

The role of radiotherapy in pancreatic cancer management

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Abstract

Pancreatic cancer represents a distinct entity in oncology, being a malignancy with poor prognosis. Although surgical resection is the only potentially curative treatment, high rates of local and loco-regional recurrence, distant metastases, along with the low overall and disease-free survival rates, underscore the importance of chemotherapy and radiotherapy in the management of the disease. The main objective of this review is to evaluate the precise role of radiotherapy in pancreatic cancer management, focusing on the stage of the disease (potentially resectable or advanced stage) and the optimal timing of its application (preoperative or postoperative). A literature review was conducted using PubMed, focusing on studies published from 1999 onwards. Outcomes assessed were overall survival, disease-free survival, locoregional recurrence and margin-negative resection rates. The results showed that there are positive prospects for neoadjuvant radiotherapy, mainly in resectable and borderline resectable disease, compared to adjuvant chemotherapy, showing benefits in overall survival (15.7 vs. 14.3, 21 vs. 12, 17.4 vs. 14.4, 29.1 vs. 13.1, and 22.4 vs. 19.5 months in separate studies), disease free survival (8.1 vs. 7.7 months), locoregional recurrence rates (32% vs. 46%), and in the achievement of clear surgical margins (71% vs. 40%, 51.8% vs. 26.1%, 52% vs. 48%, 100% vs. 40%, 70.6% vs. 64.8%, 38.9% vs. 25%, and 37% vs. 14% in various studies). Therefore, the use of radiotherapy in the treatment of pancreatic cancer, particularly in the neoadjuvant setting, appears promising. Integration of advanced radiotherapy techniques and patient-centered outcomes will be crucial for improving disease prognosis.

Keywords Radiotherapy, role, management, pancreatic cancer, review

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Introduction

Pancreatic cancer (PC) is recognized as one of the most aggressive and lethal malignancies of the gastrointestinal tract, with a dismal prognosis and a persistently high mortality rate [1]. It is the second cause of death among

gastrointestinal cancers and, at the same time, the fourth cause of all cancer-related deaths, confirming its importance in the oncologic community [2,3]. It is a disease with poor outcomes, mainly due to its late-stage diagnosis, since it is often asymptomatic in early stages or characterized by atypical symptoms. Consequently, when the diagnosis is made, only a small percentage of patients—usually less than 20%—are suitable for surgical resection, which is still the only potentially curative approach when treating these patients [4].

Although there have been many advances in both surgical techniques and perioperative care, the prognosis for patients who undergo curative surgery remains remarkably poor, with a 5-year survival rate still below 10%, portraying the aggressiveness of PC in terms of biology and progression [5]. Both locoregional recurrence (LRR) and distant metastases rates are high: a fact that translates into low overall survival (OS) as well as disease-free survival (DFS) [6]. In addition to these challenges, the anatomical complexity of the pancreas makes its treatment even more demanding. Its anatomic location, deep within the abdominal cavity (which often explains the absence of early symptoms), as well as its proximity to major vessels, place limitations on the curative strategies available [7,8]. Furthermore, a resistance to drug delivery may

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be observed, mainly due to the high density of the tumor's microenvironment and various desmoplastic reactions [9].

Taking all the above into account, it is easy to appreciate that a multimodal approach is necessary in order to improve patients' outcomes. Besides surgery, both systemic chemotherapy (CT) and radiotherapy (RT) are increasingly becoming an integral part of the treatment protocols in the preoperative (neoadjuvant), postoperative (adjuvant), or even intraoperative setting [10]. The ultimate goal is the reduction of tumor burden as far as possible, the control of microscopic disease and, finally, the achievement of a margin-negative (R0) resection. For this purpose, CT regimens relying on FOLFIRINOX and gemcitabine have shown substantial improvements in terms of survival, in both the adjuvant and neoadjuvant settings [11]. Nevertheless, the role of RT in PC management is still controversial, and its benefit in terms of local control or survival, its optimal application timing (preoperative or postoperative), or its possible combination with systemic therapies, are still subject to ongoing debate [12]. Hence, the role and possible benefits of RT in PC treatment need to be clarified with precision, and new evidence-based protocols should be established.

The primary purpose of this study is, on the one hand, to shed light on the specific role of RT in PC treatment, focusing mainly on the optimal timing of its administration, and on the other, to assist in the quest for evidence-based recommendations that may help guide clinical decision-making.

Literature search strategy

A literature search was carried out through the PubMed database, regarding the role of RT in PC management. Studies published between 2010 and 2026 were generally considered. For adjuvant RT specifically, earlier studies were also examined, mainly because of the limited data available. The main search terms - "pancreatic cancer", "pancreatic adenocarcinoma", "radiation therapy", "chemoradiotherapy", "adjuvant radiotherapy" and "neoadjuvant radiotherapy" - were combined using the Boolean operators AND/OR. Titles and abstracts of the retrieved records were independently screened by two authors, and any disagreements were resolved through discussion. Studies examined were randomized control trials, cohort studies as well as review articles that focused on adult patients with resectable, borderline resectable, or locally

advanced PC. Endpoints identified were OS, DFS, LRR and R0 resection rates. Studies in languages other than English, case reports, studies with limited clinical applicability, and studies involving non-relevant patient populations or cancer types were excluded. Case reports and studies with limited clinical applicability were also not considered. This article provides a narrative overview of the available evidence, and no formal systematic review methodology, for example the PRISMA criteria, was applied.

Adjuvant RT

Surgical resection is the treatment of choice for resectable pancreatic tumors, followed by adjuvant therapy for a duration of 6 months [13]. However, a newer approach being proposed is the combined use of postoperative CT and RT. The phase II EORTC40013/FFCD 9203/GERCOR study, in a final sample of 78 patients, showed that chemoradiotherapy (CRT) reduced LRR rates compared to CT alone (11% vs. 24%), while DFS and OS were similar between groups: DFS 11.8 (95% confidence interval [CI] 10.1-19.3) vs. 10.9 months (95%CI 8.3-16), and OS: 24.3 (95%CI 20.5-∞) vs. 24.4 months (95%CI 21.5-∞) [14]. In the RTOG 0848 study by Abrams *et al*—DFS 16 (95%CI 12-20) vs. 12 months (95%CI 9-18), and OS 27 (95%CI 25-32) vs. 31 months (95%CI 25-38)—a benefit was found in terms of DFS in patients receiving CRT, whereas OS was better in the CT alone group, although statistical significance was not provided [15]. Additionally, the study by Klinkenbijn *et al*, based on a sample of 104 patients, reported encouraging results with CRT: OS of 24.5 months ($P=0.208$) and LRR rate of 34%, statistical significance not reported [16].

In contrast, while the American Society of Clinical Oncology (ASCO) supports the use of RT, the European Society of Medical Oncology (ESMO) recommends its application only within clinical trials [13]. This is largely based on findings from the ESPAC-1 trial. This was one of the largest randomized studies, involving a total of 413 patients with PC receiving either adjuvant CT or CRT, where postoperative CRT showed no benefit and even slightly reduced OS compared to patients who received CT: 15.5 months, hazard ratio [HR] 1.18 (95%CI 0.90-1.55), vs. 19.7 months, HR 0.66 (95%CI 0.52-0.83) [17]. Similar findings were reported in a study by Neoptolemos *et al*, in which 292 patients with resectable adenocarcinoma were assigned to different treatment groups; this study found that adjuvant CT had better OS compared to adjuvant CRT: 20.1 months (95%CI 16.5-22.7) vs. 15.9 months (95%CI 13.7-19.9) [18]. In summary, opinions regarding the use of RT after surgery remain divided. While statistical significance was not consistently reached, the overall trend across most trials—including the two largest studies, ESPAC-1 and the more recent RTOG 0848—favored adjuvant CT alone over CRT in terms of OS, whereas CRT showed some benefit in LRR and DFS. These discordant results, rather than indicating true equivalence, underscore the ongoing uncertainty regarding the role of adjuvant RT (Table 1).

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Table 1 Adjuvant chemoradiotherapy vs. adjuvant chemotherapy alone

Study [ref.]	Arm	N	OS, months	DFS, months	LRR, %
Van Laethem <i>et al</i> [14]	CRT	36	24.3 (95%CI 20.5-∞)	11.8 (95%CI 10.1-19.3)	11
	CT	42	24.4 (95%CI 21.5-∞)	10.9 (95%CI 8.3-16)	24
Neoptolemos <i>et al</i> [17] (ESPAC-1)	CRT	175	15.5, HR 1.18 (95%CI 0.90-1.55)	NA	NA
	CT	238	19.7, HR 0.66 (95%CI 0.52-0.83)	NA	NA
Neoptolemos <i>et al</i> [18]	CRT	145	15.9 (95%CI 13.7-19.9)	NA	NA
	CT	147	20.1 (95%CI 16.5-22.7)	NA	NA
Klinkenbijl <i>et al</i> [16]	CRT	104	24.5 (P=0.208)	NA	34
Abrams <i>et al</i> [15] (RTOG 0848)	CRT	180	27 (95%CI 25-32)	16 (95%CI 12-20)	NA
	CT	174	31 (95%CI 25-38)	12 (95%CI 9-18)	NA

N, Number of patients; mo, months; OS, overall survival; DFS, disease-free survival; CRT, chemoradiotherapy; CT, chemotherapy; LRR, locoregional recurrence; NA, not available; HR, hazard ratio; CI, confidence interval

Neoadjuvant RT

Surgical resection followed by 6 months of adjuvant therapy remains the standard treatment for resectable pancreatic tumors [13]. However, neoadjuvant therapy combining the FOLFIRINOX regimen with CRT based on fluorouracil is gaining ground as a promising approach and may eventually replace adjuvant CT as the treatment of choice, especially in resectable and borderline resectable cases [13].

The phase III PREOPANC trial provided important evidence supporting this trend. In this study, involving 246 patients with resectable or borderline resectable PC, the group receiving neoadjuvant CRT showed significantly higher R0 resection rates—71% vs. 40%, OR 3.61 (95%CI 1.87-6.97)—as well as better DFS—8.1 vs. 7.7 months, HR 0.73 (95%CI 0.55-0.96)—while OS showed a trend toward improvement—16 vs. 14.3 months, HR 0.78 (95%CI 0.58–1.05)—although this did not reach statistical significance, compared to the group that proceeded directly to surgery followed by adjuvant gemcitabine CT [7]. Notably, the long-term follow-up of the PREOPANC trial (median follow-up 59 months) subsequently reported a statistically significant OS benefit for neoadjuvant CRT (15.7 months vs. 14.3 months, HR 0.73; P=0.025), in contrast to the non-significant trend seen at initial reporting [29].

Similar results have been reported in other clinical trials. In the study by Jang *et al*, patients with borderline resectable PC who received neoadjuvant CRT before surgery had higher R0 resection rates (51.8% vs. 26.1%, P=0.004) and better OS—21 vs. 12 months, HR 1.495 (95%CI 0.66-3.36)—compared to those who received only adjuvant CT, though the difference was not statistically significant [19]. Comparable findings of better OS and R0 resection rates with neoadjuvant CRT, though again not statistically significant, were reported by Golcher *et al* (OS 17.4 vs. 14.4, P=0.96; R0 resection rate 52% vs. 48%, P=0.81) and Fujii *et al*: OS 29.1 vs. 13.1, HR 0.323 (95%CI 0.157-0.663) and R0 resection rate 100% vs. 40% (P<0.001).

These latter studies included patients with resectable and borderline resectable PC, respectively [20,21]. In addition to this, a prospective randomized controlled trial by Casadei *et al* was in favor of CRT in the preoperative setting, showing a numerical benefit in both OS and achievement of clear surgical margins in patients with resectable disease, though this was not statistically significant: OS 22.4 (95%CI 10.2-34.6) vs. 19.5 months (95%CI 7.5-31.5); R0 resection rate 38.9% vs. 25%, (P=0.489) [22]. Similarly, in the ESPAC5 trial by Ghaneh *et al*, among the various examined arms, a benefit was shown in R0 resection, although not statistically significant, as well as in 1-year OS in the neoadjuvant CRT arm in comparison to immediate surgery arm in borderline resectable cases: R0 resection rate 37% vs. 14% (P=0.49) 1-year OS 60% vs. 39% (95%CI 24-61%) (P=0.0028) [23].

Conversely, a retrospective cohort study by Janssen *et al*, investigating patients with borderline resectable disease, emphasized the advantages of CT alone over CRT in terms of OS, although the difference was not always statistically significant—32.8 (95%CI 25.3-42) vs. 26.2 months, (95%CI 24-38.4)—and LRR (10% vs. 20%). In addition to this, especially in the management of locally advanced disease, data seem not to favor the use of RT. More specifically, the randomized LAP07 trial emphasized the advantages of CT alone over CRT in terms of OS, although the difference was not always statistically significant: 16.5 (95%CI 14.5-18.5) vs. 15.2 months (95%CI 13.9-17.3). However, CRT was superior in terms of local control (LC) [24,25].

Overall, neoadjuvant CRT appears to offer some benefits in terms of both extending survival and improving surgical outcomes, especially in resectable and borderline resectable patients – although this benefit was not confirmed in the largest borderline-resectable cohort (Janssen *et al*) or in locally advanced disease (LAP07) (Table 2). In this context, it is important to note that many of the older studies included in this review used 3D conformal RT techniques. These earlier approaches may be associated with higher toxicity and less precise LC compared with modern techniques such

Table 2 Neoadjuvant chemoradiotherapy vs. adjuvant/upfront-surgery comparators

Study [ref.]	Population	Arm	N	OS, months	DFS, months	LRR, %	R0 resection, %
Versteijne <i>et al</i> [7,29] (PREOPANC)	Resectable & borderline resectable	Neoadj. CRT	119	15.7, HR 0.73; P=0.025	8.1, HR 0.73 (95%CI 0.55-0.96)	NA	71, OR 3.61 (95%CI 1.87-6.97)
		Upfront surgery	127	14.3, HR 0.73; P=0.025	7.7, HR 0.73 (95%CI 0.55-0.96)	NA	40, OR 3.61 (95%CI 1.87-6.97)
Jang <i>et al</i> [19]	Borderline resectable	Neoadj. CRT	27	21, HR 1.495 (95%CI 0.66-3.36)	NA	35.3	51.8 (P=0.004)
		Upfront surgery	23	12, HR 1.495 (95%CI 0.66-3.36)	NA	27.8	26.1 (P=0.004)
Golcher <i>et al</i> [20]	Resectable	Neoadj. CRT	29	17.4 (P=0.96)	NA	NA	52 (P=0.81)
		Upfront surgery	33	14.4 (P=0.96)	NA	NA	48 (P=0.81)
Fujii <i>et al</i> [21]	Borderline resectable	Neoadj. CRT	21	29.1, HR 0.323 (95%CI 0.157-0.663)	NA	NA	100 (P<0.001)
		Upfront surgery	71	13.1, HR 0.323 (95%CI 0.157-0.663)	NA	NA	40 (P<0.001)
Hammel <i>et al</i> [24] (LAP07)	Locally advanced	Neoadj. CRT	133	15.2 (95%CI 13.9-17.3)	NA	32 (P=0.04)	NA
		Chemotherapy alone	136	16.5 (95%CI 14.5-18.5)	NA	46 (P=0.04)	NA
Janssen <i>et al</i> [25] (TAPS)	Borderline resectable	Neoadj. CRT	150	26.2 (95%CI 24-38.4)	NA	20	70.6 (P=0.51)
		Chemotherapy alone	150	32.8 (95%CI 25.3-42)	NA	10	64.8 (P=0.51)
Casadei <i>et al</i> [22]	Resectable	Neoadj. CRT	18	22.4 (95%CI 10.2-34.6)	NA	NA	38.9 (P=0.489)
		Upfront surgery	20	19.5 (95%CI 7.5-31.5)	NA	NA	25 (P=0.489)
Ghaneh <i>et al</i> [23] (ESPAC5)	Borderline resectable	Neoadj. CRT	17	60% (1-yr OS)†	NA	NA	37 (P=0.49)
		Upfront surgery	21	39% (1-yr OS)†, 95%CI 24-61 (P=0.0028)	NA	NA	14 (P=0.49)

† OS for Ghaneh *et al* reported as 1-year overall survival rate (%), not median OS in months as in the other studies in this table

Neoadj. CRT, neoadjuvant chemoradiotherapy; OS, overall survival; DFS, disease free survival; LRR, locoregional recurrence; mo, months; NA, not available; N, number of patients; HR, hazard ratio; CI, confidence interval; OR, odds ratio

as intensity-modulated radiotherapy (IMRT) and stereotactic body radiation therapy (SBRT). Therefore, while historical data provide valuable insights, their applicability to current clinical practice should be interpreted with caution, particularly with regard to expected toxicity and local control outcomes. Nevertheless, more research and data will be necessary if we are to encourage the addition of RT as a standard approach in the treatment regimen.

Modern radiotherapy techniques: SBRT and IMRT

While the trials discussed above largely relied on 3D-conformal RT, several more recent studies have specifically compared modern techniques, IMRT and SBRT, with conventional 3D-CRT in PC. In a retrospective single-

institution study of 104 patients with borderline resectable/potentially resectable or locally advanced PC, Abi Jaoude *et al* reported a numerically longer median OS with neoadjuvant SBRT compared with 3D-CRT/IMRT (29.6 vs 24.1 months), although this difference did not reach statistical significance on multivariable analysis (adjusted HR 0.5, 95%CI 0.2-1.3, P=0.18); Progression-free survival (PFS) was similarly comparable between groups [26]. In the multicenter, matched case-control PAULA-1 study of patients with locally advanced PC, no statistically significant differences were found between SBRT and conventionally fractionated CRT in terms of local control, distant metastasis-free survival, PFS, OS, or acute/late toxicity, supporting the non-inferiority of the more hypofractionated SBRT approach [27]. Conversely, a single-center comparison using an isotoxic high-dose SBRT protocol reported a significant OS benefit over conventional CRT

(median OS 22.5 vs 15.9 months, HR 0.39, 95%CI 0.18-0.83, $P=0.014$), along with improved PFS and 1-year local control, suggesting that dose-escalated SBRT regimens may offer an advantage over standard fractionation [28].

Taken together, these data suggest that SBRT can achieve outcomes at least comparable to, and in some dose-escalated protocols potentially better than, conventional 3D-CRT/IMRT, while offering the practical advantage of a substantially shorter treatment course (typically 3-5 fractions vs 25-30 fractions) and, in several series, a similar or improved toxicity profile. However, these findings derive exclusively from retrospective or matched cohort studies; to date, no phase III randomized trial has directly compared SBRT with conventional fractionation in PC, and SBRT is therefore not yet established as a standard of care over IMRT/3D-CRT in this setting.

Discussion

PC is still a therapeutic challenge because of its aggressive biology, late presenting symptoms and its resistance to common treatments. Although extensive research and changes in systemic therapies have been achieved, OS rates still remain at low levels, and the disease remains among the leading causes of cancer-related mortality worldwide [2]. Although surgical resection remains the only potentially curative treatment available, it is a fact that the majority of patients present with unresectable, or even metastatic disease at diagnosis, and even in those who remain candidates for surgery, the risk of both local and distant recurrence is significant [1]. Thus, it is easily understood that multimodal approaches in the perioperative setting are of great importance in order to improve outcomes when dealing with this disease.

Concerning RT, its role in PC management has changed over the years. RT was mainly used in adjuvant or palliative setting, but as large, randomized trials – from the older ESPAC-1 study to the more recent NRG Oncology/RTOG 0848 trial – have consistently failed to demonstrate a clear survival benefit for CRT over CT alone in the adjuvant setting. The discrepancies may be attributed to the different radiation techniques used, the criteria for patient selection, as well as the combination of RT with systemic therapy in the treatment regimen [17]. However, attention is nowadays once again turning to the use of RT, since various advances have been made: these include new radiation delivery techniques, such as IMRT and SBRT, as well as growing evidence supporting neoadjuvant strategies. Notably, neoadjuvant CRT can be potentially beneficial in increasing R0 resection rates and reducing LRR, as well as in improving both OS and DFS, mainly in patients with resectable and borderline resectable disease [7,19-23]. However, this benefit is not universal: the TAPS study by Janssen

, also conducted in the borderline resectable setting, found the opposite pattern, with CT alone outperforming neoadjuvant CRT in terms of both OS and LRR [25]. The studies detailed in Table 2 underscore these benefits, although the results have not always reached statistical significance in larger meta-analyses.

The rationale for neoadjuvant RT is multifold. Preoperative

therapy can target micrometastatic disease early, potentially downstage tumors, and improve the likelihood of achieving clear surgical margins. In addition, patients are often better able to tolerate aggressive multimodal therapy before rather than after major pancreatic surgery. Despite these theoretical advantages, some studies, including Janssen *et al* and the LAP07 trial, have highlighted the ongoing debate regarding the incremental benefit of the addition of RT preoperatively, when compared to adjuvant CT alone, particularly in terms of OS (Table 2) [24,25]. Adjuvant RT, on the other hand, has been less consistently associated with meaningful improvements in patient outcomes. Although the literature, including recent data from RTOG 0848, does not show consistent survival benefit from postoperative RT [14-18], and in several trials adjuvant CT alone numerically outperformed CRT, preoperative RT appears promising, with several studies reporting improvements in OS, LC, and surgical outcomes such as achieving R0 resection; however, more research is needed to confirm these results [7,19-23].

Although neoadjuvant CRT is associated with better surgical and survival outcomes, treatment-related toxicity remains an important consideration. In the studies included in this review, acute toxicities were generally manageable, with gastrointestinal side effects being the most common. More specifically, the PREOPANC trial showed low levels of perioperative morbidity, while Fujii and Jang *et al* reported that severe side-effects with the use of neoadjuvant CRT were very few [7,19,21]. These findings suggest that neoadjuvant CRT is generally tolerable in both resectable and borderline resectable PC; at the same time they stress the importance of balancing adverse events of the treatments with efficacy in disease control.

Different parameters used in all these trials including radiation dosing and techniques, patient selection, while more generally, the lack of a standardized protocol makes it very difficult to draw safe conclusions. On the one hand, reduced LRR rates have been noted, but on the other, these are not always accompanied by benefits in overall survival, not to mention that treatment-related toxicity is always a consideration [15]. However, the emergence of new RT techniques, such as SBRT, has given hope for a treatment with better LC and less toxicity [26-28]. The debate as to whether RT is beneficial in PC management can be also seen in the difference between the ASCO and ESMO recommendations, with ASCO supporting the use of RT whereas ESMO has more reservations. ASCO gives emphasis to overall survival, as well as the use of systemic treatment, while ESMO gives priority to LC, especially in borderline resectable disease. However, despite these differences, it is clear that the need for personalized treatment decisions is of vital importance [13].

Beyond radiation technique, several modern therapeutic and methodological aspects relevant to RT in PC remain unaddressed in the current review. Regarding the integration of immunotherapy, RT is hypothesized to potentiate antitumor immunity through induction of immunogenic cell death. In a single-arm phase II trial (NCT02648282), the combination of a GM-CSF-secreting allogeneic pancreatic cancer vaccine (GVAX), pembrolizumab, and SBRT following induction chemotherapy in 58 patients with locally advanced PC yielded

a median distant metastasis-free survival of 9.8 months, with 44.4% of patients undergoing resection and markedly better OS in resected versus unresected patients (29.7 vs 12.1 months) [30]. Earlier phase I/II trials combining durvalumab ± tremelimumab with SBRT reported only modest clinical benefit in unselected patients, indicating that RT-immunotherapy combinations in PC remain investigational and have not yet demonstrated a survival benefit in randomized comparisons [31]. Regarding molecular profiling and patient selection, tissue biomarkers such as SMAD4 and Krüppel-like factor 10 (KLF10)—lost in approximately two-thirds of pancreatic ductal adenocarcinoma (PDAC) cases and associated with radioresistance and early distant metastasis—have been proposed to help identify patients most likely to benefit from local RT; in a post hoc analysis of a randomized phase III trial, high KLF10 or SMAD4 expression predicted clinical benefit from adjuvant CRT [32,33]. Such biomarker-guided selection could, in principle, spare patients unlikely to benefit from the added toxicity of RT, but remains investigational and is not incorporated into any of the trials summarized in Tables 1 and 2. Targeted therapies have so far been explored mainly in the systemic, non-RT setting (e.g., PARP inhibitors in patients with homologous recombination deficiency), and prospective data on their combination with RT specifically in PC are still lacking. Finally, quality-of-life (QoL) outcomes were inconsistently reported across the studies reviewed here, and most were not designed or powered to assess QoL as a primary endpoint; more recent trials, such as PREOPANC-2, have begun to incorporate QoL as a prespecified secondary endpoint, reflecting a broader shift toward patient-reported outcomes in trial design [34]. Future studies of RT in PC should systematically incorporate QoL assessment alongside biomarker-based patient selection and RT-immunotherapy combination strategies, to better define the optimal role of RT within an increasingly personalized treatment landscape.

This study's results suggest that the greatest benefit of RT may be noticed mainly in the neoadjuvant setting, particularly when it is given in combination with more advanced CT regimens. Nevertheless, it is of great importance to realize the limitations of the current literature, including inconsistency in treatment approaches, small sample sizes and patient selection criteria, as well as the large number of retrospective analyses. In the future, the focus should be directed to large randomized controlled trials with standardized treatment protocols and carefully selected patients, so as to clarify the role of RT, especially in the neoadjuvant setting, its integration with systemic therapies and the minimization of toxicity.

In summary, although adjuvant RT has not shown consistent benefits with respect to survival rates, neoadjuvant RT, especially when combined with systemic treatment, is much more promising for improving surgical and oncologic outcomes in general when treating PC. Further research is necessary in order to design new and better strategies, as well as to clarify the specific role of every modality during the management of the disease, thus leading to individualized and much more encouraging approaches in within the PC treatment landscape.

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