

Review

Beyond the Knife: A Review of the Burden of Localized Recurrent Pancreatic Adenocarcinoma and the Potential Role of Intraoperative Radiation Therapy

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Simple Summary

Pancreatic adenocarcinoma (PDAC) has poor survival largely due to late presentation and high recurrence rates. While surgery combined with chemotherapy (and sometimes radiation) is standard for localized disease, achieving durable local control is difficult due to close margins and aggressive tumor spread, especially along nerves and vessels. Most recurrences are distant, but a meaningful portion are local and may benefit from improved local therapies. Intraoperative radiation therapy (IORT) delivers a focused, high dose of radiation directly to the tumor bed during surgery, minimizing damage to surrounding organs. Emerging evidence suggests that IORT may reduce local recurrence and improve survival without increasing complications, particularly in high-risk patients. However, more prospective trials are needed to confirm its overall benefit and to define optimal patient selection.

Abstract

Background: Pancreatic resection (Pancreatoduodenectomy, PD, distal pancreatectomy, DP, or total pancreatectomy, TP) is the standard of care for resectable pancreatic adenocarcinoma (PDAC). Despite advances in multimodal therapy, recurrence rates remain high, approaching 80%, and continue to drive poor overall survival. **Objective:** This review evaluates the burden and clinical significance of localized recurrence in PDAC and critically examines the potential role of intraoperative radiation therapy (IORT) in improving locoregional disease control. **Results:** Distant recurrence remains the predominant pattern of failure, occurring in 55–75% of patients, most commonly involving the liver, lungs, and peritoneum. However, isolated local recurrence, observed in approximately 17–32% of patients, represents a clinically meaningful subset associated with significant morbidity and potential for subsequent metastatic progression. IORT, delivered as a single high-dose radiation treatment to the tumor bed at the time of surgery, enables precise targeting of areas at highest risk for residual microscopic disease while minimizing radiation exposure to adjacent radiosensitive structures. Retrospective and meta-analytic data, while limited, suggest that IORT is associated with improved local control and modest survival benefit without a significant increase in perioperative morbidity, though interpretation is limited by study heterogeneity and lack of randomized control trials. **Conclusion:** IORT represents a rational adjunct in the multimodal management of PDAC, particularly for patients at



Academic Editor: Giusi Irma Forte

Received: 26 March 2026

Revised: 26 May 2026

Accepted: 22 June 2026

Published: 26 June 2026

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high risk of locoregional failure, including those with borderline resectable or locally advanced disease, nodal involvement, perineural invasion, or concern for margin positivity. Prospective studies are needed to better define optimal patient selection and to clarify the role of IORT in the modern treatment paradigm.

Keywords: intraoperative radiation therapy; pancreatic adenocarcinoma; radiation; pancreatectomy

1. Introduction

Pancreatic adenocarcinoma (PDAC) remains one of the most formidable malignancies, with the 5-year overall survival rate increasing from 6% in 2004 to only 12% in 2025 [1]. PDAC routinely presents clinically once the disease has already disseminated to distant sites, contributing to high morbidity and mortality. This is compounded by the persistent lack of effective early detection strategies, resulting in most patients being diagnosed at advanced, non-curable stages, underscoring the critical need for improved early diagnostic approaches [2]. For patients who present with non-metastatic disease, management is largely determined by anatomic resectability and the feasibility of achieving margin-negative resection.

PDAC can be broadly categorized as resectable, borderline resectable, locally advanced, or metastatic at presentation. Categorization of non-metastatic PDAC is largely dependent on the presence and extent of tumor contact/invasion of surrounding structures seen through imaging. Treatment decisions are guided by multidisciplinary consensus and national guidelines, incorporating surgery and systemic therapy in appropriately selected patients [3].

Currently, the recommended management of localized PDAC patients includes surgical resection (pancreaticoduodenectomy, distal, or total pancreatectomy), combined with neoadjuvant/or adjuvant chemotherapy regimens such as FOLFIRINOX or Gemcitabine-based therapies. Radiation therapy may provide additional benefit in select patient populations [4]. Specifically, external beam radiation therapy (EBRT) combined with concurrent chemotherapy is used in patients with borderline resectable or locally advanced disease. The NCCN recommends neoadjuvant chemotherapy with EBRT in this select patient population, supported by randomized controlled trials demonstrating improved R0 resection rates and increased 2- and 5-year survival outcomes [5,6].

EBRT involves the delivery of high-energy X-rays or particle beams via radiation accelerators from outside of the body to target an area of gross malignancy or areas at risk for harboring subclinical (microscopic) disease to induce tumor cell death. The primary objective is eradication of malignant cells, with applications spanning the management of preoperative treatment of resectable/borderline resectable disease, adjuvant therapy following surgical resection, and the use of a palliative measure to alleviate tumor-related symptoms. However, radiation treatment is often limited in its effectiveness due to dose limitations imposed by surrounding structures, most commonly nearby stomach, small bowel, liver, and kidneys. Consequently, dosing strategies are tailored based on the extent of disease and adjacent normal tissues [3].

In addition to EBRT, intraoperative radiation therapy (IORT) has emerged as a feasible adjunct to address challenges in the treatment for borderline resectable or locally advanced PDAC. Like EBRT, IORT utilizes high-energy radiation to target tumor tissue and reduce tumor burden (Figure 1). However, unlike EBRT, IORT is delivered directly to the tumor bed during surgery and can avoid irradiating nearby radiosensitive normal tissues, as these

can be displaced from the field during IORT. This allows precise targeting of the area at highest risk for residual disease while minimizing exposure to surrounding structures. This also allows IORT to safely deliver high doses to the target in a single treatment, rather than fractionated treatment as is done during EBRT.

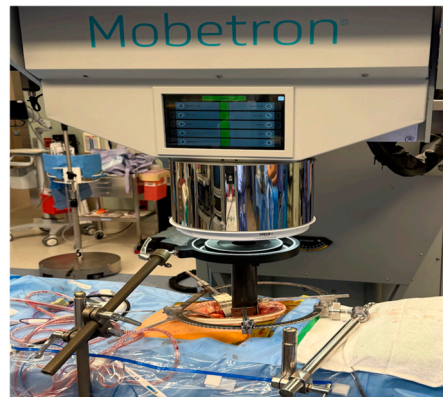


Figure 1. Intraoperative radiation therapy illustration.

Despite these multimodal treatment strategies, recurrence remains common and continues to drive the poor overall survival associated with PDAC. IORT has the potential to improve local disease control in patients at high risk for residual microscopic disease, thereby addressing a key contributor to locoregional recurrence following pancreatic resection.

2. Patterns of Recurrence

Following curative-intent resection for PDAC, recurrence may occur locally at the site of resection or distantly at metastatic sites. Reduction in distant recurrence has been a major focus of traditional and novel systemic approaches in both the neoadjuvant and adjuvant settings due to the high likelihood of this pattern of failure.

Reported rates of distant recurrence following curative-intent resection for PDAC vary among studies, reflecting differences in patient populations, surgical techniques and expertise, as well as follow-up duration. Several reports document that 55–75% of patients experience distant metastases as the first site of recurrence, with the liver being the most common organ involved [7,8]. Other common sites of distant recurrence include the lungs and peritoneum. Peritoneal dissemination represents a particularly aggressive form of metastatic spread and has prompted interest in treatment strategies such as hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC), although these approaches remain investigational in PDAC populations. Furthermore, a positive lymph node ratio > 0.2 has been seen as a strong predictor of distant disease recurrence [7].

Although distant metastasis remains the primary driver for disease-related mortality following curative resection, isolated local recurrence has increasingly become an important consideration in PDAC management. Local recurrence includes tumor regrowth within the pancreatic bed, pancreatic remnant, or mesenteric root [9].

Isolated local disease accounts for a smaller percentage of post-resection disease failure, reported in approximately 17–32% of cases [7,10–12]. While less frequent than distant recurrence, this pattern is clinically meaningful and warrants increased attention, particularly with respect to optimizing preoperative and postoperative management strategies. While isolated local recurrence after surgical resection generally manifests later than distant disease (11.7–15.5 months versus 4.6–10.4 months respectively [13]), there is a portion of the population with local-only recurrence who do not quickly progress distantly and can potentially achieve a cure or at least long-term disease control with local therapy. Unfor-

Unfortunately, though, locally recurrent disease is often not technically resectable and options for long-term disease control can be limited. This underscores the importance of achieving optimal local control in the management of PDAC. Together, these findings highlight the need to optimize strategies aimed at controlling both distant and local disease in order to improve overall survival. These estimates are largely derived from high-volume academic centers and reflect patterns of failure among patients treated with multimodal therapy. Figure 2 provides a comprehensive overview of recurrence following neoadjuvant therapy and surgery in a prospectively followed cohort of patients with locally advanced pancreatic adenocarcinoma, depicting both recurrence patterns and the distribution of recurrence sites [14,15].

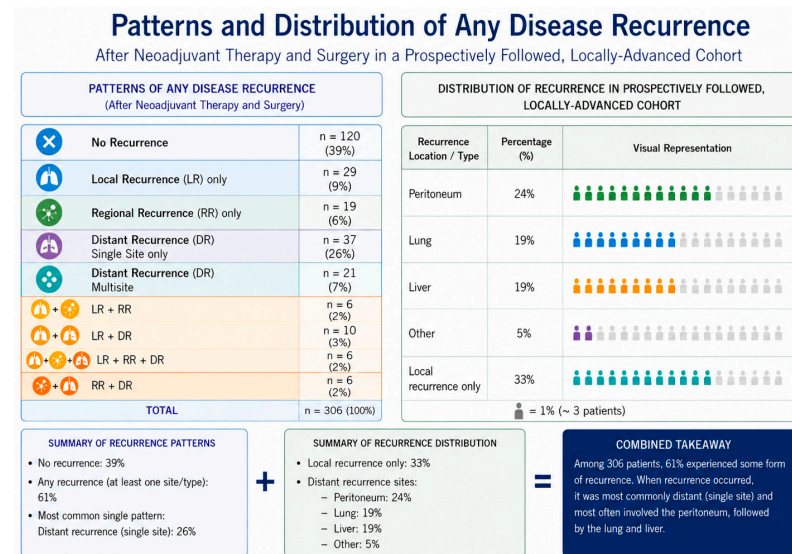


Figure 2. Patterns and Distribution of Any Disease Recurrence After Neoadjuvant Therapy and Surgery in a Prospectively Followed, Locally Advanced Cohort.

3. Biologic and Anatomic Drivers of Recurrence

PDAC demonstrates a uniquely aggressive pattern of spread, commonly infiltrating perineural, vascular, and lymphatic structures. The pancreas thus functions as a virtual hub of anatomic “highways” that facilitate malignant dissemination. Perineural invasion (PNI) refers to the presence of cancer cells surrounding pancreatic nerves and the peripheral nerve plexus within the epineural, perineural, or endoneural spaces of the neuronal sheath [16]. The incidence of PNI in PDAC approaches nearly 100% [17], contributing to increased rates of both local and regional recurrence. This propensity is largely due to the intricate anatomy of the pancreas and its surrounding nerve plexuses. The formal division of peripancreatic nerve plexuses was established by the Japan Pancreas Society (JPS) in 1986, which categorized them into six subgroups: pancreas head nerve plexus I (PLX-I) and II (PLX-II), hepatoduodenal ligament-surrounding nerve plexus (PLX-hdl), superior mesenteric artery-surrounding nerve plexus (PLX-sma), and the right and left celiac ganglion plexus (Rcg and Lcg) [17].

PNI spreads through several distinct pathways. The Phosphoenolpyruvate Carboxylase 1 (PPC1) pathway, in which cancer cells in the uncinate process of the pancreas, specifically the middle and upper regions, may spread posteriorly to the portal vein and to the right celiac ganglion. The Phosphoenolpyruvate Carboxylase 2 (PPC2) pathway, observed in 74–81% of PDAC cases, in which cancer cells in the uncinate process disseminate along the inferior posterior pancreaticoduodenal artery or the jejunal branch of the superior mesenteric vein to the mesenteric ganglion. The mesenteric pathway, in which the cancer cells in the uncinate process travel posteriorly to the inferior pancreaticoduodenal

artery leading to the mesentery of the small intestine or transverse mesocolon. Finally, the anterior pathway, in which head and neck cancer cells invade the right celiac ganglion primarily through the gastroduodenal or common hepatic arteries [17–19].

Margin status remains a key predictor of recurrence in PDAC and is classified as negative margins (R0), microscopically positive margins (R1), or macroscopically residual tumor (R2). Median overall survival and disease-free survival are increased in R0 resection (19.3 months and 14.2 months) compared to R1 resection (13.4 months and 10.9 months) respectively [20]. Achieving negative margins in PDAC remains challenging due to several factors, including early perineural and retroperitoneal spread, ill-defined tumor boundaries, and the close proximity to major vascular structures such as the superior mesenteric artery (SMA) and vein (SMV), portal vein, celiac axis, and splenic vessels.

Even in experienced hands, surgeons often find themselves “chasing” microscopic extensions of tumor along these intricate perineural and vascular highways. These biologic and anatomic factors explain why achieving durable local control in PDAC remains difficult despite technically successful surgical resections.

4. Risk Factors for Local Recurrence

Patient populations at increased risk of local recurrence include those with adverse pathologic features, operative factors, and aggressive tumor biology. Among these, lymph node involvement is the most consistently identifiable risk factor for local recurrence. Jones et al. performed a secondary analysis of the ESPAC-4 trial that reviewed the specific patterns of local, distant, and local/distant recurrence [12]. Of the 730 patients enrolled, 479 experienced disease recurrence: 238 (49.7%) developed local-only recurrence, 193 (40.3%) developed distant-only recurrence, and 48 (10.0%) experienced both local and distant recurrence. An additional 78 (10.7%) patients died with no identifiable recurrence. A positive margin was strongly associated with poorer overall survival in the main study group. Analysis of the trial demonstrated that the proportion of patients experiencing local-only recurrence increased with nodal stage, occurring in 23%, 33%, and 37% of N0, N1, and N2 disease, respectively. These findings suggest that increasing nodal disease burden is associated with a greater likelihood of locoregional failure, underscoring the potential role for therapies aimed at improving local control, such as IORT.

Other pathologic and tumor-related characteristics associated with an increased risk of local recurrence include PNI, elevated CA 19-9, resection margin status, and tumor differentiation. Interestingly, well-differentiated tumors have been associated with a higher incidence of local-only recurrence, whereas poorly differentiated tumors more commonly predict distant recurrence. This pattern suggests that well-differentiated tumors may have lower metastatic potential, but present greater challenges for achieving durable local control [21]. Similarly, Kim et al. identified PNI, resection margin status, initial CA 19-9 ≥ 200 U/mL, and N1 stage as significant independent predictors of increased local recurrence. Their analysis demonstrated that patients who exhibited two of these risk factors experienced a 3.2-fold higher locoregional failure ($p < 0.001$), while those with all four risk factors showed a 6.5-fold increase ($p < 0.001$) compared to patients that exhibited no risk factors [22]. Collectively, these findings suggest that preoperative risk stratification based on tumor biology and pathologic features may help identify patients at particularly high risk for locoregional failure, who may experience greater benefit from strategies such as IORT aimed at improving local disease control.

5. Role of Local Therapies and Radiation

Given the anatomic constraints of pancreatic resection and the high incidence of microscopic residual disease at critical margins [23,24], conventional approaches such as surgery,

chemotherapy, and EBRT/SBRT continue to face clinical limitations. Radiation therapy is particularly constrained by toxicity risks to adjacent structures. Acute toxicities generally occur within 90 days and are typically mild to moderate (Grade 1–2), most commonly presenting as fatigue, nausea, and abdominal pain. Late toxicities occurring beyond 90 days may include moderate to severe complications (Grade 3–5), such as pancreatic fistula, hemorrhage, and gastrointestinal ulceration, particularly at higher radiation doses.

Recent advances in radiation oncology have focused on dose-escalation strategies in PDAC, based on evidence that suggests delivery of higher biologically effective doses (BED) may improve local tumor control and potentially, overall survival. Modern techniques such as intensity modulated radiation therapy (IMRT) and SBRT allow for more precise and conformal radiation delivery and have enabled escalation to ablative dose ranges while also minimizing the risk of exposure to surrounding radiosensitive structures. Magnetic resonance-guided adaptive radiation therapy (MGgRT) has further expanded these capabilities by improving soft-tissue visualization and enabling daily adaptive planning, which may enhance target accuracy and facilitate safer dose escalation in anatomically complex regions such as the pancreas. Within this evolving framework of escalating radiation precision and dose intensity, several institutional studies have exhibited improved local control with BED₁₀ values exceeding 100 Gy in patients with locally advanced PDAC, although toxicity to surrounding organs including the duodenum, stomach, and small bowel remains a major limiting factor. Within this context, IORT may serve as a complementary dose-escalation strategy by allowing focused delivery of additional radiation directly to high-risk retroperitoneal and perivascular margins while adjacent organs are displaced from the operative field. This integration of external beam escalation with selective intraoperative boost therapy represents an evolving multimodal approach aimed at improving locoregional disease control [25,26].

Despite these advances, toxicity to adjacent radiosensitive structures continues to limit the safe delivery of ablative radiation doses in PDAC. IORT represents a potential strategy to address this challenge by enabling highly focused radiation delivery directly to the tumor bed during surgical resection, when surrounding organs can be mobilized or displaced from the operative field. This approach allows treatment of regions at highest risk for microscopic residual disease while minimizing radiation exposure to nearby critical structures. Although reported IORT series generally describe low rates of severe acute and late toxicity, complications such as wound-related morbidity, gastrointestinal ulceration, delayed enteric injury, neuropathy, and vascular injury have been reported, with overall incidence varying across studies due to heterogeneity in dose, technique, and reporting standards. These toxicities have generally only been observed with doses on the highest ends of the dose ranges that have been used.

6. Intraoperative Radiation Therapy (IORT)

6.1. History

The use of IORT in the United States originated in the early 1970s, when a small group of surgical oncologists began applying this novel approach to select malignancies, including recurrent rectal cancer, retroperitoneal sarcomas, pancreatic cancer, and select gynecologic and genitourinary malignancies [27]. Early implementation was challenged by significant technological and logistical constraints. Conventional linacs were fixed installations, necessitating either specially constructed, shielded operating suites or the complex and potentially risky transfer of anesthetized patients from the operating room to a designated radiation treatment area.

A major inflection point occurred in 1998 with the introduction of the first mobile linac systems for the treatment of breast cancer [28]. Adoption expanded rapidly and by

2006, approximately 30 mobile linacs had been established across the United States [27]. This transition from stationary to mobile platforms dramatically reduced operational costs, infrastructure requirements, and workflow barriers that previously limited the broader integration of IORT. As a result of this technological advancement, mobile linacs played a substantial role in facilitating the expansion and modernization of established IORT programs nationwide.

6.2. Evidence

Few studies have evaluated the effectiveness of IORT for PDAC following surgical resection. This limited evidence base is largely attributable to the absence of randomized control trials (RCTs), the sparse number of centers able to perform IORT, and the technical expertise required to deliver this modality. Nevertheless, existing retrospective analyses and institutional studies have suggested that IORT may meaningfully impact local disease control, reduce the risk of local recurrence, and maintain postoperative complication rates similar to standard surgery alone. High-volume oncologic centers with specialized radiation programs have readily implemented IORT for PDAC patients, reporting improvements in disease-free survival (DFS) and a significant decrease in local recurrence. A summary of representative studies evaluating intraoperative radiation therapy (IORT) in resected pancreatic ductal adenocarcinoma (PDAC), including key outcomes related to local disease control and overall survival, is presented in Table 1 [29].

Table 1. Key Clinical Outcomes from Selected Studies of IORT in Resected Pancreatic Ductal Adenocarcinoma.

Study	Cohort Size (n)	IORT Dose (Gy)	Treatment Approach	Primary Finding	Local Control Outcome	Median Overall Survival
Zerbi et al. [30]	90	12.5–20	Surgery ± IORT	Comparative analysis of surgery with and without IORT	Local recurrence 58.4% → 27% (>50% reduction with IORT)	12 → 19 months
Alfieri et al. [31]	46	10	Surgery ± IORT	Long-term follow-up of resected patients	5-year local recurrence 71.2% → 41.6%	10.8 → 14.3 months
Reni et al. [32]	127	10–25	Surgery + IORT	Evaluation of postoperative local disease control	Time to local failure 11 → 14 months	12 → 15.5 months
Ogawa et al. [33]	20	20–30	Surgery + IORT	High-dose IORT strategy	Local recurrence rate 16.3%	19.1 months
Valentini et al. [34]	270	7.5–25	Surgery + IORT	Large institutional experience	Time to local failure 15 months	19 months

Abbreviations: IORT, intraoperative radiation therapy; OS, overall survival.

This is adapted from Palta M et al. and the individual studies cited therein.

Jin et al. performed a retrospective analysis of 1095 studies, in which 15 studies with 834 patients were included in a meta-analysis. Among these patients, 401 underwent pancreatic resection with IORT and 433 underwent surgery alone. Patients in the IORT

group demonstrated improved overall survival (median survival rate [MSR], 1.20; 95% confidence interval [CI], 1.06–1.37, $p = 0.005$) compared to the surgery alone group [35]. Furthermore, the data also showed that the IORT group experienced a significantly reduced local recurrence rate (relative risk [RR], 0.70; 95% CI, 0.51–0.97, $p = 0.03$) compared to the non-IORT group. Postoperative complication rates (RR, 0.95; 95% CI, 0.73–1.23) as well as operation-related mortality (RR, 1.07; 95% CI, 0.44–2.63) did not differ significantly between the IORT and non-IORT groups. Importantly, this meta-analysis focused exclusively on resectable PDAC, underscoring the need for further investigation into the use of IORT among patients classified as borderline resectable or locally advanced, where the potential impact may be even more clinically meaningful.

Harrison et al. conducted a retrospective analysis of 158 BR/LA patients treated with neoadjuvant therapy—83% receiving FOLFIRINOX and 95% receiving chemoradiation prior to IORT—followed by IORT. Patients were stratified into two primary groups: those who underwent surgical resection with IORT and those who received IORT alone. Patients treated with surgical resection + IORT demonstrated significantly improved progression-free survival (PFS) and overall survival (OS) (21.5 months and 46.7 months, respectively) compared to those treated with IORT alone (14.7 months and 23 months, respectively). In terms of local disease control, only 12.7% of patients in the resection + IORT group experienced local disease progression, compared to 15% in the IORT-only group [36]. These findings strengthen the role that IORT possesses in enhancing local control and contributing to prolonged survival. Collectively, this study reinforces the value of IORT as a valuable adjunct to neoadjuvant therapy and surgical resection in the management of BR/LA PDAC.

Interpretation of the current evidence is limited by the retrospective nature of most studies, significant selection bias, and heterogeneity in patient populations, radiation dosing, and integration with systemic therapies. Furthermore, the absence of randomized control trials limits definitive conclusions regarding the survival benefit of IORT. As such, while existing data suggest improved local control, the magnitude of its impact on overall survival remains uncertain. Patients most likely to benefit from IORT include those with biologically or anatomically high-risk localized disease, particularly patients with borderline resectable or locally advanced tumors, close or microscopically positive margins (R1), nodal involvement, or a high risk of residual retroperitoneal disease where achieving durable local control is challenging despite resection and systemic therapy.

7. Radiation Delivery and Safety

IORT has generally been delivered via dedicated linear accelerator high-energy electron beams. This is in contrast to typical external beam radiotherapy that more often uses photon radiation with deeper tissue penetration. Electron beam linear accelerators typically deliver energies in the range of 6–15 MeV [29,37,38]. In these systems, a dedicated operating suite with shielding for radiotherapy is utilized. Some facilities have used a fixed, mounted electron linac, while others use a commercially available mobile electron linac [39]. A metal cylinder applicator guides the electron beam from the electron accelerator to the target tissues within the treatment field. Doses have generally ranged from 10–25 Gy, with doses on the higher end of the range reserved for R2 resections [40]. Less commonly, catheter-based high-dose-rate brachytherapy has been used as a delivery technique [41].

Radiation dosing during IORT for PDAC varies among studies; however, the median dose for resectable PDAC is approximately 10 Gy, with typical ranges between 10–15 Gy depending on surgical margin status [36,42]. The stomach, duodenum, jejunum, and liver are among the primary organs at risk for radiation toxicity in patients with PDAC. However, the radiation dose required to produce clinically significant toxicity in these organs is generally higher than the 10–15 Gy doses typically used for PDAC. For example, IORT

doses up to 30 Gy have been reported as safe for the stomach without significant acute toxicity [43]. Similarly, doses up to 20 Gy to the small bowel have been associated with minimal toxicity [44], while doses up to 15 Gy have demonstrated safety with minimal complications in the liver [45]. Additionally, although toxicity remains a concern during IORT, precautions are taken to minimize radiation exposure to surrounding organs. Surgeons first manually displace adjacent organs out of the radiation field, after which lead or aluminum protective disks are positioned between the tumor bed and underlying critical structures to provide additional shielding.

8. Future Directions

The PACER (Pancreatic Adenocarcinoma With Electron Intraoperative Radiation Therapy) Trial is a multi-institution Phase II study currently evaluating two-year survival rate, local control, median progression-free survival, and adverse events following IORT in patients who have undergone IORT following 2–3 months of chemotherapy [46]. This trial is a promising prospective study which may give additional insight into the utility of IORT for treatment of PDAC and may help further define the role of IORT as an adjunctive strategy for improving local disease control in appropriately selected patients. While it is unlikely that a randomized control trial would be completed with IORT for PDAC due to the current limited availability of the treatment, it would be ideal to have randomized data comparing patients at high risk for positive margins and/or local recurrence (e.g., the population included in the PACER Trial) randomized to induction chemotherapy, preop chemoradiation and resection with IORT versus without IORT. Perhaps with expanded adoption of the technique and increased access, this could be achieved.

Johns Hopkins conducted a Phase I trial (NCT05141513) evaluating the use of SBRT followed by IORT delivered to the “Triangle Volume” (bordered by the celiac axis, superior mesenteric artery, common hepatic artery, portal vein, and superior mesenteric vein) during pancreaticoduodenectomy. The treatment strategy aimed to achieve an ablative BED₁₀ greater than 100 Gy. Among the 20 patients enrolled, the trial reported a 1-year local progression-free survival (LPFS) of 95% [47]. These findings further support the feasibility of incorporating IORT as an adjunctive modality in the management of PDAC.

Emerging ultra-high dose rate radiation approaches, including FLASH radiotherapy and FLASH-IORT, are currently under preclinical investigation and may further expand the therapeutic window by enabling normal tissue sparing while maintaining tumoricidal dose delivery; however, clinical data in PDAC remains limited.

Looking ahead, a clearer understanding of the molecular subtype of pancreatic tumors may help guide treatment selection. Locally advanced PDAC without metastasis appears to demonstrate molecular characteristics that favor locoregional tumor dominance rather than early systemic dissemination. Data from the COMPASS trial support this concept. O’ Kane et al. reported that the classical/progenitor subtype (characterized by high GATA6 expression) was the predominant subtype in locally advanced PDAC, whereas the basal-like/squamous subtype (GATA6-low) was linked to more aggressive metastatic behavior [48]. Similarly, Hong et al. demonstrated that SMAD-4 inactivation is frequently observed in aggressive metastatic PDAC, whereas TGF- β inactivation appears to be more common among the locally advanced cancer subtype [49]. As tumor genomic profiling continues to evolve, these molecular insights may help identify specific patient populations that are more likely to benefit from intensified locoregional treatment strategies.

For patients with borderline resectable or locally advanced disease, careful biologic and anatomic risk stratification is essential to guide individualized multimodal treatment strategies. These approaches may include extended vascular resections when feasible,

neoadjuvant systemic therapy, and adjunctive local control modalities such as IORT, with the goal of maximizing margin-negative resection rates and improving local disease control.

9. Conclusions

Intraoperative radiation therapy represents a promising adjunct of treatment for PDAC following surgical resection. As systemic therapies have improved control of distant metastasis, local disease recurrence has become an increasingly important contributor to patient morbidity and mortality. Available evidence suggests that IORT, when incorporated into multimodal treatment strategies, may improve survival and outcomes by enhancing local disease control at the resection site. Patients with borderline resectable or locally advanced tumors, particularly those with high-risk pathologic features such as nodal disease, PNI, or concern for close or positive margins, may derive the greatest benefit from this approach. Further prospective investigation will be necessary to determine the optimal patient populations for IORT and to clarify its role with evolving multimodal treatment strategies for pancreatic cancer. Nevertheless, these findings are primarily derived from retrospective studies, and high-level prospective randomized data remain limited, underscoring the need for further validation before definitive conclusions regarding clinical benefit can be made.

Author Contributions: J.M.: Conceptualization, Investigation, Writing—Original Draft, Writing—Editing; B.M.: Conceptualization, Investigation, Writing—Original Draft, Writing—Editing; M.R.: Conceptualization, Investigation, Writing—Original Draft, Writing—Editing; J.A.S.: Conceptualization, Investigation, Writing—Original Draft, Writing—Editing. All authors have read and agreed to the published version of the manuscript.

Funding: This study received no external funding, and no external institutions were involved in any aspect of the research or manuscript preparation.

Informed Consent Statement: This study is a review and does not include any direct patient information or data.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable.

Conflicts of Interest: All authors report no biomedical financial interests or potential conflicts of interest.

Abbreviations

PD	Pancreatoduodenectomy
PDAC	Pancreatic Adenocarcinoma
IORT	Intraoperative radiation therapy
EBRT	External Beam Radiation Therapy
SBRT	Stereotactic Beam Radiotherapy
SMA	Superior Mesenteric Artery
RT	Radiation Therapy
PNI	Perineural invasion

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