficial for the healthcare industry. Automation will allow surgeons to do what they are best at with greater confidence, while making the best decision for the care of the patient.

Another rate-limiting step for automated surgical procedures is the regulation placed on protected health information, rightfully so. We must find a way to overcome this barrier and begin safe, confidential data sharing so that machines can begin to learn. Although it may seem far-fetched and unattainable, we must remember how laparoscopy was first viewed and how it has now become a staple of our surgical treatments. Google, Intuitive, Microsoft, Storz, and Olympus are some companies that could work towards bridging this gap of engineering and healthcare in order to safely and effectively break another barrier to improve healthcare as we know it.

Engineers are not the only ones that need to benefit from technological advancements. VR and AR were not created to exist in a silo for engineers. This technology, with the right team and handling, can advance any and every industry. The major key in taking this step forward in healthcare is establishing this crucial relationship. In the engineering world, this technology already exists and flourishes with the right amount of accessible data. For this reason, healthcare professionals and engineers must work together towards a common goal. If the two disciplines can work together, the limits and obstacles can and will be surpassed and the patient, who is the number one priority, can receive the care they deserve consistently.

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Conflicts of Interest: Moawad is a speaker for Intuitive Surgical.

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