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Breast Cancer

A Multi-Disciplinary Approach from Imaging to Therapy

Edited by
Daniele Ugo Tari

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Editor

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Editor
Daniele Ugo Tari
Department of Breast Imaging
Caserta Local Health Authority
Caserta
Italy

Editorial Office
MDPI
St. Alban-Anlage 66
4052 Basel, Switzerland

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About the Editor

Daniele Ugo Tari

Dr. Daniele Tari, MD, is the Director of the Department of Breast Imaging at Caserta LHA, Italy. After his postgraduate studies in Radiology, he specialized in breast imaging under Prof. GM Giuseppetti's mentorship in Ancona, Italy.

His research focuses on breast imaging and diseases, oncology, and public health. As a member of the Italian College of Senologists and the Italian School of Senology, he contributed to developing Italian breast cancer management guidelines. Dr. Tari emphasizes specialized training in breast imaging and promotes a multimodality approach for comprehensive early diagnoses. With over 80 published papers in national and international journals and more than 470 citations, Dr. Tari's contributions earned recognition at the 2023 EUSOBI Scientific Meeting in Valencia. He serves as an academic editor for Plos One, guest editor for MDPI, and ad hoc reviewer for high-impact journals. Dr. Tari is also affiliated with prestigious organizations like EUSOBI, ESR, and SIRM.

Current Oncology

Editorial

Breast Cancer: A Multi-Disciplinary Approach from Imaging to Therapy

Daniele Ugo Tari

Department of Breast Imaging, Caserta Local Health Authority, District 12 "Palazzo della Salute", 81100 Caserta, Italy; daniele.tari@aslcaserta.it

1. Introduction

Breast cancer (BC) is the most prevalent form of cancer among women worldwide, accounting for over 2 million diagnoses annually [1]. The impact of BC extends beyond individual patients, affecting the entire community through its implications in imaging, therapy, and its broader social, economic, and psychological consequences. In the face of ongoing challenges, a comprehensive approach is crucial to ensuring a high standard of care, particularly in the aftermath of the COVID-19 pandemic, which has brought lasting changes to medical practices [2]. The demand for personalized medicine has underscored the importance of a multidisciplinary strategy combining artificial intelligence and human expertise [3].

Early detection of breast cancer has significantly improved survival rates, enabling more effective and targeted treatments. However, a substantial gap persists when early diagnosis is not achieved, particularly among women with dense breasts or those at high risk [4,5]. Additionally, the incidence of male breast cancer has risen by 20–25% in recent decades [6]. Consequently, a multidisciplinary team and enhanced diagnostic-therapeutic pathways (DTCP) are essential for early detection and improved treatments [7].

The primary aim of this Special Issue has been to comprehensively present and discuss all aspects of breast cancer management, from imaging to therapy, addressing knowledge gaps, and exploring the psychological aspects of diagnosis and therapy. Out of nineteen submitted articles, eleven were accepted for publication after the peer-review process, resulting in a 58% acceptance rate. The published articles, briefly described in the following section, cover several topics and aspects significantly influencing breast cancer management.

2. Summary of Published Articles

In the first article of this Special Issue, Bhardwaj et al. (Contribution 1) assessed the efficacy and coordination of a multidisciplinary team (MDT) in the treatment of early-stage breast cancer using neoadjuvant chemotherapy (NAC). The retrospective study covered 94 patients and focused on the timing and outcomes of NAC, surgery, and radiation therapy. The study found significant downstaging of breast tumors in 91.4% of patients and axillary downstaging in 33% of patients. The median time from diagnosis to NAC was 37.5 days, from the end of NAC to surgery was 29 days, and from surgery to radiation therapy was 49.5 days. The study concluded that the MDT provided timely, coordinated, and consistent care, with the time to treatment aligning with national trends. It highlighted the effectiveness of multidisciplinary coordination in managing early-stage breast cancer, suggesting this as a model for other community cancer centers.

Muradali et al. (Contribution 2) synthesized the inconsistencies in the use of preoperative breast magnetic resonance imaging (MRI) following the diagnosis of breast cancer through mammography and/or ultrasound. After conducting a systematic review and meta-analysis, they recommended considering preoperative breast MRI on a case-by-case basis, especially for patients where additional information about disease extent could

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influence treatment decisions. The study substantiated that MRI improves recurrence rates, decreases reoperations, and increases detection of synchronous contralateral breast cancer. It emphasized the need for shared decision-making between care providers and patients, considering the benefits and risks of MRI as well as patient preferences. Specific recommendations are given for using MRI in various clinical scenarios, such as aiding surgical planning, identifying lesions in dense breasts, and determining the presence of muscle or chest wall invasion in certain tumors. The paper underlined the significance of MRI's high sensitivity and specificity in breast cancer diagnosis and staging, advocating for its selective use in enhancing treatment outcomes.

The study proposed by D'Angelo et al. (Contribution 3) is a retrospective investigation into the use of Magseed® (Endomagnetics, Cambridge, UK) for the preoperative localization of non-palpable breast lesions. It involved 45 patients who underwent breast-conserving surgery (BCS) between 2020 and 2022, with Magseed placement primarily under ultrasound guidance. The study boasted a high placement success rate of 97.8%, with only one instance of seed migration, and a 100% retrieval rate post-BCS. Notably, no patients required re-excision due to positive margins. The authors concluded that Magseed is an extremely effective technique for preoperative localization of non-palpable breast lesions, supporting its continued use despite acknowledging certain limitations and rare occurrences of seed migration. The study contributed valuable real-world data to the growing body of literature on Magseed, suggesting it as a viable alternative to traditional wire localization techniques.

Malainou et al. (Contribution 4) delved into the unique challenges and clinical implications of estrogen receptor-low-positive (ER-low-positive) breast cancer. This subtype, characterized by 1–9% ER expression, represents a small but significant portion of breast cancer cases, and its management is less clear-cut due to its nuanced response to standard therapies. The review consolidated various studies that discuss the prevalence, characteristics, and treatment responses of ER-low-positive BC. It highlighted that while these tumors share some similarities with ER-negative and triple-negative breast cancers, they present distinct clinical behaviors and outcomes. The review called for more research, especially randomized clinical trials, to better understand and manage this unique breast cancer subset, emphasizing the need for tailored treatment strategies and the potential of including these patients in clinical trials for more aggressive breast cancer types. This review is a call to action for the medical community to recognize the distinct nature of ER-low-positive BC and to seek more effective management strategies.

Oliveira et al. (Contribution 5) presented an observational analysis of 69 BRCA1/2 ovarian cancer survivors and their subsequent risk of developing breast cancer. The authors found that the median overall survival after ovarian cancer diagnosis was 8 years, with a significantly higher survival rate for BRCA2 patients compared to BRCA1 patients. About 13.2% of the participants developed breast cancer at a median age of 61 years. The study discussed the controversy of risk-reducing bilateral breast surgery in ovarian cancer survivors due to the associated high relapse rates and mortality of ovarian cancer. While the study acknowledged the potential benefits of surgical breast cancer risk management, it emphasized that such decisions should be tailored to individual patient characteristics and preferences, considering the balance between ovarian cancer mortality and breast cancer risk. This study contributes to the ongoing discourse on the management of cancer risks in BRCA1/2 ovarian cancer survivors, suggesting a multidisciplinary approach to decision-making.

Casella et al. (Contribution 6) presented a study exploring the clinical and aesthetic outcomes of immediate versus delayed symmetrization in skin-reducing mastectomy (SRM) for BC. The study involved a randomized observational cohort of 84 patients undergoing SRM, divided into two groups: immediate and delayed symmetrization. The study found that immediate symmetrization provided better aesthetic outcomes and higher patient satisfaction without significantly impacting the second stage of reconstruction. It highlighted immediate symmetrization as a safe and tolerable technique, improving the quality of life for patients. The research underscored the importance of considering immediate

symmetrization in reconstructive surgery planning for breast cancer patients to provide better immediate symmetry and overall satisfaction.

The next two papers evaluated the impact of radiotherapy (RT) on right and left BC, respectively. In particular, Guzeloz et al. (Contribution 7) explored the relationship between radiotherapy dose-volume parameters for right breast cancer and subsequent changes in liver function tests (LFTs), specifically alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). The retrospective analysis included 100 female patients treated across three centers, focusing on liver dosimetry during right breast or chest wall RT and its impact on LFTs pre- and post-RT. The results showed a median increase of up to 15% in AST, ALT, and GGT levels post-radiotherapy, with a significant correlation between higher liver doses and changes in LFTs. The study emphasized the importance of considering liver dose during radiotherapy planning and the necessity of regular LFT monitoring, advocating for a mean liver dose below 208 cGy to minimize potential liver damage. The study contributed to understanding the implications of RT on liver function and underscored the need for careful dose management to prevent liver toxicity, particularly in breast cancer patients with a longer life expectancy.

Antunac K et al. (Contribution 8) investigated the relationship between radiation doses to cardiac structures and the elevation of high-sensitivity cardiac troponin I (hscTnI) as an early marker of cardiotoxicity in patients receiving adjuvant radiotherapy for left-sided breast cancer along with anti-HER2 therapy. Including 61 patients, the study found that patients with an increase in hscTnI values post-radiotherapy had significantly higher mean radiation doses to the heart, left ventricle (LV), and left anterior descending artery (LAD) compared to those without an hscTnI increase. The findings suggested that higher radiation doses to these cardiac structures are associated with subclinical myocardial damage, as indicated by elevated hscTnI levels. The study underscored the importance of optimizing radiation therapy techniques to minimize cardiac exposure and the potential for early cardiac injury in breast cancer treatment.

The last three articles explored the psychological impact that a diagnosis or a potential diagnosis of breast cancer can have on women, assessing its effects on both an individual and familial level.

Oprean C et al. (Contribution 9) proposed a poignant case study of a 31-year-old woman grappling with metastatic HER2-positive breast cancer who chose to pursue pregnancy despite the known risks. The patient initially responded well to first-line treatment but vehemently refused ongoing oncological care due to her strong desire to conceive. This decision led to the cessation of treatment and the subsequent progression of her disease. Unfortunately, her pregnancy and life ended abruptly due to complications from her cancer. This case underscored the complex psychological aspects influencing patient decisions, including cognitive distortion, which led to prioritizing procreation over personal survival. The study emphasized the importance of multidisciplinary care and psychological support in managing such challenging cases, highlighting the urgent need for careful guidance and support for patients making life-altering decisions under the weight of severe illness.

Isselhard et al. (Contribution 10) provided a comprehensive evaluation of the psychological distress experienced by women who carry BRCA1/2 pathogenic variants but are not affected by cancer. This systematic review included 45 studies from 13 countries focusing on measures of distress, depression, and other psychological outcomes. Most studies observed an initial peak in distress following the disclosure of genetic test results, which tended to decline over subsequent months. While depression was frequently investigated, it was generally not found to be clinically significant among carriers. Quality of life appeared largely unaffected, though younger women showed some dissatisfaction with their role functioning. Body image was less frequently assessed, but available evidence suggested a decrease in body image satisfaction, especially after prophylactic mastectomy. The review called for future research to use standardized instruments to enhance comparability and provide more definitive conclusions about the psychological morbidity in this specific population.

Finally, Leite et al. (Contribution 11) delved into the experiences of violence endured by women from their intimate partners following mastectomy. Conducted with 16 Brazilian women who underwent breast cancer treatment, this qualitative study revealed alarming insights into the types of violence—psychological, physical, and sexual—that these women faced during their already vulnerable post-mastectomy period. The results highlighted that 50% of participants encountered psychological violence, 30% physical violence, and 20% sexual violence from their intimate partners. The research underscored the pressing need for healthcare professionals to be vigilant and proactive in identifying and addressing intimate partner violence among mastectomized women, recognizing it as a significant factor affecting their overall treatment and recovery. The study's conclusions advocated for a comprehensive, multidisciplinary approach to supporting these women, including the establishment of a protective and care network to combat the pervasive issue of violence.

3. Conclusions

The interdisciplinary nature of these discussions underscores the need for a holistic understanding and approach to breast cancer, emphasizing the importance of collaborative efforts in advancing knowledge and improving patient outcomes.

In particular, it would be desirable for scientific research to systematically compare practical experiences with extant literature, with the objective of providing empirically grounded guidance for clinical practice and meticulously embodying the principles of evidence-based medicine. Such a rigorous approach holds the potential to substantially contribute to the establishment of uniformity across diverse socio-economic contexts.

In conclusion, the imperative for further in-depth research and development remains crucial. It is vital to thoroughly understand and address the management of breast cancer diagnosis and treatment, facing new challenges with steadfast commitment and dedication.

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1. Bhardwaj, P.V.; Mason, H.; Kaufman, S.A.; Visintainer, P.; Makari-Judson, G. Outcomes of a Multidisciplinary Team in the Management of Patients with Early-Stage Breast Cancer Undergoing Neoadjuvant Chemotherapy at a Community Cancer Center. *Curr. Oncol.* **2023**, *30*, 4861–4870. https://doi.org/10.3390/curroncol30050366.
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Article

Outcomes of a Multidisciplinary Team in the Management of Patients with Early-Stage Breast Cancer Undergoing Neoadjuvant Chemotherapy at a Community Cancer Center

Prarthna V. Bhardwaj [1,*], Holly Mason [2], Seth A. Kaufman [3], Paul Visintainer [4] and Grace Makari-Judson [1]

[1] Division of Hematology—Oncology, University of Massachusetts Chan Medical School—Baystate, 759 Chestnut Street, Springfield, MA 01199 , USA
[2] Breast Surgery Section, University of Massachusetts Chan Medical School—Baystate, 759 Chestnut Street, Springfield, MA 01199, USA
[3] Division of Radiation Oncology, University of Massachusetts Chan Medical School—Baystate, 759 Chestnut Street, Springfield, MA 01199, USA
[4] Institute for Healthcare Delivery and Population Science, University of Massachusetts Chan Medical—Baystate, 759 Chestnut Street, Springfield, MA 01199, USA
* Correspondence: prarthna.bhardwaj@baystatehealth.org

Abstract: *Background:* The utilization of neoadjuvant chemotherapy (NAC) remains highly variable in clinical practice. The implementation of NAC requires coordination of handoffs between a multidisciplinary team (MDT). This study aims to assess the outcomes of an MDT in the management of early-stage breast cancer patients undergoing neoadjuvant chemotherapy at a community cancer center. *Methods:* We conducted a retrospective case series on patients receiving NAC for early-stage operable or locally advanced breast cancer coordinated by an MDT. Outcomes of interest included the rate of downstaging of cancer in the breast and axilla, time from biopsy to NAC, time from completion of NAC to surgery, and time from surgery to radiation therapy (RT). *Results:* Ninety-four patients underwent NAC; 84% were White and mean age was 56.5 yrs. Of them, 87 (92.5%) had clinical stage II or III cancer, and 43 (45.8%) had positive lymph nodes. Thirty-nine patients (42.9%) were triple negative, 28 (30.8%) were human epidermal growth factor receptor (HER-2)+, and 24 (26.2%) were estrogen receptor (ER) +HER-2−. Of 91 patients, 23 (25.3%) achieved pCR; 84 patients (91.4%) had downstaging of the breast tumor, and 30 (33%) had axillary downstaging. The median time from diagnosis to NAC was 37.5 days, the time from completion of NAC to surgery was 29 days, and the time from surgery to RT was 49.5 days. *Conclusions:* Our MDT provided timely, coordinated, and consistent care for patients with early-stage breast cancer undergoing NAC as evidenced by time to treatment outcomes consistent with recommended national trends.

Keywords: neoadjuvant chemotherapy; breast cancer; multidisciplinary team; care pathway; breast cancer therapy; breast surgery; breast radiation therapy

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1. Introduction

Modern breast cancer management has become increasingly complex and specialized over the years. A multidisciplinary approach to cancer care that brings together all pertinent disciplines to discuss optimal care is not only attractive but also promoted in cancer care guidelines [1]. Neoadjuvant chemotherapy (NAC) in breast cancer has historically been reserved for patients with large, inoperable tumors or inflammatory breast cancer, but is now being considered for women with operable disease as well. Larger clinical trials such as EORTC 10902 and NSABP B-18 have shown no differences between the same systemic therapy given pre- or post-surgery on disease-free survival (DFS) and overall survival (OS) [2–4]. However, the purpose of administering chemotherapy prior to surgery is to downstage the tumor and provide information regarding treatment response. Downstaging

the tumor may allow less extensive surgery on the breast and axilla, enabling patients to undergo breast conservation surgery instead of mastectomy, improve cosmetic outcomes, and reduce postoperative complications such as lymphedema [5,6]. Several randomized trials have shown that the frequency of mastectomies was decreased using NAC as opposed to adjuvant systemic treatment [2,7].

NAC can also eliminate axillary nodal metastases [7]. While sentinel lymph node biopsy (SLNB) is widely accepted post-NAC for patients who are clinically node-negative at presentation [8], the management of the axilla in patients who present with nodal metastases and appear to downstage with NAC remains controversial. Mamtani et al. determined the ability to avoid axillary lymph node dissections at the time of surgery in nearly 50% of patients with node-positive disease after receiving NAC [6].

NAC is also now being used to tailor adjuvant therapies for patients with human epidermal growth factor receptor (HER-2) positive and triple-negative breast cancers (TNBC) based on the presence or absence of minimal residual invasive disease in the breast or lymph nodes [9,10]. Early response after two to three cycles of NAC is thought to be a predictor of pathologic complete response (pCR) and may therefore serve as a predictor for long-term outcome [11]. Studies have also shown that the rate of pCR in patients with TNBC receiving NAC is significantly higher than that of non-TNBC patients [12,13].

Although there is common consensus on the patient subgroups most likely to benefit from NAC in breast cancer [14,15], its utilization in clinical practice remains highly variable. Candidacy for receiving NAC is carefully determined based on discussions between breast surgeons, medical oncologists, radiation oncologists, pathologists, and radiologists. Optimized care of breast cancer patients undergoing NAC requires coordination within the multidisciplinary care team (MDT) to streamline care through multiple handoffs between specialties to minimize unnecessary delays and provide consistent, continuous, coordinated, and improved care to patients with early-stage breast cancer. MDT and the collegial discussion of patient cases offer the benefits of an optimal approach to therapy in a simple and practical way. In most cases, patients feel more comfortable knowing that their situation has been evaluated and discussed by different health care professionals and the teams caring for them are communicating effectively.

While most of the data regarding patterns of NAC use in early-stage operable breast cancer are available from larger clinical trials and academic institutions, there is a paucity of real-life data describing the contemporary use of NAC in community cancer centers and the feasibility as well as outcomes of the MDT. Our study aims to evaluate the process of this MDT at our institution in the management of early-stage breast cancer patients undergoing neoadjuvant chemotherapy.

2. Methods

This was a retrospective case-series conducted at Baystate Medical Center, a 715-bed academic teaching hospital in Western Massachusetts. We included patients seen at our cancer center between October 2018 and October 2020. All patients diagnosed with early-stage operable and locally advanced breast cancer who have undergone NAC with intent for surgical resection post-treatment at our institution were included in this study. Patients with metastatic breast cancer at the time of diagnosis were excluded. Patients who underwent surgery or radiation therapy at a different facility were also excluded.

2.1. Outcomes

Outcomes included the proportion of pathologic complete response, proportion of downstaging of cancer in the breast, proportion of downstaging in the axilla, proportion of clinical trial enrollment, quality measures including timeliness of referral back to the breast surgeon during NAC, referral back to radiation oncologist, time from biopsy to NAC, time from completion of NAC to surgery, and time from surgery to radiation therapy (RT). Evaluation of our MDT was based on our quality measures or time to treatment outcomes in comparison with national standards, which is the focus of our study.

2.2. Data Collection

The total number of patients diagnosed with Stage I–III breast cancer during the study period presenting to our cancer center was obtained from our breast cancer tumor registry, which tracks all our early-stage breast cancer patients. The patients receiving NAC were obtained from our NAC registry maintained by a breast cancer intake coordinator, a unique list in our password-protected electronic health record (EHR) established for internal quality improvement purposes only.

Patient and tumor characteristics, management aspects, and outcomes measures were obtained from the EHR, Cerner-powered CIS at our institution. These data were entered into Research Electronic Data Capture (REDCap) [16]. A single author entering all the pertinent patient data ensured uniformity in data collection.

For pCR to be designated in this study, there must have been no histologic evidence of invasive cancer, either in the breast or axillary lymph nodes following definitive surgery. The presence of ductal carcinoma in-situ (DCIS) was disregarded, given that this was not thought to affect the systemic risk of recurrence [17].

We defined downstaging as decreasing the size, extent of metastases, and/or lymph node involvement of a tumor using anti-cancer therapy.

2.3. Analysis

As a case series, data analyses were limited to descriptive statistics. No hypothesis testing was conducted. We utilized descriptive statistics, including means, median, and standard deviations (SD) for continuous variables and counts and proportions for categorical variables to summarize patients' demographic and clinical characteristics.

2.4. MDT

To place MDT in context, we have summarized our conceptualization and process of modern MDT-driven care as available at our cancer center in Figure 1. Baystate Health Breast Network involves breast surgeons, medical oncologists, radiation oncologists, pathologists and radiologists who meet quarterly and are responsible for creating guidelines to standardize various breast cancer related practices across the institution. Through this endeavor, guidelines have been created for candidacy for neoadjuvant systemic therapy as described in Supplementary Table S1. All patients who undergo a breast biopsy at our institution are automatically referred to a breast surgeon, who will then determine the timing of referral to a medical oncologist based on their candidacy for neoadjuvant therapy versus upfront surgery. All potential neoadjuvant therapy candidates based on available guidelines are presented at our weekly virtual tumor board conference for a team consensus on best approach to treatment. Once it has been determined that a patient will initiate NAC, they are referred to medical oncology. A breast cancer clinical coordinator oversees the care process during the pre-operative period to ensure that patients are appropriately referred for their labs and scans, and also referred back to the surgeons more than midway through NAC to avoid delays in surgical planning. All patients who are referred to medical oncology are initially referred to radiation oncology as well. Patients are also provided with a handout with all the steps and appointments delineated in their handout at the time of their initial medical oncology visit. Samples of this handout are available in the Supplement.

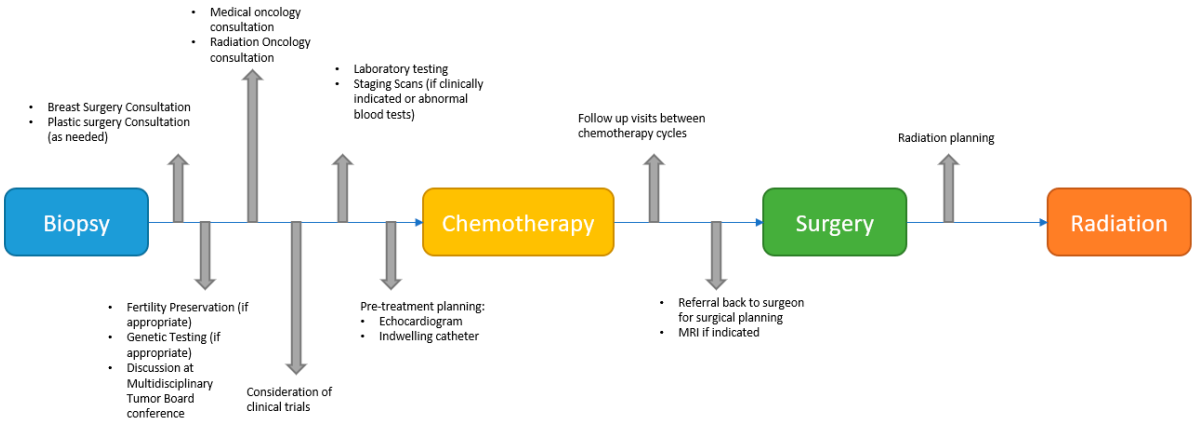

Figure 1. Clinical pathway involving multidisciplinary team-driven care for the management of patients undergoing neoadjuvant chemotherapy for early-stage breast cancer.

3. Results

A total of 54 patients were eventually diagnosed with TNBC stage II, or III between October 2018 and October 2020. Of these patients, 39 (68.4%) were referred to receive NAC. Forty patients were diagnosed with HER-2 positive breast cancer stage II, or III during the study period, of which 28 (66.6%) received NAC. Seventy-eight patients were diagnosed with ER/PR positive HER-2 negative breast cancer stage II or III, of which 24 (30.7%) underwent NAC. This study did not assess the number of patients who may have met the criteria for NAC and were not referred for NAC.

3.1. Patient and Tumor Characteristics

A total of 94 patients underwent NAC. Of these, 84% were White, 12.8% were Black and 3.2% were Asian. This demographic was reflective of all patients presenting to our cancer center with a new diagnosis of breast cancer as available from our breast cancer registry. The mean age was 56.5 years. Of these patients, 87 (92.5%) had clinical stage II or III cancer, and 43 (45.8%) had positive lymph nodes. Thirty-nine patients (42.9%) were triple negative, 18 (19.8%) were ER positive and HER-2 positive, 10 (11.0%) were ER negative and HER-2 positive and 24 (26.2%) were ER positive and HER-2 negative. The most common indications for NAC were to downstage the axilla (42.6%) and for HER-2 tailoring of treatment (25.5%). Several patients had one or more of these indications, as described in Table 1.

Table 1. Patient characteristics.

Patient Characteristics	Overall	Pathological Complete Response
N (%)	94 (100)	23 (24.5)
Age (mean)	56.5 (12.8)	54.4 (12.1)
Race		
White	79 (84.0)	19 (82.6)
Black	12 (12.8)	2 (8.7)
Asian	3 (3.2)	2 (8.7)
Ethnicity		
Hispanic	11 (11.7)	1 (4.3)
Non-Hispanic	82 (88.3)	21 (95.7)
ECOG Performance Status		
0	78 (83.0)	20 (87.0)
1	12 (12.8)	3 (13.0)
2	1 (1.1)	0 (0.0)
Not documented	3 (3.2)	0 (0.0)

Table 1. *Cont.*

Patient Characteristics	Overall	Pathological Complete Response
Prior Breast Cancer (DCIS or invasive)	11 (12.0)	2 (8.7)
Clinical Stage		
I	5 (5.3)	0 (0.0)
II	66 (70.2)	15 (65.2)
III	21 (22.3)	8 (34.8)
Clinical Tumor Stage		
TI	10 (10.6)	1 (4.3)
T2	60 (63.8)	12 (52.2)
T3	19 (20.2)	9 (39.1)
T4	3 (3.2)	1 (4.3)
Tx	2 (2.1)	0 (0.0)
Clinical Lymph Node Stage		
N0	51 (54.3)	12 (52.1)
N1	38 (40.4)	9 (39.1)
N2	4 (4.3)	1 (4.3)
N3	1 (1.1)	1 (4.3)
ER Receptor Status		
Positive	44 (46.8)	4 (17.4)
Negative	50 (53.2)	19 (82.6)
PR Receptor Status		
Positive	36 (38.3)	2 (8.7)
Negative	58 (61.7)	19 (82.6)
HER-2 Neu Receptor Status		
Positive	28 (29.8)	10 (43.5)
Negative	66 (70.2)	13 (56.5)
Chemotherapy Regimen		
DDAC/T	32 (34.0)	4 (17.4)
DDAC/TC	15 (16.0)	6 (26.1)
TC	9 (9.6)	0 (0.0)
TCHP	22 (23.4)	10 (43.5)
THP	3 (3.2)	1 (4.3)
Time from diagnosis (1st breast biopsy) to NAC (in days)—median (min, max)	37.5 (3, 150) *	41.0 (21, 98)
Indication for NAC		
Less Extensive Surgery	6 (6.4)	3 (13.0)
HER2 tailoring of treatment	24 (25.5)	9 (39.1)
Inoperable to Operable	12 (12.8)	2 (8.7)
Operable Mastectomy to BCS	12 (12.8)	1 (4.3)
Time for genetics	21 (22.3)	6 (26.1)
Time for Surgical Planning	12 (12.8)	3 (13.0)
Lymph Node positive to negative	40 (42.6)	12 (52.2)
Time from completion of NAC to surgery (in days)—median (min, max)	29.0 (9, 118) *	30.0 (13, 48)

Abbreviations: DCIS: Ductal Carcinoma In Situ, DDAC/T: Dose-dense doxorubicin and cyclophosphamide to paclitaxel, DDAC/TC: Dose-dense doxorubicin and cyclophosphamide to paclitaxel and carboplatin, TC: docetaxel and cyclophosphamide, TCHP: docetaxel, carboplatin, trastuzumab and pertuzumab, THP: paclitaxel, trastuzumab and pertuzumab, NAC: Neoadjuvant chemotherapy, ER: Estrogen receptor, HER2: Human Epidermal Growth Factor Receptor 2. * One patient did not follow through with the treatment plan regularly, resulting in delays in treatment.

3.2. Pathological Complete Response

Of the 91 patients who underwent NAC with complete data, 23 (25.3%) achieved a pathologic complete response (pCR). Of these 23 patients, 12 (52.2%) had ER-negative, HER-2-low or negative cancer, 7 (30.4%) had ER-negative HER-2-positive cancer, 3 (13.0%)

had ER-positive HER-2-positive cancer, and 1 (4%) had ER-positive HER-2-negative cancer (Table 2).

Table 2. Pathological Complete Response by Tumor Type.

Tumor Type	Total	RCB 0 [pCR]	RCB I	RCB II	RCB III
N (%)	91 (100.0)	23 (25.3)	19 (20.9)	38 (41.8)	11 (12.1)
ER + HER2 +	18 (19.8)	3 (16.7)	1 (5.6)	12 (66.7)	2 (11.1)
ER + HER2 −	24 (26.4)	1 (4.2)	2 (8.3)	14 (58.3)	7 (29.2)
ER-HER2 +	10 (11.0)	7 (70.0)	3 (30.0)	0 (0.0)	0 (0.0)
ER-HER2 −	39 (42.9)	12 (30.8)	13 (33.3)	12 (30.8)	2 (51.3)

Abbreviations: ER: Estrogen receptor, HER2: Human Epidermal Growth Factor Receptor 2, RCB: Residual Cancer Burden, pCR: Pathologic complete response.

3.3. Other Outcomes

The median time from diagnosis of breast cancer to initiation of NAC was 37.5 days (ranging between 3 and 150 days). Eighty-five (91.4%) patients had downstaging of their breast tumor, and 31 (33%) had axillary downstaging with 53 (57.6%) patients undergoing a lumpectomy while 39 (41.9%) underwent a mastectomy and 22 (23.7%) patients went on to have bilateral mastectomy. A third of patients (33%) had downstaging of axilla based on final surgical pathology (Supplementary Table S2).

All patients followed back with their surgeons before completion of NAC. The median time from completion of NAC to definitive surgery was 29 days (ranging between 9 to 118 days). Of the 78 patients who received adjuvant radiation, all had a radiation oncology consultation before surgery. However, 48 (51.1%) patients returned to see their radiation oncologist before completion of NAC, of which 67.4% were lymph node positive. The median duration of radiation therapy was 33 days (ranging between 12 to 73 days). Five patients (6.4%) underwent radiation therapy for more than two weeks beyond the expected time of completion (i.e., 4–6 weeks based on standard vs. hypo-fractionated RT). The mean time from surgery to radiation therapy was 49.5 days (ranging from 9 to 173 days) (Table 3). Time to treatment outcomes in the context of our MDT have been illustrated in Figure 2.

Table 3. Quality Metrics to assess outcomes of multidisciplinary teams.

	Overall	Clinical Node Positive	Clinical Node Negative
N (%)	94 (100.0)	43 (45.7)	51 (54.3)
Follow up with surgeon prior to completion of NAC—Yes	92 (98.9)	42 (100.0)	50 (98.0)
Follow up with radiation oncology prior to completion of NAC—Yes	48 (51.1)	29 (67.4)	19 (37.3)
Enrollment in clinical trial—Yes	5 (21.7)	3 (21.4)	2 (22.2)
Time from surgery to RT (in days)—median (min, max)	49.5 (9, 173) N = 78	55 (9, 173) N = 43	48 (25, 140) N = 35
Time to complete RT (in days)—median (min, max)	33.0 (12, 73)	39.0 (12, 73)	29.0 (21, 52)
Duration of RT for more than 2 weeks beyond expected time—Yes	5 (6.4)	4 (9.3)	1 (2.9)

Abbreviations: NAC: Neoadjuvant chemotherapy, RT: Radiation therapy. One patient did not follow through with the treatment plan regularly, resulting in delays in treatment.

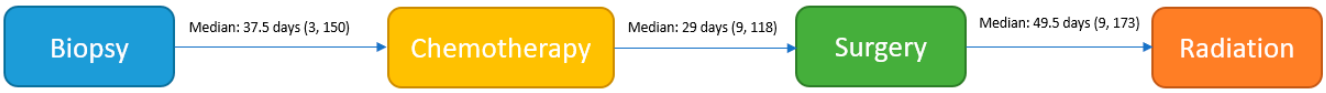

Figure 2. Time to treatment components including time from diagnosis to initiation of neoadjuvant chemotherapy (NAC), time from completion of NAC to surgery, time from surgery to radiation therapy. One patient did not follow through with appointments due to personal conflicts, reflecting the ranges in the median.

4. Discussion

In our study assessing the outcomes of an MDT in managing breast cancer, the median time from completion of NAC to surgery was less than a month. Various studies have established superior overall survival and 5-year recurrence-free survival in patients undergoing surgery within 8 weeks of completion of NAC. There has been a suggested increase in RCB class and a decline in pCR rates after a 4-week interval between chemotherapy and surgery, and worse overall survival after an 8-week interval [18–21]. This observation reinforces the importance of referring patients back to their surgeons in a timely fashion for surgical planning which was noted in our study. All patients saw radiation oncology at least once pre-operatively. Although not all patients were referred back to the radiation oncologist prior to completion of NAC, the mean time from surgery to initiation of radiation therapy was 7 weeks. It is worthy of note that a few patients required second surgeries, including re-excision of margins or complete axillary dissection based on pathology results that delayed the initiation of radiation therapy. Despite this, we were aligned with providing radiation therapy at an optimal recommended interval of within 8 weeks after surgery, which has been associated with better disease-free survival and overall survival [22,23]. The median time from diagnosis of cancer to initiation of NAC was less than 6 weeks. Time to treatment initiation is considered an important metric from a patient perspective, as delays provoke anxiety and are thought to influence long-term outcomes. This perception of longer wait times equating to poorer outcomes may be magnified by the role of mammograms whose prerogative is 'early detection saves lives'; conversely, delays are perceived to result in mortality. Various factors influence the time to start of NAC including additional testing, for e.g., MRI, staging studies, and fertility preservation as indicated. Prior studies have demonstrated no impact on long term patient outcomes so long as NAC is initiated within 8 weeks of diagnosis [24–26].

Overall pCR rates in our patients were noted to be lower than those demonstrated by larger clinical trials however similar or improved compared to other real-world studies [27–29]. Of the patients who achieved pCR, the majority were ER-negative and HER-2-negative, followed by HER-2-positive patients irrespective of ER status. Traditionally, pCR rates are highest in HER-2-positive patients [17]. pCR rates are likely influenced by multiple factors and the small sample size. While assessing treatment regimens used for patients with HER-2 positive disease in our study, a few patients did not receive dual HER-2-based therapies in the neoadjuvant setting. We hypothesize that variable physician prescribing trends during the study period could attribute to lower pCR rates in HER-2-positive patients and hence, the overall population. Despite lack of pCR, most of the patients had at least partial response in the breast and a third had axillary downstaging, resulting in a more conservative axillary approach surgically. Axillary pCR rates remain variable and are affected by age, molecular subtype, tumor grade and Ki-67 [30–32].

Coordinated care through an MDT has previously shown to improve receipt of treatment, adherence to treatment recommendations and overall survival, including in vulnerable cancer populations being treated at safety net hospitals [33–35]. It can level the playing field for patients from various socioeconomic backgrounds and thus, serve as a bridge to overcome disparities in access to care.

Our study had key limitations which include a smaller sample size, given this is a single-institution study. This study did not specifically evaluate how many patients were appropriately referred for neoadjuvant therapies as it was assumed that patients were

appropriately referred based on institutional guidelines as referenced in the Supplementary Materials. We did not collect data regarding omission of treatments in subsequent cycles or interruptions in chemotherapy cycles due to various factors, including age, co-morbidities and adverse effects which could have resulted in fewer cycles than intended, resulting in lower overall pCR rates. However, this study can serve as a model for how an MDT can be utilized in ensuring adherence to quality metrics, which can in turn improve long-term patient outcomes.

Although our small sample size did not allow for examining differences in patient subsets, using our standardized clinical pathway model for every new patient with a diagnosis of breast cancer requiring NAC allows high standards for all patients irrespective of race or ethnicity.

5. Conclusions

In our study, the multidisciplinary care process resulted in timely, coordinated, and consistent care for all patients with early-stage breast cancer undergoing NAC. All patients were referred back to the surgeon prior to completion of NAC for surgical planning. The median time to treatment initiation, time from completion of NAC to surgery and time from surgery to radiation were within recommended intervals for optimal long-term patient outcomes. NAC will likely be used in an increasing fashion as the indications expand, especially in smaller cancers that are triple negative and HER-2 positive. Hence, there is a need not only to advance systemic therapies, but also to create a streamlined process to optimize outcomes. To that effect, our multidisciplinary care pathway as described can serve as a model for growing community cancer centers to address disparities in care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/curroncol30050366/s1, Table S1: Indications for consideration of neoadjuvant systemic therapy; Table S2: Management after neoadjuvant chemotherapy.

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Informed Consent Statement: Informed consent was waived as there were no direct identifiers of individual patients for this retrospective chart review study.

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Current Oncology

MDPI

Guidelines

Preoperative Breast Magnetic Resonance Imaging: An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline

Derek Muradali [1,*], Glenn G. Fletcher [2], Erin Cordeiro [3], Samantha Fienberg [4], Ralph George [5], Supriya Kulkarni [1], Jean M. Seely [6], Rola Shaheen [7,8] and Andrea Eisen [9,*]

1 Department of Medical Imaging, University of Toronto, Toronto, ON M5T 1W7, Canada; supriya.kulkarni@uhn.ca
2 Program in Evidence-Based Care, Department of Oncology, McMaster University, Hamilton, ON L8S 4L8, Canada; gfletche@mcmaster.ca
3 Department of Surgery, University of Ottawa, Ottawa, ON K1N 6N5, Canada; ecordeiro@toh.ca
4 Ontario Health (Cancer Care Ontario), Toronto, ON M5G 2L3, Canada; samantha.fienberg@ontariohealth.ca
5 Department of Surgery, University of Toronto, Toronto, ON M5T 1P5, Canada; ralph.george@unityhealth.to
6 Department of Radiology, The Ottawa Hospital, University of Ottawa, Ottawa, ON K1N 6N5, Canada; jeseely@toh.ca
7 Department of Radiology, Queen's University, Kingston, ON K7L 3N6, Canada; rshaheen@prhc.on.ca
8 Diagnostic Imaging, Peterborough Regional Health Centre, Peterborough, ON K9J 7C6, Canada
9 Department of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada
* Correspondence: derek.muradali@unityhealth.to (D.M.); andrea.eisen@sunnybrook.ca (A.E.)

Abstract: Background: The use of preoperative breast magnetic resonance imaging (MRI) after the diagnosis of breast cancer by mammography and/or ultrasound is inconsistent. Methods: After conducting a systematic review and meta-analysis comparing preoperative breast MRI versus no MRI, we reconvened to prepare a clinical practice guideline on this topic. Results: Based on the evidence that MRI improved recurrence, decreased the rates of reoperations (re-excisions or conversion mastectomy), and increased detection of synchronous contralateral breast cancer, we recommend that preoperative breast MRI should be considered on a case-by-case basis in patients diagnosed with breast cancer for whom additional information about disease extent could influence treatment. Based on stronger evidence, preoperative breast MRI is recommended in patients diagnosed with invasive lobular carcinoma for whom additional information about disease extent could influence treatment. For both recommendations, the decision to proceed with MRI would be conditional on shared decision-making between care providers and the patient, taking into account the benefits and risks of MRI as well as patient preferences. Based on the opinion of the Working Group, preoperative breast MRI is also recommended in the following more specific situations: (a) to aid in surgical planning of breast conserving surgery in patients with suspected or known multicentric or multifocal disease; (b) to identify additional lesions in patients with dense breasts; (c) to determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumours or when invasion of the pectoralis major muscle or chest wall is suspected; (d) to aid in surgical planning for skin/nipple-sparing mastectomies, autologous reconstruction, oncoplastic surgery, and breast conserving surgery with suspected nipple/areolar involvement; and (e) in patients with familial/hereditary breast cancer but who have not had recent breast MRI as part of screening or diagnosis.

Keywords: breast cancer; magnetic resonance imaging; practice guideline

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1. Introduction

Suspected breast cancer based on clinical examination or screening mammography is generally confirmed by diagnostic mammography (with or without ultrasound) and biopsy. Surgery may be preceded by further advanced imaging of higher sensitivity or diagnostic utility, with contrast-enhanced breast magnetic resonance imaging (CE-MRI,

often referred to as MRI) being the most widely used to characterize the locoregional extent of breast cancer.

Breast MRI has a sensitivity for detecting cancer of greater than 90% and as high as 97% to 100% [1–3] in some studies of screening or for preoperative use after diagnosis. Studies published prior to 2000 had suggested poor sensitivity for ductal carcinoma in situ (DCIS); however, with improved equipment and radiologist expertise, this is no longer the case [4–6]. MRI specificity depends on study populations, technical methods, and criteria for interpretation. It is generally greater than 70%, and up to 97% has been reported [1]. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas provides standardized terminology and reporting to assist in interpretation and sets a benchmark for specificity in screening MRI at 85% to 90% [7].

The use of MRI in screening and surveillance is considered standard of care for individuals at higher risk of breast cancer due to genetic factors or previous radiation exposure for another cancer [8,9]. Some recent guidelines include personal history or dense breasts as high-risk factors warranting consideration of an MRI [10,11]. Cancer screening is dealt with in several other guidelines and was not included in the current work.

It has been established that MRI has higher sensitivity than mammography and ultrasound, as illustrated by its incorporation into high-risk screening; however, there is less consensus on whether the additional information provided by preoperative MRI subsequent to the cancer diagnosis improves patient outcomes. Use of breast MRI beyond screening is the topic of guidelines by the European Society of Breast Cancer Specialists (EUSOMA) [12], the European Society of Breast Imaging (EUSOBI) [13], and the Institut national d'excellence en santé et en services sociaux (INESSS; Quebec, Canada) [14], and a practice parameter by the American College of Radiology (ACR) [15]. Also relevant are the Canadian Association of Radiologists imaging guideline [16], which has a section on MRI, and the evidence review/medical policies by Blue Cross/Blue Shield [17]. General breast cancer guidelines such as those by the National Comprehensive Cancer Network (NCCN) [18] also have recommendations on MRI use; several of these have only a few points regarding MRI and may not be based on a review of the primary literature. It was determined that these guidelines either did not cover the most recent studies, had a different focus, or did not conduct a comprehensive review. We therefore conducted a systematic review and meta-analysis [19–21] comparing outcomes such as re-operation rates, recurrence, and survival with versus without preoperative breast MRI, followed by the development of recommendations as reported in this clinical practice guideline.

2. Materials and Methods

2.1. Background

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario), supported by the Ontario Ministry of Health. The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [22,23]. This process includes a systematic review, interpretation of the evidence, and draft recommendations by the Working Group; internal review by content and methodology experts; and external review by Ontario clinicians and other stakeholders. PEBC guideline recommendations are based on evidence of the desirable and undesirable effects of an intervention or the accuracy of a test and take into account the certainty of the evidence. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook* (https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/breast, accessed on 1 May 2023).

2.2. Guideline Objective

The primary goal was to make recommendations about whether preoperative breast magnetic resonance imaging (MRI) should be added to conventional imaging (mammog-

raphy and/or ultrasound) in patients with newly diagnosed breast cancer and to make recommendations about specific indications if evidence allowed.

2.3. Research Question

In patients with newly diagnosed breast cancer, does additional information on the extent of disease obtained by preoperative breast MRI after mammography and/or ultrasound (a) change the type or extent of surgery (breast conserving surgery (BCS), unilateral or bilateral mastectomy), the type or extent of radiation therapy, or the use of adjuvant therapy; or (b) improve patient outcomes such as recurrence, disease-free survival or event-free survival, distant metastasis-free survival, overall survival, rates of re-excision or re-operation, or quality of life?

2.4. Target Population

The target population is patients already diagnosed with breast cancer of any stage for whom additional information on disease location or extent in the breast obtained prior to surgery may influence staging, treatment, or prognosis. The guideline does not address patients diagnosed with breast cancer but without an identified cancerous lesion in the breast (occult breast cancer) or patients undergoing neoadjuvant therapy prior to surgery. Imaging for distant metastasis is the topic of a separate guideline [24].

2.5. Development Process

This guideline is based on a systematic review and meta-analysis originally completed in December 2021 [19]. The systematic review was revised to incorporate study updates until July 2022 and to include additional quality assessment using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to aid in developing the clinical practice recommendations [20]. An integrated version of the systematic review is also available [21].

The Working Group (the authors of this article) was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiology, surgery, medical oncology, and health research methodology.

2.6. Literature Search

Embase, MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched until 3 July 2019 and updated until 18 January 2021. A targeted search was conducted in July 2022 to identify any additional publications related to the included RCTs and studies identified as ongoing. Studies had to be comparative studies of MRI versus no MRI after a diagnosis of breast cancer and report rates of survival, recurrence, re-excision, reoperation, or mastectomy. One author (GGF) reviewed all studies, and co-authors were consulted in cases of uncertainty regarding inclusion.

Included were 8 randomized controlled trials (RCTs), 1 prospective cohort study, and 42 retrospective studies. The patient population was limited to those with an initial treatment plan of breast conserving surgery in 17 trials (6 RCTs). The retrospective studies included 8 with propensity-matched controls, 4 with historical or equivalent controls, 15 with multivariable/multivariate analysis of data from a single or small number of institutions, and 15 using cancer registry data and multivariable/multivariate analysis. A series of forest plots created using RevMan [25] provide graphical summaries to aid in the interpretation of the tabulated results.

Data was extracted from the included studies. Odds ratios (OR) or hazard ratios (HR) were expressed with a ratio of <1.0, indicating that the experimental group (MRI use) had a more favourable outcome than the control group. The exception to this was the case of synchronous contralateral breast cancer (CBC) detection (identified at the same time or sometimes defined as occurring within 6 months of the index cancer). Higher detection is considered a favourable outcome, but the convention is to report increased detection

with HR > 1.0. The risk of bias for randomized studies was assessed per outcome and per study using the Cochrane risk-of-bias (RoB) tool (revised version RoB2) for RCTs and ROBINS-I for non-RCTs, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [26]. The GRADE approach was used to facilitate recommendation development. The full GRADE evaluation, including risk of bias assessment, summary of findings tables, GRADE profiles, and standardized statements for each outcome, including levels of certainty, has been reported [20]. Both the original review [19] and update [20] should be consulted for further details; the review portions have been merged in a subsequent publication [21].

2.7. Recommendation Development and Review

The Working Group evaluated the systematic review and developed clinical practice recommendations. The document was then reviewed by a Patient- and Caregiver-Specific Consultation Group consisting of five people with personal experience with cancer (patients/survivors/caregivers) who participated as Patient Consultation Group members. The internal review consisted of reviews by an Expert Panel of eight content experts and by the PEBC Report Approval Panel, a three-person panel with methodology expertise. All participants approved of the document; comments were considered by the Working Group in revising the document.

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, three individuals with content expertise were identified and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline were contacted, and 41 provided feedback on the guideline recommendations through a brief online survey and additional comments. The Working Group considered all feedback in making final revisions.

3. Recommendations and Key Evidence

It has been established that breast MRI can provide additional information on lesion presence, size, location, and distribution; it is less certain in what circumstances this will lead to better patient outcomes. There are both potential benefits and harms to consider (see Table 1), and the relative importance will vary depending on patient and disease characteristics; technical considerations related to equipment and radiology team expertise; and system considerations such as cost, availability of equipment and staff, and wait lists for MRI and other procedures and consultations.

3.1. Recommendation 1

- Preoperative breast MRI **should be considered** on a case-by-case basis in patients diagnosed with breast cancer for whom additional information about disease extent could influence treatment. The ensuing decision of whether to conduct an MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.
- Stronger recommendations for specific situations are provided in Recommendations 2 and 3.

3.1.1. Qualifying Statements for Recommendation 1

- Benefits and harms (see Key Evidence and Table 1) may vary depending on patient and disease characteristics such as breast density, tumour size, tumour stage, number and distribution of tumours (multicentric or multifocal), subtype of cancer, type of surgery being considered or preferred, adjuvant treatment, and patient factors/comorbidities.
- System issues such as MRI availability may result in treatment delays that may modify the decision.
- "Treatment" in the recommendation includes surgery as well as radiation and systemic treatment.

- In patients with a strong preference for mastectomy or with contraindications to BCS, MRI is unlikely to change surgical planning in the ipsilateral breast. Breast MRI may still impact treatment if mammographically occult CBC is detected.
- Contrast-enhanced mammography (contrast-enhanced spectral mammography, contrast-enhanced digital mammography), diffusion-weighted imaging (DWI) MRI, magnetic resonance spectroscopy, or other advanced imaging techniques are known to provide additional information beyond that of conventional imaging and may be suitable instead of or in addition to CE-MRI. Potential adverse effects due to contrast agent and radiation exposure vary among these techniques, whereas many other potential benefits and harms in Table 1 would be relevant. These are mentioned briefly in the systematic review, but the evaluation was outside of scope. They are less widely available, and there is much less evidence regarding their effect on patient outcomes.

Table 1. Potential benefits and harms of preoperative MRI.

Factor	Potential Benefits	Potential Harms
High Sensitivity	• MRI is not impacted by breast density, which limits the sensitivity of mammography. • Higher cancer detection rates with MRI than mammography, with greater ability to detect occult cancer in the ipsilateral breast with multifocal and multicentric disease. • More accurate staging of the contralateral breast reduces the rate of breast cancer detected in follow-up. • Allows the detection of all cancerous lesions at the start so they can be treated at one time instead of having pre-existing cancers only detected on short-term follow-up; this can have cost benefits for patients and the health care system, reduce anxiety, and improve the quality of life of patients. • Confirmation of limited disease may allow for more conservative treatment such as partial breast irradiation (including in patients with previous radiotherapy) or the omission of systemic therapy. • May allow a longer interval between initial treatment and follow-up imaging. • Additional information from MRI reduces the frequency of reoperations to achieve clear margins and reduces the rate of unplanned (salvage) mastectomy subsequent to the initial BCS. This can have cost benefits for patients and the health care system, reduce surgical complications, reduce anxiety, and improve the quality of life of patients. • May confirm or rule out the feasibility of nipple-sparing mastectomy. • In the setting of Paget disease with negative conventional imaging studies, MRI can identify underlying breast malignancy, facilitating proper treatment planning.	• Higher breast biopsy rates, including some lesions that will be negative for cancer (i.e., false-positive by MRI). • Higher mastectomy rates with MRI when disease extent is greater than shown on conventional imaging. • Repeat (short-interval follow-up) MRIs may be required for BI-RADS 3 lesions if an MRI-guided biopsy was not conducted or with benign breast biopsies. • More aggressive surgery or other treatment due to knowledge of additional lesions may not change survival outcomes. • MRI is not necessarily more accurate in estimating tumour size than other imaging; the optimal modality may vary with tumour characteristics.
Specificity	• Specificity is generally greater than 70%, and up to 97% has been reported [1]. MRI specificity depends on study populations, technical methods, and criteria for interpretation.	• Specificity may be lower than mammography in some MRI centres or for some applications. • MRI-detected lesions require biopsy for tissue confirmation and may include false-positive lesions.
Patient Factors	• May reduce the mastectomy rate in patients initially opting for mastectomy due to fear of more extensive disease and not due to clinical factors. • Reduction in anxiety for some patients as they are more confident regarding the appropriateness of treatment planned or received.	• Some patients are not suitable for MRI (anxiety, claustrophobia, MRI does not accommodate body habitus or other patient concerns) or do not want to undergo this procedure. • Increased anxiety for some patients regarding MRI procedures or biopsies, or while waiting for these to occur or results to be reported.
Adverse Effects		• Gadolinium contrast agents may cause allergic reactions (≈0.1% of patients). • Gadolinium retention, especially after multiple MRIs, has been reported in the brain; long-term effects are uncertain but have not been reported to date. Accumulation depends on the type of contrast agent and cumulative exposure. • Nephrogenic systemic fibrosis may occur in patients with acute kidney injury or severe chronic kidney disease; the risk varies with the type and volume of gadolinium contrast agent used.

Table 1. *Cont.*

Factor	Potential Benefits	Potential Harms
Delay in Treatment		• Breast MRI use may potentially lead to delays in treatment due to both MRI scheduling and the characterization of any identified lesions (biopsies and histopathology analysis/reporting). • May increase anxiety for patients while waiting for treatment.
Equity	• Universal access to preoperative MRI would result in more health care equity, provided equivalent facilities and staffing are available.	• Breast MRI, including expertise for interpretation, is not available in all centres, and some patients may need to travel long distances.
Cost	• Better lesion characterization may reduce operative costs by reducing rates of reoperations (direct surgical costs for multiple operations, treating surgical complications, patient time), costs to treat metachronous contralateral breast cancer, and longer-term costs due to decreased recurrence.	• The addition of an MRI and subsequent biopsy of lesions will add to the initial diagnostic cost.

Abbreviations: BCS, breast conserving surgery; BI-RADS, Breast Imaging Reporting and Data System; MRI, magnetic resonance imaging.

3.1.2. Key Evidence for Recommendation 1

The literature review compared patients with and without preoperative MRI and reported the following results:

Recurrence

- Use of MRI is associated with a reduction of recurrence of any type (HR = 0.77, 95% confidence interval [CI] = 0.65 to 0.90) [moderate level of certainty]. Approximate recurrence: 8.2% versus 10.5%; 2.3% less (1% to 3.6% fewer).

Contralateral Cancer

- Use of MRI is associated with an increase in detection of synchronous CBC (prior to initial surgery) (HR = 2.52, 95% CI = 1.75 to 3.62; HR > 1 indicates increased detection with MRI) [moderate level of certainty]. Approximate synchronous CBC detection: 4.7% versus 1.9%; 2.8% more (1.4% to 4.8% more).
- Use of MRI is associated with a slight reduction in metachronous CBC (HR = 0.71, 95% CI = 0.59 to 0.85) [moderate level of certainty]. Approximate metachronous CBC: 1.7% versus 2.4%; 0.7% fewer (0.4% to 1.0% fewer).

Conversion Mastectomy

- Use of MRI is associated with a reduction in the rate of conversion mastectomy OR = 0.76, 95% CI = 0.58 to 0.99) [low level of certainty]. Approximate conversion mastectomy rate: 5.5% versus 7.1%; 1.6% fewer (95% CI = 0.1% to 2.9% fewer).

Positive Margins

- Use of MRI reduced the rate of positive margins in studies with low or low-moderate risk of bias (OR = 0.57, 95% CI = 0.36 to 0.89) [moderate level of certainty]. Approximate rate of positive margins: 6.5% versus 10.9%; 4.4% fewer (95% CI = 1.1% to 6.7% fewer).

Reoperations and Re-Excisions

- Use of MRI is associated with a reduction in the rate of reoperation (OR = 0.73, 95% CI = 0.63 to 0.85) [low level of certainty]. Approximate rate of reoperation: 14.4% versus 18.7%; 4.3% fewer (95% CI = 2.3% to 6.0% fewer).
- Use of MRI is associated with a reduction in the rate of re-excision (OR = 0.63, 95% CI = 0.45 to 0.89) [low level of certainty]. Approximate rate of re-excision: 6.9% versus 10.5%; 3.6% fewer (95% CI = 1.0% to 5.5% fewer).

Mastectomy Rates

- Use of MRI is associated with an increase in the initial mastectomy rate in patients planned (prior to MRI) for BCS (OR = 5.18, 95% CI = 2.37 to 11.29) [very low level of certainty]. Approximate initial mastectomy rate: 5.5% versus 1.1%; 4.4% more (95% CI = 3.6% to 11.5% more). Use of MRI is associated with an increase in the final mastectomy rate (OR = 1.87, 95% CI = 1.23 to 2.85) [very low level of certainty]. Approximate final mastectomy rate: 14% versus 8%; 6% more (95% CI = 1.7% to 11.9% more).
- Studies including all patients diagnosed with breast cancer (not restricted to predetermined BCS) showed that use of MRI is associated with an increase in the initial mastectomy rate (OR = 1.29, 95% CI = 1.09 to 1.35) [low level of certainty]. Approximate initial mastectomy rate: 38.0% versus 32.3%, or 5.8% more (95% CI = 1.9% to 9.9% more). The use of MRI is associated with an increase in the final mastectomy rate (OR = 1.19, 95% CI = 1.06 to 1.33). Approximate final mastectomy rate: 41.8% versus 37.6%, 4.2% more (95% CI = 1.4% to 6.9% more). There was no difference in the final mastectomy rate when the trials using registry data were excluded (OR = 0.98, 95% CI = 0.82 to 1.17).

Other Supporting Studies (Not Part of the Meta-Analysis)

- A meta-analysis of 22 studies by Brennan et al. found the incremental CBC detection rate over conventional imaging to be 4.1% [27]. This is much higher than the cancer rate of 1.4% in the High Risk Ontario Breast Screening Program [28], in which MRI is routinely used.
- Two studies that characterized mammographically occult ipsilateral lesions (>2 cm away or in different quadrants than the index tumour) found that they were larger than the index lesion in approximately 20% of cases [29,30]. In the absence of MRI, such tumours, unless detected coincidentally during the operation of the index tumour, would be untreated surgically.
- Guidelines by The Canadian Association of Radiologists [16], EUSOBI [13,31], and Blue Shield of California/Blue Cross Blue Shield Association [17,32] have similar recommendations.

3.1.3. Justification for Recommendation 1

- We consider the significant reduction in recurrence, probable improvement in disease-free survival and metachronous CBC, and reduction in reoperations (re-excisions and conversion mastectomies) evidence of benefit that outweighs the potential negative effects overall. This recommendation places a higher value on treating cancer in a single operation and avoiding recurrence than on avoiding the discomfort of an MRI and potential additional biopsies.
- While the absolute benefit is small for most outcomes and not always statistically significant, the trend is toward MRI being beneficial for each outcome, and therefore this consistency strengthens the conclusion that preoperative MRI has a positive impact in general.
- While MRI use is associated with an increase in mastectomy rate, the reasons are likely to be multifactorial, including the need to encompass additional foci of cancer, a lack of BCS/oncoplastic surgery expertise for more complex cases, and patient preferences. In retrospective studies (and some of the RCTs), MRI was used for clinical reasons that may not have been recorded or adjusted for but that could be related to mastectomy use. As mastectomy rates may vary by country, region, hospital, and surgeon, and due to patient factors such as age, relationship status, and race/ethnicity, the additional effect of MRI on mastectomy outcomes is difficult to assess.

3.2. Recommendation 2

- Preoperative breast MRI ***is recommended*** in patients diagnosed with invasive lobular carcinoma (ILC) for whom additional information about disease extent could influence

treatment. The decision of whether to conduct an MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

3.2.1. Qualifying Statements for Recommendation 2

- Risks and benefits will vary depending on patient and disease characteristics.
- System issues such as MRI availability may result in treatment delays that may modify the decision.

3.2.2. Key Evidence for Recommendation 2

Evidence for Recommendation 1 would apply, in addition to stronger evidence specifically for ILC:

- Use of MRI is associated with a reduction in the rate of conversion mastectomy in patients with ILC (OR = 0.38, 95% CI = 0.25 to 0.56) [high certainty of evidence]. Approximate conversion mastectomy rate in ILC: 5.9% versus 14.2%; 8.3% fewer (5.7% to 10.3% fewer).
- Use of MRI is associated with a reduction in the rate of positive margins in patients with ILC (OR = 0.63, 95% CI = 0.49 to 0.82) [moderate level of certainty]. Approximate rate of positive margins: 18.9% versus 27.0%; 8.1% fewer (3.7% to 11.7%).
- Use of MRI is associated with a large reduction in the rate of reoperation in patients with ILC (OR = 0.30, 95% CI = 0.13 to 0.72) [moderate level of certainty]. Approximate rate of reoperation: 12.3% versus 31.9%; 19.6% fewer (6.77% to 26.1% fewer).
- Lobbes et al. [33] found MRI increased the detection of synchronous CBC in ILC (OR = 4.07, 95% CI = 1.73 to 3.61, $p < 0.001$) (HR > 1 indicates increased detection with MRI).
- A review of the literature by Mann et al. [34] found synchronous CBC detected only by MRI in 7% of patients (95% CI = 4% to 12%). The recommendation is consistent with guidelines by EUSOBI [13], EUSOMA [12], INESSS [14], and The Royal College of Radiologists (London) [35].

3.2.3. Justification for Recommendation 2

- We consider the significant reduction in positive margins resulting in a large reduction in reoperations (including conversion mastectomy), in addition to the benefits in survival and recurrence for all patients (see Recommendation 1), to be evidence of a benefit that outweighs the potential negative effects overall. This recommendation places a higher value on treating cancer in a single operation and avoiding recurrence than on avoiding the discomfort of an MRI and potential additional biopsies. The benefit of MRI is consistent with the results of studies that reported that, compared to invasive ductal carcinoma, ILC has been found to be more difficult to detect by mammography, more likely multifocal, more often occurs with synchronous CBC, and has more involved margins after initial resection [36–41].

3.3. Recommendation 3

Preoperative breast MRI **is recommended**, based on the opinion of the Working Group, in the following situations:

(a) To aid in the surgical planning of BCS in patients with suspected or known multicentric or multifocal disease.
(b) To identify additional lesions in patients with dense breasts.
(c) To determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumours or when invasion of the pectoralis major muscle or chest wall is suspected.
(d) To aid in surgical planning for skin/nipple-sparing mastectomies or for autologous reconstruction, oncoplastic surgery, and BCS with suspected nipple/areolar involvement.
(e) Patients with familial/hereditary breast cancer who have not had a recent breast MRI as part of screening or diagnosis.

3.3.1. Qualifying Statement for Recommendation 3

Preoperative breast MRI is recommended in the above situations if additional information about disease extent could influence treatment. The decision of whether to conduct an MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

3.3.2. Key Evidence for Recommendation 3

Comparative studies meeting the evidence review inclusion criteria were not found. These uses are recommended based on the expert opinion of the authors and are consistent with recommendations in other guidelines [12–14,17,32,35,42,43]. Some of these situations are implicit in Recommendation 1; however, the authors wanted to draw attention to these uses:

(a) Most studies in the literature review [19] either excluded multicentric and multifocal disease or included these in the list of factors used to adjust results in multivariate analysis, indicating these are known to influence outcomes, but with the result that we did not find a direct comparison of outcomes according to MRI use. The presence of multicentric and multifocal disease increases the complexity of surgical planning and in older guidelines was a contraindication to BCS. When the disease is well-characterized, the possibility of BCS may be increased in some cases and ruled out in others, and the likelihood of an incidental finding during surgery decreases. The consensus of the authors is that the increased sensitivity of MRI justifies its use in suspected/known multicentric or multifocal disease if BCS is desired.

(b) Several studies mentioned in the literature review [19] reported that the sensitivity of mammography decreases as breast density increases, while the sensitivity of MRI is high and independent of breast density. The GEMMA (Gadobutrol-Enhanced MR Mammography) trials studied MRI in patients with newly diagnosed and histologically proven breast cancer. In GEMMA1, MRI sensitivity was 83% (independent of density), while the sensitivity of mammography decreased from 79% to 62% as breast density increased [44]. Corresponding results in the GEMMA2 trial were 91% (independent of density) for MRI and 82% (low density) to 64% (high density) for mammography. The Ottawa study of preoperative MRI found additional lesions changing surgical management in 31% of patients with low density (fat density) and 62% with dense breasts [45]. Screening studies reported similar variations in the sensitivity of mammography based on breast density. The Supplemental MRI Screening for Women with Extremely Dense Breast Tissue (DENSE trial) randomized 40,373 women with extremely dense breast tissue and normal screening mammography to either supplemental MRI or only mammography and found MRI reduced interval cancers by 50% in those offered MRI and 80% in those who agreed to have an MRI [46–48]. A systematic review and meta-analysis [49] found that breast density is one of the strongest risk factors for breast cancer.

(c) Tumours near the chest wall may invade the pectoralis major muscle or involve the chest wall, and thus accurate knowledge of tumour extent will influence treatment planning. MRI has been found to have high sensitivity in detecting muscle or chest wall involvement [50–53].

(d) Standard BCS may lead to fair to poor esthetic and functional results [54], and more complex oncoplastic surgery or mastectomy may be more appropriate if the optimal tumour-to-breast ratio for each quadrant is exceeded. Breast MRI or other advanced imaging (e.g., positron emission tomography/computed tomography) may be a prerequisite for extreme oncoplasty [55]. MRI is frequently used prior to nipple-sparing mastectomy, especially in the case of centrally located tumours [56–60]. MRI may rule out nipple involvement such that 2 cm is no longer considered a minimum tumour-to-nipple distance; 5 mm [61] or 1 cm [62–67] may be sufficient.

(e) Hereditary cancer patients have a high risk of synchronous and metachronous CBC. A systematic review reported 10-year CBC rates of 25% to 31% for patients with germline mutations, compared to 4% to 8% for sporadic cases [68].

3.4. Technical Factors for MRI Use

MRI is one of the most sensitive imaging techniques for detecting breast tumours, with the potential to be highly specific. Performance depends on the equipment and MRI techniques used and the expertise of those conducting the analysis. The literature review [19] identified several technical documents and standards for MRI use. Guidance on the performance of CE-MRI and biopsies by the Canadian Association of Radiologists [16], ACR [15,69–79], EUSOBI [13,80], and others may be useful; however, these were not critically reviewed or compared in this evidence summary. Several studies used technical standards for MRI set by the American College of Radiology Imaging Network (ACRIN) 6667 trial [81–84] and EUSOBI, as well as the ACRIN 6698 trial for DWI [85].

Best practice is that additional suspicious lesions detected by preoperative MRI be biopsied or otherwise confirmed if they could alter surgical procedures. Sites performing MRI should have the capacity for an MRI-directed biopsy. This minimizes the need for repeat MRIs and associated costs, delays due to transfer of care (ultimately resulting in a delay in definitive treatment) [86], and the risk of patients not receiving follow-up. Familiarity with the complete process may also result in better expertise in reading and interpreting MRI [87].

4. Discussion

In Ontario, there are currently capacity constraints that affect the availability of MRI. Additional MRI use will add system pressure unless capacity issues are resolved and may increase treatment delays beyond what are considered acceptable in some cases. Availability and accessibility vary among regions. Local availability of breast MRI and projected surgical delays due to the addition of preoperative MRI may be major issues in deciding whether MRI is used. Patients indicated that they would like to be aware of these issues and whether they were modifiable in their situation.

Limited availability and high cost are in part due to the long duration of a full MRI scan (30–45 min). Many studies have investigated whether scan time can be reduced without sacrificing sensitivity and specificity or losing other information. As MRI has been found to be beneficial in screening women at high risk of cancer [88–90], as well as those at intermediate risk [1,11,91], including patients with dense breasts [46], the majority of evidence comes from screening studies or those enriched in cancerous lesions.

The first major study of abbreviated MRI (AB-MRI) in screening by Kuhl et al. was published in 2014 [92]. Women at mildly to moderately increased risk of breast cancer with negative digital mammography underwent a full diagnostic MRI (8 pulse sequences). For AB-MRI, only the first two sequences (precontrast and first postcontrast acquisition) were read. Acquisition time for AB-MRI sequences was 3 min, compared to 17 min for the full protocol. The additional cancer yield was 18.2/1000. Sensitivity was 100%, and specificity was similar to the full protocol (94.3% vs. 93.9%). Based on this work, many other studies of AB-MRI have been conducted. Specificity was lower in some studies (though generally >80%), and variations in protocol, including additional sequences, have been investigated. Adding a T2-weighted sequence and having at least two post-contrast sequences does not increase the scan time by more than 3 to 4 min and allows improved specificity equivalent to the full protocol. Ultrafast MRI involving a fast post-contrast acquisition capturing the inflow of contrast agent may be used on its own or together with abbreviated MRI; in the latter case, it adds information but does not take additional time [93]. AB-MRI has been reported for over 5400 women in 21 studies published from 2014 to 2018 [94], with an overall sensitivity of 94% and a specificity of 90%. A later review identified 41 studies until 2020 involving 15,680 MRI examinations [95]. There is not a common definition of AB-MRI, and it sometimes refers to just the precontrast and postcontrast

sequences, sequences less than 7 to 10 min, or any protocol that is significantly shorter than the standard (full) MRI protocol.

The ACR accreditation requirements for breast MRI include a precontrast sequence (T2 weighted/bright fluid series, multi-phase T1-weighted series, and pre-contrast T1; these may be separate or combined), and early postcontrast and delayed postcontrast T1-weighted sequences [96]. Massachusetts General Hospital (Boston, Massachusetts) has used a rapid abridged multiphase (RAMP) breast MRI protocol since 2016 that meets ACR requirements and has a scan time of 10 min [97].

In Ontario, use of the full diagnostic protocol is common and requires 30 to 45 min. Some cancer centres, including those in Ottawa and London, use a shortened protocol that requires a scan time of 12 min and meets Canadian Association of Radiologists [16] and Ontario Breast Screening Program guidelines. As shorter protocols become more standardized and implemented, there is potential for cost reduction and increased patient scans. It is acknowledged that personnel, time for setup, and interpretation of results may be limiting factors until the entire workflow is rebalanced.

4.1. Limitations

This literature review referred to in this guideline included primarily retrospective studies that may have additional confounding factors for which adjustments were not made. While the benefits of MRI use in these studies are generally consistent, the magnitude of the benefit is less certain due to differences in patient populations, study designs, and methods of adjustment for confounders. Comparative studies on the use of MRI versus no MRI that met our inclusion criteria were not found for many of the subgroups of interest, including the use of systemic therapy or radiotherapy. Cost analysis was outside the scope of this work.

4.2. Review and Update

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. For the full 1–25 guideline, systematic review, and subsequent updates, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/breast (accessed on 1 May 2023).

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Article

Efficacy and Accuracy of Using Magnetic Seed for Preoperative Non-Palpable Breast Lesions Localization: Our Experience with Magseed

Anna D'Angelo [1,*], Charlotte Marguerite Lucille Trombadori [1], Flavia Caprini [1], Stefano Lo Cicero [1], Valentina Longo [1], Francesca Ferrara [1], Simone Palma [1], Marco Conti [1], Antonio Franco [2], Lorenzo Scardina [2], Sabatino D'Archi [2], Paolo Belli [1] and Riccardo Manfredi [1]

[1] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario "A. Gemelli", IRCCS, 00168 Rome, Italy
[2] Breast Unit, Department of Women, Children and Public Health Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168 Rome, Italy
* Correspondence: anna.dangelo05@gmail.com

Abstract: In this retrospective study we share our single-center experience using a magnetic seed for the preoperative localization of non-palpable breast lesions. Patients who underwent a preoperative localization with Magseed® (Endomagnetics, Cambridge, UK) placement between 2020 and 2022 were enrolled. Indications to Magseed placement have been established during multidisciplinary meetings prior to surgery and all patients underwent breast-conserving surgery (BCS). 45 patients were included. Magnetic seeds have been introduced under ultrasound guidance in 40 patients (88.9%) and under stereotactic guidance in 5 patients (11.1%). We registered a highly successful placement rate (97.8%), with only one case of migration (2.2%). After BCS, all the magnetic seeds were recovered (100% retrieval rate). The re-excision rate for positive margins was 0%. Our experience, with a highly successful placement and retrieval rate and a re-excision rate equal to 0%, is consistent with the encouraging literature published on Magseed so far, suggesting this technique to be extremely effective. Moreover, our single case of seed migration supports the existing data stating that Magseed migration is rare. In conclusion, despite acknowledging Magseed limitations, we highly value the advantages linked to this technique, and we, therefore, uphold its use.

Keywords: Magseed; breast cancer; preoperative localization; magnetic seed

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1. Introduction

Breast cancer (BC) has become the leading cause of global cancer incidence and the fifth leading cause of cancer mortality worldwide [1]. Considering the increasing of BC incidence [1], principally related to improvements in diagnostic techniques and the aging of the population, the detection of non-palpable breast lesions has become increasingly frequent.

For non-palpable BC, the treatment of choice is Breast Conserving Surgery (BCS) [2]. In order to be successful in achieving a complete excision of the lesion, a correct pre-operative localization is required. Thus, accurate and state-of-the-art localization is a pivotal step in the management of a BC patient, with an increasing demand for the development of reliable localization approaches for non-palpable lesions.

Recently, localization techniques have undergone constant improvements. One of the first types of localization technique was the wire guide localization (WGL), still widely used, consisting of locating a wire inside the lesion under ultrasound or mammography guidance. The main limitations of this procedure are the need to perform it on the same day of the surgery, the risk of displacement, and a worse aesthetic result as the breast tissue along the path of the thread must be removed.

Given the above strains, non-wire localization systems have been developed. One of the earliest non-wire systems to be implemented was the Radio-guided Occult Lesion Localization (ROLL) [3] which uses a radioactive marker. However, this localization method requires to be performed on the day of the surgery or a few days before, depending on the half-life of the radioactive molecule. Furthermore, this technique necessitates a nuclear medicine service within the hospital and determines a risk of exposure for both the operator and the patient. Therefore, over the following years, non-wire and non-radioactive localization tools have been implemented, such as the Radio-Frequency Identification tag (RFID), the Savi-Scout and the magnetic seed systems.

The RFID system uses radio frequencies and, despite some limitations [4], is considered safe and effective for non-palpable breast lesions localization, with re-excision rates similar to WGL. It can be deployed inside the lesions the day before surgery. The Savi-Scout system is another non-wire and non-radioactive alternative technique; it uses a micro-impulse infrared radar to localize the lesions and is particularly useful for patients that need MRI examinations during follow-up, without artifacts [5].

Magnetic localization techniques were developed as an alternative to the methods mentioned above [6]. The Magseed® (Endomagnetics, Cambridge, UK), a non-wire and non-radioactive paramagnetic localization tool was approved in 2016 by the Food and Drug Administration (FDA) [7]. It has the crucial advantage that it can be introduced inside the lesion and can remain in place until the time of BCS, despite the first indications that recommend the placement of Magseed up to 30 days before surgery [8]. Hence, the workload of the radiologist before the surgery is reduced as well as delays in surgical theaters due to localization procedures.

Magseed is composed of a seed of 5 × 1 mm inserted within an 18-G sterile needle (Figure 1), and its introduction can be performed either under ultrasound or mammography guidance. Following accurate disinfection of the skin and the injection of local anesthesia, the needle with the magnetic marker is inserted and centered with its distal end as proximal as possible to the target lesion, where the marker is released. A double-view mammography is performed to assess the right placement of the seed. On the day of the surgery, an ultrasound or a mammography examination is performed to evaluate the correct position of the marker, to avoid migration. The magnetic clip is then identified during surgery by the SentiMag® (Endomagnetics, Inc., Cambridge, UK) probe, which generates a magnetic field and magnetizes the seed. During surgery, the distance of the probe from the Magseed is indicated by numerical values displayed on the monitor and with audio feedback. The magnetic seed is considered detectable within a distance that is around 4 cm away from the SentiMag [9].

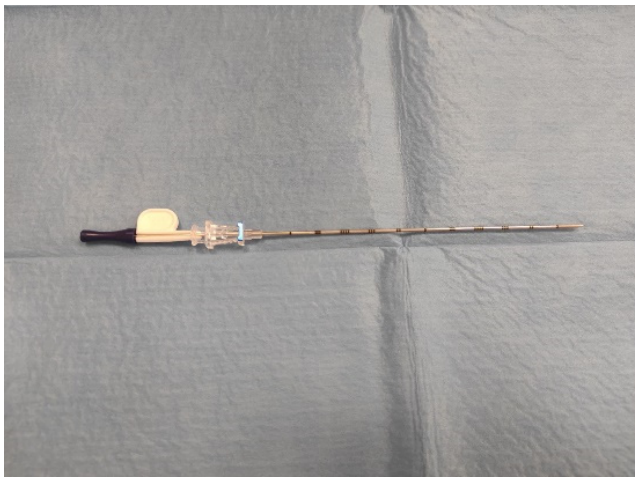

Figure 1. The 18-gauge Magseed introducer.

This retrospective study aimed to share our experience with magnetic seed and to evaluate its efficacy and accuracy for preoperative non-palpable breast lesion localizations.

2. Materials and Methods

2.1. Patients

Our institutional review board approved this single-institution retrospective study. A total of 45 patients who underwent Magseed placement between June 2020 and February 2022 were included. Inclusion criteria were: 18 years old or older, single non-palpable breast lesion and surgery performed in our center. Exclusion criteria were: palpable breast lesions and patients who underwent previous chemotherapy treatment. Each patient enrolled signed informed consent before undergoing the interventional procedure.

2.2. Procedure

The placement of Magseed was decided and approved by a multidisciplinary meeting between breast surgeons, plastic surgeons and radiologists. A total of 45 Magseeds were placed, 40 under ultrasound guidance (88.9%) and 5 under stereotactic placement (11.1%) (Figure 2). Each procedure followed accurate disinfection of the skin (chlorhexidine) and the injection of local anesthetic (Mepicain 2%); after the introduction of the magnetic seed, an ultrasound and a mammogram (two-views mammography, mediolateral oblique, and craniocaudal views) were performed, in order to document the correct position of the marker (Figure 3). On the day of the surgery, a double-view mammography is performed to verify the correct position of the seed (Figure 3).

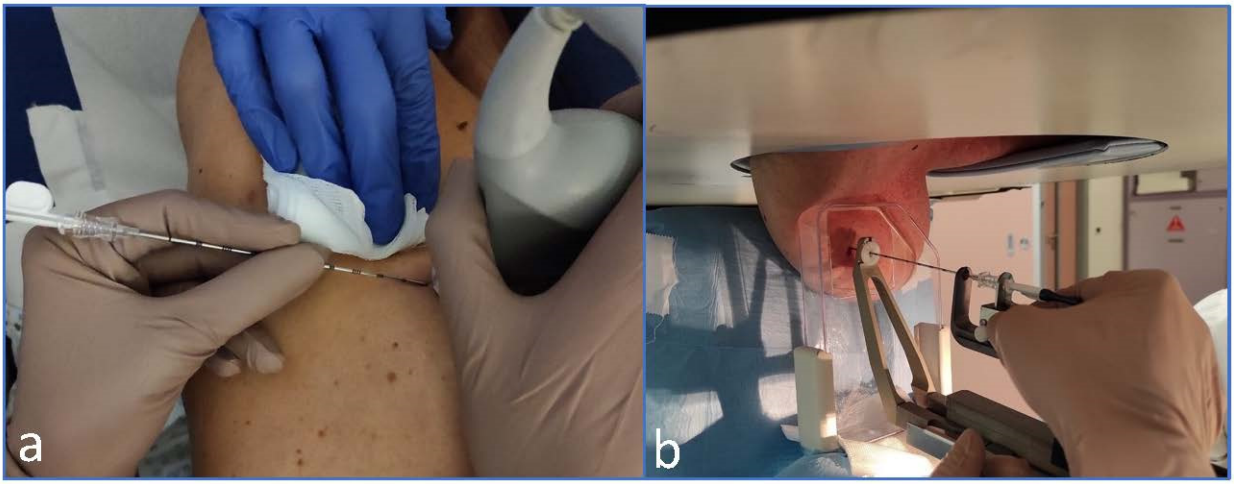

Figure 2. Magseed insertion: ultrasound (**a**) and stereotactic guidance (**b**).

The Magseed was identified during surgery using the SentiMag probe (Figure 4); the audio signal has a frequency that varies according to the intensity of the magnetic field or with the distance of the seed from the probe, helping the surgeon to find the lesion. At the end of the surgery, surgical specimen radiography in craniocaudal view with the tomosynthesis (the routine practice in our center) was performed to assess the presence of the Magseed and to evaluate the distance between the lesion and the close margins (Figures 3f and 4b). If the lesion is detected on the surgical specimen margin at the radiography, intraoperative widening is performed. After that, the surgical specimen was examined by the pathologist for the histological assessment and for the evaluation of margin status ("no ink on tumor") [10].

We evaluated patient demographics, lesions characteristics, Magseed localization features (ultrasound-guided or stereotactic-guided), seed migration, successful Magseed detection and retrieval in the surgical specimen, time of Magseed placement (in minutes) and time between Magseed placement and surgery (in days).

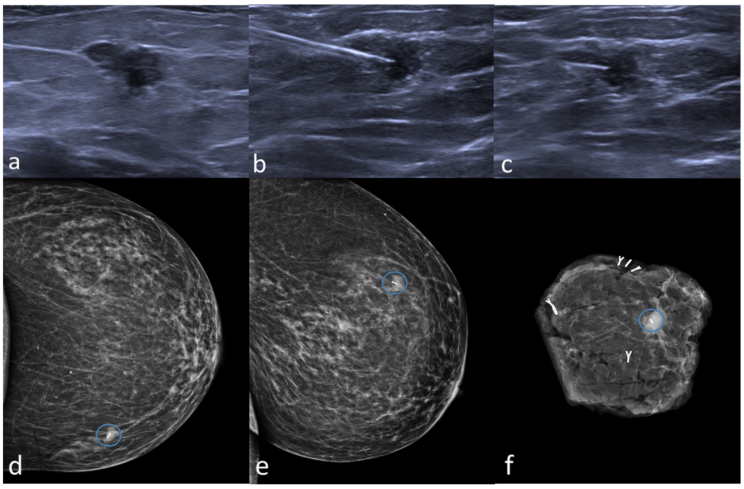

Figure 3. Magseed placement under ultrasound guidance. Preoperative ultrasound localization of a non-palpable, hypoechoic lesion (invasive ductal carcinoma) in the left upper inner quadrant (**a**), and placement of Magseed inside the lesion (**b**,**c**). Preoperative mammogram in two views confirms the correct placement of the Magseed (blue circle, (**d**,**e**)). The surgical specimen shows the presence of both the tumor and Magseed (blue circle, (**f**)).

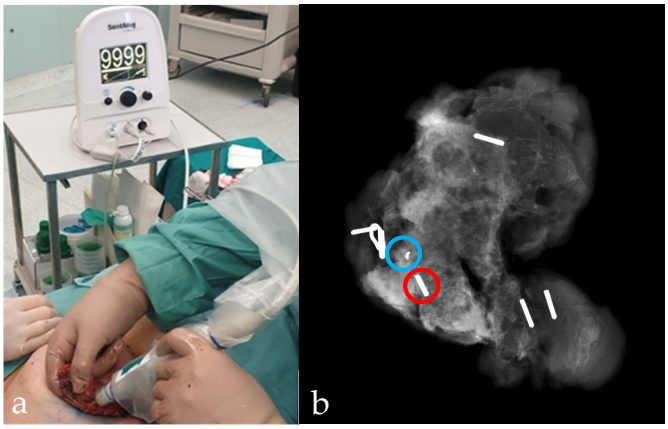

Figure 4. The SentiMag probe (**a**), used intraoperatively to locate the Magseed using a small and transient magnetic field that magnetizes the clip making it recognizable to the probe itself. In (**b**) radiographic examination of the surgical specimen shows the Magseed (red circle) adjacent to the previously clipped lesion (blue circle).

3. Results

A total of 45 patients were included in the study. The mean patient age was 57, 58 years (range 31–80). The preoperative mean size of the breast lesions was 8.8 millimeters (mm) (range 3–18 mm) (Table 1). The patients enrolled in the study underwent BCS. The intraoperative widening and the re-excision rate for positive margins were 0% (Table 1).

Table 1. Clinical and surgical data. Millimeters (mm). Ductal carcinoma in situ (DCIS). Invasive ductal carcinoma (IDC). B3 lesions according to the lexicon BI-RADS®.

Patients Age (Years)	57.58 (range 31–80)
Breast lesions dimension (mm)	8.8 (range 3–18)
Type of surgery: Lumpectomy Quadrantectomy	 3 43
Re-excision rate	0%

Table 1. *Cont.*

Intraoperative widening	0%
Post-operative histology:	
DCIS	4 (8.8%)
IDC	35 (77.8%)
B3	6 (13.4%)

The pathological examination found a prevalence of malignant lesions, of which 77.8% were invasive ductal carcinoma (IDC) and 8.8% ductal carcinoma in situ (DCIS), while the remaining 13.4% were B3 lesions [11] (Table 1).

Magseed localization features were reported in Table 2. A total of 40 magnetic seeds were placed under ultrasound guidance (88.9%) and 5 under stereotactic guidance (11.1%) (Table 2). No immediate complications after placement were observed (0.0%) and we obtained a high placement success rate (97.8%) since all markers were correctly positioned, except for one case of migration of the marker placed under stereotactic guidance (2.2%) (Figure 5). All magnetic seeds were recovered in the surgical specimens (100%) (Table 2).

Table 2. Magseed localization data. Days (d). Minutes (min).

Total Magseed Placed	**45**
Localization modality:	
Ultrasound localization	40 (88.9%)
Stereotactic localization	5 (11.1 %)
Seed migration/malpositioning	1 (2.2%)
Successful detection and retrieval	45 (100%)
Time between Magseed placement and surgery (d)	3.46
Time for Magseed placement (min)	5.5

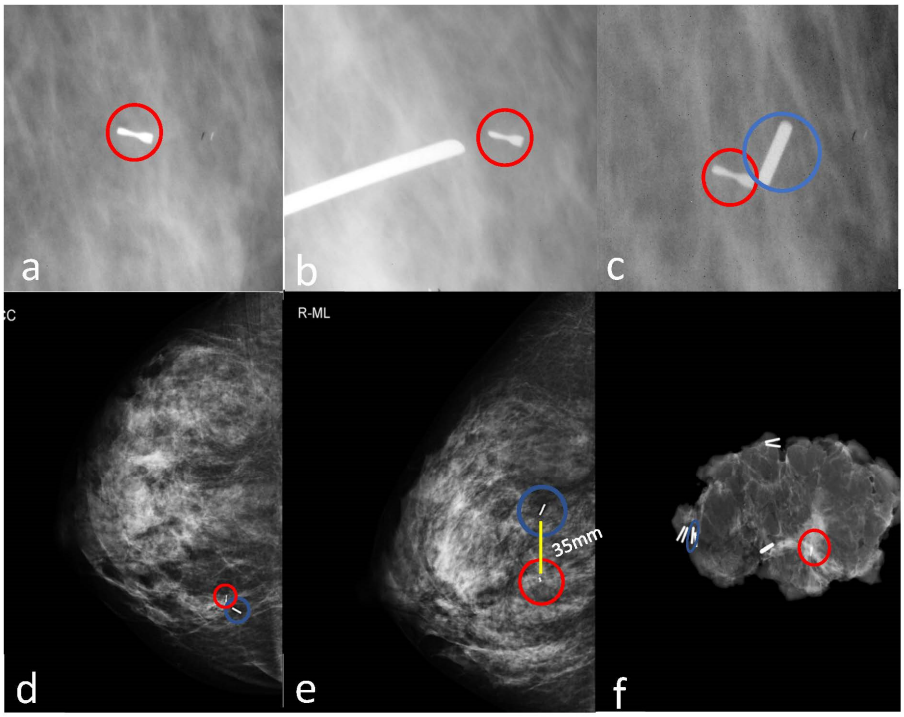

Figure 5. Misplaced Magseed. In (**a**–**c**), the placement of the Magseed (blue circle in (**c**)) under stereotactic guidance in the site of a previous stereotactic biopsy with a metallic clip (the red circles). Preoperative mammography in two views (**d**,**e**) shows a cranial displacement of the Magseed (blue circles in (**e**)) at a distance of 35 millimeters (mm) from the biopsy-clipped lesion (red circles). The surgical specimen radiogram reveals the Magseed (blue circle) and the clipped lesion (red circle) (**f**) correctly removed.

Most of the seeds were placed some days before surgery or the same day of surgery (average time was 3.46 days). On average, Magseed placement took about 5.5 min.

4. Discussion

Magseed represents one of the most promising options for the localization of non-palpable breast lesions. Recent data on its use are unarguably encouraging, proving this technique to be extremely effective.

A recent systematic review by Gera et al. [9] demonstrated the effectiveness of the Magseed in localizing non-palpable breast lesions, particularly as compared to the WGL. Indeed, the results obtained from the analysis of 16 studies, with a highly successful localization and retrieval rate (99.86%) and a relatively low re-excision rate (11.25%), support the use of this technique. In a multicenter clinical retrospective trial, Žateckýa et al. [12] evaluated a pilot use of the magnetic seed in 34 breast tumors. They reported negative margins after surgery in 29 out of 34 (85.3%) patients. Positive resection margins were found in 4 out of 34 patients (11.8%), and 1 case of seed migration was reported, with a rate of 14.7% (5/34) re-excision rate. Several studies reported no seed migration after perioperative tumor marking [13,14], being this a rare occurrence. The experience of our center is consistent with previous literature with a highly successful localization rate (97.8%); conversely, compared to other studies, our intraoperative widening and re-excision rate are lower (0%), with 0% of positive margins.

As we said above, one of the benefits of the Magseed is the possibility to deploy the seed several days ahead of surgery, enabling a more efficient and flexible organization of the workflow [15]. For this reason, the magnetic seed could be useful in case of a long follow-up, especially during neoadjuvant chemotherapy, despite the well-known signal-void MRI artifact [7]. This limitation significantly affects image quality and can, in some cases, hamper the use of the MRI for the follow-up after therapy. However, contrast-enhanced mammography can be chosen as a good and performing alternative for those patients with wider artifacts. We reported a mean time of 3.46 days between seed deployment and the day of surgery, even if most of the localizations took place on the same day of the surgery. We reported one case (2.2%) of seed migration, which is in line with the literature [14].

One limitation of the magnetic seed is related to the depth of the lesion in the breast, measured as its distance from the skin. As we stated in the introduction, Magseed is considered detectable within a distance of around 4 cm away from the SentiMag, making it harder for deeper lesions to be found [8,15]. However, many studies in literature report that intraoperatively using palpation with the detector, seeds far deeper were detected [9,15]. Given this, it may be preferable for extremely deep lesions to use WGL. Another important aspect that disincentives the use of Magseed is the cost [16]. In our analysis, we have not considered either.

This study has some limitations. The experience was limited to one center, and above all, it included a small cohort of patients. Moreover, we did not analyze some variables (e.g., depth from the skin of the breast lesion and Magseed costs), and the time between Magseed placement and surgery was short (3.46 days), probably affecting the data regarding the seed migration.

5. Conclusions

With the limits mentioned above, our single-center experience is consistent with the data reported in literature, suggesting this technique is effective in the preoperative localization of non-palpable breast lesions.

Future studies including a bigger sample size and a longer time interval between seed placement and surgery are needed to validate our results.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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

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Review

Estrogen-Receptor-Low-Positive Breast Cancer: Pathological and Clinical Perspectives

Christina Panagiotis Malainou, Nikolina Stachika, Aikaterini Konstantina Damianou, Aristotelis Anastopoulos, Ioanna Ploumaki, Efthymios Triantafyllou, Konstantinos Drougkas, Georgia Gomatou * and Elias Kotteas

Oncology Unit, Third Department of Medicine, "Sotiria" General Hospital for Diseases of the Chest, National and Kapodistrian University of Athens, 152 Messogion Avenue, 11527 Athens, Greece; ilkotteas@med.uoa.gr (E.K.)
* Correspondence: georgiagom@med.uoa.gr

Abstract: The expression of estrogen receptors (ERs) in breast cancer (BC) represents a strong prognostic and predictive biomarker and directs therapeutic decisions in early and advanced stages. ER-low-positive BC, defined by the immunohistochemical (IHC) expression of ERs from 1% to 9%, constitutes a distinct subset of total BC cases. Guidelines recommend that a low expression of ERs be reported in pathology reports since the benefit of endocrine therapy in patients with ER-low-positive BC is uncertain. Recently, several cohorts, mostly of a retrospective nature, have been published, reporting the clinicopathological characteristics and outcomes of ER-low-positive BC. However, the majority of the data focus on early-stage BC and the use of (neo)adjuvant therapy, and there is a significant lack of data regarding metastatic ER-low-positive BC. Further factors, including tumor heterogeneity as well as the potential loss of ER expression due to endocrine resistance, should be considered. Including patients with ER-low-positive BC in clinical trials for triple-negative breast cancer (TNBC) might improve the understanding of this entity and allow novel therapeutic approaches. The design and conduction of randomized clinical trials regarding this subgroup of patients are greatly anticipated.

Keywords: estrogen receptor; breast cancer; estrogen receptor-low-positive breast cancer; endocrine therapy; triple-negative breast cancer

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1. Introduction

Hormone receptors (HR), including estrogen (ER) and progesterone receptors (PR), are expressed in 70–75% of breast cancer (BC) cases and represent one of the cornerstones that direct the therapeutic decisions for patients with BC both in early and metastatic stages [1,2]. The 2020 update of the recommendations of the American Society of Clinical Oncology/College of American Pathology (ASCO/CAP) defines ER-positive BC as samples with 1% or more of tumor nuclei positive for ER expression by validated immunohistochemistry (IHC). Nevertheless, the recommendations outline that a small subset of patients with ER expression between 1 and 10% should be termed ER-low-positive BC and are not likely to benefit from endocrine therapy (ET) [3]. A lack of consensus exists regarding whether the exact 10% expression should be considered ER-low-positive or ER-positive. Hence, the definition of ER-low expression differs in the literature as either 1 to 9% or 1 to 10% [4].

ER-low BC is associated with interesting biological aspects, but it also poses several challenges regarding its management. A low expression of ERs might be observed de novo, or it might develop in the course of the disease [5,6]. In addition, it should be noted that tumors are heterogeneous entities; therefore, the expression of ERs derived from a specific biopsy might not represent the expression in the whole tumor [5]. The optimal management of patients with ER-low BC in early and metastatic settings has not been

defined yet. Several recent studies, mostly of a retrospective nature, have described the features of ER-low BC and assessed the benefit of ET, mainly in an adjuvant setting. In the present review, we attempt to summarize the literature and shed light on the biological and clinical perspectives of ER-low BC.

2. Estrogens and ER-Mediated Signaling Pathways

Estrogens, known as female sex hormones, play a crucial role in the development and function of the female reproductive system and secondary sex characteristics. They also affect other systems, such as the cardiovascular, musculoskeletal, central nervous and immune systems [7,8]. Four steroid hormones belong to the estrogen family: estrone, estradiol, estriol and estretrol [7]. Estriol and estretrol are present mainly in the course of pregnancy. Estrone is present during menopause, while estradiol is the predominant form during the reproductive years [9]. Estradiol promotes cell proliferation in the endometrium and mammary gland starting from puberty, while during pregnancy, the dominant forms prepare the mammary gland for milk production [7].

At the cellular level, estrogens act through their receptors, the estrogen receptors a (ERa) and b (ERb), which are part of the nuclear receptor family and are encoded by two different genes, *ESR1* and *ESR2* [7]. Similarly to other nuclear receptors [7], their structure enables them to bind with their ligands but also to DNA and act as transcription factors with the aid of other co-activators and co-repressors [9,10]. The isoforms ERa and ERb are highly similar except for their NH2-terminal domain (NTD), which is involved in gene transcription activation [9].

Estrogens pass through the cellular plasma membrane and interact with their receptors via their ligand binding domain (LBD). From this point, they activate several signaling pathways, which can be divided into genomic and non-genomic based on the ability of the hormone-receptor complex to bind directly to the DNA chain at specific domains, known as estrogen response elements (EREs) [9,11]. Moreover, rapid responses to estrogens have been observed, which do not involve genomic signaling and are known as indirect non-genomic signaling. They are mediated through second messenger production and protein kinase activation pathways, leading to signaling cascades that ultimately regulate gene expression. The most important intracellular cascades involve the phospholipase C/protein kinase C cascade, the mitogen-activated protein kinase (MAPK) pathway, the phosphoinositide 3-kinase (PI3K) pathway and the cyclic adenosine monophosphate (cAMP)/protein kinase A cascade [9,12]. For example, the PI3K/protein kinase B (AKT)/mammalian target of the rapamycin (mTOR) pathway, activated by non-genomic estrogen signaling, has been found to be overactive in up to 70% of BCs and is related to ET resistance after long-term estrogen deprivation [13]. Interestingly, crosstalk between non-genomic and genomic signaling pathways has been described, leading to the regulation of transcription factors by protein-kinase-mediated phosphorylation [11].

Progesterone is another steroid hormone involved in the proliferation and morphogenesis of the luminal epithelium, primarily through paracrine signaling pathways. Progesterone binds to a nuclear receptor, the progesterone receptor (PR) [14]. It should be noted that PR expression depends on estrogen levels since PR is a target gene of an ER [15]. Although the expression of the PR is routinely assessed in BC, the clinical value of PR expression is not so strongly established as it is for ER expression; rather, the presence of an intact and functionally active ER pathway is implied when the PR is expressed [16].

3. ER-Low-Positive BC

3.1. Epidemiology and Clinicopathological Characteristics

Although ER-low-positive BC represents a small subset of all patients with BC, it is important to understand its nature to provide tailored and effective treatment [5]. Lately, several studies have been published reporting the prevalence and characteristics of ER-low BC as well as their response to treatment.

The prevalence of ER-low BC varies from 1.6 to 5.1%, as reported in recent large-scale cohorts (Table 1) [4,17–24]. Interestingly, Makhlouf et al. performed a re-evaluation of ER status in cases considered ER-low-positive at initial evaluation and demonstrated that 45% of these tumors were ER-negative with repeated IHC staining, confirmed by in situ hybridization (ISH) and a quantitative polymerase chain reaction (qPCR). In particular, ER-low-positive samples derived from needle core biopsies were enriched with false-positive ER staining [4]. In the same study, they focused on tumors with precisely 10% ER expression. The results revealed that those cases were significantly lower grade and more PR-positive than tumors with an ER expression of 1–9% and did not show a significant difference from tumors with an ER expression of 11–30% [4].

Table 1. The prevalence of ER-low-positive breast cancer.

Author (Year)	*N*	Prevalence of ER-Low BC	Reference
Makhlouf (2023)	7559	1.6% (123/7559)	[4]
Moldoveanu (2023)	232,762 [a]	2.0% (4584/232,762)	[17]
Li (2023)	9082	3.29% (299/9082)	[18]
Luo (2022)	5466 [b]	5.1% (277/5466)	[19]
Yoon (2022)	2162 [b]	2.5% (54/2162)	[20]
Park (2021)	5930 [b]	2.0% (117/5930)	[21]
Schrodi (2021)	38,560 [b]	2.0% (861/38,560)	[22]
Fei (2021)	4179	2.3% (97/4179)	[23]
Poon (2020)	1824	3% (54/1824)	[24]

[a] only HER2 (–) [b] only early breast cancer cases. ER: estrogen receptor, BC: breast cancer, HER2: human epidermal growth factor receptor 2.

Regarding the characteristics of patients with ER-low BC, a study showed that ER-high-positive, ER-low-positive and ER-negative BC had no statistical difference related to the age of menarche and body mass index kg/m^2 [25]. Among patients with ER-high-positive BC, there were significantly more white patients compared to ER-low-positive BC (93.9% vs. 82.9%, $p < 0.05$) [25]. Indeed, it appears that a patient's profile is similar between ER-low and triple-negative breast cancer (TNBC), as reported in a multicenter prospective registry between 2011 and 2019. The study showed that demographic and clinical characteristics, including racial and ethnic distribution—it is well-known that TNBC is more prevalent among the African American race—and the prevalence of germline *BRCA1/2* mutations were not different between the TNBC and ER-low groups [26].

Several studies have investigated the morphological and immunohistochemical characteristics of ER-low-positive BC in relation to ER-negative and ER-high-positive BC. ER-low BCs are more likely to have a ductal phenotype of a higher histological grade compared to ER-high BCs (83.5% vs. 71.4%, $p = 0.005$) [23]. In another study, ER-low-positive cases were associated with larger tumors, higher grades, more necrosis, more stromal tumor infiltrating lymphocytes (sTILs) and a higher pathologic N stage [24]. In particular, regarding sTILs, the ER-low-positive cases were associated with more sTILs than the ER-high-positive cases, whereas no difference was found between ER-low-positive and ER-negative tumors. A further survival analysis demonstrated that higher sTIL levels are associated with reduced mortality in ER-negative and ER-low-positive BC [24]. Cases of BC with 1–9% ER expression are more likely to have a higher Ki-67 index and are more likely to be PR-negative [27–29]. Moreover, a recent study demonstrated that HER2-low expression was positively associated with the level of ER expression, and ER-low-positive tumors were enriched among HER2 0–2+ tumors [30].

Additionally, studies with further IHC and molecular analyses have demonstrated that vimentin, the epidermal growth factor receptor (EGFR), CPK5/6, and CK14 are highly expressed in ER-low-positive or negative BC and less expressed in ER-high-positive BC [5]. ER-high-positive BCs are more frequently negative for C-kit, p63 and the androgen receptor (AR) compared to ER-low-positive or ER-negative BC [24]. A decrease in vimentin expression was correlated with an increase in ER expression in an older study [31]. In addition,

the expression of the *ESR1* gene has been investigated among cases with ER-low-positive BC. Iwamoto et al. reported that the average *ESR1* expression was significantly increased in the ≥10% ER-positive group compared to the 1% to 9% ER expression or ER-negative groups [32]. Consistent findings were reported in a recent study where the average *ESR1* expression was significantly higher in the ER-high-positive cohort than in the ER-low or negative cohort [19]. However, in another study that evaluated the expression levels of a selected set of ER-regulated genes, namely *ESR1*, *PgR*, *GATA3*, *TFF1*, *FOXA1* and *XBP1* along with a panel of three reference genes, the results demonstrated that the tumors in the ER-low group were almost evenly distributed between the ER-high-positive and negative groups [33]. ER-low BCs are more likely to carry a *BRCA1* or *BRCA2* mutation, and this finding indicates the need for genetic counseling and *BRCA* testing in this subset of patients [34]. High frequencies of *TP53* but not *PIK3CA* mutations have been shown in ER-low-positive BC Furthermore, a recent study investigated the prognostic role of H3 lysine nine trimethylation (H3K9me3) in relation to ER status. ER-positive tumors were stratified by ER-low and ER-high-positive tumors, and the prognostic role of H3K9me3 was significant only among the ER-high-positive patients, indicating distinct pathogenicity among the two groups [35].

3.2. Prognosis and (Neo)adjuvant Therapy

Most data on the prognosis of ER-low-positive BC are obtained from retrospective studies mainly involving patients with early BC (Table 2). A large-scale retrospective study from Europe showed that the time to local recurrence, time to lymph node recurrence and time to metastasis among HER2-negative BC were similar in ER-low and ER-negative BC and higher compared to ER-high-positive BC [22]. Notably, in the category of HER2-positive BC, ER-low-positive, ER-negative and ER-high-positive BC did not have significant differences in terms of prognosis. The authors conclude that HER2-negative and concomitantly ER-low-positive BC resemble TNBC [22]. A large cohort from Korea reported consistent findings. In this epidemiological retrospective study, the highest 5-year disease-free survival (DFS) rate was observed in patients in the ER-high/HER2-negative cohort (94.0%), and the lowest 5-year DFS rates were in patients in the TNBC cohort (81.3%) and the ER-low/HER2-negative cohort (85.7%) [21]. The shorter DFS for the TNBC and ER-low/HER2-negative combined cohorts were significantly correlated with higher tumor stage, lymphovascular invasion, greater regional lymph node involvement, and larger tumor size [21]. The patients with ER-low BC had a statistically significant worse DFS and overall survival (OS) compared with patients with ER-positive BC, whereas no differences were reported between the ER-low and ER-negative subgroups in a meta-analysis of retrospective studies that included patients with BC who received neoadjuvant chemotherapy (NAC) [36]. However, it should be noted that a recent study from Norway that included women diagnosed with BC in 1995 or later demonstrated that the cumulative risk of death from BC was 22.3% after five years for ER expression < 1% and 8.3% for both the ER-low-positive and ER expression ≥ 10% groups, meaning that there was no apparent difference in the risk of death from BC between the ER-low-positive and ER expression > 10% groups [37].

An important and relevant question is whether adjuvant ET confers survival benefits in patients with ER-low-positive BC. In 2011, the Early Breast Cancer Trialists' Collaborative Group conducted a patient-level meta-analysis aiming to associate the levels of ER expression with the recurrence reduction with the use of 5-year adjuvant tamoxifen [38]. The results showed a significant benefit in the subgroup analysis even for patients with marginally ER-positive BC (10–19 fmol/mg cytosol protein) from tamoxifen (risk ratio ± standard error, 0.67 ± 0.08) [38]. Nevertheless, several recent retrospective studies have not confirmed this finding. In a retrospective study of 9639 patients with early BC, it was reported that (a) no significant difference was observed in recurrences between patients with ER-low and ER-negative tumors (19.4%) (p = 0.5), (b) for patients receiving ET, recurrence rates were higher in patients whose tumors were ER-low-positive compared with those that were ER-positive with ER expression ≥ 10% (17.7% versus 7.7%, p = 0.02) and (c) there

was no significant difference in total recurrences between the groups of patients who did not receive ET [39]. Another study showed that the 5-year DFS and OS did not significantly differ between ER-negative and ER-low-positive groups, irrespective of receiving endocrine treatment [40]. A lack of benefit from ET in patients with ER-low BC has recently been shown in a meta-analysis, including more than 16,000 patients. This meta-analysis indicated that patients with early BC and ER expression between 1 and 9% gained no significant survival benefit from ET but exhibited a better overall prognosis than patients with ER expression < 1% [41]. Nevertheless, a recent study demonstrated that ET was correlated with increased breast cancer-specific survival in patients with ER-low BC. No significant difference in breast cancer-specific survival was observed between patients who received 2–3 years and >3 years of ET [42]. The potential of a de-escalation strategy was also suggested in a recent propensity-matched analysis, which reported that there was no significant difference in DFS between patients who received 2–3 years and five years of ET (HR, 0.82; 95% CI, 0.51–1.33; $p = 0.43$), indicating that short-term ET for 2 to 3 years might be an alternative for patients who have ER-low-positive BC [43].

Table 2. Recent studies on prognosis of patients with early-stage ER-low BC.

Author (Year)	Type of Study	Results	Reference
Schrodi (2021)	Retrospective population-based cohort study	Significantly decreased OS of ER-low/HER2(–) compared to ER-positive/HER2(–)	[22]
Park (2021)	Retrospective unicentric cohort	DFS and OS in the ER-low/HER2(–) cohort were more similar to the TNBC cohort than those with ER-high/HER2(–) BC	[21]
Paakkola (2021)	Meta-analysis	Significantly worse DFS and OS of ER-low patients compared to patients with ER-positive BC	[36]
Skjervold (2023)	Retrospective population-based cohort study	No significant difference in prognosis (risk of death from BC) of patients with ER-low BC compared to those with ER-positive BC for patients diagnosed after 1995	[37]

OS: overall survival; ER: estrogen receptor; HER2: human epidermal growth factor 2; DFS: disease-free survival; TNBC: triple-negative breast cancer; BC: breast cancer.

In early-stage ER-positive BC, the decision to offer adjuvant chemotherapy depends on the risk of recurrence, which is assessed with clinicopathological criteria and genomic tests [1]. Assuming that a case of ER-low-positive BC is diagnosed in an early stage, without lymph nodes or with minimal node involvement (1–3 lymph nodes), it is reasonable to ask whether using genomic tests is of the same utility as for ER-high BC [44]. A recent study evaluated the role of the Oncotype Dx Breast Recurrence Score Assay in 38 patients with ER-low-positive BC [45]. The results revealed that the majority of the patients with HER2-negative/ER-low-positive BC had a recurrence score (RS) > 25, and the authors concluded that perhaps genomic tests are of limited use as most patients are likely to benefit from adjuvant chemotherapy [45].

Furthermore, NAC therapy is sometimes indicated in early ER-positive BC in order to downstage the tumor; however, it is well known that patients with ER-positive BC are not likely to achieve a pathologic complete response (pCR), contrary to patients with TNBC and HER2-positive disease. It has been reported that the pCR rate of patients with ER-low BC was intermediate between the pCR rate of patients with ER-high and ER-negative BC following NAC treatment [46]. In another study, among 358 patients receiving NAC, the pCR rates were similar for the TNBC and ER-low-positive groups (49.2% vs. 51.3%, respectively, $p = 0.808$) [26]. Moreover, in a cohort of 165 patients that received NAC, the pCR rate was comparable between the two groups (38% in the ER-negative group, 44% in the ER-low-positive group, $p = 0.498$) [47]. Interestingly, Fujii et al. identified 9.5% ER

expression as the cut-off percentage below which a pCR was likely [48]. Additionally, when comparing ER-negative, ER-low, and ER-high-positive BC in NAC clinical trial cohorts (n = 2765), the results demonstrated no significant differences in the pCR rates between women with ER-low-positive tumors and women with TNBC [49]. In general, the significant pCR rates in TNBC cases are attributed to the higher cell proliferation rates compared to ER-positive BC [50]. The addition of immunotherapy has also increased the rates of pCR in TNBC, which is mainly relevant for the immunogenic subtypes of the disease [50]. It has been suggested that patients with ER-low and HER2-negative BC could be included in the clinical trials of NAC for TNBC and potentially share the same benefit from the addition of immunotherapy, as discussed below [50].

3.3. Immune Microenvironment and Immunotherapy

Given the remarkable advances in the field of oncology immunotherapeutics, particular interest lies in the potential of immunotherapy in BC. In general, ER-negative tumors are characterized by increased sTIL infiltration, CD8 + T-cells, and a higher expression of immune-related gene sets, resulting in a more inflamed tumor microenvironment, while ER-positive BC is traditionally considered to be an immunologically "cold" tumor [51,52].

The immunological features of HER2-negative BC with low-positive (1–9%) or intermediate-positive (10–50%) ER expression were investigated in a recent study, as compared to TNBC and tumors with high ER expression (>50%) [53]. The results showed that among the groups of BC with an ER expression of 0%, an ER expression of 1–9% and an ER expression of 10–50%, the levels of stromal TILs, CD8 + T cells and PD-L1 positivity were similar [53]. Also, the expression of certain immune-related gene signatures in tumors with an ER expression of 1–9% and an ER expression of 10–50% was analogous to an ER expression of 0% and higher than in tumors with an ER expression of 51–99% and an ER expression of 100% [53]. Although there is currently no data on patients with ER-low BC who received immunotherapy in early or metastatic settings, since ER-low BC biologically mimics TNBC, it has been suggested that those patients could be included in clinical trials of TNBC and potentially derive benefit from immunotherapy [50]. However, it should be noted that TNBC exhibits a great degree of heterogeneity and includes several phenotypes, not all of which are immunogenic [50]. The presumed biological similarities between ER-low-positive BC and TNBC might be limited to particular phenotypes of TNBC and need to be further explored.

4. Knowledge and Research Gaps in ER-Low-Positive BC (Figure 1)

4.1. Early-Stage ER-Low-Positive BC

Accumulating evidence has been published questioning the benefit of adjuvant ET for patients with ER-low-positive BC; however, the data remain contradictory [38,39,41,42]. The retrospective nature of the majority of the studies, the heterogeneous design and the different endpoints limit the drawing of clear conclusions. Notably, at the 17th St. Gallen International Breast Cancer Consensus in 2021, the panel was dichotomized on the optimal ER threshold for endocrine therapy initiation [54]. The duration of ET could also be discussed, with some studies suggesting an alternative option with short-term adjuvant ET [42,43].

Besides adjuvant ET, numerous questions arise concerning the following: (a) when should NAC therapy be proposed for patients with ER-low BC and which is the optimal regimen; (b) should the majority of the patients with ER-low BC receive adjuvant chemotherapy; and (c) what is the role of adjuvant cyclin-dependent kinase (CDK)4/6 inhibitor therapy, which has been recently introduced in high-risk patients with ER-positive BC [44]. The stratification of patients according to ER status, including the ER-low-positive group, in randomized clinical trials might improve the understanding of those questions. In parallel, the introduction of patients with ER-low BC in clinical trials of TNBC may illustrate better tactics for their management. A recent phase II trial (NeoPACT) assessing the addition of pembrolizumab in carboplatin plus docetaxel in patients with TNBC

allowed for the inclusion of patients with ER-low BC, who comprised 15% of the study population [55].

4.2. Metastatic ER-Low-Positive BC

There is a significant lack of published real-world cohorts regarding patients with metastatic ER-low-positive BC. The combination of a CDK 4/6 inhibitor plus ET, the current standard of care for ER-positive BC, is theoretically indicated in these cases [2]. However, should these patients be assumed to be mostly endocrine-resistant and more chemo-sensitive? In parallel, the introduction of immunotherapy for metastatic TNBC raises the question of the potential benefit to the biologically similar ER-low-positive BC.

The latest European School of Oncology/European Society of Medical Oncology (ESO/ESMO) consensus guidelines recommend that the 2020 ASCO/CAP acknowledgment that patients with tumors with ER staining between 1% and 10% represent a new reporting category with proximity to ER-negative BC, without solid data concerning the benefit from ET, should also be adopted for patients with metastatic BC with a low ER-positive status [56]. In particular, the guidelines state that patients with ER-low-positive and HER2-negative metastatic BC should not be considered for ET exclusively and could be considered patients with TNBC for clinical trials [56].

4.3. ER Expression Heterogeneity

The identification of low ER expression in a single biopsy might not reflect the expression pattern of the whole tumor mass(es). It has been observed that BC exhibits a degree of genotypic and phenotypic heterogeneity, which could be distinguished into intertumor and intratumor heterogeneity [57]. The expression of ERs could be different between primary and metastatic lesions or in different parts of the same tumor. This phenomenon cannot be currently encompassed in a single pathology report, especially when the biopsy is small [58].

For example, the hormone receptors' conversion in metastatic BCs, either from a positive primary tumor to a negative metastasis or the opposite, has been reported as high as 18.3% for ERs and 40.3% for the PR [59]. Such discordance could mislead the selection of an effective therapy, especially when only one biopsy is available and it may not reflect the phenotype of the whole tumor [58,60]. The latest guidelines recommend considering the use of ET whenever ER expression is positive in at least one biopsy, even in cases of discordance between ER expression in primary and metastatic samples [56]. Identifying and quantifying the heterogeneity is of utmost importance, as it has a significant role in deciding the suitable therapy and predicting the outcome [57]. Perhaps the development, validation and incorporation of liquid biopsies could bypass this obstacle and lead to optimal therapeutic decisions [61,62].

4.4. ER Loss Due to Endocrine Resistance

Endocrine resistance, either primary or secondary, is a major challenge that could occur during the therapy of ER-positive BC [63]. It has been proposed that a proportion of ER-negative and ER-low-positive cells stem from ER-positive cells that lose their ER expression [64]. This alteration could happen spontaneously, due to the selective pressure caused by the absence of estrogen, or even as an adaptive response against specific pharmacological agents [64]. More specifically, it has been shown that a loss of ER expression occurs in approximately 10–20% of the cases during disease progression [63].

The mechanisms involved in the suppression of ER expression include genetic or epigenetic changes in the *ESR1* gene, post-translational modifications or altered receptor tyrosine kinase signaling and cell cycle regulation [63,65,66]. Perhaps the identification of ER-low-positive BC during the disease course could be attributed to ER loss due to endocrine resistance. With an "out-of-the-box" approach, mainly in the pre-clinical research field, we could assume that the finding of ER-low positivity might not preclude ET but rather guide a strategy aiming to reverse this process and re-sensitize the tumor to ET [64].

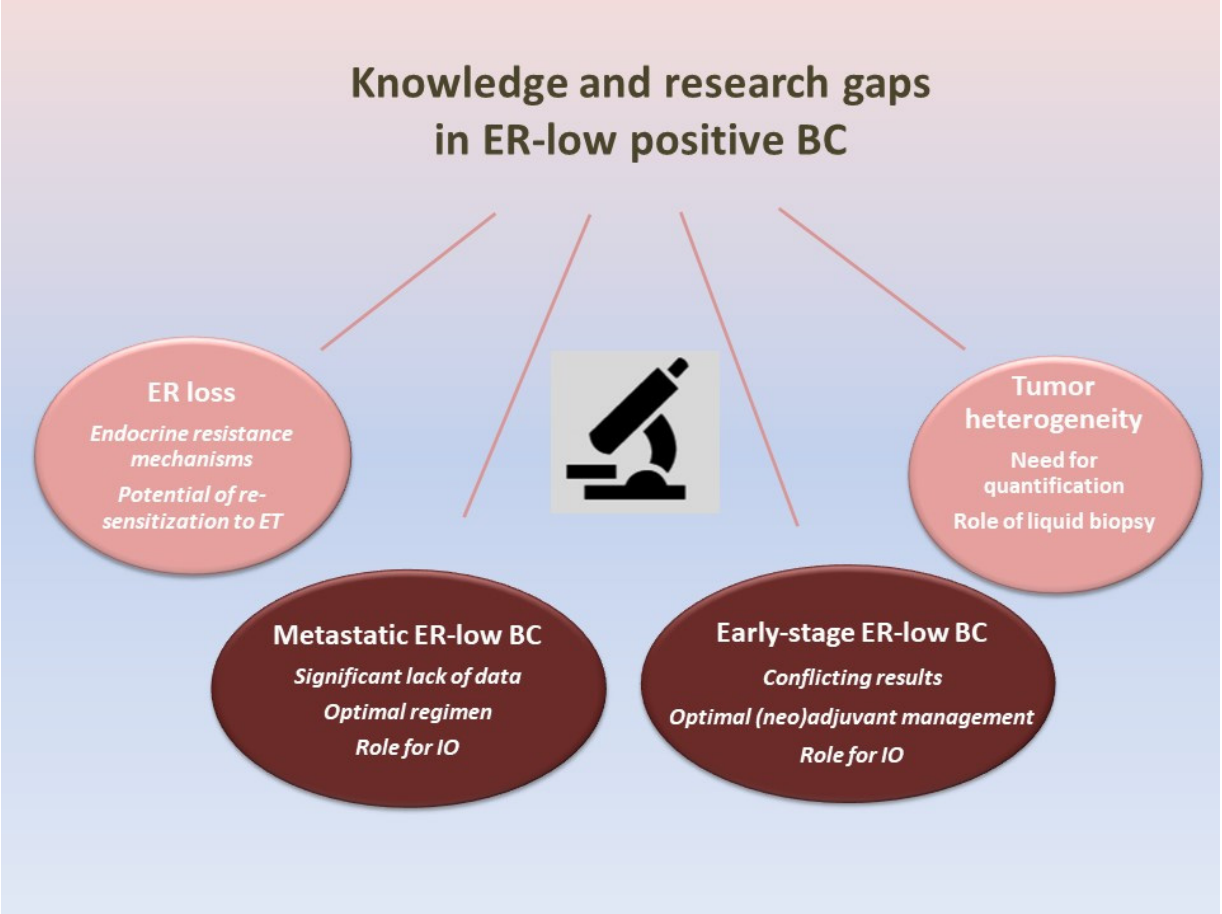

Figure 1. The figure illustrates the research and knowledge gaps regarding ER-low-positive BC. Knowledge and research gaps regarding ER-low-positive BC include the interpretation of conflicting data on early-stage ER-low-positive BC, the significant lack of data on metastatic ER-low BC and incorporating aspects of ER heterogeneity and ER loss due to endocrine resistance. ER: estrogen receptor; BC: breast cancer; ET: endocrine therapy; IO: immunotherapy.

5. Conclusions

ER-low-positive BC comprises a small subgroup of the total BC cases but represents a challenging entity with unclear management. Given the conflicting results leading to uncertainty in clinical practice, the role of biomarkers for predicting the benefit of different therapies should be evaluated, including the expression of PR, HER2 or other immune-related biomarkers, such as the sTILs. The inclusion of those patients in clinical trials for TNBC might provide valuable information regarding better management options; however, the significant heterogeneity of TNBC should be taken into account. Finally, well-designed randomized clinical trials for this well-characterized population are greatly anticipated.

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Abbreviations

AKT: Protein Kinase B; AR: Androgen Receptor; ASCO: American Society of Clinical Oncology; BC: Breast Cancer; BRCA1/2: Breast Cancer gene 1/2; cAMP: cyclic Adenosine Monophosphate; CAP: College of American Pathology; CDK: Cyclin-dependent Kinase; CK14: Cytokeratine 14; CPK 5/6: Creatine Phosphokinase; DFS: Disease-Free Survival; DNA: Deoxyribonucleic Acid; EGFR: Epidermal Growth Factor Receptor; ER: Estrogen Receptor; ERE: Estrogen Response Elements; ESMO: European Society of Medical Oncology; ESO: European School of Oncology; ESR1: Estrogen Receptor 1; ET: Endocrine Therapy; FOXA1: Forkhead Box A1; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormone Receptor; IHC: Immunohistochemistry; IO: Immunotherapy; ISH: In Situ Hybridization; LBD: Ligand-Binding Domain; MAPK: Mitogen-Activated Protein Kinase; mTOR: mammalian Target Of Rapamycin; NAC: Neoadjuvant Chemotherapy; NTD: NH2-Terminal Domain; OS: Overall Survival; P63: Protein 63; pCR: pathologic Complete Response; PD-L1: Programmed Death-Ligand1; PgR: Progesterone Receptor; PI3K: Phosphoinositide-3 Kinase; PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; H3K9me3:H3 Lysine 9 Trimethylation; PR: Progesterone Receptor; qPCR: quantative Polymerase Chain Reaction; RS: Recurrence Score; sTILs: stromal Tumor Infiltrating Lymphocytes; TFF1: Trefoil Factor 1; TILs: Tumor-Infiltrating Lymphocytes; TNBC: Triple-Negative Breast Cancer; TP53: Tumor Protein 53; XBP1: X-box Binding Protein 1.

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Current Oncology

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Brief Report

Is There a Role for Risk-Reducing Bilateral Breast Surgery in *BRCA1/2* Ovarian Cancer Survivors? An Observational Study

Daniela Oliveira [1,2,3], Sofia Fernandes [4], Isália Miguel [4,5], Sofia Fragoso [6] and Fátima Vaz [4,5,*]

1 Medical Genetics Unit, Centro Hospitalar e Universitário de Coimbra, 3000-602 Coimbra, Portugal; danielaoliveira@chuc.min-saude.pt
2 University Clinic of Genetics, Faculdade de Medicina, Universidade de Coimbra, 3000-548 Coimbra, Portugal
3 Clinical Academic Center of Coimbra, 3004-561 Coimbra, Portugal
4 Familial Cancer Risk Clinic, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal; sffernandes@ipolisboa.min-saude.pt (S.F.); imiguel@ipolisboa.min-saude.pt (I.M.)
5 Medical Oncology Service, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal
6 Molecular Pathobiology Research Unit, Instituto Português de Oncologia de Lisboa Francisco Gentil, 1099-023 Lisboa, Portugal; afragoso@ipolisboa.min-saude.pt
* Correspondence: fvaz@ipolisboa.min-saude.pt

Abstract: Background: Risk-reducing surgeries are an option for cancer risk management in *BRCA1/2* individuals. However, while adnexectomy is commonly recommended in breast cancer (BC) survivors, risk-reducing bilateral breast surgery (RRBBS) is controversial in ovarian cancer (OC) survivors due to relapse rates and mortality. Methods: We conducted a retrospective analysis of *BRCA1/2*-OC survivors, with OC as first cancer diagnosis. Results: Median age at OC diagnosis for the 69 *BRCA1/2*-OC survivors was 54 years. Median overall survival was 8 years, being significantly higher for *BRCA2* patients than for *BRCA1* patients (p = 0.011). Nine patients (13.2%) developed BC at a median age of 61 years. The mean overall BC-free survival was 15.5 years (median not reached). Eight patients (11.8%) underwent bilateral mastectomy (5 simultaneous with BC treatment; 3 RRBBS) at a median age of 56.5 years. The median time from OC to bilateral mastectomy/RRBBS was 5.5 years. Conclusions: This study adds evidence regarding a lower BC risk after *BRCA1/2*-OC and higher survival for *BRCA2*-OC patients. A comprehensive analysis of the competing risks of OC mortality and recurrence against the risk of BC should be individually addressed. Surgical BC risk management may be considered for longer *BRCA1/2*-OC disease-free survivors. Ultimately, these decisions should always be tailored to patients' characteristics and preferences.

Keywords: ovarian cancer; breast cancer; hereditary cancer; *BRCA*; risk-reducing bilateral breast surgery

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1. Introduction

Women with hereditary breast and ovarian cancer syndrome have an increased risk of developing cancer, mainly breast cancer (BC)—absolute risk > 60% for *BRCA1/2* carriers—and ovarian cancer (OC)—absolute risk of 39–58% for *BRCA1* and 13–29% for *BRCA2* carriers [1].

Currently, breast imaging, such as ultrasound, mammography and/or magnetic resonance imaging (MRI), is widely recommended to detect malignant lesions at an early stage in *BRCA1/2* women [1]. However, the most significant approach to reduce BC risk in *BRCA1/2* carriers is risk-reducing bilateral breast surgery (RRBBS) [2]. Some previous reports stated that there was a BC risk reduction of 90 to 95% in *BRCA1/2* women that underwent RRBBS, although no significative reduction in mortality was observed [3]. Likewise, risk-reducing adnexectomy is strongly recommended, typically between 35 and 40 years, to manage OC risk in *BRCA1/2* women [1]. In addition to a profound decrease

in OC incidence, risk-reducing adnexectomy also leads to a substantial reduction in all-cause and OC-related mortality [3]. While risk-reducing adnexectomy is still commonly recommended in *BRCA1/2*-BC survivors, RRBBS is controversial in *BRCA1/2*-OC survivors, due to the high relapse rate and mortality associated with OC. In fact, there is a lack of thorough recommendations concerning BC risk and the role of RRBBS in *BRCA1/2*-OC survivors. In this study, we evaluate the incidence of BC after *BRCA1/2*-OC and report our experience with RRBBS in these patients.

2. Materials and Methods

All consenting women testing positive for *BRCA1* or *BRCA2* were invited to participate in long-term prospective follow-up in the Familial Risk Clinic of IPO Lisboa. Patients are kept under surveillance until death, loss to follow-up or consent withdrawal. For this study, patients with OC as first cancer diagnosis and a *BRCA1/2*-positive test between January 2000 and August 2022 were selected. Women who had had another cancer before OC were excluded. Data before testing were retrospectively collected from available clinical reports. The start of the follow-up period was defined as the date of OC diagnosis. The overall and BC-free survival were calculated using the Kaplan–Meier method. The log-rank test was used to compare survival and BC incidence between different groups. Overall survival was considered as the time from OC diagnosis to the time of death, whereas BC-free survival was defined as the time from OC to BC diagnoses. Statistical analysis was conducted using SigmaPlot software, version 15.0.

3. Results

Over a period of 22 years, a total of 69 women, from 63 different families, were diagnosed with *BRCA1/2*-OC. The median age at OC diagnosis was 54 years (range: 18–85 years). Most patients for whom data were available were diagnosed with epithelial serous OC (75.9%) and at a III or IV FIGO stage (73.7%). Regarding molecular testing, 33 (47.8%) individuals were identified with a germline *BRCA1* variant and 36 (52.2%) with a germline *BRCA2* variant. Of the 36 *BRCA2* patients, 9 (25%) had the founder variant of Portuguese origin *BRCA2*:c.156_157insAlu. Among the 69 patients, 55 (79.7%) had at least one relative with BC, while 14 (20.3%) had no known relatives diagnosed with BC. Among those with positive family history of BC, 38 (69.1%) had an affected first-degree relative (Table 1). In the subgroup of nine patients who developed BC, eight (88.9%) reported positive family history, and only one (11.1%) patient had no family history of BC. Among those eight with a positive family history of BC, half had an affected first-degree relative (Table 2).

The median duration of follow-up for all patients since OC diagnosis was 6 years (range: 1–22 years). In this group, there were a total of 35 deaths from all causes (all-cause mortality rate: 50.7%) throughout the follow-up period. Death occurred at a median age of 59 years (range: 40–89 years), at a median of 4 years (range: 1–16 years) after OC diagnosis, and, in 94.3% of the cases (33 patients), within the first 10 years of follow-up. For the entire cohort, the median overall survival was 8.0 years (mean: 11.6 years), being significantly higher for *BRCA2*-OC patients (median: not reached; mean: 14.3 years) than for *BRCA1*-OC patients (median: 5 years; mean: 8 years) ($p = 0.011$).

Further, one of the 69 patients was lost to follow-up more than two years before death, so she is not considered when assessing BC (or other cancer types) risk in this cohort. A total of nine (13.2%) patients developed BC after the OC at a median age of 61 years (range: 44–68 years). The median BC-free survival could not be calculated via Kaplan–Meier survival analysis because of the small number of patients who were diagnosed with BC after OC, with the mean BC-free survival in the total population being 15.5 years (Figure 1). The difference in BC-free survival between *BRCA1*-OC women (median: not reached; mean: 12.9 years) and *BRCA2*-OC women (median: not reached; mean: 15.9 years) did not reach statistical significance ($p = 0.440$). The difference in the overall survival between *BRCA1/2*-OC women with BC (median: not reached; mean: 16.4 years) and *BRCA1/2*-OC

women without BC (median: 8.0 years; mean: 9.9 years) was also not statistically significant ($p = 0.107$).

Table 1. Characterization of the cohort.

CHARACTERISTIC	
Number of patients	69
Number of families	63
MOLECULAR RESULT	
BRCA1	33 (47.8%)
BRCA2	36 (52.2%)
BRCA2:c. c.156_157insAlu	9 (25%)
OVARIAN CANCER	
Median age [range]	54 y [18–85 y]
FIGO stage	
I	11 (18.0%)
II	5 (8.2%)
III	34 (55.7%)
IV	11 (18.0%)
Unknown	8
Histology	
Epithelial serous	44 (75.9%)
Epithelial endometrioid	3 (5.2%)
Epithelial mucinous	1 (1.7%)
Epithelial transitional cell	1 (1.7%)
Mixed epithelial serous and endometrioid	2 (3.4%)
Mixed epithelial serous and transitional cell	1 (1.7%)
Poorly differentiated	6 (10.3%)
Unknown	11
NUMBER OF DEATHS (all causes)	35 (50.7%)
Median age [range]	59 y [40–89 y]
Median time after OC [range]	4 y [1–16 y]
Death within the first 10 years of follow-up	33 (94.3%)
FAMILY HISTORY OF BC	
Positive—all known relatives	55 (79.7%)
First-degree relatives	38 (69.1%)
Negative	14 (20.3%)

Table 2. Characterization of BC diagnosed in the cohort.

BREAST CANCER	9 (13.2%)
Median age [range]	61 y [44–68 y]
Median time after OC [range]	5 y [2–14 y]
RECEPTORS	
ER and PR negative	2 (22.2%)
ER and/or PR positive	7 (77.8%)
Her2 negative	7 (77.8%)
Triple negative	2 (22.2%)
FAMILY HISTORY OF BC	
Positive-all known relatives	8 (88.9%)
First-degree relatives	4 (50.0%)
Negative	1 (11.1%)

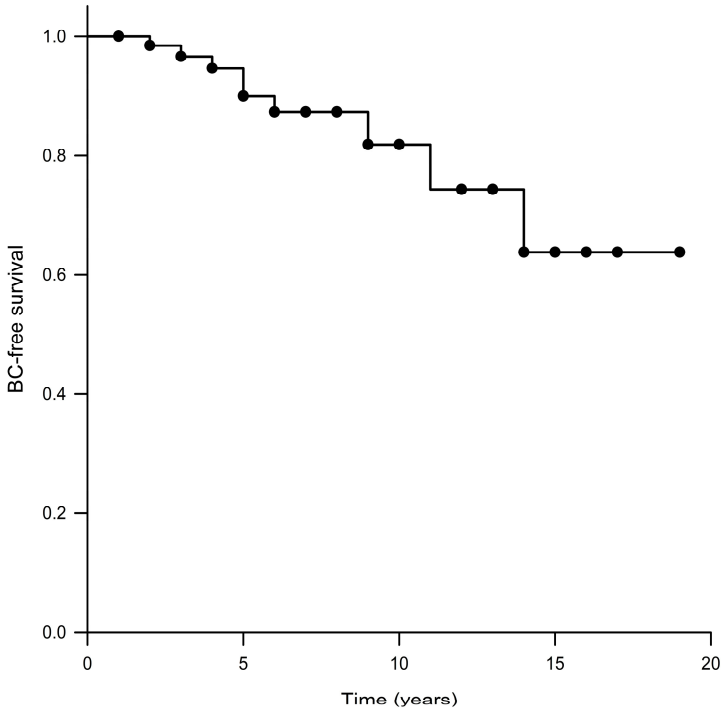

Figure 1. Kaplan–Meier analysis of BC-free survival.

All diagnosed BCs were unilateral, and two of them were triple-negative (both *BRCA1* patients). Of the nine patients with BC, five (55.6%) had a *BRCA1* variant, whereas four (44.4%) had a *BRCA2* variant (two with the Portuguese founder variant). Three out of the nine *BRCA1/2*-OC women with BC died at a median age of 51 years (range: 50–61 years) and at a median time of 7 years after the OC diagnosis (range: 5–9 years). The cause of death of these three patients was unrelated to BC: 1—ovarian cancer progression; 2—refractory leukemia; 3—overdose in a patient in remission of both cancers. The characterization of BC diagnosed in our cohort is detailed in Table 2.

Five (7.4%) patients underwent bilateral mastectomy in a unilateral BC context (Table 3). Bilateral mastectomy was performed at a median age of 54 years (range: 44–69 years) and at a median of 6 years (range: 2–15 years) after the OC diagnosis. Three (4.4%) patients, without personal history of BC, were submitted to RRBBS at a median age of 58 years (range: 55–61 years) (Table 3). The median time from OC diagnosis to RRBBS was 5 years (range: 3–15 years).

Table 3. Characterization of bilateral mastectomy and RRBBS in the cohort.

BILATERAL MASTECTOMY	5 (7.4%)
Median age [range]	54 y [44–69 y]
Median time after OC [range]	6 y [2–15 y]
RRBBS	3 (4.4%)
Median age [range]	58 y [55–61 y]
Median time after OC [range]	5 y [3–15 y]

In this cohort, five other cancers were diagnosed during the follow-up period—a squamous cell carcinoma of the tongue at the age of 51 (one patient), a synchronous high-stage serous carcinoma of the endometrium at the age of 75 (one patient) and basal cell carcinomas of the skin at ages of 59 and 72 (two patients). One patient was diagnosed with acute myeloid leukemia, secondary to chemotherapy for ovarian cancer, at the age of 60 and BC at the age of 61.

4. Discussion

In this study, we observed an incidence of 13.2% of BC in a cohort of 68 *BRCA1/2*-OC women during a median follow-up period of 6 years. The mean BC-free survival in the total population was 15.5 years (median: not reached), with no significant difference for *BRCA1*-OC, as compared to *BRCA2*-OC patients. While we observed a significantly higher overall survival for *BRCA2*-OC patients as compared with *BRCA1*-OC patients, the difference in overall survival between *BRCA1/2*-OC women with BC and *BRCA1/2*-OC women without BC was not found to be statistically significant.

The incidence of BC in our cohort was slightly higher than that reported in previous studies, such as that described by Vencken et al. [4], who identified 8 primary BCs in 79 *BRCA1/2*-OC women (10.1%) during a mean period of 6.7 years, and by Domchek et al. [5], who reported 11% of BCs (18 patients) in a group of 164 during a mean follow-up of 5.8 years. Similarly, Gangi et al. [6] described an incidence of 8.9% of BC (12 women) in 135 patients with a mean follow-up period of 6.6 years, and Fong et al. [7] identified 8.3% (16 patients) in 192 *BRCA1/2*-OC women. More recently, a larger cohort of 502 patients was characterized by Safra et al. [8], who reported a lower incidence (6.2%) of BC in 502 *BRCA1/2*-OC women, with a median follow-up of 5.0 years. The small number of *BRCA1/2*-OC women included in most of the studies, including our own, is a limitation regarding conclusions about the incidence of BC in this specific population. However, caution should also be taken when drawing conclusions, as inclusion criteria and mutational *BRCA1/2* patterns differ among these studies. For example, Safra et al. [8] included women with BC and other cancers diagnosed prior to OC (representing 17.5% and 1.6% of the cohort, respectively) in their cohort. In our study, any type of cancer diagnosed before OC was an exclusion criterion. Another note that must be emphasized is that women who underwent RRBBS were maintained in our cohort, even after prophylactic surgery. Even after RRBBS, there is a remaining BC risk, and, in our registry, patients are kept in surveillance until death, are lost to follow-up or withdraw their consent.

Regarding mutational *BRCA1/2* patterns, our study is the first where the numbers of *BRCA2*-OC women are higher than *BRCA1*-OC patients (*BRCA2*: 52.2% vs *BRCA1*: 47.8%). In all previous studies, *BRCA1*-OC patients represented more than 70% of the cohort [4–8]. As we discuss below, data are conflicting regarding *BRCA1* and *BRCA2* as biomarkers for better survival when compared with sporadic OC. However, a relevant finding in our study is the increased overall survival observed in the *BRCA2*-OC subgroup when compared to *BRCA1*-OC patients (14.3 years vs. 8 years, $p = 0.011$). This observation was previously described in a pooled analysis of 26 studies [9].

Vencken et al. [4] reported a BC risk of 3%, 6% and 11% in *BRCA1/2*-OC survivors in the following 2, 5 and 10 years after OC diagnosis. The same study reported a signif-

icantly higher BC risk in unaffected variant carriers during the same follow-up period (6%, 16% and 28%, respectively) [4]. Domchek et al. [5] also reported a less-than-10% risk of developing BC in the 10-year follow-up period (12% for *BRCA1* carriers and 2% for *BRCA2* carriers). In a more recent study, McGee et al. [10] reported a risk of 7.8% of developing BC in a 10-year interval, conditional on OC survival and other causes of death. Despite the fact that data are still limited and larger studies are needed, *BRCA1/2*-OC survivors appear to have a significantly lower risk of developing BC after OC than unaffected individuals. Previous studies suggested several reasons for the apparent lower BC risk in *BRCA1/2*-OC survivors compared to unaffected women. One of the reasons is the premature termination of ovarian function due to salpingo-oophorectomy, usually performed in an OC treatment context [4–6]. In line with that, previous studies reported that risk-reducing adnexectomy reduces the risk of BC in *BRCA1/2* patients, mainly if performed at a premenopausal age [4,5,11,12]. Another aspect that is likely to contribute to a lower rate of BC in this subgroup is the effect of the therapy for OC. Some authors argue that platinum-based chemotherapy usually used for OC treatment could contribute to eradicating submicroscopic breast disease, leading to a lower number of BCs in these patients [4–6].

Although there are conflicting data in the literature, some studies reported that carrying a *BRCA1* or *BRCA2* variant leads to better responses to both platinum- and non-platinum-based chemotherapies, as well as better progression-free and overall survival in OC patients [13]. Nonetheless, McLaughlin et al. [14] demonstrated that *BRCA1* or *BRCA2* variants could be an advantage in OC patients to short-term survival but not to long-term survival. Although there is a trend for increasing OC survival due to recent advances in therapeutic approaches, OC 5-year and 10-year survival rates remain poor (63% and 35%, respectively) [4]. In our study, we report a mortality rate of 50.7% at a median age of 59 years, which is similar to those previously reported (53.2%, 51.1%, 40.7% and 36.3%) [4,6,8,10]. Moreover, most patients in our cohort (74.6%) were diagnosed with a high-stage OC, which is comparable to the 76% reported in Vencken et al. [4] and the most prevalent stage IIIC in Gangi et al. [6]. Currently, patients' outcome is essentially determined by OC mortality rate and the risk of relapse, mainly during the first years after diagnosis. Noteworthily, 94.3% of deaths in our cohort occurred within the first 10 years of follow-up after OC diagnosis. We registered three deaths among *BRCA1/2*-OC women with BC but none were linked to the diagnosis of BC. Similarly, Domchek et al. [5] and Safra et al. [8] also stated that none of the deaths in their cohorts of women with OC and BC were related to BC. In the Fong et al. [7] study, only one patient died of BC.

Taking all data into consideration, we propose that BC after *BRCA1/2*-OC would still require specific surveillance, especially in those women who have better prognosis. Based on simulation studies, McGee et al. [10] concluded that the risk of death from BC after OC is about 1%, and breast MRI screening and RRBBS will have a very small impact on survival. For example, among all *BRCA1/2* women diagnosed with stage III/IV OC at the age of 50, breast MRI screening and RRBBS will reduce, by 1% and 2%, respectively, the chance of dying by the age of 80. However, these effects could be greater if OC was diagnosed at an early age or at lower stages, leading several authors to propose that RRBBS or breast MRI screening should be recommended to all patients diagnosed with stage I or II OC and those patients with stage III or IV OC diagnosed at or before the age of 50 and surviving at least 10 years without relapse [10]. It is of note that in our study, eight patients underwent BC risk-reducing surgery, but for five of these patients, surgery was decided in the context of a BC diagnosis and regarding contralateral BC risk reduction.

We are aware that several limitations of this study, particularly the small cohort and the lack of a control group, should be considered when conclusions are discussed. Data regarding individual treatment and OC relapse were also not included in the current discussion. However, this study adds data to the discussion regarding the risk of developing BC in a population of *BRCA2*-enriched OC survivors. With recent advances in treatment, the number of *BRCA1/2*-OC survivors may increase in the near future, and this information may

help clinicians to provide more accurate counseling regarding BC risk and risk management options to these patients. We are looking forward to in-depth future collaborative studies, including larger cohorts, so as to obtain more robust recommendations for this subgroup.

5. Conclusions

During the early period after OC diagnosis, OC mortality and recurrence rates are significantly high, and BC risk appears to be lower than in unaffected *BRCA1/2* individuals. With that in mind, invasive BC risk management could bring an inappropriate burden without significant benefits to these patients. However, with the positive survival impact of new therapeutic advances, we expect a rising number of *BRCA1/2*-OC survivors with health professionals having to face the dilemma of RRBBS in the context of a potentially life-limiting OC diagnosis. We propose a comprehensive analysis of the competing risks of OC mortality and OC recurrence against the risk of BC that should be individually addressed, particularly in those patients with longer disease-free survival. Ultimately, decisions regarding preventive measures should always be tailored to patients' characteristics and preferences.

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Institutional Review Board Statement: Ethical review and approval were waived for this observational study, since all patients included consented previously in data collection during prospective, non-interventional, follow-up. Data collection during follow-up of patients with a positive genetic testing was approved by the Ethics Committee of our Institute (Comissão de Ética do Instituto Português de Oncologia de Lisboa, EPE). Of note, after implementation of the European 679/2016 Regulation, data collection and consent forms were reviewed and approved by the same Ethics Committee.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. All genetic records are protected with restricted access, as per Portuguese law. All forms related to this study were approved by the Ethics Committee of our Institute (Comissão de Ética do Instituto Português de Oncologia de Lisboa, EPE).

Data Availability Statement: Data are contained within the article.

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

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Controlateral Symmetrisation in SRM for Breast Cancer: Now or Then? Immediate versus Delayed Symmetrisation in a Two-Stage Breast Reconstruction

Donato Casella [1], Daniele Fusario [2,*], Dario Cassetti [3], Anna Lisa Pesce [2], Alessandro De Luca [4], Maristella Guerra [5], Roberto Cuomo [6], Diego Ribuffo [7], Alessandro Neri [8] and Marco Marcasciano [9]

1 Department of Medicine, Surgery and Neurosciences, Unit of Breast Cancer Surgery, University of Siena, 53100 Siena, Italy
2 Department of Medicine, Surgery and Neurosciences, Unit of General Surgery and Surgical Oncology, University of Siena, 53100 Siena, Italy
3 Unit of General Surgery, USL Toscana Sud-Est, Valdarno Hospital Santa Maria alla Gruccia, 52025 Arezzo, Italy
4 Department of Surgery, Sapienza Università di Roma, 00185 Rome, Italy
5 Unit of Plastica Surgery, Polo Ospedaliero Santo Spirito ASL/RME, 00193 Rome, Italy
6 Department of Medicine, Surgery and Neurosciences, Unit of Plastic and Reconstructive Surgery, University of Siena, 53100 Siena, Italy
7 Department of Plastic Reconstructive and Aesthetic Surgery, Sapienza Università di Roma, 00185 Rome, Italy
8 Unit of Breast Surgery, USL Toscana Sud-Est, San Donato Hospital, 52100 Arezzo, Italy
9 Unit of Plastic and Reconstructive Surgery, University of Catanzaro "Magna Graecia", 88100 Catanzaro, Italy
* Correspondence: dani.fusario@gmail.com

Abstract: *Introduction:* The timing of contralateral symmetrisation in patients with large and ptotic breasts undergoing a unilateral skin-reducing mastectomy (SRM) is one of the most debated topics in the reconstructive field. There is no evidence to support the advantage of immediate or delayed symmetrisation to help surgeons with this decision. The aim of this study was to investigate the clinical and aesthetic outcomes of immediate symmetrisation. *Methods*: A randomised observational study was conducted on patients who underwent an SRM for unilateral breast cancer. Based on a simple randomisation list, patients were divided into two groups: a delayed symmetrisation group versus an immediate symmetrisation group. The postoperative complications, BREAST-Q outcomes and reoperations were compared. *Results:* Out of a total of 84 patients undergoing an SRM between January 2018 and January 2021, 42 patients underwent immediate symmetrisation and 42 patients had delayed symmetrisation. Three implant losses (7.2%) were observed and we reported three wound dehiscences; one of these was in a contralateral breast reconstruction in the immediate symmetrisation group. The BREAST-Q patient-reported outcome measures recorded better aesthetic outcomes and a high patient satisfaction for the immediate symmetrisation group. *Conclusions*: Simultaneous controlateral symmetrisation is a good alternative to achieve better satisfaction and quality of life for patients; from a surgical point of view, it does not excessively impact on the second time of reconstruction.

Keywords: breast reconstruction; skin-reducing mastectomy; implant-based breast reconstruction; subcutaneous implant positioning; controlateral breast symmetrisation

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1. Introduction

In 1991, Toth et al. [1] first described a skin-sparing mastectomy (SSM). By preserving the breast envelope and inframammary fold, a much more satisfactory cosmetic outcome could be achieved during a reconstruction.

Rice and Stickler in 1951 [2] described an "adeno-mammectomy" for benign diseases and Freeman in 1962 [3] presented the term "subcutaneous mastectomy": these are the first

descriptions of a nipple-sparing mastectomy (NSM). An NSM is similar to an SSM for the dissection of skin flaps, but considers the NAC.

In patients with large and ptotic breasts that are higher than the second degree according to the Regnault classification [4], it is difficult to approach a mastectomy because an excellent satisfactory aesthetic outcome is hard to obtain [5].

Carlson et al. [6] in 1997 described four types of incision that could be used for an SSM; in particular, the Wise pattern is used for those patients with medium-sized or large ptotic breasts. Therefore, these authors first described a technique that combined a skin-sparing mastectomy with a simultaneous reduction of the breast envelope. For many years, this was not universally known; thus, in 2006, Nava et al. reproposed and renamed this technique the skin-reducing mastectomy (SRM) [7].

Although the results were reassuring, patients with macromastia and ptotic breasts remained a stimulating group to treat; the timing of contralateral symmetrisation remains one of the most debated topics in the breast reconstruction field [8–10].

Nowadays, breast surgeons regularly try to perform a symmetrical and aesthetically pleasing breast reconstruction to achieve a better outcome.

Despite the pros and cons of immediate versus delayed symmetrisation being well-documented, the ideal moment for performing a contralateral surgical procedure remains debated [11].

Currently, immediate symmetrisation is a questioned procedure. On one hand, a few surgeons prefer delayed symmetrisation to reduce the operating times and blood loss, thus potentially decreasing the morbidities. Additionally, important fat necrosis or partial flap losses may impose a change in the plan for reconstructed and contralateral breasts. On the other hand, several surgeons prefer immediate symmetrisation in order to give the patient immediate psychological wellness and increase their quality of life by the immediate reduction of asymmetry and, furthermore, to reduce the number of postoperative expansions needed to the reach the final volume and to avoid another operation.

The purpose of this study was to investigate the clinical and aesthetic outcomes of immediate symmetrisation and to suggest our indication in an attempt to help surgeons with this operative decision.

2. Materials and Methods

This was a randomised observational study conducted on a population of patients with a diagnosis of unilateral breast cancer who underwent an SRM with a prepectoral tissue expander (Mentor CPX4, Mentor Worldwide LLC, Irvine, CA, USA) reconstruction implanted with specific covering devices (TiLoop® Bra, PFM medical, Cologne, Germany) followed by a substitution with a silicon-based implant at a later stage [12,13]. The enrolment started in January 2018 and ended in January 2021 at the Unit of Oncological Breast Surgery, University of Siena.

All women had a confirmed breast cancer diagnosis, were aged 18 years or older, met the criteria suggested by Nava et al. [7] for an SRM (patients with medium to large breasts with breast ptosis and at least grade II from the Regnault classification) and had a Pre-BRA score [14] from five to eight, indicating the implant of a prepectoral tissue expander and a subcutaneous definitive prosthesis from a second-time surgery.

The exclusion criteria were clinical evidence of axillary metastases or skin or chest wall tumour involvement, a body mass index greater than 35 kg/m^2, pregnancy, active smokers, connective tissue disease, diabetes, previous thoracic radiotherapy and previous breast surgery.

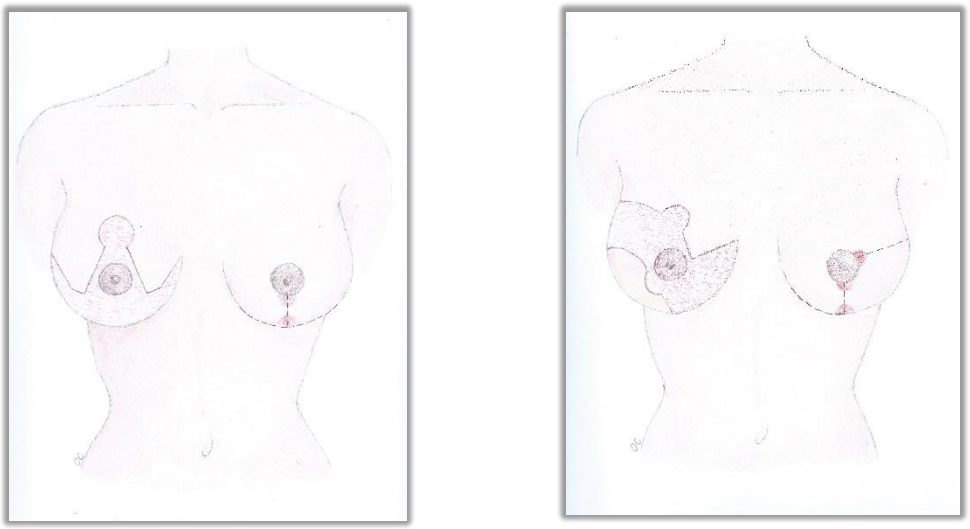
All data were collected upon informed consent acceptance and when the patients enrolled had accepted contralateral symmetrisation. We then divided the patients into two groups: one with delayed symmetrisation and one with immediate symmetrisation, based on a simple randomisation list using a dedicated computer program.

The patient data (including the age, body mass index and treatment characteristics as well as the indication for surgery, including the type of cancer, axillary surgery and

locoregional or systemic recurrence, surgical complications and aesthetic outcomes) were collected from our specifically designed database.

The study was accomplished according to the ethical standards of the Declaration of Helsinki. Ethics approval was not required because the different timings of contralateral symmetrisation did not require any modifications to the standard therapeutic protocols.

All SRMs were conducted by a Wise pattern incision or a modified Wise pattern incision used to remove the skin overlying or infiltrated by the tumour in the lateral quadrants of the breast, as shown in Figure 1; in all cases, the nipple–areola complex (NAC) was removed at the beginning of the surgical procedure and reimplanted with the free-nipple graft (FNG) technique at the end of the surgical operation.



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

Figure 1. (**a**) Wise pattern incision for SRM; (**b**) modified Wise pattern incision for SRM used to remove the skin overlying or infiltrated by the tumour in the lateral quadrants of the breast.

For the symmetrisation procedure, the patients underwent a reduction mammoplasty performed by a Wise pattern incision.

All the patients underwent an intraoperative sentinel lymph node (SLN) examination by a one-step nucleic acid amplification (OSNA) assay (Sysmex, Kobe, Japan) [15].

A health-related quality of life (HRQOL) evaluation was conducted using the preoperative and postoperative BREAST-Q modules. It has been largely corroborated for research in breast reconstruction and is routinely used at our institutions [16,17].

After a consultation with the oncology and plastic surgeon, the enrolled patients received the preoperative questionnaire 1 month before surgery. The BREAST-Q postoperative modules were administered 1 year after the breast reconstruction. All aspects of the BREAST-Q reconstructive modules (satisfaction with the breasts, satisfaction with the outcome, psychosocial wellbeing, physical wellbeing and sexual wellbeing) were considered [18].

SPSS software version 27.0 (IBM Corp., Armonk, NY, USA) was used for the simple descriptive statistics, accounting for the patient sociodemographic and clinical characteristics as well as the complications and capsular contracture grade.

The BREAST-Q scores for each patient were converted from the survey scores (1 to 5) to a continuous range from 0 to 100 using QScore Scoring Software. A higher score indicated grater satisfaction or a better HRQOL. To verify the normal distribution of the continuous variables, we used the Shapiro–Wilk test; we then analysed the BREAST-Q scores and expert scores as the continuous variables with a Student's *t*-test. The discrete variables were analysed with the χ^2 test. *p*-Values less than 0.05 were considered to be statistically significant.

3. Results

We enrolled 84 patients who underwent an SRM with the FNG technique and a prepectoral tissue expander reconstruction implanted with specific covering devices (TiLoop® Bra, PFM medical, Cologne, Germany) between January 2018 and January 2021 in our centre and divided them into two groups using a simple randomisation list. In the first group, 42 patients underwent immediate symmetrisation; in the second group, 42 patients underwent delayed symmetrisation (performed after a median of 9 months).

The characteristics of the study population are collated in Table 1. In the immediate group, the median age was 55.5 years and the average BMI was 24.9; in the delayed group, the median age was 55.8 years and the average BMI was 25.3.

Table 1. Characteristics of the study population.

Characteristics of the Study Population		Immediate Sy.		Delayed Sy.	
		No. of Cases	%	No. of Cases	%
Patients		42		42	
Age		55.5		55.8	
BMI		24.9		25.3	
Histology	Invasive ductal carcinoma	29	69%	28	66.6%
	DCIS	5	11.9%	6	14.2%
	Invasive lobular carcinoma	3	7.2%	4	9.6%
	Invasive ductal carcinoma + DCIS	5	11.9%	4	9.6%
Tumour size	pT1a	1	2.4%	2	4.8%
	pT1b	10	24%	11	26.2%
	pT1c	19	45%	17	40.2%
	pT2	11	26.2%	10	24%
	pT3	1	2.4%	2	4.8%
Pre-BRA	5	7	16.6%	8	19%
	6	14	33.4%	16	38%
	7	12	28.6%	10	24%
	8	9	21.4%	8	19%

The histology most represented was, in both groups, an invasive ductal carcinoma, with 29 cases (69%) in the immediate symmetrisation group and 28 cases (66.6%) in the delayed symmetrisation group.

In the immediate symmetrisation group, we performed an axillary resection on 10 patients (23.8%) with a macrometastasis at the SNL examination with an OSNA, on 4 after a neoadjuvant CHT and on 32 after sentinel lymph node biopsies (76.2%) (Table 2).

In the delayed symmetrisation group, we performed an axillary resection on 11 patients (26.2%) with a macrometastasis at the SNL examination with an OSNA, on 4 after a neoadjuvant CHT and on 26 after sentinel lymph node biopsies (61.9%) (Table 2).

The median follow-up time after surgery was 22 months (from 1 to 4 years). The postoperative morbidity is shown in Table 2. Complications requiring a second operation occurred in seven cases: in the immediate symmetrisation group, we reported two wound dehiscence cases (4.8%)—one on the mastectomy side and one on the symmetrisation side—as well as one seroma (2.4%) and one case of skin-nipple necrosis (2.4%), both on the mastectomy side; in the delayed symmetrisation group, we reported one infection (2.4%),

one seroma (2.4%) and one case of skin-nipple necrosis (2.4%). We had to remove the tissue expander in three cases because of implant exposure; one in the immediate symmetrisation group and two in the delayed group. In the case of the removal of the prepectoral tissue expander, in two cases a salvage surgery was performed with a submuscular replacement of the tissue expander with the selective denervation of the pectoralis major muscle [5,6] and in one case the tissue expander was removed and a surgical revision was made supplemented with an antibiotate pulse lavage of the pocket surface and a new definitive implant placement [19].

Table 2. Characteristics of the study population.

Characteristics of the Study Population	Immediate Sy.		Delayed Sy.	
	No. of Cases	%	No. of Cases	%
Axillary dissection (following neoadjuvant CHT)	4	9.50%	4	9.50%
Axillary dissection (without neoadjuvant CHT)	6	14.30%	7	16.70%
Sentinel lymph node biopsy	32	76.20%	31	73.90%

Regarding disease recurrence, we reported one case of locoregional cancer recurrence (2.4%) in the delayed symmetrisation group and one case of systemic recurrence (2.4%) in each group. No statistical difference was found between the two groups. The safety and oncological outcomes are reported in Table 3.

Table 3. Safety and oncological outcomes.

Safety and Oncological Outcomes.		Immediate Sy.				Delayed Sy.	
		No. of Cases	%			No. of Cases	%
Tumour Recurrence							
	Locoregional	0	0%			1	2.4%
	Systemic	1	2.4%			1	2.4%
	No recurrence	41	97.6%			40	95.2%
				Symmetrisation side			
Complications	Skin-nipple necrosis	1	2.4%	0	0%	0	0%
	Infection	0	0%	0	0%	1	2.4%
	Wound dehiscence	1	2.4%	1	2.4%	1	2.4%
	Seroma	1	2.4%	0	0%	1	2.4%
Implant Loss		1	2.4%			2	4.8%

As shown in Table 4, we reported two cases (4.8%) in each group significative of capsular contractures (Baker III–IV grade) and in these cases we corrected this issue during the surgical procedure of the definitive implant. We observed a rippling in five cases (12%) in both groups 12 months after the primary surgery. Expander rippling was documented

in five breasts (11.9%) in the immediate symmetrisation group and four breasts (9.5%) in the delayed symmetrisation group 12 months after the primary surgery.

Table 4. Aesthetic complications.

Aesthetic Complications.		Immediate Sy.		Delayed Sy.	
		No. of Cases	%	No. of Cases	%
Capsular Contracture					
	Grade I	35	83.3%	29	69.0%
	Grade II	5	11.9%	10	23.8%
	Grade III	2	4.8%	1	2.4%
	Grade IV	0		1	2.4%
Rippling		5	11.9%	4	9.5%
Complication Requiring Reoperation		7	16.6%	6	14.3%

Measure of the HRQOL and Aesthetic Outcomes

All the patients answered the five domains of the survey. The results are reported, divided for the two different groups, in Table 5. The survey was administered during a follow-up visit 1 year after surgery. The patients scored a high level of satisfaction about the outcomes within each group.

Table 5. BREAST-Q results.

BREAST-Q	Delayed Sy.	Immediate Sy.	*p*-Value
Satisfaction: breasts	73 ± 10	78 ± 11.9	0.04 *
Psychosocial wellness	76.6 ± 12	79.2 ± 14.2	0.36
Sexual wellness	60.7 ± 12.9	65.3 ± 14.7	0.13
Physical impact	56.5 ± 13.2	58.8 ± 11.8	0.40
Satisfaction with outcome	73 ± 12.1	75 ± 10.7	0.42

* Statistically significant ($p < 0.05$).

The scores in all the domains were higher in the immediate symmetrisation group, but only the satisfaction with the breasts score had a statistically higher result than the delayed symmetrisation group ($p < 0.05$).

4. Discussion

Although the study of breast cancer and its surgical treatment have paved the way for numerous discoveries in the field of oncology [20], there are still technical innovations in both the demolition and reconstructive fields [21,22].

Breast reconstruction during oncological surgery is, today, a recommended practice that provides optimal aesthetic satisfaction to patients and surgeons [13,17]. In an era where continuous innovations such as 3D printing can aid surgical planning [23,24], the search for new materials can radically change surgical tactics. The introduction of biological and synthetic devices aimed at providing an additional layer between the prosthesis and subcutaneous tissue has contributed to prepectoral reconstructions as a predominant role among the reconstructive techniques, reducing the complication rate and increasing the possibility of refining the shape of the breast with fat grafting [25–27]. Recent studies in the

literature report a small complication rate for this technique with the advantage of a more natural aesthetic result compared with submuscular implants [28–34].

In this context, SRMs with an FNG for an immediate breast reconstruction are nowadays a preferred surgical strategy for selected patients [7], allowing both a safe oncological clearance and an improved cosmesis [35,36].

The prepectoral approach requires the placement of the tissue expander and the reconstruction to occur in two stages in a few cases when the vascularisation of the skin is not optimal and patients have risk factors such as diabetes, a history of smoking, obesity and a previous RT treatment [14,37].

In the last decade, the need to achieve increasingly satisfactory aesthetic outcomes has led breast surgeons to consider the treatment of the opposite breast as an important aspect of postmastectomy breast reconstructions [38–40].

This study aimed to demonstrate the improved outcomes that can be derived from the immediate symmetrisation of the healthy breast during an oncoplastic procedure. Currently, there are no indications of this type of surgical strategy in the literature [11]; however, in our experience, it appeared to us that we were able to guarantee patients a better aesthetic aspect due to the symmetry of the two breasts, especially after a procedure such as an SRM where the asymmetry in quite evident.

Giordano et al. [10] demonstrated that performing immediate symmetrisation at the time of a breast reconstruction was a reasonable and safe option in autologous latissimus dorsii breast reconstructions.

We analysed the satisfaction concerning the cosmetic and functional aspects of patients undergoing a unilateral SRM with an FNG and a prepectoral tissue expander reconstruction through a comparison between the results of patients subjected to immediate symmetrisation and the ones who were candidates for delayed symmetrisation.

We did not find significant differences in the analysis of the clinical outcomes between the two groups in the study or between these populations and the ones reported in the literature [19,41–43]. In two cases, a reintervention was required for implant exposure: one in the symmetrisation group and one in the immediate group.

We also reported an acceptable number of patients with aesthetic complications that required a second surgery; in the majority of cases, a lipofilling with a small quantity of fat grafting was sufficient to correct them [27,44,45]. A high-grade capsular contracture was reported only in 4.8% of cases in each group, according to the literature [46].

In the immediate symmetrisation group, compared with the patients with an SRM and an FNG without symmetrisation, there was a higher subjective satisfaction rate as it improved the aesthetic results by reducing negative self-perception.

5. Conclusions

This is, to the best of our knowledge, the first study evaluating immediate symmetrisation during a subcutaneous reconstruction for demolitive surgery. Our findings suggested that immediate symmetrisation was a possible, safe and highly tolerable technique of reconstruction in terms of the aesthetic outcome and the quality of life of the patients. Moreover, immediate symmetrisation did not delay the adjuvant oncological treatments compared with the choice of symmetrisation at the second time of reconstruction.

Furthermore, the consolidated use of covering devices in prepectoral reconstructions in selected patients confirmed how this technique could be applied with a low rate of complications.

This technique, providing patients an aesthetic result in terms of immediate symmetry, allowed us to better manage the waiting times for the second reconstructive surgery whilst still providing an excellent result, even if it was not definitive. Moreover, at the time of the definitive reconstruction, it was possible to evaluate the natural ageing process of the symmetrised breast in order to accordingly adjust the definitive implant of the reconstructed breast. In conclusion, even if not indicated in the literature, it seems to us that the choice of immediate symmetrisation is a viable choice to provide immediate better

satisfaction and quality of life for patients and does not excessively impact, from a surgical point of view, on the second time of the reconstruction.

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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.

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Dose Volume and Liver Function Test Relationship following Radiotheraphy for Right Breast Cancer: A Multicenter Study

Zeliha Güzelöz [1,*], Oğuzhan Ayrancıoğlu [2], Nesrin Aktürk [3], Merve Güneş [2] and Zümre Arıcan Alıcıkuş [2]

[1] Department of Radiation Oncology, Health Science University Tepecik Training and Research Hospital, İzmir 35100, Türkiye
[2] Department of Radiation Oncology, İzmir Tınaztepe University Galen Hospital, İzmir 35001, Türkiye; oguzhan.ayrancioglu@tinaztepe.com (O.A.); merve.gunes@tinaztepe.com (M.G.); zumre.arican@tinaztepe.edu.tr (Z.A.A.)
[3] Department of Radiation Oncology, Katip Çelebi University Atatürk Training and Research Hospital, İzmir 35150, Türkiye; nesrin.akturk@saglik.gov.tr
* Correspondence: z.guzelozcapar@saglik.gov.tr; Tel.: +90-5064019642

Abstract: Objective: The liver is a critical organ at risk during right breast radiotherapy (RT). Liver function tests (LFTs) such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) serve as biochemical markers for hepatobiliary damage. In this multicenter cross-sectional study, the effects of liver dose–volume on changes in LFTs pre- and post-RT in patients treated for right breast cancer were evaluated. Materials and Methods: Between January 2019 and November 2022, data from 100 patients who underwent adjuvant right breast RT across three centers were retrospectively assessed. Target volumes and normal structures were contoured per the RTOG atlas. Patients were treated with a total dose of 50 Gy in 25 fractions to the CTV, followed by a boost to the tumor bed where indicated. The percentage change in LFT values in the first two weeks post-RT was calculated. Statistics were analyzed with SPSS version 22 software, with significance set at $p < 0.05$. Statistical correlation between liver doses (in cGy) and the volume receiving specific doses (Vx in cc) on the change in LFTs were analyzed using Kolmogorov–Smirnov, Mann–Whitney U test. Results: The median age among the 100 patients was 56 (range: 29–79). Breast-conserving surgery was performed on 75% of the patients. The most common T and N stages were T1 (53%) and N0 (53%), respectively. None of the patients had distant metastasis or simultaneous systemic treatment with RT. A total of 67% of the treatments utilized the IMRT technique and 33% VMAT. The median CTV volume was 802 cc (range: 214–2724 cc). A median boost dose of 10 Gy (range: 10–16 Gy) was applied to 28% of the patients with electrons and 51% with IMRT/VMAT. The median liver volume was 1423 cc (range: 825–2312 cc). Statistical analyses were conducted on a subset of 57 patients for whom all three LFT values were available both pre- and post-RT. In this group, the median values for AST, ALT, and GGT increased up to 15% post-RT compared to pre-RT, and a median liver D_{mean} below 208 cGy was found significant. While many factors can influence LFT values, during RT planning, attention to liver doses and subsequent regular LFT checks are crucial. Conclusion: Due to factors such as anatomical positioning, planning technique, and breast posture, the liver can receive varying doses during right breast irradiation. Protecting patients from liver toxicity secondary to RT is valuable, especially in breast cancer patients with a long-life expectancy. Our study found that, even in the absence of any systemic treatment or risk factors, there was an average increase of nearly 15% in enzymes, indicating acute liver damage post-RT compared with pre-RT. Attention to liver doses during RT planning and regular follow-up with LFTs is essential.

Keywords: right breast; radiotherapy; liver function tests; dose–volume; toxicity

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1. Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide [1]. Adjuvant radiation therapy (RT) plays a pivotal role in the treatment of breast cancer [2,3].

There has been an observed increase in locoregional control in patients undergoing breast-conserving surgery with adjuvant RT and selected patients receiving mastectomy [4,5]. Following breast-conserving surgery, RT to the preserved breast halves the local recurrence rate and lowers breast cancer mortality by approximately one-sixth [5].

The success achieved in locoregional control with RT has also reflected positively in survival rates [4–6]. Variations in local treatments that have a significant impact on local recurrence rates would, under the assumption of no other causes of death, prevent approximately one breast cancer-related death within the next 15 years for every four avoided instances of local recurrence, consequently leading to a decrease in overall mortality over the course of 15 years [5]. Nowadays, due to the diffusion of breast cancer screening programs and advancements in imaging technology, breast cancer diagnoses are being made at younger ages [7,8]. This means that younger-patient populations need to be followed for many years. Advances in both RT and systemic treatments have improved the prognosis of these patients, emphasizing the importance of the quality of life and preservation of normal tissue. Particularly with the increasing young patient population, there has been a growing emphasis on the need for better protection of normal tissues during RT. Protecting these long-surviving patients from acute side effects is just as crucial as minimizing secondary cancer risks in the long term.

For many years, numerous studies have been conducted on radiation-induced liver disease (RILD). Especially in patients undergoing abdominal RT, the liver stands as one of the priority normal tissues to be protected [9]. In right breast RT practices, due to anatomical proximity, the liver is one of the normal tissues at risk. However, the etiology of RILD is multi-factorial, with a central role of veno-occlusive processes and, although as low dose exposure may as well exert some effects, no specific liver dose constraints have been defined in the setting of adjuvant breast irradiation [10].

The liver, being a metabolic organ with vital functions, has liver function tests (LFTs) such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT), which are biochemical indicators of hepatobiliary damage for various reasons. The normal ranges for ALT, AST, and GGT are 0–45 IU/L, 0–35 IU/L, and 0–45 IU/L, respectively [10]. In the literature, there are limited studies examining long- and short-term changes in LFTs post-RT [11–14]. Grade 3–4 hepatotoxicity was not identified in these few studies. However, a correlation was found between irradiated liver volume and ALT and ALP tests [11]. A significant increase was detected in IL-6 level [12]. An increase in median AST and ALT values was observed after radiotherapy [13].

In this multicentric cross-sectional study, the aim was to evaluate the impact of liver dose–volume on changes in LFT values before and after RT in patients treated for right breast cancer.

2. Patients and Methods

2.1. Patient Selection

In this study, data from 100 female patients aged 18 and over who underwent RT to the right breast or right chest wall following breast-conserving surgery or mastectomy between January 2019 and November 2022 in three centers with identical RT protocols were retrospectively evaluated. These patients had a diagnosis of invasive breast carcinoma without distant organ metastasis and had pre-radiation therapy (preRT) and post-radiation therapy (postRT) liver function test values (AST, ALT, GGT). Staging was performed according to the American Joint Committee on Cancer tumors, lymph nodes, and distant metastases TNM staging system (8th ed., 2017). Patients diagnosed with stage IV or in situ carcinoma, those who received neoadjuvant chemotherapy, those undergoing concurrent systemic treatment, or those with chronic liver or biliary tract disease were excluded from this study. The study protocol was approved by the national ethics committee (Health Science University Tepecik Training and Research Hospital Ethics Committee approval number: 2023/07-05).

2.2. Radiation Therapy

2.2.1. Simulation

All patients were planned in a supine position using a breast board with arm support. Tomographic slices were acquired at intervals of 3 mm. In the acquired topographies, the entire liver was included in the imaging field.

2.2.2. Contouring of Target Volumes

Target volumes and at-risk normal tissues were contoured on the tomographic slices taken at a 3 mm slice thickness according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) guidelines [15]. For patients who underwent breast-conserving surgery, the entire right mammary glandular tissue and skin were determined as breast CTV (clinical target volume). Lumpectomy cavities and seromas were included in the CTV. For patients who underwent mastectomy, the chest wall including the incision scar and skin was contoured. PTV (planning target volume) was obtained by giving a five mm margin to CTV.

2.2.3. Contouring of the Liver

The liver was contoured based on the RTOG upper abdomen normal tissue contouring guidelines [16]. The entire liver in the slice area was contoured in the abdomen window level range. The gallbladder was excluded. The portal vein, branches of the portal vein, and other vessels were included within the liver (except inferior vena cava) contour according to the guidelines [17].

2.2.4. Radiotherapy Prescription and Planning

Patients received a total of 50 Gy RT over 25 fractions of CTV using FIF (field in field)/IMRT (intensity-modulated radiotherapy)/VMAT (volumetric arc therapy) techniques. Where necessary, an additional dose (boost) was given to the tumor bed using either electron or photon energy. The energy of 6–10 MVX was utilized. It was aimed to keep the volume of the right lung receiving 20 Gy below 30%.

2.2.5. Liver Dose–Volume

Assessment from the dose–volume histogram, values for the D_{max} (maximum dose, D_{min} (minimum dose), D_{mean} (mean dose), and (V_x) the volume of the liver (cc) receiving a certain dose (x) were (V_5, V_{10}, V_{20}, V_{30}, V_{40}, and V_{50}) recorded. According to normal tissue dose limitations, the mean dose to the liver was aimed to be below 30–32 Gy [18].

2.3. Laboratory Tests

ALT, AST, and GGT blood values from two weeks before the initial fraction of RT (preRT) and two weeks after the last fraction of RT (postRT) were obtained from hospital and national medical record systems.

2.4. Statistics

The percentage difference (Δ%) for each of the three parameters between preRT and postRT was calculated using the formula $\Delta\% = (\text{postRT} - \text{preRT})/\text{preRT} \times 100$. Based on this formula, a positive percentage difference indicated an increase in LFTs after RT, while a negative value indicated a decrease post-RT. The effects of liver doses (cGy) and volumes (Vx) (cc) on Δ% were evaluated. Statistics were analyzed with SPSS© 22 software (Statistical Package for the Social Sciences), with significance set at $p < 0.05$. Statistical correlation between liver doses (in cGy) and the volume receiving specific doses (Vx in cc) on the change in LFTs were analyzed using Kolmogorov–Smirnov, Mann–Whitney U test.

3. Results

The demographic and treatment data of the patients can be seen in Table 1.

Table 1. Demographics and treatment data of patients.

Median Age	56 (29–79)
Median CTV volume	802 (214–2724) cc
Surgery modality	
breast conserving	75%
mastectomy	25%
T Stage	
T1	53%
T2	39%
T3	-
T4	-
Tx	8%
N Stage	
N0	53%
N1	25%
N2	-
N3	-
Nx	22%
RT technics	
FIF/IMRT	67%
VMAT	33%
Deep inspiration breath hold	25%
RT boost dose (median)	10 (10–16) Gy
RT boost	
Electron	28%
IMRT	31%
VMAT	20%
Patient not received boost	21%

CTV: Clinical target volume; RT: Radiotherapy; FIF: Field in field; IMRT: Intensity-modulated radiotherapy; VMAT: Volumetric arc therapy.

After radiotherapy, it was observed that AST values were above the normal range in 12 patients (ranging from 45 to 1107 IU/L), ALT values in 12 patients (ranging from 35 to 365 IU/L), and GGT values in 12 patients (ranging from 49 to 414 IU/L).

No patient received systemic therapy or tamoksifen concurrent with RT. The median liver volume was 1423 cc, with a range of 825–2312 cc. The median D_{min} was 3.4 cGy (range: 0–206.1 cGy), the median D_{max} was 4814 cGy (range: 110–206.1 cGy), and the median D_{mean} was 203 cGy (range: 15–1497 cGy). The observed dose–volume values were as follows: Median V_{50} was 0 cc (range: 0–68), V_{40} was 0.76 cc (range: 0–87.2), V_{30} was 2.14 cc (range: 0–180.7), V_{20} was 6 cc (range: 0–387.7), V_{10} was 11.7 cc (range: 0–949.1), and V_5 was 21.2 cc (range: 0–1352).

For the statistical analyses, 57 patients were included, for whom all three LFTs were completely obtained in both the pre- and post-RT periods. In this patient group, the median CTV volume was 806 cc (range: 214–2519 cc) and the median liver volume was 1457 cc (range: 825–2218 cc). The D_{max}, D_{min}, and D_{mean} dose values are presented in Table 2 and Figure 1, while the liver $V_{5–50}$ dose values are shown in Table 3 and Figure 1.

Table 2. Liver Dosimetric Values (cc) of 57 patients.

Liver Dx	D_{max} (cGy)	D_{min} (cGy)	D_{mean} (cGy)
Dose (median)	5005 (110–5969)	5.8 (0–206.1)	208 (15–1497)

D_{max}: Maximum dose; D_{min} Minimum dose; D_{mean}: Mean dose; cGy centi Gray.

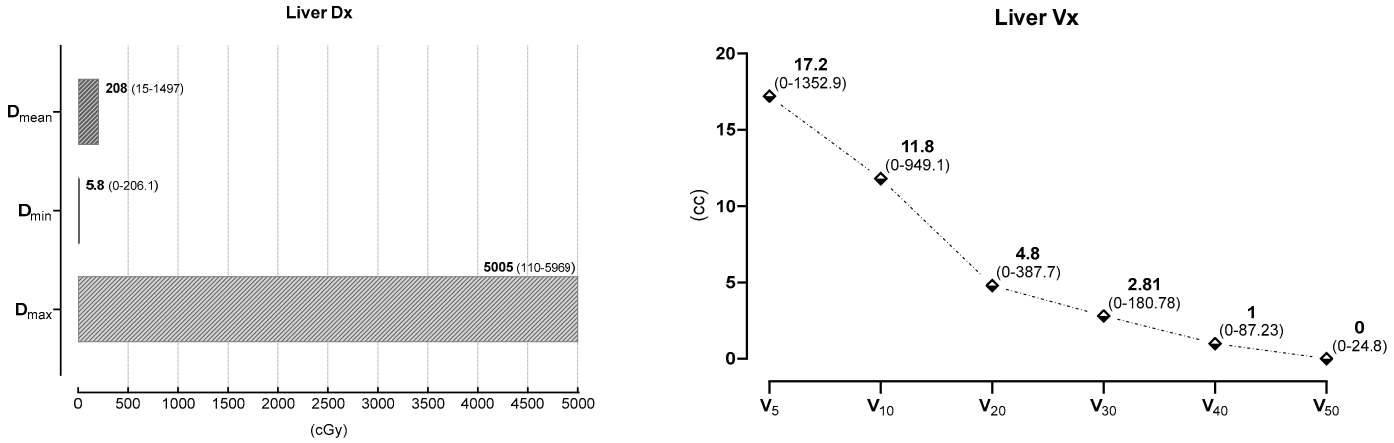

Figure 1. Liver Dosimetric and $V_{5–50}$ Values.

Table 3. Liver $V_{5–50}$ Values (cc) of 57 patients.

Liver V_x	V_5	V_{10}	V_{20}	V_{30}	V_{40}	V_{50}
cc (median)	17.2 (0–1352.9)	11.8 (0–949.1)	4.8 (0–387.7)	2.81 (0–180.78)	1 (0–87.23)	0 (0–24.8)

$V_{5/10/20/30/40/50}$ liver volume receiving 5/10/20/30/40/50 Gy.

The median values and percentage changes in ALT, AST, and GGT tests prior to and following RT are provided in Table 4 and Figure 2.

Table 4. Median and percentage change in liver function test (LFT) values of 57 patients.

Liver Test	Median (U/L)	Median Percentage Change (%)
AST		
preRT	19 (11–35)	13% (−120 to 54.5)
postRT	21 (10–52.32)	
ALT		
preRT	18 (1.97–39)	3.03% (−292 to 46.1)
postRT	20 (8- 55)	
GGT		
preRT	20 (12–44)	−6% (−93.18 to 42.86)
postRT	19 (10–85)	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; preRT: pre-radiation therapy; postRT: post-radiation therapy.

When examining the effect of liver dose–volume on the percentage change between preRT and postRT in LFT, a statistically significant adverse effect was observed with higher liver D_{mean} ($p = 0.03$) values solely for ALT and for AST with both liver D_{min} ($p = 0.007$) and D_{mean} ($p = 0.023$) values. For GGT, all liver dose–volume values, namely D_{min} ($p = 0.014$), D_{max} ($p = 0.023$), D_{mean} ($p = 0.006$), V_{50} ($p = 0.009$), V_{40} ($p = 0.03$), V_{30} ($p = 0.03$), V_{20}

(p = 0.001), V_{10} (p = 0.02), and V_5 (p = 0.008), were found to be statistically significant. However, the RT technique, CTV volume, the addition of boost, and its technique did not demonstrate a statistically significant effect. The statistically significant values, effect of liver dose–volume and the percentage change are presented in Table 5.

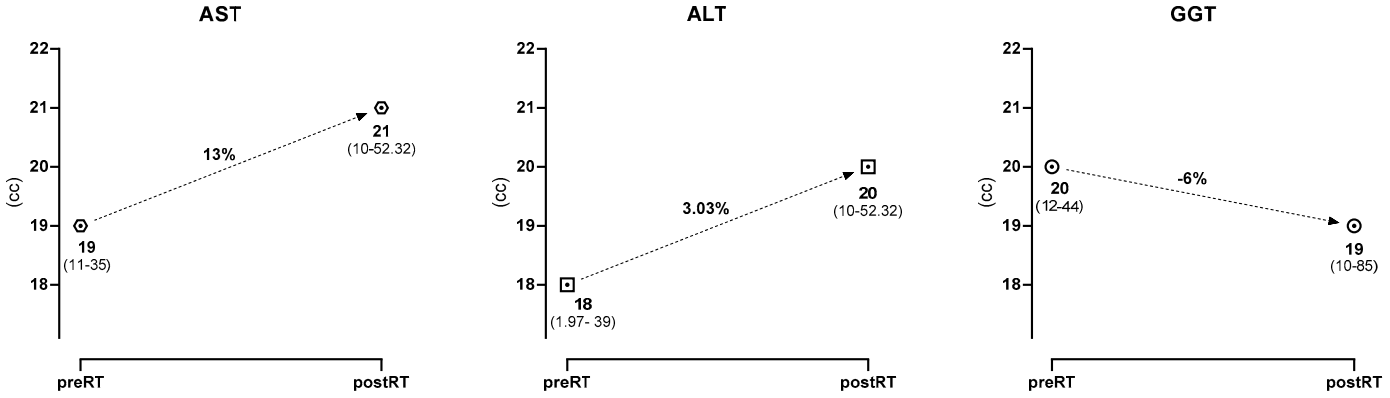

Figure 2. Median and percentage change in liver function test (LFT) values of 57 patients.

Table 5. Significant values of dose–volume and percentage chance on LFT.

Liver Test	Dose–Volume Parameters	p Value
ALT	D_{mean}	0.03
AST	D_{mean}	0.023
	D_{min}	0.007
GGT	D_{mean}	0.006
	D_{min}	0.014
	D_{max}	0.023
	V_{50}	0.009
	V_{40}	0.03
	V_{30}	0.03
	V_{20}	0.01
	V_5	0.02

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; D_{max}: Maximum dose; D_{min}: Minimum dose; D_{mean}: Mean dose; $V_{5/10/20/30/40/50}$ Liver volume receiving 5/10/20/30/40/50 Gy.

4. Discussion

Radiation in the early phase results in DNA damage, oxidative stress, and an accumulation of free oxygen radicals in the environment, leading to acute inflammation and hepatocellular apoptosis [19]. This scenario creates vascular damage that subsequently results in an increased synthesis of collagen, negatively impacting growth factors, TNF-alpha, TNF-beta, and other elements involved in liver damage regulation and repair [20]. Clinically, this situation is recognized as radiation-induced liver disease (RILD).

Classic RILD is observed between 2 weeks and 4 months post-radiation in patients who have received 30–35 Gy through conventional fractionation of the liver [21]. It arises due to veno-occlusion associated with fibrosis secondary to RT. Its presentation involves an ALP level increased by $\geq$2 times. With advancements in radiation technology, such as image-guided RT techniques, VMAT plans, IMRT plans, and stereotaxic body radiotherapy, classic RILD has become less common. Instead, non-classic RILD is more frequently observed. In this scenario, even with a lower radiation dose, there can be a rise in LFTs, possibly due to diminished liver regeneration capacity, which may be associated with conditions like cirrhosis or hepatitis [10,21]. In such cases, AST and ALT levels may elevate to $\geq$5 times [13].

Anatomically, the liver is near the radiation treatment area during breast or chest wall irradiations, particularly on the right side, making it an at-risk organ. Current dose restrictions used in planning RT for right breast cancer recommend a D_{mean} value of 28–32 for the liver [18]. This dose carries a 5% risk of developing RILD [22]. However, when considering the anatomy and the conventional dose of 50 Gy given to the entire breast, this prescribed dose for the liver seems excessively high and is not reflective of reality. Considering the ALARA principle "As Low As Reasonably Achievable", these theoretically appropriate dose limitations pose different challenges in clinical practice. This principle aims at minimizing the risks associated with radiation exposure, thus striving to keep radiation doses in diagnostic and therapeutic processes as low as reasonably achievable. Within the framework of this principle, the use of radiation at necessary therapeutic doses aims to minimize acute and chronic side effects that may occur following RT. Consequently, the objective is to reduce the long-term risk of secondary cancer development attributed to RT.

In studies assessing liver doses in patients diagnosed with breast cancer and treated with right breast irradiation, the mean liver dose was found to be between 1.94 and 4.34 Gy [11,13,14]. The maximum liver dose averages at 26.9 Gy and in some cases reaches as high as 51.7 Gy [14]. There are limited studies in the literature that focus on liver function alterations due to the dose received by the liver during right breast irradiation. You can see these studies in Table 6.

Table 6. Studies examining LFT changes following right breast irradiation.

	The Number of Patients/RT Dose/Timing of Blood Test	**Liver Dose**	**Hepatic Blood Test Results**
Lauffer et al. [11]	34 right side 42.5 Gy/16 fr or 50 Gy/25 fr ±16 fr boosts Before and last week of RT	MLV: 1270.2 cc (918.5–2233.2) MLD: 1.94 Gy (0.2–9)	Correlation between irradiated liver volume and ALT (p = 0.05) and ALP (p = 0.006)
Courtier et al. [12]	52 right side, 100 left side 40 Gy/15 fr Before and during 4 weeks after RT	Mean $V_{10:}$ 226 cm^3 (19%) Mean $V_{50:}$ 92 cm^3 (8%) Mean $V_{90:}$ 62 cm^3 (5%)	V_{10} and IL-6 (p = 0.001)
Park et al. [13]	47 right side, 78 left side 42.56–50 Gy/16–25 fr ± 10–14 Gy boost 1 week before vs. 6 months after	$D_{mean\_right\ breast}$ 434.1 cGy $D_{mean_left\ breast}$260.6 cGy V_{10} 3% V_{20} 1% V_{30} 0%	AST_{median}: 23.2 ± 5.3 vs. 29.6 ± 14.6 ALT_{median}: 20.2 ± 7.7 vs. 25.6 ± 20.0
Quintin et al. [14]	27 right side or bilateral, 29 left side Median follow-up 5.4 years	D_{mean} 2.8 Gy (0.3–16.6) D_{max} 26.9Gy (0.7–51.7)	no grade 3 hepatotoxicity Three patients (6%) with grade 2 delayed hepatotoxicity

RT: Radiotherapy; Gy: Gray; ALT: Alanine aminotransferase; AST:Aspartate aminotransferase; MLV: Mean lung volume; MLD: Mean lung dose; D_{max}: Maximum dose; D_{mean}: Mean dose; $V_{10/20/30/50/90}$ volume of liver irradiated 10/20/30/50/90% of prescription dose.

In our study, unlike in the literature, early changes in LFTs were calculated as a percentage change using a mathematical formula, and the relationship between this value and dose–volume values was evaluated. It was determined that, as the mean dose received by the liver increases, there is a significant increase in ALT and AST values (p = 0.03, p = 0.023 respectively). Furthermore, it has been shown that the higher the minimum dose the liver receives, the greater the increase in AST value (p = 0.007). Therefore, keeping the mean and minimum dose received by the liver as low as possible is seen as one of the essential parameters to avoid LFT increase. A statistically significant decrease in percentage change and GGT values was observed after RT. This could be attributed to the GGT levels not being negatively affected during the acute phase of RT.

In the current study, no significant relationship between percentage difference (Δ%) and a certain volume dose (VxGy) was not detected. In the literature, it is recommended

that the liver receives a dose below 30 Gy (V_{30} < 100%). It is argued that a dose above 30 Gy is an indicator of RDIL [17,23–25]. In our study, the median V_{30} value was found to be 2.81 cc, which corresponds to approximately 2% of the median value. We think that, since such a low value was found, there was no clinical change and no relationship was detected with DVH. One of the key points should be the actual clinical impact of low-dose exposure to the liver. The liver is well-know for its ability to regenerate after multiple kinds of damage. Several previous experiences demonstrated that, although RT could result in increased LFT, it did not meet the criteria for RILD [13] and delayed hepatotoxicity was negligible, questioning the definition of liver as an OAR [14]. In a study by Park et al. evaluating LFTs in patients diagnosed with breast cancer undergoing RT, it was reported that 53.6% of the patients had a V_{30} value of 0 and the maximum V_{30} value was 2.6%, and RILD was not observed in any patients. Based on this, it has been suggested to use a liver $D_{mean} \leq 3$–4 value as the liver normal tissue dose limitation for right breast irradiation and can be considered as a cut-off value [13]. The similar low doses found in our study and absence of changes in LFTs support this thesis.

Survival rates have increased in patients diagnosed with breast cancer due to advancements in RT techniques and progress in systemic treatments. It is possible to observe the long-term stochastic effects of radiation, which are independent of dose, in the patient group monitored with a breast cancer diagnosis. Therefore, the incidence of secondary cancers after breast cancer irradiation during follow-up is higher than that for other types of cancer [26,27]. Even if the results do not manifest clinically as an increase in LFTs, considering the long-term effects of the received radiation, normal tissues should be exposed to the lowest possible radiation dose, as discussed in accordance with the ALARA principle [28]. Radiation-induced cancer is classically defined as a stochastic process, although recent studies developed more complex models; therefore, there is no threshold point and even low doses may increase second neoplasms risk. This phenomenon is relevant especially for long-term survivors and has been extensively investigated for lymphoma and breast cancer patients, mostly focusing on second lung, breast and thyroid malignancies [29–31]. Nonetheless, some studies defined the risk of secondary liver cancer after breast irradiation, with conflicting results: while in some models, the lifetime attributable risk (LAR) for liver cancer induction after breast radiotherapy was extremely low [32], in other experiences high LAR estimates were obtained for liver in case of right-sided targets [33].

Currently, the deep inspiration breath hold (DIBH) is employed as standard in left breast and chest wall irradiation. This technique is used in left breast cancer RT to ensure that cardiac tissues and coronary arteries receive a lower dose [34–36]. The DIBH technique has not yet become standard for right breast or chest wall RT. There are fewer studies on the benefits of the DIBH technique in right breast irradiation. While there are studies that determined that it reduces the dose to the heart, lungs, and liver dosimetrically [37], there are also studies that argue it is effective in reducing liver doses only in cases with hepatomegaly while reducing doses to the heart and LAD (left anterior descending artery) [38]. In the study of Loap and colleagues, although there was no significant change in cardiac structures and the right lung in right breast irradiations using DIBH compared to the free breath technique with VMAT, a significant reduction was observed in the mean liver dose (from 2.54 to 0.87 Gy $p = 0.001$). Therefore, it has been emphasized that, instead of routine use, it should be used in selected patients [39].

Due to its retrospective design, our study inherently possesses some limitations. Despite the availability of 100 patients that met the study criteria, statistical analysis was performed on the 57 patients with data for all three liver function test parameters. None of the patients included in the study received concurrent chemotherapy and tamoxifen alongside RT. Some patients received neoadjuvant or adjuvant chemotherapy. As per our protocol, RT begins approximately 3–4 weeks after chemotherapy. The reason for conducting LFTs just before RT is to assess the reduction in potential toxicity that could occur due to chemotherapy during this period. Furthermore, since the primary focus of our study is on the changes occurring in the acute phase before and after radiation therapy, the

effect of chemotherapy has not been separately evaluated. On the other hand, according to the literature, it is known that hormonal therapies used in the post-menopausal period (like letrozole and exemestane) do not have an effect that will reflect on the clinic and tests [40,41]. Although there is a viewpoint that minimal changes in LFTs may not have clinical implications, it is essential to remember that slight elevations in AST, ALT, and GGT due to scattered radiation may indicate potential risks concerning non-RILD and secondary cancers in the long run.

There is a dearth of research in the literature that examines early changes in LFTs after right breast irradiation. We aimed to address this gap. The multicentric design of our study, its evaluation using modern RT techniques, the detailed examination of DVH parameters, and the articulation of LFT changes through a mathematical formula constitute this study's strengths.

5. Conclusions

In conclusion, liver damage can manifest as a spectrum ranging from subtle laboratory abnormalities to severe liver insufficiency. Due to factors such as anatomical positioning, planning technique, and breast posture during right breast irradiation, the liver can receive variable doses. For breast cancer patients with a longer survival expectancy, safeguarding them from potential liver toxicity secondary to RT is of paramount importance. Our findings indicate that, in patients who did not undergo any systemic treatment or had no risk factors, there was an average increase of nearly 15% in enzymes, indicative of acute liver damage post-RT compared with pre-RT. It was deemed significant to maintain liver D_{mean} under 208 cGy. Given the myriad of factors influencing LFT values, our study underscores the necessity for meticulous attention to liver doses during RT planning. We advocate for maintaining the mean dose below 208 cGy and emphasize the importance of regular LFT monitoring during follow-up.

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Institutional Review Board Statement: The study was designed with the World Medical Association Declaration of Helsinki guidelines, after obtaining local institutional ethics committee approval (No: Tepecik TRH-2023/07-05).

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 the request from the corresponding author.

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

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Correlation of High-Sensitivity Cardiac Troponin I Values and Cardiac Radiation Doses in Patients with Left-Sided Breast Cancer Undergoing Hypofractionated Adjuvant Radiotherapy with Concurrent Anti-HER2 Therapy

Katarina Antunac [1,*], Ljiljana Mayer [2], Marija Banovic [3] and Lidija Beketic-Oreskovic [1,4]

[1] Division of Oncology and Radiotherapy, University Hospital for Tumours, Sestre Milosrdnice University Hospital Centre, Ilica 197, 10000 Zagreb, Croatia; lidijabeketicoreskovic@gmail.com
[2] Department of Medical Biochemistry in Oncology, University Hospital for Tumours, Sestre Milosrdnice University Hospital Centre, Ilica 197, 10000 Zagreb, Croatia; ljiljana.mayer@kbcsm.hr
[3] Polyclinic Leptir, Ilica 253, 10000 Zagreb, Croatia; mabanovi@gmail.com
[4] Department of Clinical Oncology, School of Medicine University of Zagreb, Salata 3 B, 10000 Zagreb, Croatia
* Correspondence: katarina.antunac@gmail.com

Abstract: Anti HER2 therapy and left breast adjuvant radiation therapy (RT) can both result in cardiotoxicity. The aim of this study was to evaluate the influence of radiation dose on cardiac structures on the values of the early cardiotoxicity marker high-sensitivity cardiac troponin I (hscTnI) in patients with HER2-positive left breast cancer undergoing adjuvant concomitant antiHER2 therapy and radiotherapy, and to establish a correlation between the hscTnI values and cardiac radiation doses. Sixty-one patients underwent left breast hypofractionated radiotherapy in parallel with anti-HER2 therapy: trastuzumab, combined trastuzumab–pertuzumab or trastuzumab emtansine (T-DM1). The hscTnI values were measured prior to and upon completion of radiotherapy. A significant increase in hscTnI was defined as >30% from baseline, with the second value being 4 ng/L or higher. Dose volume histograms (DVH) were generated for the heart, left ventricle (LV) and left anterior descending artery (LAD). The hscTnI levels were corelated with radiation doses on cardiac structures. An increase in hscTnI values was observed in 17 patients (Group 1). These patients had significantly higher mean radiation doses for the heart ($p = 0.02$), LV ($p = 0.03$) and LAD ($p = 0.04$), and AUC for heart and LV ($p = 0.01$), than patients without hscTnI increase (Group 2). The patients in Group 1 also had larger volumes of heart and LV receiving 2 Gy ($p = 0.01$ for both) and 4 Gy ($p = 0.02$ for both). LAD differences were observed in volumes receiving 2 Gy ($p = 0.03$), 4 Gy ($p = 0.02$) and 5 Gy ($p = 0.02$). The increase in hscTnI observed in patients receiving anti-HER2 therapy after adjuvant RT was positively associated with radiation doses on the heart, LV and LAD.

Keywords: HER2-positive breast cancer; adjuvant radiotherapy; radiotherapy dose hypofractionation; cardiotoxicity; high-sensitivity cardiac troponin I; trastuzumab; pertuzumab; trastuzumab emtansine

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1. Introduction

Breast cancer adjuvant radiotherapy reduces the risk of disease recurrence (from 35% to 19.3% in 10 years) and the risk of breast cancer death (from 25.2% to 21.4% in 15 years) [1]. However, the incidental exposure of the heart during left breast irradiation increases the risk of ischemic heart disease that starts about 5 years after radiotherapy and continues up to the third decade upon its completion. The ischemic heart disease rate is proportional to the mean dose to the whole heart; it increases linearly by 7.4% per Gray (Gy) and no threshold has been defined [2]. The risk of radiation-induced heart disease is not only dose-dependent but also correlates with the volume of the cardiac structure receiving a certain radiation dose [3]. Therefore, it was shown that the volume of the left ventricle (LV) receiving 5 Gy was the most important prognostic dose-volume parameter for the

development of an acute coronary event [4]. A mean dose on the left anterior descending (LAD) artery higher than 5 Gy was associated with an increased requirement for coronary intervention in LAD [5].

Troponin is a contractile apparatus component in both cardiac and skeletal myocytes. Troponin I and T isoforms are highly specific to cardiac myocytes; their detection in serum is a specific marker of cardiac damage [6]. The prognostic value of small changes in high sensitivity cardiac troponins, those below the 99th centile, has been shown in diseases affecting the cardiac muscle, such as coronary disease [7]. Radiation-induced cardiac cell damage could be a consequence of changes in cardiac vasculature and inflammation caused by radiation or could be the direct effect of radiation on the destruction of myocyte membranous structures [8,9].

A meta-analysis of eight randomised trials evaluated whether high-sensitivity cardiac troponin T (hscTnT) can be used as an early diagnostic marker of cancer-treatment-related cardiac dysfunction. A correlation between elevated hscTnT levels and cancer-treatment-related cardiac dysfunction was found and hscTnT testing improved the accuracy of the diagnosis. Still, it was not possible to define exact cut-off values of hscTnT for the early diagnosis of cardiac dysfunction [10].

A correlation between radiation doses on cardiac structures and the increase in troponin I levels during and after radiotherapy has been shown in patients undergoing adjuvant irradiation of the left breast. The patients in this trial did not receive chemotherapy or anti-HER2 therapy [11].

Patients with early HER2-positive breast cancer receive anti-HER2 systemic therapy based on trastuzumab in both neoadjuvant and adjuvant settings. The overall treatment time is usually 1 year and adjuvant radiotherapy of the breast cancer is most often applied concomitantly with anti-HER2 therapy. The most common side effect of trastuzumab is cardiotoxicity, presenting as an asymptomatic decrease in the left ventricular ejection fraction (LVEF), occurring in about one fourth of patients. It mainly occurs during the first three months of the treatment and leads to the treatment discontinuation in about 5% of patients [12]. In 14% of patients receiving trastuzumab, an increase in troponin I levels has been observed A multivariate analysis showed that observed troponin increase was an independent predictor of cardiotoxicity and in these patients LVEF did not recover. Therefore, troponin I elevation can identify patients who are at risk of developing cardiac disfunction that might not be recovered [13].

Little is known about the cardiotoxicity of pertuzumab and trastuzumab emtansine. Pertuzumab is a recombinant humanised monoclonal antibody targeting HER. It is always given in combination with trastuzumab. Its cardiotoxic effect is far less known. An APHINITY trial evaluated the effectiveness and safety of pertuzumab when added to combination of chemotherapy and trastuzumab (dual blockade) in the adjuvant treatment of breast cancer patients. After 6 years of follow up, the incidence of primary cardiac events was less than 1% in both groups of patients. No new safety signals regarding the cardiotoxicity of dual blockade have been detected [14,15]. However, in a meta-analysis of eight randomised controlled trials that included 8420 patients, pertuzumab was associated with an almost two-fold increased risk of heart failure. No other cardiotoxic effects were observed [16].

T-DM1 is a combination of trastuzumab, a HER2 antibody, and emtansine, which is an anti-microtubule agent. Data on its cardiotoxicity are scarce. It was compared to trastuzumab in a KATHERINE trial that enrolled 1486 patients with HER2 breast cancer that did not achieve a complete pathological response on primary systemic therapy. After a median follow up of 41 months, the cardiac events rate was 0.6% in patients receiving trastuzumab and 0.1% in patients receiving T-DM1 [17–19]. In a pooled analysis of seven trials including over 1900 patients receiving T-DM1, the cardiac event rate was about 3%. This included congestive heart failure, LVEF drop, cardiac arrhythmias and cardiac ischemia. In almost 80% of patients, the events resolved upon treatment discontinuation [20]

According to the current position statement of the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology, in patients with breast cancer that should receive anti-HER2 cancer therapies, a baseline cardiovascular risk assessment should be performed, based on previous cardiovascular disease (heart failure or cardiomyopathy, myocardial infarction or CABG, severe valvular heart disease, LVEF value, arrhythmias, stabile angina), cardiac biomarkers (troponin, BNP or NT-proBNP), demographic and cardiovascular risk factors (age, hypertension, diabetes mellitus, chronic kidney disease), current cancer treatment regimen (including anthracyclines before HER2-targeted therapy), previous cardiotoxic cancer treatment (including anthracyclines and chest radiotherapy) and lifestyle risk factors (smoking, obesity) [21].

In patients with breast cancer receiving both anthracyclines and trastuzumab, a measurement of troponin is recommended at baseline, before the commencement of trastuzumab-based therapy and after every four/three/two cycles of trastuzumab according to baseline cardiovascular risk assessment (low/medium/high) [7].

It is not clear whether a heart exposed to trastuzumab is more prone to radiation damage, since the data are equivocal [22,23]. In a retrospective trial of patients undergoing trastuzumab therapy in parallel with radiotherapy of either the right or left breast, radiation doses on the right ventricle (RV), LV and LAD were evaluated. Patients with left-sided breast cancer more often had arrhythmias and cardiac ischemia compared to patients with cancer of the right breast. Also, radiation dose on the RV, LV and LAD was positively correlated with LVEF decline [24].

In this study, we have enrolled patients with HER2-positive left breast cancer undergoing hypofractionated adjuvant left-breast radiotherapy concomitantly with anti-HER2 therapy: trastuzumab, a combination of trastuzumab and pertuzumab or trastuzumab emtansine (T-DM1). Values of high-sensitivity cardiac troponin I (hscTnI), as an early cardiotoxicity biomarker, have been measured prior to and upon completion of radiotherapy. Dose volume histograms (DVH) were generated for cardiac structures and correlated with the increment of hscTnI values in order to define acceptable radiation doses on the heart, left ventricle (LV) and left anterior descending artery (LAD).

2. Materials and Methods

2.1. Patient Population

In this single centre, cohort, prospective, observational trial, 61 female patients with HER2-positive early stage left breast cancer were enrolled. Patients underwent either breast-conserving surgery or mastectomy with axillary lymph node dissection or sentinel lymph node biopsy. Patients were treated with forward intensity-modulated radiotherapy. Clinical target volume consisted of the left breast or chest wall, with or without axillary or supraclavicular lymph nodes. All patients were receiving anti-HER2 therapy: trastuzumab, a combination of trastuzumab and pertuzumab or trastuzumab emtansine (T-DM1) concomitantly with irradiation. Exclusion criteria were myocardial infarction, symptomatic heart failure, chronic atrial fibrillation, malignant cardiac arrhythmias, pacemaker therapy, pulmonary embolism and renal failure.

The study was approved by the Institutional Ethics Committee and all patients signed their informed consent prior to recruitment. It was conducted from January 2022 to April 2023.

2.2. Radiation Therapy

Patients underwent 3D computer tomography treatment simulation during free breathing. Patients were placed on breast board in supine position with arms above their heads. CT slices were 2 mm thick and no intravenous contrast was used. Clinical target volume (CTV) consisted of left breast in 46 patients and left thoracic wall in 15 patients. In 1 patient, both breasts were irradiated. In 31 patients, regional lymph nodes were included in CTV, supraclavicular lymph nodes in 19 patients and both supraclavicular and axillary lymph

nodes in 12 patients. Planning target volume (PTV) was created by adding 1 cm margin to account for intra- and inter-fraction movement. DVHs were generated for target volumes, lungs, spinal cord, heart, LV and LAD. In order to avoid interobserver variability, the same radiation oncologist contoured all structures (KA).

Radiation technique was forward intensity-modulated radiotherapy (fIMRT, field-in-field technique). Prescribed dose was 40.05 Gy in 15 fractions of 2.67 Gy over 3 weeks. Patients were irradiated during free breathing. Patient positioning was controlled using electronic portal-imaging device (EPID) prior to first five fractions and, thereafter, prior to every other fraction.

2.3. High-Sensitivity Cardiac Troponin I Analysis

HscTnI was analysed using Architect STAT Troponin I immunoassay (Abbott Laboratories, Abbott Ireland, Longford, Ireland). Serum samples were taken immediately before the first radiation fraction and immediately after the last radiation fraction. All samples were taken in the morning to avoid the influence of possible diurnal changes on hscTnI values. Patient samples were collected into CAT Serum Sep Clot Activator Vacuette with separator gel (Greiner Bio-One) and processed within 2 h of collection. The samples were centrifuged at 3000× *g* for 10 min. Analysis were performed on the Abbott Architect i2000 using reagents, calibrators and controls of the same manufacturer. Lowest detection limit was 1 ng/L.

Clinically significant increase was defined as a second value > 30% from the baseline and higher than 4 ng/L. Upon data completion, patients were divided in two groups: Group 1 with clinically significant hscTnI increase and Group 2 without clinically significant hscTnI increase.

2.4. Statistical Analysis

Quantitative data distribution normality was tested using Kolmogorov–Smirnov test. Qualitative features distribution was shown in contingency tables and differences in distribution were analysed using Fisher's exact test. Data were expressed as arithmetic means and standard deviation for normally distributed variables and as medians with interquartile range (IQR) for variables with significant deviation from normal distribution. Differences in distribution of numerical variables were analysed using Mann–Whitney U test and Wilcoxon test. The ROC curve was used to determine the optimal threshold value. Correlation of radiation doses and hscTnI increase was analysed using Spearman's rank correlation test. Data are shown as tables and figures. All statistical analyses are interpreted on a significance level of 5%.

3. Results

3.1. Patients' Characteristics

In total, 61 patients were enrolled in this trial. Their characteristics are shown in Table 1. There was no difference between the groups regarding their age, menopausal status, baseline hscTnI values, frequency of anthracycline based therapy, time since the last anthracycline cycle application, cardiac therapy and ACE inhibitors therapy. Besides ACE inhibitors, cardiac therapy also included angiotensin II receptor blockers, beta blockers, calcium channel blockers, imidazoline receptor agonists, diuretics and anti-aggregation agents.

Table 1. Patients' and treatments' characteristics.

	All N = 61	Group 1 N = 17	Group 2 N = 44	*p*-Value
Age (x +/− SD)	58 ± 11	55 ± 12.3	59 ± 10.5	0.2767
Premenopausal	16 (26%)	7 (41%)	9 (20%)	0.1018
hscTnI (ng/L) baseline (M,IQR)	4 (2–7)	5 (3–7)	4 (2–7)	0.8336
Anthracycline use	30 (49%)	11 (65%)	19 (43%)	0.1811
Time between anthracycline and RT in days (M,IQR)	208.5 (188–227)	216 (190–245)	208 (185–219)	0.3015
Hormonal therapy	44 (72%)	13 (76.5%)	31 (70%)	0.1811
Tamoxifen	11 (25%)	4 (30.8%)	7 (22.6%)	0.7221
AI (anastrozole, letrozole)	31 (70%)	8 (61.5%)	23 (74.2%)	0.7979
Goserelin + tamoxifen	2 (5%)	1 (7.7%)	1 (3.2%)	0.5208
Clinical target volume				
Left breast	29 (47.5%)	6 (35.4%)	23 (52.3%)	0.6069
Left breast/thoracic wall + lymph nodes	31 (51%)	10 (58.8%)	21 (47.7%)	0.8099
Both breasts	1 (1.55%)	1 (5.8%)	0	-
Cardiac therapy	26 (43%)	8 (47%)	18 (41%)	0.6658
ACE inhibitors	17/61 (28%)	5/17 (29%)	12/44 (27%)	0.8684

During radiotherapy, 72% of all patients received hormonal therapy, 76.5% in the group with hscTnI increase and 70% in the group without hscTnI increase (no difference between the two groups, $p = 0.1811$). Within the group of patients receiving hormonal therapy, 70% were taking aromatase inhibitor (AI, either anastrozole or letrozole), 25% were receiving tamoxifen and 5% a combination of LHRH agonist goserelin and tamoxifen. No difference between the study groups regarding frequency or type of hormonal treatment has been observed.

In 6 patients in Group 1 (35.4%) and 23 patients in Group 2, the clinical target volume consisted of breast only. In 10 patients in Group 1 (58.8%) and 21 patients in Group 2 (47.7%), regional lymph nodes were also involved in CTV. In one patient in Group 1, both left and right breast were irradiated. There was no statistically significant difference between the groups in terms of clinical target volume comprehensiveness.

Data are shown in Table 1.

3.2. Anti-HER2 Treatments' Characteristics

Before the commencement of radiotherapy, patients received either trastuzumab alone (28%), a combination of trastuzumab and pertuzumab (49%), T-DM1 (1%) or combination of trastuzumab and pertuzumab followed by T-DM1 (21%). No difference between the two groups has been shown regarding the type of anti-HER2 regimen or number of cycles of anti-HER2 therapy prior to radiotherapy.

During radiotherapy, patients received either trastuzumab alone (31%), a combination of trastuzumab and pertuzumab (46%) or T-DM1 (23%). Again, no difference between the two groups has been shown regarding the frequency of any anti-HER2 regimen. There was no difference observed between the two groups in terms of the day (fraction) of radiotherapy treatment on which anti-HER2 therapy was administered.

Data are shown in Table 2.

Table 2. Anti-HER2 therapy before and during radiotherapy.

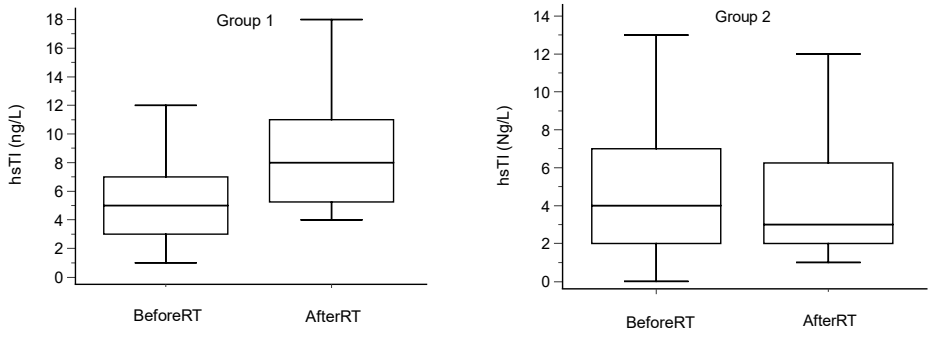
Anti-HER2 Therapy	All N = 61	Group 1 N = 17	Group 2 N = 44	*p*-Value
Before radiotherapy				
Trastuzumab	17 (28%)	4 (23%)	13 (30%)	1.0000
Trastuzumab/pertuzumab	30 (49%)	9 (53%)	21 (48%)	1.0000
T-DM1	1 (2%)	-	1 (2%)	-
Trastuzumab/pertuzumab T-DM1	13 (21%)	4 (23%)	9 (20%)	1.0000
Number of cycles of anti-HER2 therapy before RT (M,IQR)	7 (5–8)	7 (5–8.25)	7 (5.25–8)	0.9934
During radiotherapy				
Trastuzumab	19 (31%)	4 (23.5%)	15 (34%)	0.7665
Trastuzumab/pertuzumab	28 (46%)	9 (53%)	19 (43%)	0.8024
T-DM1	14 (23%)	4 (23.5%)	10 (23%)	1.0000
RT fraction with anti-HER2 therapy application (M,IQR)	9 (5–12)	10 (4.75–12)	8 (5.5–12)	0.8590

3.3. High-Sensitivity Cardiac Troponin I Values

For the whole study population, the median (IQR) hscTnI values were 4 (2–7) ng/L before radiotherapy and 5 (3–10) ng/L after radiotherapy. A clinically significant increase in hscTnI, defined as a second value > 30% from baseline and higher than 4 ng/L, occurred in 17 patients (Group 1). The median values (IQR) were 4 (2–7) ng/L before RT and 8 (5–11) ng/L after RT. For Group 2, the baseline values were 4 (2–7) ng/L and 3 (2–6) ng/L upon treatment completion (Table 3). The values are shown in Table 1. Data are graphically presented in Figure 1.

Table 3. High-sensitivity cardiac troponin I values.

	All N = 61	Group 1 N = 17	Group 2 N = 44	*p*-Value
hscTnI (ng/L) baseline (M,IQR)	4 (2–7)	5 (3–7)	4 (2–7)	0.8336
hscTnI (ng/L) after RT (M,IQR)	5 (3–10)	8 (5–11)	3 (2–6)	0.0053



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

Figure 1. High-sensitivity cardiac troponin I values. Box plot figures to describe hscTnI before and after radiotherapy in (**a**) patients with increase (Group 1, 17 pts) and (**b**) in patients without an increase (Group 2, 44 pts). Borders of the box present Q1 and Q3, middle lines present medians and error bars above and below present maximums and minimums.

3.4. Cardiac Doses

The dose volume histograms for heart, left ventricle (LV) and left anterior descending artery (LAD) for Group 1 and Group 2 are shown in Figure 2. The cardiac doses for both

groups are shown in Table 4. Since the risk of cardiac radiation damage correlates with the volume of the cardiac structure receiving a certain radiation dose, besides mean and maximal doses, we have also selected 10 dose volume points for each cardiac structure. For all observed structures, the mean radiation doses were significantly higher in the Group 1 patients with hscTnI increase ($p = 0.02$ for heart, $p = 0.03$ for LV and $p = 0.04$ for LAD). A statistically significant difference between the groups was observed for AUC for heart and left ventricle ($p = 0.01$ for both), for volume of heart receiving 2 Gy and 4 Gy radiation dose ($p = 0.01$ and $p = 0.02$, respectively) and for volume of left ventricle receiving 2 Gy, 4 Gy and 38 Gy radiation doses ($p = 0.01$, $p = 0.02$ and $p = 0.03$, respectively), all values being higher for Group 1. Also, in Group 1, larger volumes of LAD received 2 Gy, 4 Gy and 5 Gy radiation doses ($p = 0.03$, $p = 0.02$ and $p = 0.02$, respectively), compared to Group 2. In conclusion, in the patients in Group 1 who had an increase in hscTnI levels, larger volumes of the heart, LV and LAD received low radiation doses than in patients in Group 2 (patients without hscTnI increase).

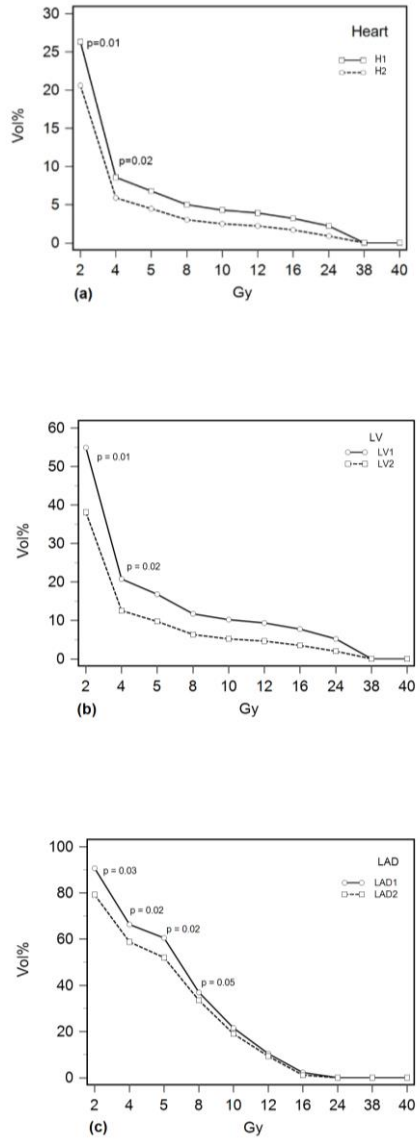


Figure 2. DVH curves for (**a**) heart, (**b**) left ventricle (LV) and (**c**) left anterior descending artery (LAD) in patients with high-sensitivity cardiac troponin I (hscTnI) increase (Group 1, 17 pts) and in patients without hscTnI increase (Group 2, 44 pts).

Table 4. Radiation doses on heart, left ventricle (LV) and left anterior descending artery (LAD) in patients with high-sensitivity cardiac troponin I (hscTnI) increase (Group 1, 17 pts) and in patients without hscTnI increase (Group 2, 44 pts).

Cardiac Structure	Group 1 (N = 17) Median (IQR)	Group 2 (N = 44) Median (IQR)	*p* Mann–Whitney U
Heart			
Dmean (Gy)	2.4 (1.9–3.9)	1.8 (1.5–2.5)	0.02
Dmax (Gy)	38.3 (35.3–39.6)	37.4 (33.8–38.6)	0.22
V2 (%)	26.3 (21.1–35.2)	20.5 (18.9–23.6)	0.01
V4 (%)	8.6 (6–16)	5.8 (4.4–8.9)	0.02
V5 (%)	6.8 (4–13.8)	4.5 (3.2–7.1)	0.07
V8 (%)	5 (2.3–10.7)	3 (1.5–5)	0.08
V10 (%)	4.3 (1.7–9.5)	2.5 (1–4.2)	0.08
V12 (%)	3.9 (1.3–8.5)	2.1 (0.8–3.7)	0.08
V16 (%)	3.2 (0.8–7)	1.6 (0.5–3)	0.09
V24 (%)	2.2 (0.3–4.4)	0.8 (0.1–4.7)	0.10
V38 (%)	0 (0–0.3)	0 (0–0)	0.27
V40 (%)	0 (0–0.3)	0 (0–0)	0.74
AUC (%)	72.9 (72.1–74.3)	51.4 (51.4–54.3)	0.01
LV			
Dmean (Gy)	4.7 (2.8–6.1)	2.9 (2.3–4.2)	0.03
Dmax (Gy)	38.4 (35.3–39.6)	37.2 (33.5–38.5)	0.13
V2 (%)	54.9 (41.3–62.8)	34.8 (32.3–48.3)	0.01
V4 (%)	20.8 (12.7–27.7)	12.5 (10.4–16.1)	0.02
V5 (%)	16.8 (9–22.8)	9.7 (6.3–15.6)	0.06
V8 (%)	11.7 (5.2–17.5)	6.3 (3.2–10.8)	0.08
V10 (%)	10.2 (3.9–15.7)	5.2 (2.1–9.2)	0.08
V12 (%)	9.3 (3.1–14.4)	4.6 (16–8.1)	0.08
V16 (%)	7.7 (1.8–12.3)	3.7 (0.8–6.5)	0.08
V24 (%)	5.2 (0.7–8.7)	2 (0.2–4.2)	0.09
V38 (%)	0.1 (0–0.6)	0 (0–0)	0.03
V40 (%)	0 (0–0)	0 (0–0)	0.8
AUC (%)	67.8 (67.1–72.9)	51.4 (51.4–52.9)	0.01
LAD			
Dmean (Gy)	6.8 (6.3–19.2)	6.2 (5.1–6.9)	0.04
Dmax (Gy)	22.4 (16–37.8)	19.1 (17.2–25)	0.21
V2 (%)	90.7 (82.2–99.9)	79.2 (71.8–88.9)	0.03
V4 (%)	66.3 (61.8–74.1)	58.8 (48–67.8)	0.02
V5 (%)	60.5 (55.6–70.6)	52 (41.3–63)	0.02
V8 (%)	37 (31.1–55.7)	33.5 (16.3–38.4)	0.05
V10 (%)	21.5 (16.1–53.3)	19.1 (6.6–23.2)	0.07
V12 (%)	10.4 (6.1–51.3)	9.2 (2.5–16.1)	0.08
V16 (%)	2.2 (0–48.2)	1.1 (0.1–3.5)	0.24
V24 (%)	0 (0–44.3)	0 (0 –0)	0.16
V38 (%)	0 (0–0)	0 (0–0)	0.19
V40 (%)	0 (0–0)	0 (0–0)	0.54
AUC (%)	63.2 (58.6–68.6)	60 (57.1–63.6)	0.12

LV—left ventricle, LAD—left anterior descending artery, hscTnI—high sensitivity cardiac troponin I, Dmean—mean radiation dose to the structure, Dmax—maximal point radiation dose in the structure, V 40/38/24/16/12/10/8/5/4/2—the volume of structure receiving 40 Gy, 38 Gy, 24 Gy, 16 Gy, 12 Gy, 10 Gy, 8 Gy, 5 Gy, 4 Gy and 2 Gy doses, AUC—area under curve.

Dose volume constraints for hscTnI increase are shown in Table 5.

Table 5. Dose volume constraints for hscTnI increase (ROC curve data).

Radiation Dose (Gy)	Heart Dose-Volume Constraint (%)	LV Dose-Volume Constraint (%)	LAD Dose-Volume Constraint (%)
2	>19.7	>38.7	>86.4
4	>10.2	>12.1	>59.6
5	>8.6	>14.5	>52.4
8	>4.7	>10	>16.7
10	>3.9	>8.2	>7.1
16	>2.6	>7.3	>1.6
38	>0.1	>0.1	>0
40	>0.1	>0.2	≤0

LV—left ventricle, LAD—left anterior descending artery, V 40/38/24/16/12/10/8/5/4/2—the volume of structure receiving 40 Gy, 38 Gy, 24 Gy, 16 Gy, 12 Gy, 10 Gy, 8 Gy, 5 Gy, 4 Gy and 2 Gy radiation dose. Dose-volume constraint—the threshold value for hscTnI value increase.

4. Discussion

Upon completion of left breast radiotherapy, hscTnI levels increased in about one fourth of patients and that increase was correlated with radiation doses on the heart and its structures, LV and LAD suggesting subclinical myocardial damage caused by irradiation. After lower radiation doses, such as those observed in our study, the underlying mechanism is microvasculature damage and inflammatory changes. They lead to focal ischemia resulting in myocyte damage and subsequent troponin release [8]. Based on data from the literature, troponin elevation during cancer treatment is correlated with the later development of cancer-treatment-related cardiac dysfunction that might not recover [10,13,25,26]. Although cut-off values of high-sensitivity cardiac troponin are yet to be defined, its evaluation during cancer treatment can identify patients that require a more thorough follow-up of cardiac function.

In our study, no difference between the groups has been observed regarding patients' age, menopausal status, prior cardiac therapy and the use of ACE inhibitors.

Anthracyclines are cytostatic antibiotics that have been in use in oncology since the 1960s. The risk for developing cardiotoxicity caused by anthracyclines is proportional to their cumulative dose; it occurs in up to 5% of patients with doses of 400 mg/m^2. It can occur years after therapy with anthracyclines and its incidence rises with the time flow from the last application. It is more common in older patients, patients with previous heart conditions, in patients that underwent radiotherapy of the thorax and, in last two decades, in breast cancer patients receiving trastuzumab. The underlying mechanism of anthracycline-caused cardiotoxicity is still not clear. It presents with hypokinetic cardiomyopathy diagnosed by a decrease in left ventricle ejection fraction (LVEF) and eventually leads to heart failure. The early diagnosis and early onset of therapy with ACE inhibitors and beta blockers can result in LVEF improvement. If diagnosed at a later stage, anthracycline-caused cardiotoxicity is usually irreversible and has poor prognosis [27].

Anthracycline-based chemotherapy is known to elevate troponin levels. That elevation is transitional and correlates with the development of cardiotoxicity, including a decline in left ventricular ejection fraction [25,26]. In our study, one half of the patients received anthracycline-based chemotherapy; 65% in Group 1 and 43% in Group 2 ($p = 0.1811$). The median times from the application of the last cycle of anthracycline and the commencement of radiotherapy were 216 days for Group 1 (IQR: 190–245) and 208 days for Group 2 (IQR: 185–219), $p = 0.3015$. In conclusion, no statistically significant difference between the groups in terms of anthracycline use has been observed. Therefore, we did not attribute the hscTnI increase observed in Group 1 to previous anthracycline use.

Trastuzumab itself can also increase troponin levels. As with anthracyclines, troponin increment caused by trastuzumab is transitional and was shown to be predictive of later cardiotoxicity [13]. In our study, no difference between the groups regarding number of anti-HER2 therapy applications prior to radiotherapy has been observed; in both groups,

the median number of cycles was 7 (IQR: 5–8.25 for Group 1 and 5.25–8 for Group 2; $p = 0.9934$).

Also, there was no difference regarding the type of anti-HER2 therapy, either before or during radiotherapy. Prior to radiotherapy, patients were receiving trastuzumab, a combination of trastuzumab and pertuzumab, T-DM1 or combination of trastuzumab and pertuzumab followed by T-DM1. During radiotherapy, patients were given either trastuzumab, a combination of trastuzumab and pertuzumab or T-DM1. That is in concordance with most of the literature data showing no difference in cardiotoxicity regarding the type of anti-HER2 treatment [14,15,17–20]. One exception is the meta-analysis of eight randomised controlled trials revealing a higher risk of heart failure associated with pertuzumab [16]. However, although patients in these trials were irradiated concomitantly with anti-HER2 therapy, data on the radiation doses on cardiac structures are lacking.

To exclude the possible acute effect of the application of anti-HER2 therapy during radiotherapy on hscTnI release, we have recorded the radiation fraction with which anti-HER2 therapy was administered. Again, no difference between the groups has been observed. The median radiotherapy fraction values were 10 for Group 1 (IQR: 4.75–12) and 8 for Group 2 (IQR: 5.5–12), $p = 0.859$. Based on the abovementioned, we have excluded the effect of anti-HER2 therapy application on hscTnI levels.

In terms of hormonal therapy, this was prescribed in about three fourths of patients during radiotherapy. About 75% of the patients in each group that were receiving hormonal therapy were given aromatase inhibitor. No difference between the groups has been shown regarding either the use or type of hormonal therapy. Therefore, it is not likely that hormonal therapy might have influenced hscTnI release.

The clinical target volume was either left breast (in the case of breast-conserving surgery), with or without lymph nodes or left thoracic wall with lymph nodes. If included in CTV, lymph nodes were either supraclavicular or both supraclavicular and axillary lymph nodes. The target volumes were determined according to the current guidelines and based on the initial clinical stage of the disease, the type and extent of axillary surgery and the pathohistological report. In one patient in Group 1, both breasts were irradiated upon breast-conserving surgery due to bilateral breast cancer. Although the proportion of patients with lymph nodes included in the target volume was slightly higher in Group 1, 58.8%, compared to 47.7% in Group 2, this was not statistically significant.

The two groups differed only in radiation doses on cardiac structures. The mean heart dose median was 2.4 Gy for Group 1 (IQR: 1.9–3.9) vs. 1.8 Gy for Group 2 (IQR: 1.5–2.5). This is in accordance with the finding that the risk of major cardiac event is proportional to the mean dose to the whole heart and increases linearly by 7.4% per Gray [2]. When analysing DVHs, the measured dose volume points were different for low doses: V2 (volume of heart receiving 2 Gy) and V4 (volume of heart receiving 4 Gy), meaning that, in Group 1 with hscTnI increase, larger volumes of the heart were exposed to more radiation than in Group 2. Though it is still unclear what is more detrimental, a lower dose for a larger volume or a higher dose for a small volume, our data indicate that a low dose applied on a larger volume contributed to acute myocyte damage, resulting in subsequent troponin release.

For the left ventricle and left anterior descending artery, the findings were similar. There was a statistically significant difference for mean doses between the two groups. For LV, the medians were 4.7 for Group 1 (IQR: 2.8–6.1) and 2.9 Gy for Group 2 (IQR: 2.3–4.2). The two groups differed for V2 and V4, but also for V38, with all volumes being larger in Group 1.

LAD is the most anterior part of the heart situated near the clinical target volume. According to data from the literature, the mean dose on LAD higher than 5 Gy was connected with an increased requirement of coronary intervention in LAD years after the completion of radiotherapy [5]. In our study, the median dose on LAD was higher than 5 Gy in both groups: it was 6.8 Gy for Group 1 (IQR: 6.3–19.2) and 6.2 Gy for Group 2 (IQR:

5.1–6.9). The measured dose volume points were different for low doses, with V2, V4 and V5, again, being higher in Group 1 with hscTnI increase.

Radiation-dose-dependent troponin release during irradiation of the left breast has already been described in the literature. High-sensitivity cardiac troponin T was measured prior to, during and after left breast radiotherapy. In patients with increased hscTnT values, higher radiation doses on the whole heart and LV were reported, as well as V15 and V20 for LAD [11]. However, the patients in this trial did not receive chemotherapy prior to irradiation or anti-HER2 therapy either prior to or during irradiation. Lymph nodes were not included in the target volume and, also, fractionation schemes were different than in our study; patients received either 50 Gy in 2 Gy daily fraction over 5 weeks or 42.56 Gy in 2.66 Gy fractions over 3.5 weeks. According to the institutional guidelines based on the data in the literature, the patients in our trial received 40.05 Gy in 2.67 Gy fractions over 3 weeks—a hypofractionated regimen [28,29]. Therefore, the applied radiation dose in our patients was somewhat lower and the overall treatment time was shorter.

Numerous trials did not show any difference in cardiotoxicity between the conventional radiotherapy (CFRT) and hypofractionated radiotherapy (HFRT). In START trials, schedules of 41.6 Gy or 39 Gy in 13 fractions over 5 weeks and 40 Gy in 15 fractions over 3 weeks were compared to the conventional fractionation scheme of 50 Gy in 25 fractions over 5 weeks. After 10 years of follow-up, there was no difference in the frequency of ischemic heart disease between the groups of patients that received HFRT and the patients irradiated with conventional fractionation [29]. Long-term data from a Canadian trial comparing 42.56 Gy in 16 fractions over 22 days with 50 Gy in 25 fractions over 5 weeks are similar; after 12 years of follow-up, few cardiac-related deaths were observed in both groups of patients. There was no increase in cardiac-related deaths in patients who were irradiated with a hypofractionated schedule [30]. In a meta-analysis that was published in 2020, the authors analysed the data from 25 clinical trials that enrolled 3871 postmastectomy patients and compared HFRT with CFRT in terms of both treatment efficacy and toxicity. No difference in late cardiac toxicity between the schedules was observed [31]. In an analysis of the data of 510 breast cancer patients irradiated between 2002 and 2006, either conventionally or with a hypofractionated schedule, cardiac toxicity was evaluated. The rate of ischaemic cardiac disease was low in both group of patients. According to the trial data, the fractionation schedule had no influence on the frequency of cardiotoxicity [32].

The strengths of our study are the clear inclusion criteria that reduce uncertainty and error factors, and the well-balanced subgroups of patients. The limitations could be the possibly confounding effect of anthracycline use, though groups were balanced in this regard and there was a variability of cardiac therapy.

Based on the abovementioned data, we have calculated dose-volume constraints for the whole heart, LV and LAD in order to define the radiation doses above which troponin release as a result of radiation damage can be expected. They should not be considered absolute safe cardiac doses for this patient population, but rather as guidance that might be considered for treatment planning. However, patients with troponin increase should be followed more carefully for the early diagnosis of cardiac dysfunction and timely implementation of cardioprotective treatment strategies in order to improve both oncological and cardiovascular outcomes. It is yet to be explored if this hscTnI increase can predict the future risk of cardiovascular morbidity and mortality in this group of patients.

5. Conclusions

In patients with HER2-positive breast cancer undergoing adjuvant hypofractionated left breast radiotherapy concomitantly with anti-HER2 therapy, high-sensitivity cardiac troponin I is being released, dependent on the radiation dose on the heart and its structures. The results of this study can partially contribute to understanding early cardiotoxicity development and detection.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets analysed or generated during the current study are available from the corresponding author upon reasonable request.

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

Abbreviations

hscTnI	high-sensitivity cardiac troponin I
Gy	Gray
LN	lymph nodes
ROC	receiver operating characteristics
RT	radiation therapy
DVH	dose volume histograms
LAD	left anterior descending artery
LV	left ventricle
LVEF	left ventricular ejection fraction
T-DM1	trastuzumab emtansine
CFRT	conventional fractionated radiotherapy
HFRT	hypofractionated radiotherapy

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Current Oncology

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Case Report

Pregnancy in a Young Patient with Metastatic HER2-Positive Breast Cancer—Between Fear of Recurrence and Desire to Procreate

Cristina Marinela Oprean [1,2,3], Andrei Dorin Ciocoiu [2], Nusa Alina Segarceanu [2,3], Diana Moldoveanu [2,3], Alexandra Stan [4], Teodora Hoinoiu [5,6,*], Ioana Chiorean-Cojocaru [7], Daciana Grujic [8], Adelina Stefanut [9], Daniel Pit [6] and Alis Dema [1]

1 ANAPATMOL Research Center, 'Victor Babes' University of Medicine and Pharmacy of Timisoara, 300041 Timisoara, Romania
2 Department of Oncology, ONCOHELP Hospital Timisoara, Ciprian Porumbescu Street, No. 59, 300239 Timisoara, Romania
3 Department of Oncology, ONCOMED Outpatient Unit, Ciprian Porumbescu Street, No. 59, 300239 Timisoara, Romania
4 Department of Oncology, City Clinical Emergency Hospital of Timisoara, Victor Babes Blvd. No. 22, 300595 Timisoara, Romania
5 Department of Clinical Practical Skills, "Victor Babes" University of Medicine and Pharmacy, Eftimie Murgu Sq. Nr. 2, 300041 Timisoara, Romania
6 Center for Advanced Research in Cardiovascular Pathology and Hemostaseology, "Victor Babes" University of Medicine and Pharmacy, 300041 Timisoara, Romania
7 Department of Obstetrics and Gynaecology, Faculty of Medicine and Pharmacy, "Victor Babes" University of Medicine and Pharmacy, 300041 Timisoara, Romania
8 Department of Plastic and Reconstructive Surgery, "Victor Babes" University of Medicine and Pharmacy, Eftimie Murgu Sq. Nr. 2, 300041 Timisoara, Romania
9 Department of Psichology & Sociology, West University, Timisora, Blvd. No. 4, Vasile Pârvan, 300223 Timisoara, Romania
* Correspondence: tstoichitoiu@umft.ro

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Abstract: Breast cancer is the most frequent neoplasm among women and the second leading cause of death by cancer. It is the most frequent cancer diagnosed during pregnancy. Pregnancy-associated breast cancer is defined as breast cancer that is diagnosed during pregnancy and/or in the postpartum period. Data about young women with metastatic HER2-positive cancer who desire a pregnancy are scarce. The medical attitude in these clinical situations is difficult and nonstandardized. We present the case of a 31-year-old premenopausal woman diagnosed in December 2016 with a stage IV Luminal HER2-positive metastatic breast cancer (pT2 N0 M1 hep). The patient was initially treated by surgery in a conservative manner. Postoperatively, the presence of liver metastases was found by CT investigation. Consequently, line I treatment (docetaxel l75 mg/m^2 iv; trastuzumab 600 mg/5 mL sq) and ovarian drug suppression (Goserelin 3.6 mg sq at 28 days) was administered. After nine cycles of treatment, the patient's liver metastases had a partial response to the therapy. Despite having a favorable disease evolution and a strong desire to procreate, the patient vehemently refused to continue any oncological treatment. The psychiatric consult highlighted an anxious and depressive reaction for which individual and couple psychotherapy sessions were recommended. After 10 months from the interruption of the oncological treatment, the patient appeared with an evolving pregnancy of 15 weeks. An abdominal ultrasound revealed the presence of multiple liver metastases. Knowing all the possible effects, the patient consciously decided to postpone the proposed second-line treatment. In August 2018, the patient was admitted in the emergency department with malaise, diffuse abdominal pain and hepatic failure. Abdominal ultrasound found a 21-week-old pregnancy which had stopped in evolution, multiple liver metastases and ascites in large quantity. She was transferred to the ICU department where she perished just a few hours later. Conclusions/Discussion: From a psychological standpoint, the patient had an emotional hardship to make the transition from the status of a healthy person to the status of a sick person. Consequently, she entered a process of emotional protection of the positive cognitive distortion type,

which favored the decision to abandon treatment and try to complete the pregnancy to the detriment of her own survival. The patient delayed the initiation of oncological treatment in pregnancy until it was too late. The consequence of this delay in treatment led to the death of the mother and fetus. A multidisciplinary team worked to provide this patient with the best medical care and psychological assistance throughout the course of the disease.

Keywords: metastatic breast cancer; pregnancy; trastuzumab; chemotherapy; pregnancy-associated breast cancer; PABC

1. Introduction

Breast cancer is the most common malignancy amongst women. It is the second leading cause of death by cancer [1]. In the US, approximately 11% of 230,000 new cases of invasive breast cancer are diagnosed in women under the age of 45 [2]. In recent years, there has been an increase in the incidence of breast cancer in women under 40 [3]. In the last five decades, since the 1970s, there has been a trend in postponing pregnancies to a more mature age (delaying childbearing) [4]. As the incidence of breast cancer increases with age, more and more women are diagnosed with cancer during pregnancy, and on the other hand, despite being diagnosed with cancer, some women want a child at any cost [5]. Pregnancy-associated breast cancer (PABC) is defined as breast cancer that is diagnosed during pregnancy and/or the postpartum period (Shao 2020). Breast cancer is the most common malignancy diagnosed during pregnancy, with an increase in incidence in recent decades [6]. The incidence of breast cancer in pregnancy is estimated at 1/3000 pregnancies, about 3% of all breast cancers [7–9]. Pregnancy that occurs before or concurrently with a diagnosis of breast cancer is more likely to result in death and decreased disease-free survival [10]. Breast cancer during pregnancy should be treated as much as possible following the recommendations of the guidelines for breast cancer in nonpregnant women. Chemotherapy is contraindicated in the first trimester of pregnancy due to an increased risk of induction of fetal malformation, as it is the period in which oncogenesis is formed [6]. The most common fetal malformations are deafness, gonadal malformations, cardiac complications (arrhythmias, ischemia and thrombocytopenia), or cognitive disabilities [11]. Moreover, administering chemotherapy in the first trimester of the pregnancy carries a 17% risk of inducing a miscarriage [12]. Chemotherapy can be safely administered during the second and third trimesters of pregnancy [5,13]. The use of chemotherapy during the second and third trimesters of pregnancy may be associated in approximately 10–20% of cases with an increase in the number of obstetric and fetal complications, including hypertensive disorders, restriction of intrauterine growth and premature birth [13]. Anthracycline-based chemotherapy is the standard therapy and can be safely administered to pregnant breast cancer patients during the second and third trimesters of pregnancy. Clinical experience in the use of taxanes in this subtype of patient is limited [13,14]. Endocrine therapy as well as anti-HER2 therapy (the monoclonal antibody trastuzumab) should be avoided during pregnancy, and treatment with these agents should be postponed until after birth [6]. Anti-HER2 therapy is associated with an increased risk of anhydramnios (absence of amniotic fluid leading to fetal lung hypoplasia and postpartum respiratory distress or even intrauterine death) [15–17].

Psychological Implications of Breast Cancer Diagnosis

The diagnosis of breast cancer has implications not only on a physical level but also on a psychological level that are closely related to the disease itself but also to the specifics of the treatments applied. Thus, although the efficacy of these treatments has increased over time, one third of patients do not follow an adjuvant treatment, because they refuse it [18]. Understanding the psychological reality of these patients as well as the factors that contribute to refusing or stopping treatment is particularly important.

They may have a reaction of distrust or of denial; they may face a feeling of uncertainty. During this transition period, patients face multiple stressors, and the lack of similar experiences in their own life or in the life of those in their families makes the coping process difficult [19].

Regarding treatment compliance, among the factors that can influence it, we include the existence of depression, the level of medical knowledge, beliefs about treatment and the trust in the medical system [20]. In the case of young women diagnosed with breast cancer, the psychological problem presented above is frequently added to the desire to have children. In general, women's desire to have children can be emotionally grounded or may be the result of society's expectations; it may be based on the desire to please their life partner [21], or it may mean the end of loneliness because the mother has a person who can love her [22]. In addition, the diagnosis of breast cancer can intensify this desire and give it a new symbolic meaning, such as being normal and able to achieve something beautiful, as opposed to death [23]. In the context of breast cancer, young women face a strong sense of injustice derived from the fear of not being able to give birth and the need to change their future plans regarding having a child, which can affect the achievement of life goals [24].

It is also worth noting that young women newly diagnosed with breast cancer report that their most important concerns are children and family, even at the expense of their own survival [25]. A study involving breast cancer survivors and their partners shows that the experience of the disease did not diminish the motivation to have a biological child for either women or their husbands [23].

Data about young women with metastatic HER2-positive cancer who desire a pregnancy are scarce. The medical conduct in these clinical situations is difficult and nonstandardized. Patients need strong emotional support to help them make a decision about procreation and fear of recurrence. To the best of our knowledge, this is the first case report about an unfavorable outcome of a pregnant mother with metastatic HER2-positive breast cancer.

2. Case Presentation

We present the case of a premenopausal, employed, unmarried, urbanite, nulliparous, 31-year-old patient with a negative personal and familial medical history. In December 2015, she was diagnosed clinically and by imaging with a tumor formation in her left breast, in the lower inner quadrant of 25/13/16 mm. The patient delayed the definite diagnosis by performing the biopsy 1 year later, in November 2016. The pathology examination revealed a hormone-dependent (ER = 90, PR = 30%), Ki67 = 30%, HER2 = 3 + (positive) infiltrative ductal breast carcinoma (IDC), G2, with an "in situ" ductal component of the comedo type. The preoperative assessment consisted of performing a bilateral mammogram and a bilateral breast MRI, thus avoiding the diagnosis of liver metastases at the time of diagnosis. The patient was initially clinically staged T2N0, being considered a nonmetastatic disease. On 8 December 2016, a left breast conserving surgery and a sentinel node biopsy was performed. Postoperative histopathological examination confirmed a infiltrative ductal carcinoma with components of "in situ" breast carcinoma; Nsn = 0/2 lymph nodes examined (pT2Nsn0). Immunohistochemistry (IHC) revealed an RE = 80%, RP = 20%, Ki 67 = 30% and HER2 = 3 + (positive) profile. On the CT scan performed during the pretherapeutic assessment on 19 December 2016, two liver metastases of 31 mm and 12 mm were observed in the 4th and 2nd segment (Figure 1). The CA15-3 tumor marker had a value of 86.8 U/mL. First-line treatment with docetaxel 75 mg/m^2 iv, trastuzumab 600 mg/5 mL sq./21 days and medical ovarian suppression (goserelin 3.6 mg sq./28 days) was initiated. The treatment was well tolerated by the patient, with no significant side effects. The CT scan performed in May 2017, after six cycles of treatment, highlighted a partial response: the liver lesion in the 4th segment had decreased dimensions (15 mm vs. 31 mm), and the lesion in segment II was in complete remission (Figure 2). The treatment was continued for three more cycles. The PET-CT performed in July 2017 described a single liver lesion of 22.3 mm in the 2nd segment, intensely metabolically active (SUV = 6.4) (Figure 3).

Transaminases, both after the 6th and 9th cycle, were within normal limits. For the remaining liver injury, the patient performed, in August 2017, two ablation sessions with an MW of 6 and 4 min at 32 W with a temperature set at 96 degrees. Due to the favorable evolution of the disease and the strong desire to have a child, the patient refused to continue any oncological treatment, including ovarian ablation and the recommended hormone therapy (tamoxifen). The psychiatric consultation highlighted an anxious and depressive reaction for which individual and couple psychotherapy sessions were recommended. The patient only attended regular individual psychotherapy sessions, because at that time she had no life partner. Three months later, in January 2018, the CT scan highlighted a progressive disease of the 4th liver segment lesion (from 33 mm to 55 mm) (Figure 4). She was proposed a 2nd-line treatment with the resumption of the ovarian suppression with goserelin, but the patient refused any additional oncological treatment. In July 2018, the patient presented to the clinic after an emergency consultation, being pregnant for 15 weeks and complaining of abdominal pain. Ultrasound revealed multiple hepatic lesions suggestive of metastases. Tumor marker CA 15-3 had a value of 2400 U/mL, and the common liver tests were slightly above the normal limit (AST = 50 U/L; ALAT = 80 U/L, TB = 1.8 mg/dL). Although the patient was informed about the prognosis at this stage of the disease and about the potential vital risks in case of pregnancy, she wanted to keep the pregnancy, being aware of the consequences of this decision on the evolution of the disease and survival. She did not consult with her parents or with her life partner. Psychological counselling was carried out individually only with the patient, who did not want the family present at the counselling sessions. The psychiatric evaluation performed did not find the existence of any psychiatric pathology that would affect her decision making. We proposed the initiation of chemotherapy, but the patient refused, wanting to go abroad for a second-opinion consultation. She hoped that this consultation would give her a lifesaving solution for the clinical situation she was in. At the end of August 2018, the patient was transported to the emergency department with an affected general state, diffuse abdominal pain and liver failure (AST = 6017 U/L, ALT = 782 U/L; TB = 6.67 mg/dL). The abdominal ultrasound that was performed in the OBGYN department revealed a 21-week-old pregnancy halted in evolution, the absence of fetal heartbeat, biometrics corresponding to an 18-week-old pregnancy, amniotic fluid in normal quantity, multiple liver metastases that almost entirely occupied the liver parenchyma and ascites in large quantities. Given the serious general condition and the impossibility of evacuating the pregnancy by surgery (uterine curettage or total hysterectomy) due to the very high risk of anesthetic death, she was transferred to the intensive care unit where she died a few hours later.

The psychological aspects involved in this case are, first of all, the postponement by the patient of the investigations that could specify the diagnosis with certainty. This postponement was justified by the patient on the basis of the belief that it could not be a serious illness considering her young age. With the initiation and then continuation of chemotherapy, its side effects also appeared. Although the patient's body tolerated the medication well, the psychosocial impact of the disease and treatment was considerable. The patient was a very active person and the social and professional limitations resulting from her illness changed not only her life routine but also reduced her access to the situations that could create meaning and significance. These limitations also contributed to the reduction in social support. The patient was the only child in the family, so she thought it was her duty to protect her parents from the negative psychological impact of finding out the diagnosis. Therefore, she presented the situation to her parents in a much better light than it was in reality, and when the treatment was stopped, they thought that it was no longer necessary to continue it. This state of affairs had the consequence of depriving the patient from adequate support from her parents.

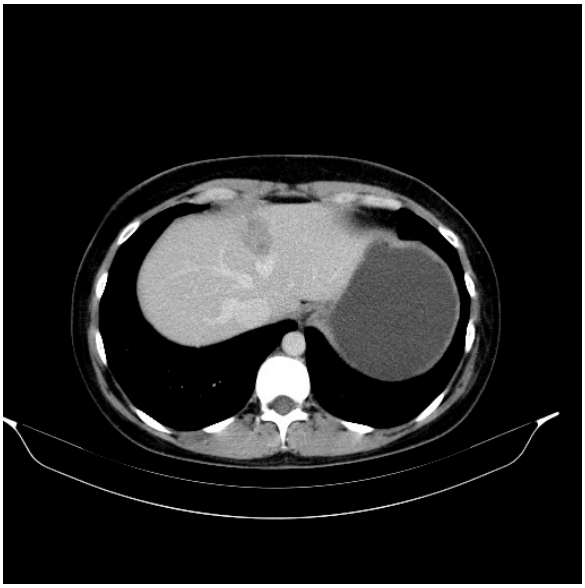

Figure 1. Liver metastasis in 31-year-old women with infiltrative ductal breast carcinoma (IDC), G2, with an "in situ" ductal component of the comedo type. Axial noncontrast abdominal CT image performed in 2016 shows a liver metastasis (31 mm diameter) with an ill-defined area of low attenuation and faint high attenuation.

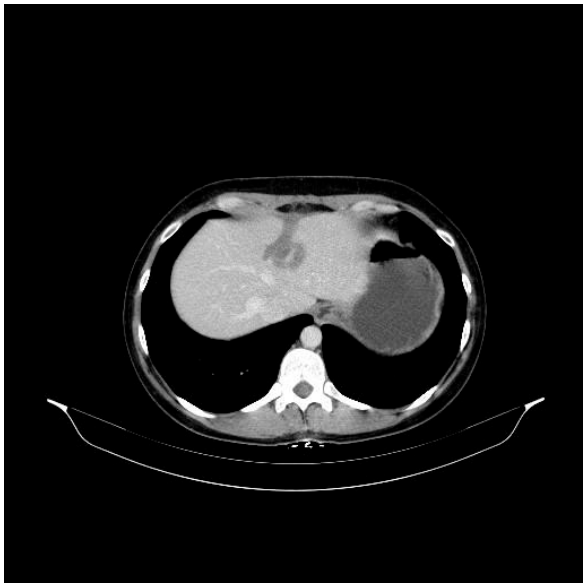

Figure 2. Aspect on the abdominal CT in 2017 after medication with docetaxel 75 mg/m^2 iv, trastuzumab 600 mg/5 mL sq./21 days and medical ovarian suppression (goserelin 3.6 mg sq./28 days) with the liver metastasis (15 mm diameter).

The patient expressed positive beliefs about herself and about her ability to overcome the disease. She also expressed an optimistic view of the course of the disease, believing that it could be stopped even if she interrupted treatment—this view being in fact a way of denying the severity of the disease. Even though she generally acknowledged the severity of the disease, she could not accept that she herself could be in a serious situation.

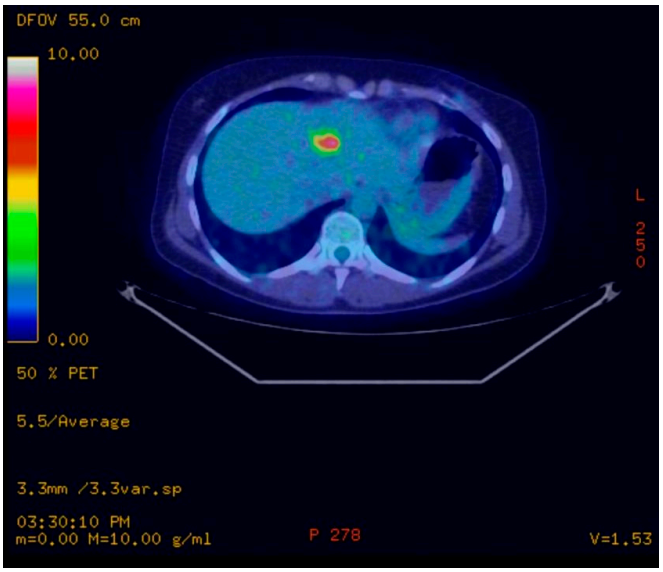

Figure 3. PET/CT scans performed in 2017 showing a single liver lesion of 22.3 mm in the 2nd segment with intense metabolic activity (SUV = 6.4) described as a single liver metastasis.

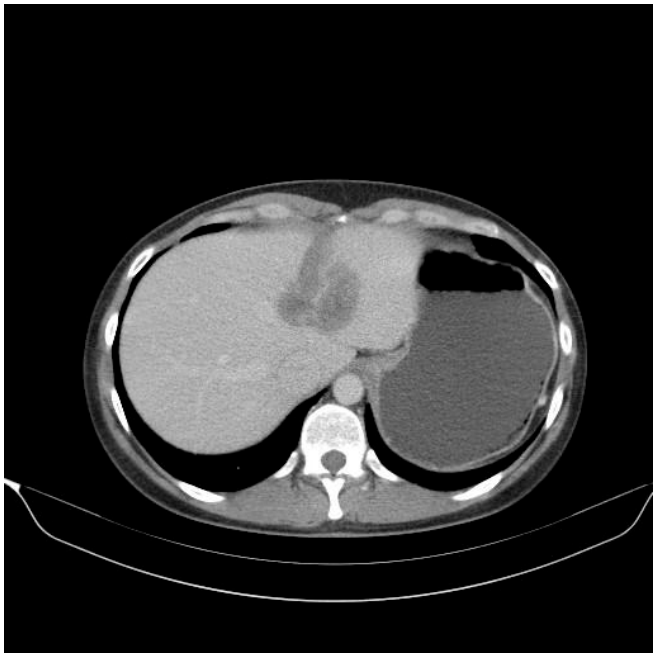

Figure 4. Follow-up abdominal CT performed in 2018 at 6 months after two ablation sessions of the liver metastasis with an MW of 6 and 4 min at 32 W with a temperature set at 96 degrees highlights a progressive disease of the liver metastases at 55 mm diameter.

Although physically the treatment was well tolerated by the patient, she stated that the treatment "does her no good" and that it "changes" her. The way she perceived herself had changed, and she was not satisfied with this new situation. She did not complain about the bodily changes that occurred, but she pointed out the fact that before she was a cheerful, active, full-of-life person, and now she felt deprived of energy and permanently tired. In an attempt to return to her previous condition, once the treatment was stopped, she resumed her professional life, although she could have benefited from another 8 months of medical leave. Involvement in a relationship and then the onset of pregnancy are part of the same attempt to return to her previous life when she was a healthy person.

3. Discussion

Breast cancer, malignant melanoma, cervical cancer, lymphoma and acute leukemia are the most common cancers diagnosed in pregnancy. The occurrence of pregnancy in a patient with metastatic or recurrent disease is a rare and difficult clinical situation. There are few publications in the literature that present these clinical situations. The vast majority of published cases present clinical situations in which the evolution was favorable and the pregnancy was completed. Mauricio Burotto presents such a case in a patient with metastatic malignant melanoma [26]. Clinical cases with successful outcome have also been published: pregnancy in a patient with recurrent ovarian angiosarcoma [27], pregnancy in a patient with recurrent and high-grade metastatic osteosarcoma [28]. Isolated cases have been published in the literature on pregnant patients treated with trastuzumab. Thus, Michelle A. Fanare described a case of HER2-positive metastatic breast cancer in a 27-week-pregnant woman treated with trastuzumab and vinorelbine weekly. Although she suffered an anhydramnios as a side effect, the patient managed to give birth to a healthy baby [16]. One of our explanations would be that since this patient was 27 weeks pregnant, the exposure to trastuzumab during pregnancy was not long-lasting. In our patient, anti-HER2 therapy may not have been a treatment option, requiring longer-term exposure to trastuzumab and probably with more severe side effects. Most likely, our treatment option would have been the use of anthracyclines or taxanes (especially considering the good response to taxanes we had at the first administration), while the use of trastuzumab would have been postponed until after birth.

Pregnancy associated with breast cancer is defined differently in different clinical trials, and this difference explains the inhomogeneous results related to the prognosis of these patients. A recent meta-analysis of 54 articles with 76 included clinical trials that analyzed the prognosis of patients with pregnancy associated with breast cancer concluded that this clinical situation is associated with poor prognosis. However, whether PABC has a worse prognostic is controversial [29]. A meta-analysis published in 2016 showed an increased risk of death in women with PABC compared with non-PABC [10]. Other recent studies found no significant difference in the prognostic of PABC compared with women with non-PABC [30–33]. Case-control studies found that the prognosis is more unfavorable in breast cancer in pregnancy, but when analyzing the data on the TNM stage of the disease, it was observed that the prognosis is not significantly different [34]. For patients who received chemotherapy during pregnancy, the survival data were comparable to those of nonpregnant patients [35,36]. Most children exposed to chemotherapy during intrauterine life have no significant complications [37].

In the case of our patient, the initiation of oncological treatment during pregnancy was postponed until it was too late, which required a multidisciplinary collaboration between the oncologist and obstetrician for the relative benefits of the fetus. Clinical trials have shown that chemotherapy can be safely administered in the second and third trimesters, starting at week 16 of pregnancy. In the selection of treatment, the criteria involve the time of diagnosis, hormonal status and trimester of pregnancy [12]. One of the open questions would be "if we had started chemotherapy, would the patient have managed to complete the pregnancy?" Among the negative prognostic factors present in this case, we mention pregnancy, stage of the disease (patient with metastatic disease at onset), progressive disease at the time of pregnancy, young age and overexpression of HER2. We can assume that if we had initiated chemotherapy, there would have been a chance that the patient would have completed the pregnancy. Unfortunately, the consequence of the delay of the oncological treatment resulted in the death of the fetus and the mother.

The cause of fetal death in utero may be due to hypoxia due to placental detachment with disseminated intravascular coagulation [38] or placental metastases that may affect the fetal circulation if they exceed the villous space of the placenta or may not affect the fetus if they remain at that level [39]. Other causes can be intrauterine growth restrictions or even fetal malformation. Placental metastases are rarely described in the literature, occurring in approximately 17% of cases (4 cases out of 24) [40].

If we refer to the psychological implications associated with this case, we note that finding a diagnosis of a potentially fatal disease can greatly change a person's assumptions about the world and about themself. Reconstructing the worldview requires both emotional and cognitive processing, at a time when the enormity of the threat and emotions can be overwhelming [41]. Young patients newly diagnosed with breast cancer report this passage through various emotional states, which they describe as an "emotional rollercoaster" [19]. From a cognitive perspective, people can resort to three different processes to keep negative emotions aside: cognitive avoidance, emotional avoidance and cognitive distortion. Cognitive avoidance refers to concentrating attention voluntarily or automatically elsewhere to avoid thoughts or images that create distress. Emotional avoidance is a dissociative mechanism by which the person is able to talk about stressful, serious events without having emotional reactions. The last type of avoidance—cognitive distortion—refers to the tendency to operate within a positive bias expressed, for example, by overestimating the probability of experiencing positive events [42].

In the case presented in this study, the hypothesis is that in trying to protect herself emotionally from the implications of the severe diagnosis she was facing, the patient resorted to cognitive distortion. The patient's beliefs about herself before the disease outlined the image of a strong, active person with multiple resources, able to face adversity. These beliefs, which are the basis of an optimistic vision, and which support a fighting spirit against the disease, can make an easy and imperceptible transition to an optimism that is not objectively sustained. This transition was probably made when she gave up treatment, considering the personal resources available to her ensured her success in dealing with the disease. It is also possible that this transition was triggered by the news of encouraging treatment results, known to be the mechanism involved in cognitive distortion through which a person filters a certain category of information (in this case, the negative ones) and focuses on other categories of information (in this case positive). However, the consequence of excluding negative information can be extremely harmful, because it leads to a reduction in the perception of the threat and to the endangerment of the person. Another aspect that can be observed in this case is the fact that the extremely positive assumptions about herself that existed before the diagnosis was made were not changed after the diagnosis or during the treatment. The discrepancy between self-image and the reality of the disease, in which there were aspects that were out of her personal control, created an emotional discomfort expressed by the patient. However, this discomfort was solved not by updating her self-image by integrating the fact that there are situations that are not under one's control but by the positive cognitive distortion of reality as we described previously. An explanatory hypothesis for this way of resolving the internal conflict may be that the acceptance of the personal lack of control in the context of the disease would have led to an intensified perception of the disease threat at a level that the patient would not have been able to cope with. This loss of control and the feeling of being trapped in a system that dictates what to do is reported in the literature by young patients diagnosed with breast cancer [19].

In the present case, the protective attitude that the patient adopted towards the family also draws attention. Although the family was informed of the diagnosis, the situation presented was better than the real one. This position may also be based on the positive beliefs about oneself presented above and is also observed in other young patients with breast cancer [19].

Even in the case of women with early stage breast cancer, the usual medical recommendation is to wait at least two years after the end of the treatment before becoming pregnant, due to the fact that most recurrences occur during this time [42]; when the pregnancy occurred, our patient decided to try to complete it. Despite the risks to her own health, she made the decision, saying that she "wants to leave something behind", which suggests the possible motivation for a symbolic immortality, as evidenced in the literature [23].

4. Conclusions

Pregnancy generally appears to be safe for fetuses, newborns and mothers, without requiring the need for some long-term clinical trials to provide more and more reliable information to doctors and patients [43]. We are, in fact, faced with an enormous challenge. Pregnancy after cancer is an area still being explored and is a fascinating stimulus of knowledge to dedicate oneself to oncology and women's health.

Our conclusion is that in the present case, an important role from a psychological point of view was played by the patient's difficulty to make the transition from the status of a healthy person to the status of a sick person, as well as not updating her self-image according to the new context. This had, as a consequence, an entry into emotional protection processes, such as positive cognitive distortion, which favored the decision to abandon the treatment and the attempt to complete the pregnancy at the expense of her own survival. The patient delayed the initiation of oncological treatment in pregnancy until it was too late. The consequence of this delay in treatment led to the death of the mother and fetus. A multidisciplinary team was committed to providing this patient with the best medical care and psychological assistance throughout the course of the disease. Maybe a strong family and social support, together with more intensive psychological intervention, would have made the evolution of this case different.

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Current Oncology

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Systematic Review

Assessing Psychological Morbidity in Cancer-Unaffected *BRCA1/2* Pathogenic Variant Carriers: A Systematic Review

Anna Isselhard [1,*], Zoë Lautz [1], Kerstin Rhiem [2] and Stephanie Stock [1]

[1] Institute of Health Economics and Clinical Epidemiology, University Hospital Cologne, 50935 Cologne, Germany
[2] Center for Hereditary Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University Hospital, 50937 Cologne, Germany
* Correspondence: anna.isselhard@uk-koeln.de

Abstract: Female *BRCA1/2* pathogenic variant carriers have an increased lifetime risk for breast and ovarian cancer. Cancer-unaffected women who are newly diagnosed with this pathogenic variant may experience psychological distress because of imminent health threat. No comprehensible review on psychological morbidity in cancer-unaffected *BRCA1/2* pathogenic variant carriers is currently available. This review aims to give an overview about all available the studies in which psychological outcomes have been assessed in cancer-unaffected *BRCA1/2* pathogenic variant carriers, whether as a primary outcome or secondary measurement. A systematic search across four databases (Web of Science, PubMed, ScienceDirect, and EBSCO) was conducted. Studies had to report on cancer-unaffected pathogenic variant carriers (exclusively or separately) and use a validated measure of psychological morbidity to be eligible. Measures were only included if they were used in at least three studies. The final review consisted of 45 studies from 13 countries. Distress measures, including anxiety and cancer worry, were most often assessed. Most studies found a peak of distress immediately after genetic test result disclosure, with a subsequent decline over the following months. Only some studies found elevated distress in carriers compared to non-carriers in longer follow-ups. Depression was frequently investigated but largely not found to be of clinical significance. Quality of life seemed to be largely unaffected by a positive genetic test result, although there was some evidence that younger women, especially, were less satisfied with their role functioning in life. Body image has been infrequently assessed so far, but the evidence suggested that there may be a decrease in body image after genetic test result disclosure that may decrease further for women who opt for a prophylactic mastectomy. Across all the outcomes, various versions of instruments were used, often limiting the comparability among the studies. Hence, future research should consider using frequently used instruments, as outlined by this review. Finally, while many studies included cancer-unaffected carriers, they were often not reported on separately, which made it difficult to draw specific conclusions about this population.

Keywords: *BRCA1*; *BRCA2*; breast cancer; anxiety; distress; cancer worry; patient experience

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1. Introduction

BRCA1 and *BRCA2* are tumor suppressor genes that encode proteins, which are responsible for repairing disruptions in damaged DNA that could otherwise result in tumor formation [1,2]. Inheriting a pathogenic variant in either of the two genes leads to erroneous DNA repair and, subsequently, a high risk for breast and ovarian cancer in women [1–3]. For breast cancer, the lifetime risk is roughly five to seven times higher for *BRCA1/2* pathogenic variant carriers compared to women in the general population [3]. For ovarian cancer, the risk is roughly 20 times higher for *BRCA2* and 40 times higher for *BRCA1* pathogenic variant carriers [3]. Albeit independent, a pathogenic variant in either gene is inherited from parent to offspring in autosomal dominant heredity. Therefore, cancer-unaffected members of families with a known *BRCA1/2* pathogenic variant are generally

offered genetic counseling and testing [4]. Likewise, index patients of families with a high incidence of breast and ovarian cancers with unknown pathogenic variant status may be offered genetic counseling and testing based on a familial risk assessment. Upon reasonable probability of carrying a pathogenic variant, a blood sample is preferentially drawn from a cancer patient (index patient) and tested. The test result may be positive (individual is a *BRCA1/2* pathogenic variant carrier), negative (individual is a *BRCA1/2* pathogenic variant non-carrier in a *BRCA1/2*-positive family), non-informative (no pathogenic variant was detected in a particular gene), or inconclusive (no pathogenic variant in *BRCA1/2* was found, but a variant of unknown significance (VUS) was) [5]. Pathogenic variant carriers are confronted with difficult decisions in the case of a positive genetic test result on how to deal with their personal cancer risk. Women without previous breast or ovarian cancer history have to make difficult decisions on which risk-reducing strategy to adopt. For breast cancer, this may mean a risk-reducing bilateral mastectomy or participation in intensified surveillance programs [6–8]. While a risk-reducing bilateral mastectomy may reduce breast cancer incidence for carriers of both pathogenic variants, as well as mortality for *BRCA1* pathogenic variant carriers [8,9], worsening of body image and sexual satisfaction have been reported, even with immediate reconstruction [10–13]. On the other hand, breast surveillance is less invasive and can provide survival benefits [14] but cannot reduce breast cancer risk. Both of these options might, therefore, induce distress and worsen psychological wellbeing, as both options come with significant downsides [15]. For ovarian cancer, the only option for effective risk management is a prophylactic bilateral salpingo-oophorectomy [16–18]. For surgical options in particular, female carriers must decide whether to opt for them at all and at what point in their life depending on age-dependent risk, since surgical procedures impact the possibility of bearing or breastfeeding children.

Consequently, undergoing genetic testing, receiving a positive genetic test result, and sharing the test results friends and families may influence levels of psychological morbidity [19,20]. Some women go as far as describing genetic test result disclosure as traumatic [21]. Various studies have assessed psychological wellbeing and morbidity in *BRCA1/2* pathogenic variant carriers, both qualitatively [19,21–24] and quantitatively [25–27]. Previous reviews have attempted to condense the evidence available [12,20,26,28–31]. However, these reviews (1) have focused on the efficacy of psychosocial interventions [28,29], (2) have focused on the psychological effects of different risk-management strategies [12,31], (3) have only included cancer-affected *BRCA1/2* carriers [30], or (4) have reported men and women or cancer-unaffected and cancer-affected *BRCA1/2* pathogenic variant carriers combined [20,26]. This is problematic, as there appears to be a non-negligible difference between cancer-affected compared to cancer-unaffected pathogenic variant carriers [26,32].

To the best of our knowledge, no comprehensive systematic review about the psychological morbidity that female cancer-unaffected *BRCA1/2* pathogenic variant carriers experience after genetic test result disclosure is available thus far. Therefore, the aim of this review is to fill this gap in the literature and explore the short- and long-term psychological consequences of receiving a positive genetic test result for *BRCA1* or *BRCA2* in women without a personal cancer history. To reach these aims, this review sets out to answer two questions:

- How is the psychological morbidity in cancer-unaffected *BRCA1/2* pathogenic variant carriers, both immediately after genetic test result disclosure and long-term?
- Which instruments are frequently employed to assess these psychological morbidities?

2. Materials and Methods

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized for this review [33]. Four bibliographic databases (Web of Science, PubMed, ScienceDirect, and EBSCO) were systematically searched for studies published from 1997 to January 2023. The search terms included the following keywords, and PubMed medical subject headings (MeSHs) were included individually and in combination depending on the database: *BRCA*, *BRCA1/2*, psychosocial impact,

psychosocial distress, coping, anxiety, depression, mental health, psychological adjustment, and mental disorder. The review was not prospectively registered, but the authors will provide protocol upon request.

2.1. Eligibility Criteria

Studies were deemed eligible if they were written in English and if they fulfilled the criteria, as determined by the PICOS framework [34,35].

- Participants: the review focused on cancer-unaffected female adults (age $\geq$ 18 years) with a confirmed pathogenic variant in either *BRCA1* or *BRCA2*.
- Intervention: no special intervention was specified.
- Comparison: studies that compared BRCA pathogenic variant carriers with women who received negative or inconclusive BRCA genetic test results, as well as studies that compared cancer-affected vs. cancer-unaffected pathogenic variant carriers were also included.
- Outcomes: the review included short-term and long-term psychological consequences that were measured with validated instruments.
- Study design: only quantitative studies, irrespective of study design (randomized or non-randomized trials, longitudinal cohort, cross-sectional, or case control), were included; qualitative studies were excluded from the present review.

2.2. Exclusion Criteria

Exclusion criteria consisted of studies not written in English, books, qualitative studies, literature reviews, case reports, or letters to the editor. Studies were also excluded if there was no reporting of psychological consequences or if studies did not specifically identify the population as (1) female, (2) cancer-unaffected, and (3) definitive *BRCA1/2* pathogenic variant carriers. Therefore, studies grouping results for cancer-unaffected with cancer-affected pathogenic variant carriers, carriers with non-carriers, or female with male carriers or those not defining the pathogenic variant as BRCA1/2 were excluded. Additionally, to provide the most value, studies were only included if they measured psychological morbidity with a validated questionnaire that at least three studies used.

2.3. Data Extraction, Data Synthesis, and Quality Assessment

After removal of duplicates, a stepwise approach was undertaken: first, two authors screened titles and abstracts independently (AI and ZL). Conflicts in screening were resolved by discussion. If the disagreement could not be solved quickly, the record went through a full-text review. Next, two authors (AI and ZL) independently screened the full-text articles. Disagreements during this process were solved by discussion. The included studies were analyzed according to the predefined PICOS criteria (see Section 2.1). For each included study, one author (ZL) extracted the following information: full reference, study design, duration of follow-up, and participant characteristics (sample size, age, *BRCA1/2* pathogenic variant status, and psychological outcome). Information extraction was overseen and quality-controlled by one author (AI). The findings were divided and grouped into the outcomes utilized within the studies. The goal of this review was a descriptive data analysis and synthesis of evidence. We, therefore, clustered outcomes with their respective validated instruments.

The quality of the included studies was assessed with the AXIS tool [36]. This tool was developed for non-experimental research and includes 20 discrete-choice questions that may be answered with yes or no (e.g., "Was the target population clearly defined?" or "Was ethical approval or consent of participants attained?"). Two reviewers (AI and ZL) rated each item independently and resolved disagreements in the process via discussion. A point was assigned for an item if methodological quality was met, resulting in a score from 0 to 20 for each study, with higher scores indicating higher study quality. The full AXIS assessment can be found in Supplementary Material File S1.

3. Results

The full flow-chart for the review process is displayed in Figure 1. The initial search yielded 810 records. After duplicates were removed, 478 records were screened for eligibility, and 264 records went through full-text review. Additionally, five records were identified by hand search. Forty-five studies met the eligibility criteria and were included in this review. The total number of participants from all the included studies was n = 2442, with an age range of 18–83. Overall, the studies showed good quality (see quality assessment 3.5), with some exceptions. Some studies only partially reported outcomes separately for cancer-affected versus cancer-unaffected pathogenic variant carriers. All the studies included in the review are shown in Table 1.

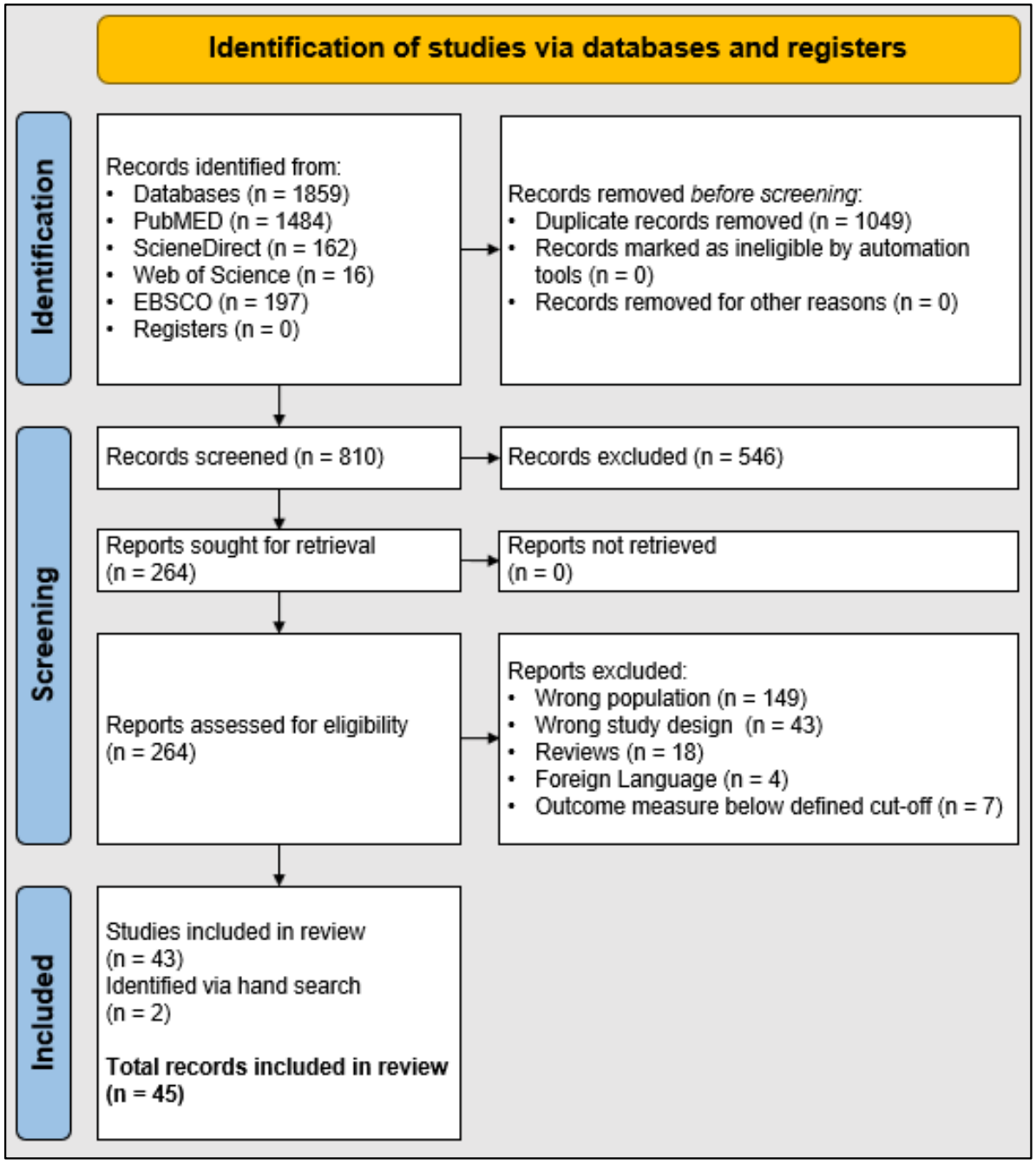

Figure 1. PRISMA flow chart for the identification of studies.

Table 1. Descriptive data of the studies (n = 45) and measures used.

First Author, Year	Country	Participant Characteristics [1]	Study Design, Follow-Up Length	BHS	BIQ	BSI	CES-D	CWS	HADS	IES	GHQ	SF-12/36	STAI
Borreani et al., 2014 [37]	Italy	n = 27 Age range: 26–75	Longitudinal, 15 months					√	√			√	
Brand et al., 2021 [38]	Germany	n = 48 Age mean: 40	Cross-sectional					√					
Buchanan et al., 2017 [39]	U.S.	n = 97 Age range: 25–40+	Cross-sectional							√		√	√
Carpenter et al., 2014 [40]	U.S.	n = 26 Age mean: 42.9	Experimental							√			
Claes et al., 2005 [41]	Belgium	n = 34 Age range: 19–61	Longitudinal, 1 year							√			√
Croyle et al., 1997 [42]	U.S.	n = 13 Age range: 19–83	Longitudinal, 2 years							√			√
Dagan and Gil, 2004 [43]	Israel	n = 36 Age mean: 54.1	Retrospective			√							
Dagan and Shochat, 2009 [44]	Israel	n = 17 Age mean: 51.4	Case control			√		√				√	
Dorval et al., 2006 [45]	Canada	n = 19 Age mean: 48	Longitudinal, 36 months							√			
Ertmanski et al., 2009 [46]	Poland	n = 56 Age range: 18–56+	Longitudinal, 1 year							√			√
Finch et al., 2013 [47]	Canada	n = 59 Age range: 35–69	Longitudinal, 1 year			√				√		√	
Foster et al., 2007 [48]	U.K.	n = 53 Age range: 23–72	Longitudinal, 3 years					√			√		
Geirdal and Dahl, 2008 [49]	Norway	n = 68 Age mean: 42	Cross-sectional						√				
Geirdal et al., 2005 [50]	Norway	n = 68 Age mean: 42	Cross-sectional	√					√	√	√		
Gopie et al., 2013 [51]	Netherlands	n = 44 Age mean: 37.1	Longitudinal, 21.7 months		√					√		√	
Graves et al., 2012 [52]	U.S.	n = 47 Age mean: 54.1	Longitudinal, 5 years			√				√			√

Table 1. *Cont.*

First Author, Year	Country	Participant Characteristics [1]	Study Design, Follow-Up Length	BHS	BIQ	BSI	CES-D	CWS	HADS	IES	GHQ	SF-12/36	STAI
Isern et al., 2008 [53]	Sweden	*n* = 27 Age range: 25–51	Longitudinal, 42 months						√			√	
Isselhard et al., 2023 [54]	Germany	*n* = 130 Age range: 24–60	Cross-sectional						√	√			
Julian-Reynier et al., 2010 [55]	France	*n* = 244 Age range: <30–50+	Longitudinal, 60 months		√		√			√			
Kinney et al., 2005 [56]	U.S.	*n* = 19 Age range: <40–50+	Longitudinal, 1 year				√	√		√			√
Landau et al., 2015 [57]	Israel	*n* = 56 Age mean: 49.6	Intervention, 12 weeks			√		√					
Lapointe et al., 2013 [58]	France	*n* = 221 Age range: 20–60	Longitudinal, 2 years				√			√			
Lodder et al., 2001 [59]	Netherlands	*n* = 25 Age range: 19–68	Longitudinal, 1–3 weeks						√	√			
Lodder et al., 2002 [60]	Netherlands	*n* = 26 Age mean: 38.8	Longitudinal, 12 months		√				√	√			
Low et al., 2008 [61]	U.S.	*n* = 7 Age mean: 44.7	Longitudinal, 6 months							√			
Madalinska et al., 2007 [62]	Netherlands	*n* = 160 Age range: 35–50+	Longitudinal, 12 months					√		√		√	
Maheu et al., 2012 [63]	France	*n* = 217 Age range: <35–50+	Longitudinal, 2 years				√			√			
Maheu et al., 2014 [64]	France	*n* = 232 Age mean: 40.7	Longitudinal, 12 months				√			√			
Meiser et al., 2002 [65]	Australia	*n* = 30 Age mean: 40	Longitudinal, 12 months							√			√
Metcalfe et al., 2012 [66]	Canada	*n* = 22 Age range: 25–70	Longitudinal, 2 years							√			
Metcalfe et al., 2017 [67]	Canada	*n* = 150 Age range: 25–60	RCT, 12 months							√			
Metcalfe et al., 2020 [68]	Canada	*n* = 576 Age range: 25–55	Cross-sectional							√			

Table 1. *Cont.*

First Author, Year	Country	Participant Characteristics [1]	Study Design, Follow-Up Length	BHS	BIQ	BSI	CES-D	CWS	HADS	IES	GHQ	SF-12/36	STAI
O'Neill et al., 2009 [69]	U.S.	*n* = 14 Age range: 27–68	Longitudinal, 1 year							√			
Reichelt et al., 2004 [70]	Norway	*n* = 80 Age mean: 43.9	Longitudinal, 6 weeks	√					√	√	√		
Reichelt et al., 2008 [71]	Norway	*n* = 58 Age mean: 45.4	Longitudinal, 18 months	√					√	√			
Schwartz et al., 2002 [72]	U.S.	*n* = 35 Age mean: 45	Longitudinal							√			
Shochat and Dagan, 2010 [73]	Israel	*n* = 17 Age mean: 51.4	Cross-sectional			√		√					
Smith et al., 2008 [74]	U.S.	*n* = 20 Age range: 22–70	Longitudinal, 6 months				√			√		√	√
Spiegel et al., 2011 [75]	U.S.	*n* = 51 Age range: 25–60	Longitudinal, 6 months					√	√				
Van Dijk et al., 2006 [76]	Netherlands	*n* = 22 Age range: <30–50+	Longitudinal, 6 months					√		√			
Van Egdom et al., 2020 [77]	Netherlands	*n* = 96 Age mean: 41.4	Cross-sectional						√				
Van Oostrom et al., 2003 [78]	Netherlands	*n* = 23 Age mean: 41.9	Longitudinal, 4–6 years		√			√	√	√			
Van Oostrom et al., 2007 [79]	Netherlands	*n* = 49 Age mean: 42.3	Longitudinal, 12 months					√		√			
Van Roosmalen et al., 2004 [80]	Netherlands	*n* = 68 Age mean: 37.6	Longitudinal, 2 weeks				√			√			√
Watson et al., 2004 [81]	U.K.	*n* = 91 Age range: 23–72	Longitudinal, 12 months					√		√	√		

[1] Sample size *n* refers to number of cancer-unaffected female *BRCA1/2* carriers in the sample and does not represent total sample size.

3.1. Study Characteristics

The studies were published from 1997 to January 2023. Most studies included participants from the U.S. (10 studies), the Netherlands (9 studies), Canada (5 studies), Norway, France, and Israel (4 studies each). Other countries included Italy, Belgium, Poland, the U.K., Sweden, France, and Australia. Most studies employed a (prospective) longitudinal cohort design (thirty-two studies), ranging in follow-up from one week to six years after test result disclosure. Additionally, studies with cross-sectional designs (eight studies) and randomized controlled intervention designs (two studies), as well as one experimental, one retrospective, and one case-control study, were included. Study populations had high heterogeneity in their sample sizes, from $n = 7$ to $n = 576$ cancer-unaffected pathogenic variant carriers. The age ranges in the studies were between 18 and 83 years old. In total, 11 measures were examined within this review (see Table 2).

Table 2. General outcomes and respective measures included in this review.

General Outcome	Specific Measure
Distress	Impact of Event Scale (IES) [82,83]
	Hospital Anxiety and Depression Scale (HADS) [84]
	Cancer Worry Scale (CWS) [85,86]
	Spielberger State-Trait Anxiety Inventory (STAI) [87]
	Brief Symptom Inventory (BSI) [88]
	General Health Questionnaire (GHQ) [89]
Depression	Hospital Anxiety and Depression Scale (HADS) [84]
	Beck's Hopelessness Scale (BHS) [90]
	Center for Epidemiologic Studies Depression Scale (CES-D) [91]
Other	Short Form Health Survey (SF-36/SF-12) [92,93]
	Body Image Questionnaire (BIQ) [60]

3.2. Distress Measures

The anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) [84], the Cancer Worry Scale (CWS) [85,86], the Spielberger State-Trait Anxiety Inventory (STAI) [87], the Brief Symptom Inventory (BSI) [88], the General Health Questionnaire (GHS-28) [89], and the Impact of Event Scale (IES) [82] were characterized as psychological distress parameters.

3.2.1. Impact of Event Scale

By far the most used questionnaire to measure distress was the IES, which was used by 34 studies [39–42,45–47,50–52,54–56,58–72,74,76,78–81]. The IES consists of two subscales for intrusion and avoidance. The revised IES-R additionally has a hyperarousal subscale. Twenty-eight studies used the original version of the questionnaire (IES), whereas three studies used the revised version (IES-R) [54,61,79], and three studies used the intrusion subscale only [62,70,71]. While cut-off values have been reported for different populations, they vary by version used and have been criticized for providing little clinical significance. Fourteen studies report higher IES scores in carriers compared to non-carriers within six months of test result disclosure [42,45,58,59,61,63,65,69,70,72,74,76,80,81]. Of these studies, five reported that distress remained significantly higher in carriers for up to one year after disclosure [58,65,72,76,81]. Contrarily, one study reported that, while carriers experienced higher distress immediately after genetic test result disclosure, there was no significant difference in the distress of non-carriers after 6 months [63]. Two long-term follow-ups with an average time of five years since genetic test result disclosure similarly found no difference between carriers and non-carriers [52,78]. One study reported that, even though distress was higher in carriers, carriers experienced a decrease from before to immediately after test result disclosure, indicating that knowing the test result regardless of the outcome may provide relief [42]. However, this was the only study with this particular result. In fact, four other studies found increases from before to immediately after test result disclosure in carriers [60,65,66,79]. Longitudinal studies among carriers suggested a de-

crease in distress anywhere between 6 months and two years after disclosure [60,66,67,79]. Higher distress was associated with higher adherence to recommendations about risk-reducing strategies [39] and, among those strategies, higher likelihood to opt for a bilateral mastectomy [60] or a salpingo-oophorectomy [55,62]. Five other studies reported significant decreases in distress after undergoing such risk-reducing surgeries [47,51,66,68,79]. Higher scores were significantly associated with general psychological distress [54] and with receiving a psychological consultation [64], providing some evidence for the real-world validity of the IES. In terms of validity, however, one author pointed to the importance of the definition of the "event" in question: test result disclosure or cancer itself [45]. In fact, one study found differences between carriers and non-carriers in distress when the IES was framed for ovarian cancer but not when it was framed for breast cancer [41]. Therefore, precise wording is important for the interpretation and comparability of results.

3.2.2. Hospital Anxiety and Depression Scale—Anxiety Subscale

Twelve studies assessed anxiety with the anxiety subscale of the HADS (HADS-A) [37,49,50,53,54,59,60,70,71,75,77,78]. Among the studies that compared anxiety in carriers with anxiety in non-carriers, two studies reported differences [59,60]. Both studies were written by the same authors and presumably reported on the same population, with one being focused on anxiety 1–3 weeks after test result disclosure [59] and the other being a one year follow-up [60]. The first of the two studies showed that non-carriers experienced a reduction in anxiety from before genetic testing to shortly after test result disclosure, whereas carriers showed an increase in anxiety [59]. A subgroup analyses based on high and low baseline anxiety was performed and identified a diverging pattern of results: pathogenic variant carriers with high pre-test anxiety remained highly anxious after receiving test results, whereas non-carriers with high pre-test anxiety showed a decrease in anxiety. Further, pathogenic variant carriers with low pre-test anxiety showed an increase in anxiety, whereas non-carriers with low pre-test anxiety showed unchanged levels of anxiety post-test. The second study showed that, at 1 year after receiving test results, anxiety levels for carriers and non-carriers were similar and that those with clinically high scores shortly after test result disclosure remained anxious at 1 year after disclosure [60]. Indeed, many studies found that pre-test anxiety levels were a good predictor of anxiety longitudinally [37,60,75,78]. One study specifically showed that, even after 5 years, current anxiety was best predicted by anxiety pregenetic test result disclosure, regardless of carrier status [78]. The authors of this particular study reported that anxiety in carriers spiked to just sub-clinical levels right after genetic test result disclosure but returned to the level of non-carriers after six months. They noted an increase in anxiety 5 years after genetic post-result disclosure that was present for carriers and non-carriers alike [78]. In contrast to these findings, two other studies found scores well below the clinical threshold for carriers and showed that anxiety scores in carriers were lower compared to women from high-risk families with an absence of demonstrated pathogenic variants [49,50]. Roughly half of the studies included percentages of potential clinical cases (HADS-A score $\geq$ 8) and reported that roughly one-in-four to one-in-five-carriers (19–24%) showed clinical anxiety [49,53,54,59,60,70,71]. One study reported almost half (49%) of participants scoring in the clinical anxiety range [75]. However, this higher occurrence may have been found because the sample in this study consisted of carriers who were or were not recalled after a suspicious MRI report in intensified breast cancer screening. The anxiety might, therefore, be a result of this recall and not of the genetic test result itself, as the recalled group showed significantly higher anxiety than the non-recalled group. It was shown that, even among recalled carriers, the scores returned to below baseline 6 months after genetic test result disclosure. Three studies were identified that compared carriers opting for different preventive options (risk-reducing surgery vs. surveillance) [37,60,77]. One study reported scores on the higher end of the normal range for both women who opted for surveillance and women who opted for surgery, with women in the surveillance group showing marginally, but not significantly, higher scores [37]. Another study showed a contrary result, with carriers

who opted for prophylactic mastectomy showing significantly higher anxiety compared to carriers opting for surveillance [60]. A reduction in anxiety from immediately after test result disclosure to 1 year after result disclosure was reported regardless of preventive option but was steeper for women who opted for a mastectomy. Finally, one study compared women opting for surveillance or bilateral prophylactic mastectomy with immediate breast reconstruction and found no difference in anxiety between the two [77].

3.2.3. Cancer Worry Scale

Thirteen studies measured cancer worry utilizing different versions of the CWS [37,38,44,48,56,57,62,73,75,76,78,79,81]. There was high heterogeneity in the versions used, with one study using a single-item version [76], two studies using a three-item version [37,56], five studies using a four-item version [38,44,73,75,79], two studies using a five-item version [62,78], and two studies using a revised six-item version [48,81]. One study did not specify which version was used [57]. Two studies did not report results relevant to the population [56,57]. Three studies identified no difference in cancer worry in carriers when compared to non-carriers from high-risk families [48,73,78]. In contrast, eight studies identified increased cancer worry, each with unique comparators [37,38,44,62,75,76,79,81]. Three studies compared carriers with non-carriers from high-risk families and found higher cancer worry in those with pathogenic variants for up to one year after genetic test result disclosure [44,79,81]. One of these studies further specified that, especially, carriers under the age of 35 experienced higher levels of cancer worry compared to carriers over 50 years one month after genetic test result disclosure [81]. This difference, however, was no longer significant at one year after genetic test result disclosure. This may be indicative of the complexity of decision making in premenopausal women immediately after genetic test result disclosure. Two other studies provided additional evidence for this by displaying an increase in cancer worry for up to one month after disclosure, with a subsequent decline in cancer worry at six months after genetic test result disclosure [76,79]. Another study compared carriers opting for different preventive strategies (prophylactic surgery vs. intensified breast cancer screening) [62]. The results revealed that, specifically, the surgery group showed an increase in cancer worry symptoms. Further, in another study [75] there was an increase in cancer worry over time. However, the study compared carriers who were recalled after a first MRI with women who were not recalled. Although there was no difference in cancer worry symptoms at the first MRI appointment, there was a significant increase in cancer worry symptoms in the recalled group. The non-recalled group did not exhibit this pattern, indicating that imminent cancer diagnosis may be relevant to the genesis of higher cancer worry.

3.2.4. Spielberger State-Trait Anxiety Inventory

Nine studies measured anxiety using the STAI [39,41,42,46,52,56,65,74,80], eight of which used the state anxiety subscale only. Only one study used both the state and the trait subscales [46]. While this study found no increase in state anxiety right after result disclosure, as well as at one year after, women with the highest trait anxiety also experienced the highest spike in state anxiety after genetic test result disclosure [46]. No specific outcome was reported in one study [52]. Three studies found that non-carriers experienced significantly less state anxiety after genetic test result disclosure, whereas carriers remained at a stable level or experience slightly more anxiety [41,56,65]. In fact, two studies found significantly higher state anxiety in carriers compared to non-carriers at 1–2 weeks after genetic test result disclosure [42,80]. Another study found higher state anxiety at three months after genetic test result disclosure in carriers compared to non-carriers but no longer at six months [74]. Likewise, another study found no differences between carriers and non-carriers at 4 months and 12 months after genetic test result disclosure [65]. One study found that anxiety was not related to adherence to recommended risk management [39].

3.2.5. Brief Symptom Inventory

Six studies assessed psychological distress via the BSI [43,44,47,52,57,73]. Different versions were used, with 1 study utilizing the 53-item version [43], 2 studies utilizing the 48-item version [44,73], 2 studies utilizing the 18-item version [47,57], and 1 study using the anxiety subscale only [52]. For one study, no outcome was specified [52]. Scoring schemes and subsequent cut-off values varied depending on the version used. One study found subclinical levels in carriers after genetic test result disclosure and no change at a three month follow-up [57]. Two studies did not identify an increase in distress in carriers compared to non-carriers from high-risk families [44,57,73]. Conversely, two other studies found that the scores of the somatization subscale were increased in carriers compared to non-carriers of all age groups [43], as well as in premenopausal carriers compared to postmenopausal carriers [47]. High scores on the somatization subscale represent a high focus on physical dysfunction (e.g., pain, fatigue, dizziness, numbness, or tingling) that may, in turn, cause psychological distress. Identifying differences in psychological distress was not related to the version of the BSI used.

3.2.6. General Health Questionnaire

Four studies assessed generalized psychological distress via the GHQ-28 [48,50,70,81]. A score ≥ 5 indicates clinically significant distress [89]. All the included studies reported below this cut-off score, albeit some only marginally [48,81]. Two studies found lower psychological distress in identified carriers compared to untested members of high-risk families [50,70]. Two other studies reported an increase in psychological distress from before genetic testing to 12 months [81] or 3 years after result disclosure [48]. Even though the reported means did not tangent the cut-off score, one of these studies reported that almost 20% of the study participants scored above the cut-off score three years after genetic test result disclosure [48]. Another study identified that carriers aged 35–49 experienced significantly higher psychological distress than high-risk non-carriers 1 month after genetic test result disclosure [81].

3.2.7. Summary Distress Outcomes

In conclusion, many studies found a slight elevation in distress outcomes shortly after genetic test result disclosure. The majority of the studies reported that up to one-fourth of carriers experienced symptoms of anxiety disorder after genetic test result disclosure, irrespective of the instrument used. Longitudinal studies suggested that, even though anxiety symptoms peaked after genetic test result disclosure, they usually declined to the level of non-carriers over time. However, carriers with high pre-test anxiety may experience clinical anxiety, even at longer follow-ups. Some studies provided limited evidence for age dependence, with younger women showing higher distress than older women, especially immediately after genetic test result disclosure. Furthermore, there was some degree of evidence to suggest that those with higher distress were more likely to opt for surgery, albeit the causative nature of this relationship remains unclear. Therefore, sensitive screening tools to identity this subgroup may be beneficial to alleviate long-term distress and prevent the manifestation of anxiety disorders. Finally, some studies showed that carriers showed lower anxiety compared to untested women, suggesting that receiving a definitive test result, regardless of if a pathogenic variant was in fact found, may provide a relief in anxiety.

3.3. Depression

The depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) [84], the Center for Epidemiologic Studies Depression Scale (CES-D) [91], and the Beck Hopelessness Scale (BHS) [90] were characterized as measures of depression.

3.3.1. Hospital Anxiety and Depression Scale—Depression Subscale

Ten studies assessed depression with the HADS-D [37,50,53,54,59,70,71,75,77,78]. Analogous to the anxiety subscale, a score ≥8 indicates signs of clinical depression. All the studies reported means well below this cut-off. Among the studies that reported a percentage of cases, the numbers ranged from 2–12.5% of possible clinical depression cases, indicating that depression was as prevalent as in the general population [50,53,54,59,75]. In fact, two studies found that the depression scores in carriers were significantly lower than in the healthy population [50,70]. One of these studies compared collected data from carriers with published normative data [70], whereas one study simultaneously collected data from carriers, non-carriers, and controls and found that carriers had fewer depressive symptoms compared to the other two groups [50]. Furthermore, two other studies found no difference between carriers and non-carriers in terms of depression [53,78]. One study that compared carriers and non-carriers from before to after genetic test result disclosure found an increase from before to after genetic test result disclosure for carriers and the opposite effect for non-carriers [59]. Two studies compared the depression scores of women opting for surveillance vs. risk-reducing surgeries and found no difference [37,77]. Finally, one study found that carrier depression scores were not affected by recall after a suspicious MRI [75], suggesting that depression was not influenced by imminent danger of cancer.

3.3.2. Center for Epidemiologic Studies Depression Scale

Seven studies assessed depression utilizing the CES-D [55,56,58,63,64,74,80], of which all but two reported outcomes relevant to the population [56,64]. Different cut-off scores have been put forward, ranging from scores ≥16 to ≥23 indicating a clinical case of depression. One study identified higher depressive symptoms in carriers compared to the general female population at baseline, with 21.3% of women scoring in the clinical depression range (scores ≥ 23) [55]. Three studies found increases from before to after genetic test result disclosure [58,74,80]. One of these studies reported means over the cut-off score of 16 at one week and three months after genetic test result disclosure, with no difference between carriers and non-carriers [74]. Similarly, another study found no differences between carriers and non-carriers but identified an increase in depression from pre-test result disclosure to 15 days after, with a subsequent decrease to pre-test levels after one year [58]. One study looked at risk management behaviors and found that women with fewer depressive symptoms were more likely to conduct regular breast self-examination [63].

3.3.3. Beck Hopelessness Scale

Three studies assessed hopelessness and associated suicidal ideation using the BHS [50,70,71]. A score between 4 and 8 generally indicates mild hopelessness, whereas a score of ≥9 suggests more severe hopelessness that predicts the presence of at least some suicidal ideation. Two of the studies reported mean scores in the higher end of the normal range [50,70]. One study did not specify the mean for the sample but reported a significant association to psychological distress in general [71].

3.3.4. Summary Depression Outcomes

The patterns of the results from these depression measures suggested that carriers did not show increased depressive symptoms following test disclosure, and some studies remarkably even identified levels of depression that were lower than those in the normal population. Of these depression measures, the CES-D appeared to be the most sensitive in detecting depression in *BRCA1/2* carriers. However, even studies using this instrument showed that depressive symptomology decreased over time, and no lasting effects were found. Only one study showed that depression scores remained above pre-test levels for up to two years. Studies using the other questionnaires indicated that hopelessness or suicidal ideation were generally not a clinical problem in this population.

3.4. Other Psychological Outcomes

Quality of life and body image were categorized as other psychological outcomes that were frequently investigated. Quality of life was assessed using the Short Form Health Survey (SF) [92,93], while body image was assessed using the Body Image Questionnaire (BIQ) [60] following recommendations from Cull on sexual function in cancer patients [94].

3.4.1. Short Form Health Survey

Eight studies assessed quality of life with some version of the SF questionnaire, with four studies utilizing the original SF-36 [44,51,53,74], three studies utilizing the SF-12 [37,39,47], and one study using two subscales of the SF-36 [62]. One study did not report outcomes relevant to the population [53]. The original SF-36 has eight subscales (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) that may be summarized into a physical and a mental composite score. Two studies compared quality of life in carriers with non-carriers [44,74]. One study found lower quality of life in some domains, especially in premenopausal women (emotional role functioning, physical role functioning, and physical functioning) [44], whereas the other found no differences [74]. The other studies assessed quality of life in terms of risk management strategies. One study found that higher physical functioning was associated with higher adherence to recommended risk management strategies, but higher mental functioning was not [39]. In terms of opting for one strategy over the other, one study found no difference in quality of life between carriers opting for surgery or surveillance [37], whereas one study found that carriers with lower general health perceptions were more likely to opt for a salpingo-oophorectomy [62]. After risk-reducing surgeries, one study found lower physical quality of life six months after bilateral mastectomy but higher mental quality of life [51], whereas another study found no differences in either composite score after salpingo-oophorectomy [47].

3.4.2. Body Image Questionnaire

Four of the studies included body image as measured by the BIQ [51,55,60,78]. Two of the studies found that body image satisfaction was lower in carriers compared to non-carriers [51,78]. Longitudinally, body image satisfaction of carriers further declined as time after genetic test result disclosure passed [51,78]. One study found that body image satisfaction was unrelated to prophylactic mastectomy uptake [55]. However, two studies showed that undergoing prophylactic mastectomy, mostly combined with immediate reconstruction, may result in lower body image [51,60]. One study specified that those with lower BMI and higher cancer distress at baseline showed lower body image after finishing reconstruction, whereas higher general physical health predicted better body image over time [51]. However, it is unknown how long ago these study participants were found to carry a pathogenic variant and how that might have impacted results.

3.4.3. Summary Other Outcomes

Quality of life seemed to be largely unaffected by a positive genetic test result, although there was some evidence that especially younger women were less satisfied with their role functioning in life. It seems plausible that this was related to distress, which was also found to be slightly more prominent in premenopausal women (see Section 3.2.7). In terms of body image, the results were extremely heterogeneous and only provided limited insight. From the studies identified, it could be concluded that body image may decrease slightly after genetic test result disclosure but was generally unrelated to further decision making.

3.5. Quality Assessment

All the studies included in this review met at least 11 of 20 AXIS points (range: 11–20). The overall quality of the studies was adequate: most of the studies clearly stated the aims of the study, identified a clearly defined target group per inclusion criteria, and

included a good description of the basic data with justified conclusions. All but four studies discussed the limitations of the study and the results. Nonetheless, the included studies have some methodological weaknesses: most of the studies did not justify their sample size or did not run a priori power analyses. Additionally, although most studies took a sample from an appropriate frame with an appropriate sampling method, more than half (60%) of the 45 studies expressed concerns about the representativeness or indicated that a bigger sample size would have been desirable. Only 19 studies included information about non-responders, with 10 of these identifying differences between responders and non-responders. A common difference identified was that non-responders were less likely to have a partner, which is a factor to be considered in interpreting results. All AXIS results can be seen in Supplementary Material File S1.

4. Discussion

To the best of our knowledge, this is the first time a systematic review investigated not only the psychological outcomes of cancer-unaffected *BRCA1/2* pathogenic variant carriers, but also the instruments that were used to assess these outcomes. Due to the high heterogeneity of measures used by the different studies, it was challenging to draw comprehensive conclusions about all the psychological outcomes. The differences in the design and analyses in the presented studies may underlie this non-conclusive pattern of results.

The psychological outcomes that were most often assessed were distress, anxiety, and cancer worry. Most studies showed an increase in those outcomes, mainly cancer worry and anxiety, after genetic test result disclosure. This appeared to be slightly more prominent in premenopausal women under the age of 50 [44,47,81]. This seems logical considering family planning and breastfeeding decisions for women of childbearing age. In fact, qualitative studies with premenopausal *BRCA1/2* pathogenic variant carriers have confirmed that family planning often competes with risk-reducing surgical procedures [22,95]. This may in turn increase anxiety and distress in this younger group. Longitudinally, most studies showed a steady decline in the months after genetic test result disclosure and a complete return to baseline roughly after one year. Only a few studies reported higher frequency of distress one year after genetic test result disclosure. In terms of decision making, it seemed that women deciding for prophylactic surgeries experienced slightly higher levels of distress. This may be the reason why these women opted for risk-reducing surgeries in the first place. In terms of depressive symptomatology and quality of life, merely mild or no negative outcomes at all were identified. Regarding body image, no conclusive results could be drawn due to the small number of studies using a validated measure. Two reviews on various body image outcomes showed that decreased body image and changes in sexuality were common after prophylactic mastectomy [96,97]. However, a recent review reported that sexual health remained understudies in the context of *BRCA1/2* testing [98].

Limitations and Recommendations for Future Research

While this review was the first review to systematically investigate the effects of *BRCA1/2* pathogenic variant carrier status on psychological outcomes, there are a few limitations that need to be addressed. Firstly, the oldest study included in the review was published 1997, and many others were published in the early 2000s. Breast and ovarian cancer risk may have been communicated differently in those years compared to today, as they were not as well-researched and long-term data were not yet available. This may, in turn, influence the level of psychological morbidity. Secondly, the majority of the studies in the review were conducted in the United States or Europe and investigated mainly well-educated white women. Studies that specifically looked at minorities were very few. Only one study in the review examined an African-American population [56]. Thus, further and larger studies investigating such underrepresented groups are necessary. Moreover, we suspect that at least a few studies reported on the same population over several years,

which may taint the results. Two studies reported from Rambam Health Care Campus in Israel [43,44]; two further studies reported baseline and follow-up data from a sample at Rotterdam University Hospital in the Netherlands [59,60]; four studies reported from Oslo University Hospital in Norway within a close timeframe [49,50,70,71]; and finally, four studies utilized the GENESPO study cohort from France [55,58,63,64]. We were unable to exclude the possibility that more studies reported on these or other populations across different publications. Lastly, most studies reported on small study populations, with the majority of the studies including less than 100 cancer-unaffected carriers. This may impact the generalizability of our results.

As discussed above, there have been attempts to condense results from various outcome sources (e.g., integrative reviews on body image [96,97]), but the consequent and continuous use of established and validated instruments is often lacking. Future research could improve data on psychological morbidity in cancer-unaffected *BRCA1/2* pathogenic variant carriers by (1) using validated measures, (2) not conflating cancer-unaffected with cancer-affected carriers or cancer-unaffected carriers with the general population when reporting results, (3) reporting precisely how long carriers knew of their risk status when reporting results, and (4) diversifying the sample populations. Additionally, while *BRCA1/2* pathogenic variants have been known the longest and are well-studied because they are also found comparatively frequently in individuals at risk, several other pathogenic variants in less frequently identified genes exist that have similarly high risks associated with them, such as *PALB2* [99]. Future research should address these pathogenic variants equally in researching psychological morbidity in the hereditary cancer field.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/curroncol30040274/s1, Supplementary Material File S1: AXIS Report.

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Intimate Partner Violence against Mastectomized Women: Victims' Experiences

Franciéle Marabotti Costa Leite [1,*], Andreia Gomes Oliveira [2], Bruna Lígia Ferreira de Almeida Barbosa [3], Mariana Zoboli Ambrosim [4], Neiva Augusta Viegas Vasconcellos [4], Paulete Maria Ambrósio Maciel [4], Maria Helena Costa Amorim [4], Lorena Barros Furieri [4] and Luís Carlos Lopes-Júnior [1,*]

1 Graduate Program in Public Health, Health Sciences Center, Federal University of Espírito Santo (UFES), Vitoria 29075-910, ES, Brazil
2 Prefeitura Municipal de Vitória, Vitoria 29050-945, ES, Brazil
3 Western New South Wales Primary Health Network-WNSWPHN, Dubbo, NSW 2830, Australia
4 Nursing Department, Federal University of Espírito Santo (UFES), Vitoria 29075-910, ES, Brazil
* Correspondence: francielemarabotti@gmail.com (F.M.C.L.); lopesjr.lc@gmail.com (L.C.L.-J.); Tel.: +55-27-3335-7280 (F.M.C.L. & L.C.L.-J.)

Abstract: Exposure to situations of domestic violence during the treatment for breast cancer may compromise the treatment and quality of life of women patients, so it is essential that health professionals act in tracking this phenomenon in the approach to and care of women with breast cancer. The purpose of this study was to examine experiences of violence against women by their intimate partners after mastectomy. This is an exploratory descriptive study, with a qualitative approach, carried out in the Rehabilitation Program for Mastectomized Women in a Brazilian reference hospital for oncological treatment. Semi-structured interviews were conducted with 16 mastectomized women. For data analysis, a content analysis technique was performed. The women interviewed were predominantly brown, with a minimum age of 44 years and maximum of 72 years. They presented with low education, were married, and had a mean period of five years of breast cancer diagnosis. The participants reported that after mastectomy, they experienced episodes of violence at a time when they were extremely vulnerable due to the various cancer treatments. Three major thematic categories emerged from interview data across the data collection: (1) experiences of psychological violence, (2) experiences of physical violence, and (3) experiences of sexual violence. Psychological violence took the form of humiliation and contempt for their condition. Physical violence involved assault and sexual violence in the form of forced sex by coercion. Violence was a phenomenon present after mastectomy, practiced in the domestic environment by the intimate partner. We emphasize the importance of health professionals in screening for this issue by listening to and welcoming women, recording cases, exposing this situation, and contributing to prevention.

Keywords: breast neoplasms; violence against women; mastectomy; violence

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1. Introduction

A global public health problem, cancer places a high psychosocial and economic burden on individuals, families, and health systems [1]. The projections of the World Health Organization for the period 2018 to 2040 are 29.5 million new cases for all types of cancer across all ages and both sexes [2]. Among the chronic noncommunicable diseases, malignant neoplasms are the second leading cause of death in developed countries and are among the top three causes of death in adults in developing countries [3,4].

The latest report on the global burden of cancer, using the GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, which focuses on geographical variability in 185 countries worldwide, anticipated an incidence of 19.3 million new cases of cancer and 10 million deaths for 2020 [4]. The report pointed out that the most frequently diagnosed cancer and the main cause of death

from cancer vary substantially between countries and within each country, depending on the degree of economic development, social factors, and lifestyle [4]. Breast cancer is the most common cancer among women globally. In 2018, there were 2.1 million new cases, equivalent to 11.6% of all estimated cancers. This value corresponds to an estimated risk of 55.2/100,000 [4,5].

According to data from the latest estimate made by the National Cancer Institute José Alencar Gomes da Silva (INCA), 625,000 new cases of cancer are expected to occur in Brazil for each year of the triennium 2020–2022 [6]. Specifically for women, 66,280 new cases of breast cancer are anticipated for each year of that triennium, which corresponds to an estimated risk of 61.61 new cases per 100,000 women. Excluding non-melanoma skin tumors, female breast cancer is the most common in all Brazilian regions, with an estimated risk of 81.06/100,000 in the Southeast region [6]. In the state of Espírito Santo, for the triennium 2020–2022, 790 cases of female breast cancer per 100,000 inhabitants are forecast [6].

The treatment of breast cancer has made substantial advances in recent years, resulting in the increase in the overall and relative survival rate of patients with this neoplasm. A good prognosis for breast cancer is directly related to early diagnosis, the rapid initiation of treatment, and technological advances in therapy, such as measures for early detection; personalized care; multidisciplinary, interdisciplinary, and specialized teams; combined protocols; target-molecular therapy; and the progress of clinical and translational research in oncology [7–13]. Currently, the 5-year relative survival rate for breast cancer can vary from 72% to 100% depending on staging, early detection, and type of treatment received in a timely manner and in specialized centers [6,7,10].

The diagnosis and treatment of breast cancer damage women's daily lives, especially in relation to their sexuality, femininity, and body image [13]. In that sense, the psychological suffering women go through transcends the suffering of the disease itself, since it is linked to representations and meanings attributed to the disease throughout the history and culture and enters dimensions of the feminine being, interfering many times in the woman's interpersonal relationships [14].

In this context, the family is very important, and the revelation of a diagnosis of cancer, although not always unexpected, is a difficult experience that causes feelings of deep sadness. Each family member reacts in a different way, with feelings of shock, fear, anguish, sadness, or even insecurity due to the stigma attributed to cancer as a painful and incurable disease [15].

It is therefore important to highlight that a healthy family relationship can help provide women with a favorable environment in which to face breast cancer, since any demonstration of care and attention coming from the children and the partner are only beneficial [16]. Reinforcing this statement, a recent study on the perceptions of breast cancer and its repercussions on daily life shows that breast cancer leads to significant changes in a couple's lives and that mutual support is essential for better coping with the pathology, followed by family support [17].

It is important to highlight that women generally receive the diagnosis of breast cancer without their partners. This scenario is maintained throughout the treatment, perpetuating a condition in which the husband is sidelined in all the phases, from the diagnosis to the end of the treatment. This situation hinders the emotional support for the woman, since the partner collaborates in the process of psychological adaptation to the breast cancer [18].

The participation of the partner in all the stages is fundamental, since it will lead to an understanding of the process, enabling the partner to contribute to the reduction in the negative repercussions of breast cancer in the sexual, psychological, and social spheres [18,19].

A recent systematic review on exposure to violence among breast cancer patients showed how much this phenomenon causes harm to the victim [19]. Women diagnosed with breast cancer are victims of violence, have a higher occurrence of depression, as well as have damage to their physical, emotional, and functional well-being, which contributes to a worse prognosis of the neoplasm. In addition, it is important to highlight the underreporting of violence in the group of women with breast cancer, as this topic is still a taboo among patients, making it even more difficult to reveal it [19].

Exposure to situations of domestic violence during the treatment for breast cancer may compromise the treatment and quality of life of women patients, so it is essential that health professionals act in tracking this phenomenon in the approach to and care of women with breast cancer [19].

Hence, this study aimed to examine women's experience of violence against them by their intimate partner after mastectomy.

2. Materials and Methods

2.1. Ethical Approval

The research project was approved by the Research Ethics Committee (CEP) of the Federal University of Espírito Santo under number 2,207,822. All ethical criteria were met, respecting the recommendations of Resolution 466/2012, which refers to research involving human beings.

2.2. Study Design

This was a descriptive study with a qualitative approach, conducted in a Rehabilitation Program for Mastectomized Women (PREMMA), which operates in a Brazilian reference hospital for oncological treatment in the municipality of Vitória, Espírito Santo state, in the Southeast Region of Brazil.

2.3. Participants and Recruitment

The participants were 16 women diagnosed with breast cancer who had submitted to mastectomy, following the criterion of data saturation, which occurs when no new element is found, and the addition of new information is no longer necessary because it does not change the understanding of the phenomenon studied. This is a criterion that allows the validity of a data set to be established in qualitative studies [20].

2.4. Data Collection

The women were invited to participate in the research after receiving care from the nursing sector offered by the Program. It is important to highlight that only those who signed the Informed Consent Form were admitted into the study, after the purpose of the study had been explained to them and they had been advised of their freedom to withdraw at any time. Only the researcher and the interviewee participated in data collection.

The interviewers were female, health professionals, who were not part of PREMMA and who have extensive experience in studies with a qualitative approach.

The interviews were carried out with the application of semi-structured interviews that required sociodemographic data and the following guiding question: "After breast cancer, did you experience violence from your intimate partner?" A pilot study was conducted with ten women in order to verify the suitability of the instruments for conducting the research. The data from this pilot study were not included in this research.

At the end of the interview, each participant received a folder explaining the phenomenon of violence against women and the networks of protection.

2.5. Data Analysis

The characterization data (age, education, marital status, family income, and time of diagnosis) of the participants were recorded and analyzed by obtaining measures of raw and relative frequency. The data concerning the women's reports were recorded, transcribed, and analyzed according to the content analysis technique proposed by Bardin [21]. This analysis includes a set of systematic procedures to describe the content of messages in order to enable inference of knowledge related to the conditions of production/reception of these messages, covering the steps of pre-analysis, exploration of the material, treatment of results, and interpretation [21]. The narratives of the women interviewed were categorized into three thematic units on the basis of their experience of violence: (1) experiences of psychological violence, (2) experiences of physical violence, and (3) experiences of sexual violence. In order to preserve the anonymity of the women interviewed, the code I was used for "interviewee" followed by a number; thus, I1 was used to refer to interviewee number 1.

3. Results

Sixteen mastectomized women participated in the study. The minimum age was 44 years and the maximum 72. Most had an incomplete elementary school education, a partner, and a family income of 1 to 2 minimum wages; the mean time of diagnosis was five years (Table 1).

Table 1. Participants' characteristics. Vitória, Espírito Santo, Brazil, 2018.

Codification	Age	Education *	Marital Status	Family Income **	Time of Diagnosis (Years)
I1	52	2	Married	1	1
I2	64	3	Divorced	1	3
I3	62	1	Married	1	10
I4	68	4	Married	3	9
I5	47	1	Married	2	3
I6	47	1	Married	2	7
I7	45	1	Married	1	<1
I8	47	1	Stable union	1–2	1
I9	52	1	Married	3–4	4
I10	55	1	widow	2	4
I11	44	1	Married	3	<1
I12	56	3	Married	1–2	10
I13	72	3	Married	2	15
I14	49	1	Single	2	5
I15	46	3	Married	1	<1
I16	55	1	Married	1–2	6

I = Interviewee; * Illiterate = 1, Incomplete Elementary = 2, Complete Elementary = 3, Higher Education = 4; ** In Brazilian minimum wage. Brazilian minimum wage corresponds to USD 231.73 (quote on 15 September 2022).

The interviewed women's statements were grouped into three thematic categories depending on their experience of violence: (1) experiences of psychological violence, (2) experiences of physical violence, and (3) experiences of sexual violence.

The analysis of the data related to the guiding question: "After the breast cancer, did you start to experience situations of violence on the part of your intimate partner?" The interviewees' narratives revealed that 50.0% experienced psychological violence, 30% experienced physical violence, and 20.0% experienced sexual violence.

3.1. Experiences of Psychological Violence

With regard to the experience of psychological violence, the comment of I1, married and diagnosed a year ago with breast cancer, indicate the presence of this problem practiced by the intimate partner, who sees the treatment as unnecessary, relating cancer to death.

[...] Sometimes inside the house he would say: there, you are taking treatment for nothing, you are really going to die [...] (I1).

For I12, diagnosed 10 years ago, the diagnosis of breast cancer and the surgery generated changes in the relationship with her partner, as she reported:

[...] From the moment he (the husband) found out I had cancer, that I had breast surgery, he changed completely. He kept saying things to humiliate me, like, "Oh, you are not my wife, I have no wife like that, thin, bald, without both breasts" (pause for crying) [...] (I12).

Breast cancer is a stigmatizing disease, which places female body image, especially after a mastectomy, in opposition to the parameters imposed by society, of what is expected of the female body. I3 reported having been deprecated as "mutilated." A statement such as this reveals the degree of psychological violence by the intimate partner as a result of the breast removal surgery.

[...] I was totally despised when I was "mutilated," right. Mutilated in the breasts... The first time I took off my blouse near him, he said that if he had known that "they were going to" cut me like that, he would have done it himself. (pause)... sometimes I was changing my clothes and he called me a "cripple" [...] (I3).

Participant I8 used resources based on coping and focused on emotion to deal with psychological violence; that is, she "pretended" not to be experiencing such a situation.

[...] What struck me most in all this was the contempt. The worst thing he did was that. I pretended not to hear, but it hurt. It hurts. Sometimes, if it was a stranger, it wouldn't hurt me so much [...] (I8).

3.2. Experiences of Physical Violence

In this category, there were reports of physical aggression by the intimate partner, with incidents that ranged from a pinch, a push, or a punch to the use of a knife as a weapon. Despite the physical vulnerability due to the treatment, there was confrontation with and mastery over fear of the situation in pursuit of the preservation of their physical integrity, with the intervention of neighbors, as shown in the reports:

[...] He pinched me and pushed me. I faced him and said that I am not afraid, I am not afraid of dying, I am not afraid of anything [...] (I1).

[...] There was a moment when he pulled the wig off my head and burned the wig [...] (I8).

[...] He came out of his room with a knife, when I went to get up, he came to punch me I got up and he came with the knife [...] (I12).

The interviewees expressed indignation when questioning the justice of the application of the Maria da Penha Law, given the payment of bail for the release of the aggressor.

[...] I didn't have the physical strength to fight with him. Then it got to the point where he beat me and the neighbors "got involved" and he "went" to jail, but when he got there, he paid bail and got out because to justice, a life is nothing, it's nothing [...] (I12)

3.3. Experiences of Sexual Violence

Reports of sexual practices without consent, which characterizes sexual violence, were present. It was reported by women who, because of fear or economic dependence, felt coerced by their intimate partner to submit to a sexual act.

[...] He came to "get me" and go up against me by force. He said either I gave in or he would not buy anything else for the house [...] (I1).

[...] I slept with my room locked, but three times he broke the door down and forced me to have sex. I did it for fear of him doing something worse than what he was already doing to me, understand? [...] (I12)

[...] I had sex out of fear [...] (I6).

4. Discussion

This study aimed to uncover the violence against women practiced by their intimate partners after mastectomy. The analysis of the statements revealed three thematic categories: (1) experiences of psychological violence, (2) experiences of physical violence, and (3) experiences of sexual violence.

Intimate partner violence (IPV) is a public health concern. A study conducted with users of primary care in the municipality of Vitória, Espírito Santo, Brazil, revealed the prevalence of psychological, physical, and sexual violence perpetrated against women by their intimate partners in the last 12 months: 25.3% (95% CI 22.6–28.2), 9.9% (95% CI 8.1–11.9), and 5.7% (95% CI 4.3–7.3), respectively [22]. The data indicate that this is a topical problem in Brazil, not only because of its magnitude, given the significant number of women affected, but also because of the social problems generated by gender violence, which implies the weakened autonomy of women affected by a relationship of domination and control by their partner [23].

A study conducted with women with breast cancer revealed that psychological violence was the most prevalent, with the partner cited as the main aggressor and the house the most frequent place in which the violence was perpetrated [24]. As noted in the present research, expressions of humiliation and feelings of fear and low self-esteem, as well as contempt exhibited by the intimate partners, reinforce how much psychological violence is present in the daily lives of women who have undergone mastectomies, with the partner as the most commonly cited aggressor.

It is important to emphasize that the experience of violence involves a range of feelings, often ambiguous and contradictory. The victims live between fear, anger, indignation, and surprise in relation to the aggressive actions of their partners, but the violence is perceived as negative [25]. Even so, the naturalization of violence, especially within the domestic space, is legitimized by male domination. This violence, marked by power over and oppression of women, leads us to reflect on the definitions and typology of violence against women emphasized by the Maria da Penha Law in Brazil; this reflection could facilitate a (re)conceptualization of violence in the unequal power relations that circumscribe the cruel dynamics in affective and marital relationships [26].

The breakup of a violent relationship can take years, given that many women continue with their partners due to financial dependence, fear of dying, waiting for a change in their partner's behavior, the shame of assuming the failure of the relationship, or emotional dependence [27]. In the absence of economic factors, aspects such as intimacy and the centrality of the relationship can function to prevent the termination of the relationship [28]. Many women fail to report violence because they have the perception that they are not entitled to autonomy over their lives, because they believe they are guilty of the violence suffered, or because they do not even realize they are in a violent relationship [29].

A study conducted with 553 women diagnosed with breast, cervical, or colorectal cancer showed that domestic violence negatively influenced all health indicators related to cancer, suggesting that the identification of IPV and other stressors can provide important information to health professionals in order to contribute to the better planning of assistance, disruption of violence, and improvement in the well-being of these women [30].

The present study noted the experience of sexual violence in the reports of participants who highlighted coerced sexual practices, committed without consent, or motivated by fear of their partner. These results show how fundamental it is that health professionals take into consideration the complex interaction between the cultural, relational, and subjective aspects of the sexual experience after breast cancer in order to provide better care in the context of oncological assistance [31–40].

Provision of comprehensive care to women with breast cancer experiencing violence requires the construction of a network of services to confront that violence, this network being one of the most important and challenging strategies for dealing with a problem that is complex and multifaceted, so that the network contributes to the strengthening of victims and professionals, and so that they will feel supported and encouraged to act [41].

It is worth considering as a limitation of this study the fact that it did not investigate whether the women had already experienced tensions that interfered with their relationships prior to the disease. However, this does not prevent us from concluding that there is a need for professionals to assist these women and to provide holistic care capable of uncovering previous or current cases of violence, which are often omitted by women because they feel inhibited, ashamed, or too insecure to report what has happened, in order to contribute to their comprehensive care and record their cases, playing an important role in their care and the prevention of this phenomenon.

5. Conclusions

This is one of the few studies that we know of that has approached violence against woman in a context of the great vulnerability that is the experience of mastectomy resulting from a diagnosis of breast cancer. It was observed that the physical, sexual, and psychological violence practiced by their intimate partners may be present in this phase, considered a time of great need for family and social support.

The results of this study reaffirm the importance of health professionals in the care of women with breast cancer, and especially those in situations of violence. Health professionals have a role of immense relevance not only in the reception of victims, but also and especially in the recording of this problem, giving women the opportunity of inclusion in a network of protection and care and thereby enabling the removal of this phenomenon. It is important to emphasize that it is essential that women be assisted by a multidisciplinary and interprofessional team, given the complexity of violence and the demands that arise in different bio-psycho-social areas resulting from the experience of this serious public health phenomenon that is violence against women.

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