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Chemoradiation in Pancreatic Adenocarcinoma: A Literature Review

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ABSTRACT

Adenocarcinoma of the exocrine pancreas has an annual incidence of 7,400 cases in the U.K. In comparison with other common cancers of solid organs, namely, breast, colorectal, and prostate cancer, pancreatic cancer has a high morbidity and mortality. Radical resection is possible in only 15%–20% of patients, and only 3%–4% of all patients presenting with this condition achieve long-term control and cure. Various strategies in the form of neoadjuvant and adjuvant treatment have been employed over the years to improve outcome, with limited success. Systemic chemotherapy remains the gold standard in the metastatic setting in good performance status patients, and adjuvant chemotherapy after resection of localized and locally advanced cancer has been found to improve outcome. The role of radiotherapy, however, remains controversial and is an area that merits further investigation in well-conducted multicenter trials at various stages of the disease in combination with systemic agents and exploiting recent advances in the delivery of radiotherapy. In this article, we review the published literature on the use of chemoradiation as a modality in various stages of pancreatic adenocarcinoma and highlight areas that future trials in this field should target for a way forward in this malignancy. ***The Oncologist*** 2010;15:259–269

INTRODUCTION

Pancreatic cancer is the tenth most common cancer in the western world and has become the fourth leading cause of cancer-related death. In the U.S., for 2009, an expected incidence of 42,470 new cases was accompanied by 35,240 pancreatic cancer–related deaths for a mortality rate of 82.9% [1]. In the U.K., an annual incidence of 7,400 cases was accompanied by a mortality rate of 98% [2]. These figures underline the paucity of effective treatments available. Apart from the obvious need for new breakthroughs, it is noteworthy that there remains a significant amount of uncertainty and controversy over the optimal use of even the conventional modalities at our disposal, despite years of research.

Here, we comprehensively review the published literature on the role of chemoradiation (CRT) as a strategy at

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Table 1. Neoadjuvant treatment of pancreatic adenocarcinoma

Study	*n*	Neoadjuvant treatment	Resection rate (%)	Median survival, all patients (mos)	Median survival, resected patients (mos)
Evans et al. (2008) [3]	86	EBRT with Gem	74	22.7	34
Varadachary et al. (2008) [4]	90	Cis + Gem followed by EBRT with Gem	66	17.4	31
Le Scodan et al. (2008) [5]	41	EBRT with Cis + 5-FU	63	9.4	NR
Takai et al. (2008) [6]	32	EBRT with Cis + 5-FU or EBRT with Gem	75	NR	20.5
Moutardier et al. (2004) [7]	39	EBRT with 5-FU	59	NR	26.6
Joensuu et al. (2004) [8]	34	EBRT with Gem	60	NR	25
Calvo et al. (2004) [9]	15	EBRT with Tegafur	60	17	23
Aristu et al. (2003) [10]	47	EBRT with Cis + 5-FU + taxanes	19	10	23
Wilkowski et al. (2003) [11]	33	EBRT with Cis + Gem	48	10	11.7
Mehta et al. (2001) [12]	15	EBRT with 5-FU	60	NR	30
Snady et al. (2000) [13]	68	EBRT with Cis + 5-FU + STZ	29	23.6	32.3
Wanebo et al. (2000) [14]	14	EBRT with Cis + 5-FU	64	9	19
White et al. (2001) [15]	111	EBRT with 5-Fu + MMC + Cis	35	NR	NR
Hoffman et al. (1998) [16]	53	EBRT with 5-FU + MMC	45	9.7	15.7
Spitz et al. (1997) [17]	91	EBRT with 5-FU with or without IORT	45	19	19.2
Staley et al. (1996) [18]	39	EBRT + IORT with 5-FU	100	19	NA
Coia et al. (1994) [19]	27	EBRT with 5-FU/MMC	48	3-yr survival, 19%	3-yr survival, 43%
Ishikawa et al. (1994) [20]	23	EBRT alone	74	NR	NR
Evans et al. (1992) [21]	28	EBRT with 5-FU with or without IORT	61	NR	NR

Abbreviations: 5-FU, 5-fluorouracil; Cis, cisplatin; EBRT, external-beam radiotherapy; Gem, gemcitabine; IORT, intraoperative radiotherapy; MMC, mitomycin C; NA, not applicable; NR, not recorded; STZ, streptozocin.

several stages of the disease, highlighting questions, research into which may optimize outcomes.

Neoadjuvant (Preoperative) CRT

Preoperative treatment of resectable or borderline resectable cancer has several attractive benefits (Table 1) [3–21]. First, any partial response to treatment reduces the tumor volume, potentially increasing the likelihood of an R0 resection. Second, the resected tumor can serve as its own biological "marker" of treatment response. Third, the undisturbed tumor microenvironment permitting better oxygenation of tumor tissue may enhance treatment effects. Finally, multimodality therapy is likely to be better tolerated prior to, rather than after, a radical pancreaticoduodenectomy [22]. Patients who develop unresectable or metastatic disease during the induction treatment phase are also spared the morbidity of such a radical procedure. The main drawbacks are the comparatively low response rate to multimodality treatments in advanced pancreatic cancer (APC) and the potentially higher complication rate, which could result in the delay of potentially curative surgery.

CRT in Resectable Pancreatic Cancer

In a recent phase II study [3], preoperative radiotherapy was given to 86 patients at a dose of 30 Gy in 10 fractions over 2 weeks with 7 weekly gemcitabine doses at 400 mg/m^2. Seventy-three patients (85%) went to surgery and 13 patients were found to have either progressive disease or a deterioration in performance status. At surgery, nine patients were found to have metastatic disease and 64 patients (74%) underwent radical surgery. The median survival times and 5-year overall survival rates in the whole population, resected patients, and unresectable patients were

22.7 months and 27%, 34 months and 36%, and 7 months and 0%, respectively. The same group conducted a further study [4] in which similar gemcitabine-based CRT was preceded by induction chemotherapy with four cycles of cisplatin and gemcitabine as 2-weekly schedules in a cohort of 90 patients. Although 88% of patients completed the whole course of treatment and 66% underwent the planned R0 resection, the median survival time was not improved upon (Table 1).

CRT in "Borderline Resectable" Pancreatic Cancer

The definition of "borderline resectable" is an evolving entity not founded on evidence-based criteria that have been shown to select similar patients in a validated prospective sense. Existing data, therefore, have to be viewed with caution especially because they span almost three decades, during which surgical and staging techniques have progressed substantially. Tumors that are encasing the superior mesenteric artery (SMA), celiac artery (CA), aorta, or inferior vena cava are considered unresectable. In addition, tumors with encasement of the superior mesenteric vein (SMV) or portal vein (PV) $>180°$ over an extended segment are also considered unresectable. Tumors in which the PV and SMV are patent and there is a clear fat plane between the tumor and SMA and CA are deemed primarily resectable [23]. Borderline resectable patients are, therefore, those that fall in between these two groups. They often have abutment or encasement of the PV, SMV, or SMA over $\leq 180°$ or short-segment (≤ 1.5 cm) encasement of the SMV or PV, which is amenable to partial resection of the vein and reconstruction [24, 25]. These patients are, however, more likely to have R1 or R2 resections, and hence a neoadjuvant strategy could be employed to increase the prospect of an R0 resection.

Radiotherapy

One of the earlier studies in this group of patients employed external-beam radiotherapy (EBRT) alone [26]. Seventeen patients were treated with radiation at doses of 40–46 Gy over 4–5 weeks. The response rate was 29% and six patients (35%) became resectable. Only two patients (12%) had an R0 resection, and they survived for 5 years. To circumvent the dose limitations of EBRT imposed by the need to limit the dose to normal organs, strategies have been developed to deliver a higher dose to the tumor, such as intraoperative radiation therapy (IORT) and brachytherapy. Roldan et al. [27] employed a combination of EBRT and IORT versus EBRT alone in unresectable cancers. Although the local control rate at 2 years was significantly better for the combination arm (66% versus 20%; $p < .0005$), this did not translate into a survival benefit. A similar lack of survival benefit but higher toxicity was reported by the Memorial Sloan-Kettering Cancer Center group with ^{103}Pd brachytherapy in unresectable patients [28].

Combining Chemotherapy with Radiotherapy

Fluoropyrimidines. Because escalation of the radiation dose in locally APC did not translate into longer survival, focus shifted to employing multiagent chemotherapy with conventional radiation, especially because a small randomized trial (RCT) from the Gastrointestinal Tumor Study Group (GITSG) [29] had demonstrated the superiority of 5-fluorouracil (5-FU)–based CRT over radiotherapy alone in locally advanced unresectable disease (discussed in detail below). Hoffman et al. [30] performed pilot studies with 50.4 Gy of radiation with a combination of 5-FU (1,000 mg/m^2 per day continuous infusion on days 2–5 and days 29–32) along with mitomycin-C (10 mg/m^2). In 34 patients treated with this regimen, 25 went for surgery. Eleven had a pancreaticoduodenectomy and 10 had an R0 resection, with a 45-month median survival duration. Based on these promising results, a phase II study was set up by the Eastern Cooperative Oncology Group, which included 53 patients. The resection rates were similar to those in the pilot phase, but the median survival time was shorter [16].

Gemcitabine. The clinical primacy of gemcitabine [31] in APC has led to preclinical studies with human pancreatic and colon cancer cell lines that have shown its potency as a powerful radiosensitizer [32, 33]. Phase I trials of gemcitabine with 50.4 Gy of radiation given in 1.8-Gy fractions established dose-limiting hematologic and gastrointestinal toxicities at a dose of 700 mg/m^2 weekly. Responses were observed at doses >500 mg/m^2, but late duodenal strictures were noted [34] at doses >400 mg/m^2. Crane et al. [35] analyzed a retrospective series of 53 patients with unresectable pancreatic cancer treated with weekly gemcitabine doses of 250–300 mg/m^2 for 7 weeks with concurrent radiation of 30–33 Gy in 10 fractions versus 61 patients treated with concurrent infusional 5-FU and radiation. The radiotherapy volumes were large and included at-risk uninvolved lymph node stations at the porta, celiac axis, and superior mesenteric vessels. The toxicity rate in the gemcitabine arm was significantly higher (23% versus 2%). Resectability was achieved in 9% of patients in the gemcitabine group, as opposed to 2% of patients in the 5-FU arm. There was, however, no significant difference in the median survival times (11 months versus 9 months). The safe weekly dose of gemcitabine, therefore, needs to remain <400 mg/m^2 when used with conventional radia-

Table 2. Adjuvant chemoradiation in pancreatic adenocarcinoma

Study	*n*	Treatment	Median survival (mos)	Study conclusion
GITSG (1985) [42]	21 22	5-Fu + EBRT (sc) + 5-FU Obs	21 10.9	Significantly longer median survival
EORTC (1999) [43]	60 54	5-FU + EBRT (sc) Obs	17.1 12.6	Nonsignificantly longer median survival
ESPAC-1 (2001) [44]	145	CRT	15.8	Nonsignificantly shorter survival with CRT, significantly longer with CT
Pooled analysis	144	No CRT	17.8	
	147	CT	20.1	
	142	No CT	15.5	
ESPAC-1 (2004) [45],	69	Obs	16.9	Same conclusion
2 × 2 subanalysis	75	CT	21.6	
	73	CRT (sc)	13.9	
	72	CRT (sc) + CT	14.2	
RTOG 97-04 (2006) [46]	187 194	5-FU + CRT + 5-FU Gem + CRT + Gem	16.9 20.6	Significantly longer median survival for pancreatic head carcinoma
Mornex et al. (2007) [47], phase II	54	Induction CT: Gem + Ox followed by Gem + EBRT	1-yr survival, 71%	
Wang et al. (2009) [48], retrospective	18	CRT with 5-FU, Gem, Cape	21.6	

Abbreviations: 5-FU, 5-fluorouracil; Cape, capecitabine; CRT, chemoradiotherapy; CT, chemotherapy; EBRT, external-beam radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; Gem, gemcitabine; GITSG, Gastrointestinal Tumor Study Group; Obs, observation; Ox, oxaliplatin; RTOG, Radiation Therapy Oncology Group; sc, split course.

tion, which is a suboptimal dose for systemic disease control. Subsequent studies with a smaller radiotherapy volume to include the primary tumor and involved nodes only have successfully used full doses of gemcitabine, at 1,000 mg/m^2 weekly, with acceptable toxicity. Encouragingly, locoregional nodal failure outside the radiation volume was rare [36]. Gemcitabine combinations with other chemotherapy agents like cisplatin [11] and paclitaxel [37] given concurrently with radiation have resulted in R0 resections in up to 30% of patients with acceptable toxicity and no difference in the postsurgical complication rate.

A recurrent theme of neoadjuvant CRT studies is that 10%–30% of patients experience disease progression during preoperative treatment, which in turn has led to the suggestion that a period of induction chemotherapy could potentially superselect patients suitable to undergo CRT. A retrospective analysis of 323 patients with locally APC at the MD Anderson Cancer Center showed a longer median overall survival time (11 months versus 8.5 months; $p < .001$) in patients receiving a median of 2.5 months of gemcitabine-based upfront combination chemotherapy than in patients receiving CRT alone [38]. Fogelman et al. [39], at Columbia University, used three cycles of gemcitabine, docetaxel, and capecitabine over a 9-week period followed by CRT in a series of 14 patients with locally APC. Only one patient progressed in the induction phase and eight patients (57%) became resectable, and all had R0 resections.

Adjuvant CRT in Pancreatic Adenocarcinoma

The relatively high rate of both locoregional and distant recurrence following surgery for pancreatic cancer makes a strong case for effective adjuvant therapy [40, 41]. RCTs of CRT are limited, and the available data are boosted by some phase II and single-institution studies. They are summarized in Table 2 [42–48].

The first prospective, multicenter trial of CRT versus observation alone was performed by the GITSG [42]. Resected pancreatic cancer patients with R0 margins were assigned to receive either split-course radiotherapy over 6 weeks with a 2-week gap in between, with concurrent 5-FU on week 1 and week 5 followed by maintenance 5-FU for 2 years or until progression or no active treatment. In 1974–1982, only 49 patients were randomized. At an interim anal-

ysis, patients in the CRT arm had a significantly longer median survival time (21 months versus 11 months). A further 32 patients were added to the treatment cohort in a nonrandomized fashion following the interim analysis, and the final analysis showed a median survival time of 18 months with 2- and 5-year survival rates of 46% and 17%, respectively [49]. Following that trial, adjuvant CRT became the standard of care in the U.S. The study, however, has been criticized in other quarters for its poor accrual, low statistical power, suboptimal radiotherapy schedule, lack of radiotherapy quality assurance, and noncompliance with maintenance chemotherapy in 75% of patients.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a similar study of CRT versus observation in Europe between 1987 and 1995 [43]. The radiation schedule was similar but the 5-FU was delivered as an infusion and there was no maintenance chemotherapy. It included pancreatic and periampullary cancers and both R0 and R1 resections, but did not prestratify for primary site or resection margin status. The trial did not show any significant benefit in terms overall survival in the whole population or in patients with pancreatic head cancer. The statistical analysis of that trial has been criticized, and it could have given a significant result if the design was more appropriate [50].

The European Study Group for Pancreatic Cancer (ESPAC) conducted the largest phase III RCT in this setting between 1994 and 2000. Five hundred forty-one patients were randomized to: (a) chemotherapy versus observation, (b) CRT versus observation, and (c) a 2×2 factorial design of observation versus chemotherapy versus CRT versus CRT plus maintenance chemotherapy. The radiotherapy schedule was similar to that used in the EORTC study and the chemotherapy agent was bolus 5-FU. Both R0 and R1 patients were included. At an early intent-to-treat analysis at 10 months, there was a statistically significant survival benefit for patients receiving chemotherapy (median survival time, 19.7 months versus 14 months; $p = .0005$) but no benefit for patients treated with CRT (median survival time, 15.5 months versus 16.1 months; $p = .24$) [44]. The mature results of ESPAC-1 [45] with analysis restricted to the 2×2 arm of the study showed a significant 5-year survival benefit for chemotherapy versus no chemotherapy (21% versus 8%; $p = .009$), but no benefit for CRT versus no CRT (10% versus 20%; $p = .05$). The conclusion from that trial was that adjuvant chemotherapy significantly improved survival, whereas CRT had a detrimental effect on survival because it delayed systemic chemotherapy. The results generated substantial controversy and the trial was criticized because of a suboptimal radiotherapy schedule, lack of central radiotherapy quality assurance, wide variation in the radiotherapy doses employed, in violation of the protocol, and the allowance of background therapy with chemotherapy or CRT prior to randomization, which could all potentially influence the final analysis.

A subsequent meta-analysis of adjuvant therapy by the Pancreatic Cancer Meta-analysis Group (PCMG) in 2005 looked at individual patient data from five randomized studies of chemotherapy and CRT along with previously unpublished results of the ESPAC-1 study [51]. They concluded that: (a) chemotherapy alone reduced the risk for death by 25% (hazard ratio [HR], 0.75; confidence interval [CI], 0.64–0.90; stratified $p = .001$), (b) CRT had no significant impact (HR, 1.09; CI, 0.89–1.32; stratified $p = .43$), and (c) subgroup analyses showed CRT as more effective than chemotherapy in patients with R1 resections. However, that meta-analysis was heavily influenced by ESPAC-1 data.

A further PCMG meta-analysis looking at the influence of resection margin status and treatment on survival suggested that resection margin involvement was not a significant factor for survival (HR, 1.10; CI, 0.94–1.29; $p = .24$) [52]. The 2- and 5-year survival rates were 33% and 16% for R0 and 29% and 15% for R1 patients, respectively. CRT in R1 patients resulted in a 28% lower risk for death (HR, 0.72; CI, 0.47–1.10) and there was a 19% higher risk for death in R0 patients (HR, 1.19; CI, 0.95–1.49). Chemotherapy, on the other hand, resulted in a 4% higher risk for death in R1 patients (HR, 1.04; CI, 0.78–1.40) and a 35% lower risk for death in R0 patients (HR, 0.65; CI, 0.53–0.80).

The latest trial of CRT (Radiation Therapy Oncology Group trial 97–04) was conducted between 1998 and 2002 [46]. The analysis was conducted on 442 of 538 patients randomized between 3 weeks before and 3 months after CRT with 5-FU and 3 weeks before and 3 months after CRT with gemcitabine. The CRT part in both arms delivered 50.4 Gy in 28 fractions, with concurrent 5-FU as a 250-mg/m^2 per day continuous infusion. Only 5% of the patients had an unacceptable deviation from protocol. Patients were stratified for surgical margin, tumor diameter, and nodal status. At the final analysis, 381 patients with pancreatic head tumors only had a significant benefit from gemcitabine in terms of the median survival time and 3-year survival rate (20.6 months versus 16.9 months and 32% versus 21%, respectively). There was no significant difference when tumors of the body and tail were included as well.

The ESPAC group recently reported data from ESPAC-3 in their latest abstract, showing equivalence of gemcitabine and 5-FU plus leucovorin as adjuvant therapy, with a better safety profile in favor of gemcitabine [53]. ESPAC-4 has now been launched comparing gemcitabine with gemcitabine plus capecitabine in the adjuvant setting

because the assessment of the ESPAC group is that CRT offers no benefit in this setting. Nevertheless, the issue of the optimal treatment of patients with positive resection margins is still far from clear.

In light of the above findings, it is difficult to formulate a "one-size-fits-all" strategy in the adjuvant setting for pancreatic cancer. Good quality trials are still needed, targeting surgical subgroups, especially because more aggressive surgery of "borderline" cases will lead to a greater number of R1 resections.

The advent of biologicals is interesting, but it is as yet difficult to see where they fit in the combination radiotherapy and adjuvant settings, given disappointing results in APC patients to date.

CRT in Locally Advanced Nonresectable Pancreatic Adenocarcinoma

Locally advanced nonresectable pancreatic adenocarcinoma (LANPC) as an entity presents a significant dilemma to multidisciplinary teams involved in the management of pancreatic cancer. The chance for a cure is low with radiation alone. Combination with chemotherapy is logical, but it can be associated with significant toxicity.

The GITSG demonstrated the superiority of 5-FU–based CRT over radiotherapy alone in locally advanced unresectable disease [29]. The median survival time was 5.7 months in the 60-Gy radiotherapy alone arm, compared with 10 months in the arms receiving bolus 5-FU with 40 Gy and 60 Gy of radiation. That trial also raised the possibility that, with chemotherapy, a higher dose of radiation is perhaps not necessary because the 1-year survival rates in the 60-Gy arm and 40-Gy arm with concurrent 5-FU were similar. This is a significant finding in terms of keeping the total radiation dose to a minimum and thereby reducing the rate of serious adverse events. Since the publication of that trial in 1981, several single-institution and cooperative group studies have employed CRT in LANPC patients with similar median survival figures (Table 3) [29, 54–65]. The rates of grade 3 and 4 toxicities were consistently higher in the CRT arms of these trials, and when compared with trials employing chemotherapy alone CRT is likely to cause a significant dip in quality of life, at least in the short term.

With the introduction of gemcitabine, the emphasis shifted to the use of chemotherapy alone because it seemed that the survival rate achieved with this drug matched the survival rates seen in earlier trials of CRT using 5-FU. A recent French group trial [64] showed that CRT with concurrent 5-FU and cisplatin followed by maintenance gemcitabine provided a much higher toxicity rate and poorer survival rate than with induction chemotherapy alone with gemcitabine followed by maintenance gemcitabine in a group of 119 patients with LANPC. However, the dose intensities of both the chemotherapy and radiotherapy in the combined-modality arm and the use of large fields of radiation, including uninvolved nodes, are questionable as a strategy. The trial also showed a higher than expected survival duration of 14.3 months in the chemotherapy alone arm. In contrast, the Eastern Cooperative Oncology Group [65] recently reported on a trial comparing CRT with concurrent gemcitabine followed by maintenance gemcitabine with gemcitabine alone. Although the trial was stopped after only 74 of a planned 316 patients were entered as a result of slow accrual, it still showed a significant median survival advantage in favor of the radiotherapy arm. That trial employed more acceptable total doses of radiation and chemotherapy, and the radiation fields were smaller, planned using a conformal technique. As a result, the rates of grade 3 and 4 toxicities were low and these were manageable (Table 3). These data highlight the need for strict quality assurance of radiation techniques and call for the necessity of a uniform approach to radiotherapy of this sensitive anatomical area.

Techniques of Radiation Therapy Planning and Delivery

In order to reduce the toxicity associated with radiotherapy to the pancreas newer techniques have been employed which look at excluding as much normal tissue as feasible and thereby escalate the dose to influence local control and ultimately survival.

IORT

IORT has the advantage of delivering radiotherapy to the tumor/tumor bed under direct vision and reducing toxicity by shielding dose-limiting normal organs. Methods of IORT included either implantation of iodine-125 seeds or intraoperative electron beam radiotherapy (IOERT). IOERT has been the favored approach in most studies. A trial by the National Cancer Institute showed better local control with 20 Gy of IORT following surgical therapy than with observation. Several phase II studies have tried to exploit the radiobiological and anatomical advantages of IOERT (Table 4) [66–70]. A further strategy of brachytherapy used colloidal phosphorus-32 infusion in the tumor interstitial space followed by EBRT with concurrent 5-FU. All five patients treated with this technique showed local control or regression, with three patients surviving for 24 months and one patient surviving for 36 months [71]. Although most have shown better local control, survival was not shown to be superior to that seen with EBRT alone.

Table 3. Chemoradiation in locally advanced nonresectable pancreatic cancer

Study	Treatment plan	*n*	Median survival (mos)	1-Yr survival
Childs et al. (1965) [54]	35–40 Gy EBRT + saline versus 35–40 Gy EBRT + 5-FU	25	5.4 versus 7.0	11.6% versus 30.8%
Moertel et al. (1969) [55]	35–40 Gy EBRT versus 35–40 Gy EBRT + 5-FU	64	6.3 versus 10.4*	5% versus 25%
Moertel et al. (1981) [29]	40 Gy SCRT + 5-FU versus 60 Gy SCRT + 5-FU versus 60 Gy SCRT alone	194	9.6 versus 9.2 versus 5.2*	40% versus 40% versus 12%*
Hazel et al. (1981) [56]	5-FU + CCNU versus 46 Gy EBRT + 5-FU + CCNU	30	7.8 versus 7.8	
Klaassen et al. (1985) [57]	5-FU versus 40 Gy EBRT + 5-FU	91	8.2 versus 8.3	28% versus 30%
GITSG (1985) [58]	60 Gy SCRT + 5-FU versus 60 Gy SCRT + doxorubicin	157	8.4 versus 7.5	
GITSG (1988) [59]	SMF versus 54 Gy EBRT with 5-FU + maintenance SMF	42	8.0 versus 10.5	19% versus 41%*
Earle et al. (1994) [60]	40–60 Gy SCRT + 5-FU versus 40–60 Gy SCRT + hycanthone	87	7.8 versus 7.8	35% versus 28%
Mehta et al. (2001) [61]	54–60 Gy EBRT + 5-FU (PVI) versus 54–60 Gy EBRT + 5-FU (bolus)	54		34% versus 18%
Shinchi et al. (2002) [62]	50.4 Gy EBRT + 5-FU versus 5-FU	31	13.2 versus 6.4*	53.3% versus 0%*
Li et al. (2003) [63]	50.4–61.2 Gy EBRT + PVI 5-FU versus 50.4–61.2 Gy EBRT + Gem concurrent with and after EBRT	34	6.7 versus 14.5*	31% versus 56%*
FFCD/SFRO (2008) [64]	60 Gy EBRT + 5-FU + Cis (concurrent) + maintenance Gem versus Gem alone	119	8.4 versus 14.3*	32% versus 53%*
ECOG 4201 (2008) [65]	50.4 Gy EBRT + Gem (concurrent) + maintenance Gem versus Gem alone	74	11.0 versus 9.2*	

*Statistically significant.
Abbreviations: 5-FU, 5-fluorouracil; CCNU, lomustine; Cis, cisplatin; EBRT, external-beam radiotherapy; Gem, gemcitabine; SCRT, split-course radiotherapy; SMF, (streptozocin, mitomycin, 5-FU); PVI, peripheral venous infusion.

Stereotactic Radiotherapy

Stereotactic radiotherapy (SRT) aims to deliver one to five high-dose fractions to the area of gross disease, in comparison with conventional EBRT. Such an advantage could potentially be exploited by delivering SRT to the tumor only, preceded or followed by conventional radiation to the tumor volume and at-risk area. Hoyer et al. [72], in a phase II study of SRT, used 45 Gy in three fractions in a space of 5–10 days in 22 patients with LANPC. There were unacceptable acute gastrointestinal toxicities, with 4.5% of patients experiencing gastric perforation. A trial by the Stanford group [73] used a single fraction of SRT delivering 25 Gy to a limited radiation field and demonstrated an 81% local control rate. The same group studied the effect of SRT as a boost to EBRT, yielding a very impressive 94% local control rate [74]. Gastrointestinal toxicity, however, still remained a significant issue, with a 12.5% rate of late duodenal ulceration. Despite a major improvement in local control, no difference in the median survival time was noted in these studies.

Intensity-Modulated Radiotherapy

Intensity-modulated radiotherapy (IMRT) is delivered as conformal radiation but with varying intensities within each radiation field. This has the advantage of mapping the dose to a high-dose volume within the tumor and its vicinity and

Table 4. Phase II trials of IOERT in locally advanced pancreatic cancer

Study	Treatment arm	*n*	Median survival (mos)	2-yr survival (%)
Tepper et al. (1991) [66]	5-FU, 50.4 Gy EBRT, IOERT	51	9	–
Garton et al. (1993) [67]	Bolus 5-FU, 50–54 Gy EBRT, IOERT[a]	27	14.9	27
Garton et al. (1993) [67]	Bolus 5-FU, 50–54 Gy EBRT, IOERT[b]	56	10.5	6
Mohiuddin et al. (1995) [68]	Bolus 5-FU and leucovorin, 55 Gy EBRT, IOERT	49	16	22
Nishinura et al. (1997) [69]	Various chemotherapy regimens, 50–60 Gy EBRT, IOERT	31	8.2	14
Gunderson et al. (1997) [70]	Bolus 5-FU, 35–39.6 Gy EBRT, IOERT	68	13	12

[a]Preoperative chemoradiotherapy.
[b]Postoperative chemoradiotherapy.
Abbreviations: 5-FU, 5-fluorouracil; EBRT, external-beam radiation therapy; IOERT, intraoperative electron radiation therapy.

at the same time keeping the dose low in the regions of at-risk normal structures. It may also allow for dose escalation and a consequent greater tumor control probability. Milano et al. [75], in an efficacy and toxicity finding study of IMRT in pancreatic and bile duct cancer, treated 25 patients with IMRT and concurrent 5-FU. IMRT was well tolerated and reduced the mean dose to the liver, kidneys, stomach, and small bowel, with 80% of patients experiencing grade 2 toxicity only. In a separate study [76], 15 patients with adenocarcinoma of the pancreas were treated with IMRT and concomitant capecitabine. The IMRT was delivered to a dose of 54 Gy to the gross tumor and 45 Gy to the draining lymph nodes in a simultaneous boost method. The study reported a 7% grade 3 toxicity and 0% grade 4 toxicity rate. Thus, with superior planning techniques and better and effective monitoring of toxicities, IMRT is likely to be safely delivered to patients with pancreatic cancer concurrently with systemic chemotherapy. The position of IMRT and that of SRT vis à vis local control and other concurrent or sequential systemic treatment needs RCTs with conventional comparators.

Induction Chemotherapy Prior to CRT

The majority of LANPC patients recur at distant sites. Hence, to improve prognosis in this group, effective systemic chemotherapy is necessary to control micrometastases. Induction chemotherapy is a logical tactic allowing resistant cancer biology to declare itself before offering CRT as a more definitive approach.

At the MD Anderson Cancer Center, in a retrospective analysis of 318 patients [38] with LANPC between 1993 and 2005, 73 patients receiving a median of 2.5 months of induction chemotherapy before proceeding to CRT had a significantly longer overall time to local and distant progression than 245 patients receiving CRT as their first treatment.

A phase I/II study by Brade et al. [77] of induction chemotherapy with gemcitabine followed by concurrent gemcitabine and radiotherapy showed that 22% of patients (six of 27) had disease progression on induction chemotherapy and hence could be spared further treatment with CRT.

A recent audit report [78] showed that patients with LANPC who had stable disease after induction chemotherapy before CRT had a significantly longer survival duration (11.8 months versus 6.6 months; $p = .01$).

In a recently published nonrandomized series, 181 patients [79] were treated with gemcitabine-based chemotherapy for 3 months, and those with stable disease (128 patients) were treated with CRT or chemotherapy alone. The median survival time was significantly longer in patients receiving CRT (15 months versus 11.7 months). This shows a probable benefit of CRT in patients who have achieved stable disease with induction chemotherapy.

These data as a whole seem promising, but there is a clear need for a RCT designed to test these hypotheses, especially the two strategies of gemcitabine-based CRT followed by gemcitabine versus gemcitabine induction followed by gemcitabine-based CRT.

Conclusion

In terms of the positioning of CRT, our review highlights a number of priority issues that the oncological community needs to address. First, the quality assurance of delivered radiotherapy and agreement on similar standards of what

constitutes a radical treatment field in the two settings of an in situ primary and a resected primary are seen as a sine qua non for the success of any trial in this area. Second, the position of CRT in patients with initially resectable disease on first intent ending up with R1 margins needs further study, for example, in an RCT evaluating gemcitabine-based CRT with or without extended adjuvant chemotherapy. Third, the "neoadjuvant" approach using CRT for patients with a borderline resectable primary given the high likelihood of R1 or R2 margins would also benefit from an RCT. Fourth, for LANPC, the two most promising strategies of gemcitabine-based CRT followed by gemcitabine or the reverse need further study in a head-to-head RCT. Finally, the position of IMRT and that of SRT need RCT approaches (e.g., phase IIb trials) with conventional comparators. The failure of biologicals to have an impact on APC treatment means that we cannot at present see a role for these in the CRT setting other than in early-phase (I and II) trial work.

Author Contributions

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