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REVIEW

Changing paradigm of radiation therapy for the treatment of pancreatic cancer

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Abstract

The evidence supporting the use of radiation therapy (RT) for pancreatic cancer (PC) treatment is highly variable, with studies both showing and failing to show that RT provides a survival benefit. Trials exploring the use of RT for PC treatment dates back to the 1960s with various dosing and fractionation schemes, as well as various chemotherapeutic combinations. Collectively, large retrospective studies using cancer databases have shown an overall survival benefit with the addition of RT. The combination of RT with efficacious chemotherapy regimens synergistically improves the benefits of RT. More recent studies have evaluated the use of stereotactic body radiation therapy in either single- or multi-fraction regimens. Modern studies using multifractionated stereotactic body radiation therapy have demonstrated maintenance of local control and safe toxicity profiles with shorter therapeutic regimens allowing for improved integration with other therapeutic modalities. Although the use of RT has been evaluated for ≥50 years for PC treatment, the heterogeneous nature of the studies carried out and the advancement of complementary chemotherapeutic regimens makes it difficult to clearly identify the direct effect of RT. Herein, we provide a comprehensive overview of the evidence for the use of RT in PC treatment, including a comparison of conventionally fractionated RT versus stereotactic body radiation therapy.

KEYWORDS

external beam radiation therapy, pancreatic cancer, stereotactic body radiation therapy

1 | PANCREATIC CANCER

Despite our best efforts, pancreatic cancer remains one of the most lethal types of cancer in the USA, with little improvement in survival rates over the past 50 years. In addition, unlike most other cancers, its incidence has remained steady or has even increased over the past decade.[1] This combination creates a demoralizing situation for many patients that are diagnosed with pancreatic cancer. The high morbidity and mortality of pancreatic cancer is at least in part attributable to the typically late or advanced stage at presentation of most patients. A patient's only chance for cure from this devastating disease relies on them being a surgical candidate; however, a majority of patients are no longer considered resectable at the time of diagnosis due to either their disease being either locally advanced or metastatic. The advanced nature and unresectability of most pancreatic cancer forces clinicians and patients to turn to systemic chemotherapy and radiation therapy for treatment. Both of these realms have been advancing rapidly in an attempt to find better therapeutic regimens for patients that both maximize disease-free and overall survival, and minimize the potentially devastating side-effects of the treatments. Previous autopsy studies have shown that although 70% of patients died with widely metastatic disease, 30% of patients succumbed to their disease with only local disease, suggesting a potentially significant role for radiation therapy in the treatment of pancreatic cancer.[2] Additionally, multiple recent studies have shown that neoadjuvant chemoradiation can reduce tumor burden and convert borderline or unresectable tumors into resectable tumors.[3] Therefore, identifying the most efficacious radiation regimens in the context of adjunct chemotherapy and surgical interventions will improve patient outcomes and limit toxicity.

2 | RADIATION THERAPY IN PANCREATIC CANCER

The evidence supporting the use of radiation therapy for the treatment of pancreatic cancer is highly variable, with numerous studies both showing and failing to show survival benefits of radiation therapy. Radiation can be used in a neoadjuvant or adjuvant setting in the context of resectable or borderline resectable tumors. In locally advanced or unresectable disease, radiation with concurrent chemotherapy can be a significant contributor to definitive treatment with or without induction chemotherapy. Finally, in metastatic or recurrent tumors, radiation therapy can be applied for salvage therapy or with palliative intent. Further complicating the research evaluating the efficacy of radiation therapy is the potential to combine radiation with other therapies, including surgery, chemotherapy, and targeted therapeutics, that can be applied in various combinations and with variable timing.

Radiation therapy has been most well-studied as adjuvant and definitive therapy. More recently, the use of radiation as neoadjuvant therapy has been examined. While still in early phases of evaluation, multiple studies have shown some benefit or at least equivalent outcomes in patients receiving chemoradiation before surgical resection.[4–6] In fact, in some cases, patients with borderline or unresectable pancreas tumors transitioned to being resectable after neoadjuvant chemoradiation.[3] Radiation therapy has also shown promise for use as palliative therapy in patients with clearly unresectable pancreatic cancer. These patients typically undergo combination therapy with chemotherapy and radiation, with new regimens and combinations being examined in recent years.[7,8] Unfortunately, the rapid advancement of combination regimens, while beneficial for the progression of the field, has contributed to conflicting results in studies evaluating the efficacy of radiation therapy in pancreatic cancer.

Despite radiation therapy being commonly used in the treatment of pancreatic cancer, there are several studies that have failed to show its efficacy. The Eastern European Cooperative Oncology Group study failed to show any benefit of chemoradiation consisting of a "split course" of 40 Gy and 5-fluorouracil (FU) versus chemotherapy with 5-FU alone. In this study, the median survival was <10 months for all groups, and higher toxicities were associated with the chemoradiation versus chemotherapy group.[9] Additionally, the European Study Group for Pancreatic Cancer 1 trial and Fédération Francophone de Cancérologie Digestive (FFCD)/Société Francophone de Radiothérapie Oncologique (SFRO) studies showed no additional benefit, and possible harm with increased toxicities and a shorter overall survival with the addition of radiation therapy. In the European Study Group for Pancreatic Cancer 1 trial, patients were prospectively randomized into one of four groups: chemoradiation (20 Gy and 5-FU) alone, chemotherapy (leucovorin/folinic acid and 5-FU) alone, chemotherapy and chemoradiation, or observation.[10,11] Patients receiving combination chemoradiation and chemotherapy had the most adverse events, followed by chemotherapy alone, with chemoradiation alone having the fewest adverse events out of the three treatment branches. Criticism for this study includes the substandard levels of total radiation given to the patients assigned to receive chemoradiation therapy, and a relatively high percentage of patients who were stratified to the observation- or chemotherapy-only groups receiving some radiation therapy as well. At the other end of the spectrum, in the FFCD/SFRO study, patients received either chemoradiation consisting of 60 Gy/30 fractions with concomitant 5-FU infusion and cisplatin over the course of 6 weeks versus chemotherapy only with induction gemcitabine. Maintenance gemcitabine was given in both arms until disease progression or toxicity. This study showed increased toxicity and shorter overall survival in the chemoradiation arm versus the chemotherapy only arm.[12] Criticism of this trial largely cites the particularly high dose of radiation therapy given.

The most notable negative trial for radiation therapy was the large LAP07 study published in 2016 that failed to reproduce previous results showing an increase in survival with the addition of radiation therapy for definitive treatment of pancreatic cancer. In this study, patients with locally advanced pancreatic cancer received induction chemotherapy with either gemcitabine alone or gemcitabine plus erlotinib. Patients with stable disease after induction therapy were then randomized to continued chemotherapy or chemoradiation consisting of 54 Gy with concurrent capecitabine. Chemoradiation therapy showed decreased local progression, increased interval to subsequent therapy, and had no increase in grade 3 or 4 toxicities; however, median overall survival was not increased with chemoradiation versus chemotherapy only, questioning the overall benefit of radiation therapy in pancreatic cancer.[13]

In contrast, trials showing benefit from the addition of radiation therapy for the treatment of pancreatic cancer can be found dating back to the 1960s. Early trials by the Gastrointestinal Tumor Study Group (GITSG) in the 1960s and 1970s showed increased median survival with the addition of chemoradiation consisting of 40–60 Gy plus 5-FU for the treatment of pancreatic cancer;[14,15] however, the benefit of this combination and the interaction between chemotherapy and radiation therapy was poorly understood. Later trials carried out by GITSG evaluated the efficacy of post-resection adjuvant chemoradiation therapy versus observation of pancreatic adenocarcinoma (GITSG 9173). The chemoradiation therapy included concurrent and maintenance 5-FU. A total dose of 40 Gy radiation was given in a "split course," with two courses of 20 Gy each, with the courses separated by 2 weeks. The chemoradiation group showed an increased median overall survival of 20 months versus 11 months in the observation group (Table 1).[16] GITSG recruited an additional 30 patients to receive the chemoradiation adjuvant therapy, which confirmed the previous results with a median overall survival of 18 months.[17] Further randomized trials by GITSG showed improved survival of patients who received chemoradiation adjuvant therapy versus radiation or chemotherapy alone.[18] A phase III trial by the Gastrointestinal Tumor Cancer Group of the European Organization for the Research and Treatment of Cancer showed a trend for increased survival benefit of chemoradiation versus observation; however, the results were not statistically significant. This study (European Organization for the Research and Treatment of Cancer 40891) used a similar radiation protocol to previous GITSG studies (40 Gy split course), but updated the

TABLE 1 Early studies of radiation therapy in pancreatic cancer

Study (ref. no)	Study design					Outcomes			PMID
	Phase (no. patients)	Type of Tx	Surgery	Dose (Gy)/ fractions	Chemo	1 year LC %	mOS (months)	Conclusions	
Kalser *et al*., 1985 GITSG 9173[16]	Prospective, randomized (43)	Adjuvant	43/43	40 split course (20/10 + break + 20/10)	5-FU^{C+M}	–	20	Benefit of adjuvant chemoRT *vs* surgery alone	4015380
GITSG 9173	Confirmation arm (30)	Adjuvant	30/30	40 split course (20/10 + break + 20/10)	5-FU^{C+M}	–	18	Confirmation of findings in GITSG 9173	
Klinkenbijl *et al*., 1999 EORTC 40891[19]	Prospective, randomized (218)	Adjuvant	218/218	40 split course (20/10 + break + 20/10)	5-FU^{C}	–	21.6	No benefit of chemoRT *vs* chemo	10615932 16858208 17968163
Neoptolemos *et al*., 2001 ESPAC-1[10]	Prospective, randomized (541)	Adjuvant	541/541	40 split course (20/10 + break + 20/10)	5-FU^{C}	–	15.9	No benefit of chemoRT *vs* chemo in OS	11716884 15028824

Chemotherapy codes: C, concurrent; M, maintenance. Chemo, chemotherapy; CFRT, conventionally fractionated radiation therapy; EORTC, European Organization for the Research and Treatment of Cancer; ESPAC-1, European Study Group for Pancreatic Cancer 1 trial; GITSG, Gastrointestinal Tumor Study Group; LC, local control; mOS, median overall survival; Tx, treatment.

chemotherapy dosing of concurrent 5-FU and eliminated the maintenance chemotherapy. Notably, a stronger benefit of combination chemoradiation was noted for patients with cancer within the head of the pancreas versus those with periampullary cancer.[19]

Another more recent study carried out by the Eastern Cooperative Oncology Group evaluated the outcomes in patients with unresectable, localized pancreatic cancer either receiving gemcitabine alone or gemcitabine with radiation therapy (50.4 Gy/28 fractions). Median survival was increased with chemoradiation therapy to 11.1 months versus 9.2 months in the chemotherapy only arm; however, there was also significantly more toxicity in the combination chemoradiation treatment group.[20] Limitations of this study included the small number of patients enrolled and the combination of radiation therapy with gemcitabine, a combination that has been shown in multiple studies to have significant toxicities. Additionally, utilizing a chemotherapeutic regimen with gemcitabine alone is considered a substandard, outdated chemotherapeutic regimen.

However, in single-institute retrospective studies, the evidence largely supports a potentially significant increase in survival with the addition of adjuvant radiation therapy. A retrospective study of patients with pancreatic adenocarcinoma who underwent complete resection at the Mayo Clinic between 1975 and 2005 showed that adjuvant chemoradiation was associated with better outcomes than without adjuvant therapy.[21] In patients treated at Johns Hopkins Hospital between 1993 and 2005 that underwent surgical resection for pancreatic adenocarcinoma, those that received adjuvant chemoradiation had better outcomes than those that did not receive adjuvant therapy, even when controlling for high-risk features.[22] A small cohort of patients treated at Moffitt Cancer Center with resected pancreatic adenocarcinoma showed significantly increased survival with the addition of adjuvant chemoradiation therapy versus chemotherapy alone or observation, with median overall survival of 21.6 months versus 11.3 months.[23]

Recent post-hoc, retrospective evaluations of patients with pancreatic cancer from national databases have confirmed these findings, and have largely all shown a survival benefit with the addition of adjuvant radiation therapy for the treatment of pancreatic cancer. A post-hoc evaluation of patient outcomes from the National Cancer Database in patients with resected pancreatic adenocarcinoma diagnosed between 1998 and 2002 showed that the combination of chemoradiation outperformed chemotherapy alone and observation as adjuvant approaches.[24] These results were shown using both propensity-matched cohorts and whole cohort analyses. Interestingly, chemotherapy alone did not improve survival over observation, but the combination of chemoradiation decreased the HR to 0.70 (95% confidence interval 0.61–0.80) based on the propensity-matched analysis.[24] In another study, patients with locally advanced pancreatic cancer that received radiation therapy had improved survival (HR 0.773, 95% CI 0.687–0.782) based on data within the Surveillance, Epidemiology, and End Results registry dataset from 2004 to 2011. Of note, radiation therapy was associated with younger patients, smaller tumor sizes, and less lymph node involvement, suggesting that other factors might be confounding these findings; however, the survival benefit was confirmed using a propensity score-matched cohort to account for potential confounders, and on multivariate analysis, radiation therapy remained a significant factor independently associated with improved patient outcomes.[25] A similar analysis carried out using data from the National Cancer Database that queried patients with locally advanced pancreatic cancer diagnosed between 2004 and 2014 showed that adjuvant chemoradiation was associated with improved survival compared with adjuvant chemotherapy alone.[26] Additionally, chemoradiation appeared to be particularly effective in patients that had previously received multiagent induction chemotherapy. This is consistent with earlier prospective studies that showed that the efficacy of chemoradiation therapy was improved if implemented after induction chemotherapy.[27,28]

More recent studies have applied new strategies to better stratify patients that are more likely to benefit from chemoradiation regimens. These studies were based on retrospective analyses that showed the benefit of chemoradiation appeared to be greater in patients after induction therapy with chemotherapy that showed stable and nonmetastatic disease after induction therapy. In the Groupe Coordina-

teur Multidisciplinaire en Oncologie phase II studies,[29–32] all patients completed induction therapy with multi-agent chemotherapeutic regimens (leucovorin, FU, and gemcitabine or gemcitabine ± oxaliplatin) for at least 3 months. Subsequent chemoradiation was recommended for all patients with stable disease; however, nearly half of providers/patients chose to continue with chemotherapy instead, allowing for a comparison of outcomes in both groups in a follow-up retrospective analysis. Patients that received combined chemoradiation had a progression-free survival of 10.8 months versus 7.4 months in the chemotherapy only group. Additionally, median overall survival was 15 months versus 11.7 months, respectively.[33] This retrospective analysis was followed by a prospective phase III trial to further evaluate these results, which confirmed the findings.[34] In this study, patients received induction chemotherapy for 2 months with gemcitabine and oxaliplatin followed by chemoradiation with 45 Gy radiation + 10 Gy boost, along with daily 5-FU infusions and weekly oxaliplatin. Consistent with previous results, patients that received the full chemoradiation regimen showed the longest progression-free survival and overall survival.[34] This is based on the concept that radiation therapy is largely beneficial for local and regional control of the tumor. By identifying patients that are less likely to already have disseminated metastatic disease, these patients are the most likely to benefit from radiation therapy aimed at reducing or eliminating their localized disease. Consistent with this, more efficacious chemotherapy likely increases the benefit of radiation therapy by increasing the value of the local control.

3 | STEREOTACTIC BODY RADIATION THERAPY

With the advent and increasing use of stereotactic body radiation therapy (SBRT) for the treatment of various types of cancer, and the question over net patient benefit of radiation therapy with the effects of life quantity versus quality in mind, the need to evaluate the potential for SBRT to improve outcomes in patients with pancreatic cancer has arisen. The first studies using SBRT for the treatment of pancreatic cancer were carried out at Stanford University and evaluated the efficacy of using a single fraction of radiation. A phase I dose escalation study showed that a single fraction of 25 Gy could be delivered to patients without significant acute GI toxicity.[35] A subsequent study evaluated the efficacy of using a single fraction of 25 Gy via Cyberknife given between cycles 1 and 2 of chemotherapy with gemcitabine in patients with locally advanced pancreatic cancer.[36] Although the efficacy of this high-dose single-fraction regimen remained high with comparable survival rates to more conventional radiation regimens and excellent rates of local control, the patients also experienced an increase in significant GI toxicities.[36] Similar results were found in a follow-up study of 77 patients, which confirmed maintenance of high levels of local control and overall survival, but with increased levels of GI, specifically duodenal, toxicity.[37,38]

Our experience with SBRT in pancreatic cancer started in 2008 when enrollment opened for patients in a phase I dose-escalation trial (NCT01068327) to evaluate the safety and efficacy of multifraction SBRT regimens in borderline or unresectable patients.[50] When this clinical trial was initiated, only the Stanford study describing the use and safety of the single fraction of 25 Gy radiation therapy had been published. The trial was closed to accrual in 2013, and the final results of our study were published in 2019. Our trial showed increased efficacy of multifraction regimens (5 fractions) of 7–8 Gy per fraction over lower doses with 5–6 Gy per fraction in unresected patients (median survival was 16 *vs* 10 months, $P = 0.002$) with no increase in toxicity. Local control for the entire group was 85%. Interestingly, two patients developed late pseudoaneurysms and subsequent GI bleeds after treatment. This is an unreported side-effect of SBRT delivered within the abdomen, and suggests the possibility that avoidance of vascular structures might be vital to limit toxicity when treating with SBRT.

Other groups were also evaluating the intermediate approach where radiation was administered in fewer, higher-dose fractions than conventional regimens, but still in multifraction regimens. Studies evaluating the administration of total radiation doses of 24–45 Gy in three to six fractions revealed maintenance of local control with decreased GI toxicity.[39–43] Notably, a retrospective review of patients with unresectable pancreatic cancer treated at Stanford between 2002 and 2013 with single- (25 Gy/1 fraction) or multifraction (33 Gy/5 fractions) radiation therapy showed that multifraction SBRT reduced GI toxicity relative to single fraction treatment without sacrificing efficacy, as local recurrence and overall survival were similar between groups.[44] Another retrospective study carried out at Johns Hopkins showed that the use of SBRT (25-33 Gy/5 fractions) after induction chemotherapy for the treatment of locally advanced or borderline resectable pancreatic cancer had minimal toxicity and good efficacy.[45] A prospective, phase II study evaluated the efficacy of combination gemcitabine chemotherapy followed by a week-long break for SBRT (33 Gy/5 fractions) and maintenance gemcitabine until disease progression or toxicity for locally advanced, unresectable pancreatic cancer. This study showed good local control and overall survival consistent with previous studies with low levels of GI toxicity (8% with grade ≥3).[46] Current clinical trials are underway to evaluate the use of modified FOLFIRINOX with or without SBRT (40 Gy/5 fractions) therapy (clinical trial: NCT01926197).

A pooled meta-analysis of 19 studies with >1000 cumulative patients with locally advanced pancreatic cancer reaffirmed previous findings suggesting high levels of local control can be obtained without significant toxicity with the use of SBRT.[47] Surveys of the patients from these studies showed a good quality of life and reduced GI toxicities compared with the single dose SBRT trials.[48] Thus, the use of SBRT regimens have allowed for the same level of efficacy in regard to local control with shorter lengths of treatment allowing for earlier transition to other therapeutic modalities.

Using SBRT as neoadjuvant therapy has also recently been examined, particularly in the context of locally advanced or borderline resectable pancreatic cancer. In one study, patients underwent 2–3 months of induction chemotherapy followed by 30 Gy radiation to the tumor and 40 Gy radiation to adjacent tumor-vessel interfaces in a total of five fractions. These patients were then re-evaluated

for surgical resection. This method showed an increased rate of patients able to have surgical resection, high rates of negative margin resections, and low levels of toxicity with 7% of grade ≥3 toxicities recorded, suggesting this approach is safe and effective.[49] Additionally, patients that underwent surgical resection showed significantly improved survival, highlighting the potential benefit of implementing neoadjuvant therapies to increase the rates and extent of resection and survival in pancreatic cancer. A subsequent study carried out at Johns Hopkins showed similar results in that neoadjuvant induction chemotherapy with FOLFIRINOX and SBRT correlated with a higher probability of subsequent resection, and those that underwent resection had a longer median overall survival.[49]

4 | CONVENTIONAL RADIATION THERAPY VERSUS STEREOTACTIC BODY RADIATION THERAPY

Although prospective studies to date have not directly compared SBRT with conventionally fractionated radiation, there are several factors that suggest SBRT might be beneficial. First, the biological effects of using a larger dose per fraction might confer additional therapeutic benefit compared with the smaller doses of conventionally fractionated therapy, particularly in tumors with a low α/β ratio. This might provide improved local control and subsequent lengthened progression-free and overall survivals. Additionally, the shorter radiation treatment course required for SBRT allows for improved integration of radiation therapy with concomitant or subsequent chemotherapy regimens and consolidation of treatment regimens.

In an attempt to compare these two methods, extensive efforts have been initiated to evaluate the efficacy and toxicities of both SBRT and conventionally fractionated radiation therapy. The toxicity profiles of conventionally fractionated radiation therapy vary from those seen in SBRT. With conventional fractionation, toxicity can be seen in the spinal cord, liver, kidney, and small bowel (Table 3), whereas SBRT toxicity is largely constrained to the GI tract, specifically the duodenum and stomach (Table 5). The limited field of irradiation with SBRT limits the number of structures at risk for toxicity; however, it potentially opens up the opportunity for local failure. One study evaluating the patterns of local failure after SBRT identified that a majority of local failures were close to the radiation field in the region of other important structures, namely the celiac trunk and superior mesenteric artery, as well as the retroperitoneal space, highlighting the balance required to ensure the entire tumor and full clinical target volume, including relevant, suspicious lymph nodes, is treated with radiation therapy, while limiting radiation therapy to key nearby structures.[51] In contrast, a retrospective review of our institutional experience of local and regional failures after SBRT for pancreatic cancer showed a higher percentage of in-field failure compared with near field failures, suggesting the field coverage is sufficient and failures are more likely related to radioresistence of the tumor more so than inadequate coverage.[79] Additionally, multiple studies have shown high rates of local control after SBRT, suggesting local control is comparable or improved relative to conventional radiation therapy. Local control rates after conventionally fractionated radiation therapy for pancreatic cancer have been reported to be 50–90% with a majority of studies showing rates near or greater than 70% (Table 2).[4,5,13,28,52–56] In comparison, local controls rates after SBRT range from 41.2 to 100%, with the average and median rate of local control in these studies being approximately 80% (Table 4).[35–37,39–46,49,50,57–70]

Even though no direct comparative studies have been carried out evaluating the efficacy of conventionally fractionated radiation versus SBRT, retrospective analysis of data from the National Cancer Database has shown improved survival with SBRT.[71,72] Additionally, a prospective multi-institutional phase II study evaluating the efficacy of gemcitabine followed by SBRT compared its findings with historical results of conventionally fractionated radiation therapy contained within the LAP07 study, and showed improved local control with SBRT compared with the levels previously reported with conventionally fractionated radiation therapy.[46] In our review of the literature, the median overall survival for patients receiving conventionally fractionated radiation therapy is highly variable and ranges from 8.6 months to 47.4 months[4–7,12,13,20,28,52–56,73–76] versus 5.7 to 47.2 months with SBRT,[35–37,39–46,49,50,57–70,77,78] with the large variability being attributable to the context of the treatment (neoadjuvant, definitive *vs* adjuvant), as well as whether or not surgical resection was included in treatment.

Median survival for patients undergoing neoadjuvant therapy including conventionally fractionated radiation where a majority or all patients also underwent resection was 17.4–47.4 months,[4–6,74–76] whereas it was 7–17 months for those not undergoing resection.[4,12,13,74,75] After neoadjuvant SBRT, the median survival ranged from 10.6 to 47.2 months, with highly variable rates of patients also receiving surgical resection.[45,49,50,65,7039,41,77] Median survival for patients who received conventionally fractionated radiation as part of their adjuvant therapy after surgical resection ranged from 20.5 to 42.3 months.[53,54,73]

Patients who received conventionally fractionated radiation as part of their definitive therapy had a median survival of 11.1–19.2 months.[7,20,28,52,55,56] Whereas, patients that received SBRT as part of their definitive therapy had a median survival of 5.7–20 months.[35–37,40,42–44,46,57–64,66–69,78]

In conclusion, the current evidence suggests that SBRT has equivalent to improved local control and overall survival while being a shorter and therefore more convenient and cost-effective regimen for patients. Future studies will continue to add to the body of evidence delineating the benefit and role for SBRT versus conventionally fractionated radiation therapy in the treatment of pancreatic cancer.

5 | DISCUSSION

Overall, our current understanding of radiation therapy in pancreatic cancer largely reinforces that radiation therapy has a role in the treatment of pancreatic cancer; however, determining the appropriate patient, tumor, and situations that will derive the largest benefit from

TABLE 2 Local control and overall survival in CFRT clinical trials

	Study design					Outcomes			
Study (ref. no)	Phase (No. patients)	Type of Tx	Surgery	Dose (Gy)/ fractions	Chemo	1 year LC %	mOS (months)	Conclusions	PMID
Rich *et al*., 2004 RTOG 9812[7]	II (109)	Definitive	0	50.4/28	Paclitaxel[C]	–	11.2	No comparison	14758134
Ko *et al*., 2007[28]	II (25)	Definitive	0	50.4/28	Gemcitabine[I] Cisplatin[I] Capecitabine[C]	50%*	13.5 (overall) 17.0 (received all therapy)	No comparison	17363191
Chauffert *et al*., 2008[12]	III (119)	Neoadjuvant	0	60/30	5-fluorouracil[C] Cisplatin[C] Gemcitabine[P]	–	8.6	No benefit of chemoRT *vs* gemcitabine for induction	18467316
Evans et al., 2008[4]	II (86)	Neoadjuvant	64/86	30/10	Gemcitabine[C]	89%*	22.7 (all), 34 (resected), 7 (unresected)	No comparison	18640930
Loehrer *et al*. 2011, E4201 NCT00057876[20]	III (74)	Definitive	0	50.4/28	Gemcitabine[I,C]	–	11.1	Benefit of chemoRT *vs* chemo. Increased toxicity with chemoRT	21969502
Katz *et al*. 2011 NCT00068575[73]	II (28)	Adjuvant	28/28	50.4/28	Interferon-alfa-2b[C] Cisplatin[C] 5-fluorouracil[C,P]	–	42.3 (resected)	No comparison	21701927
Crane *et al*., 2011 NCT00338039[52]	II (67)	Neoadjuvant/ Definitive	7/67	50.4/28	Cetuximab[I] Gemcitabine[I] Oxaliplatin[I] Capecitabine[C] Cetuximab[C]	77.2%	19.2	No comparison	21709185
Regine *et al*., 2009 and 2011 RTOG 9704 NCT00003216[53,54]	III (451)	Adjuvant	451/451	50.4/28	5-fluorouracil[I,P] or Gemcitabine[I,P] 5-fluorouracil[C]	72–77%*	20.5	No difference between 5-FU *vs* gemcitabine in chemoRT	21499862 18319412
Cetin *et al*., 2013 NCT00424827[74]	II (11)	Neoadjuvant	4/11	50.4/28	5-Fluorouracil[C] Gemcitabine[C,P] Cetuximab[C,P]	–	47.4 (resected) 17 (unresected)	No comparison	24312684
Kim *et al*., 2013 NCT00456599[75]	II (68)	Neoadjuvant	43/68	30/15	Gemcitabine[C] Oxaliplatin[C]	–	18.2 (all), 27.1 (resected), 10.9 (unresected)	No comparison	23720019
Van Buren *et al*. 2013 NCT00557492[76]	II (59)	Neoadjuvant	43/59	30/10	Gemcitabine[I] Bevacizumab[I] Bevacizumab[C]	–	16.8 (all) and 19.7 (resected)	No comparison	23904005

(Continues)

TABLE 2 (Continued)

Study (ref. no)	Study design					Outcomes			PMID
	Phase (No. patients)	Type of Tx	Surgery	Dose (Gy)/ fractions	Chemo	1 year LC %	mOS (months)	Conclusions	
Mukherjee *et al.* 2013[55] Hurt *et al.*, 2017[56] SCALOP	II (74)	Definitive	0	50.4/28	Gemcitabine[I] Cisplatin[I] Gemcitabine[C] or Capecitabine[C]	65.8 (GEM-RT) and 67.6 (CAP-RT)	14.6 (GEM-RT) and 17.6 (Cap-RT)	Benefit of capecitabine vs gemcitabine in chemoRT	23474363 28376080
Golcher *et al.*, 2015 NCT00335543[6]	II (66)	Neoadjuvant	A: 23/33 B: 19/33	55.8/31 (tumor), 50.4/28 (LNs)	Gemcitabine[C] Cisplatin[C]	-	17.4 (chemoRT) 14.4 (surgery alone)	Neoadjuvant chemoRT safe with trend towards OS benefit	25252602
Hammel *et al.*, 2016 LAP07 Trial[13]	III (269)	Neoadjuvant	12/269	54/30	Gemcitabine[I] ± erlotinib[I] Capecitabine[C]	68% *(Benefit)	15.2	No benefit of chemoRT vs chemo in OS	27139057
Katz *et al.*, 2016 NCT01821612[5]	I (22)	Neoadjuvant	15/22	50.4/28	FOLFIRINOX[I] Capecitabine[C]	90%	21.7	No comparison	27275632

Chemotherapy codes: C, concurrent; I, induction; M, maintenance; P, postsurgery/adjuvant.
*Local control based on lack of local disease progression/first site of recurrence in local tumor bed. CFRT, conventionally fractionated radiation therapy; Chemo, chemotherapy; chemoRT, chemoradiotherapy; LC, local control; mOS, median overall survival; Tx, treatment.

radiation therapy with the least side-effects is still evolving. Based on previous studies, this is likely to be in patients without disseminated disease, which might be selected for by using induction chemotherapy initially with subsequent stable disease. The role of various chemotherapeutic regimens for induction, as well as concomitant treatment for both the selection of patients for radiation therapy and the sensitizing effects of chemotherapy for radiation therapy, is still poorly understood. As our knowledge of chemotherapy advances, we will continue to identify combinations of chemotherapy and radiation regimens that have improved efficacy with fewer side-effects. Numerous studies have recently been initiated to evaluate the efficacy of radiation therapy in the context of various newer chemotherapeutic regimens. These studies include the SCALOP trial evaluating the use of gemcitabine versus capecitabine,[55,56] an additional phase III trial that is ongoing to evaluate the benefits of a modified FOLFIRINOX with and without SBRT for the treatment of locally advanced pancreatic cancer (clinical trial: NCT01926197), and another study evaluating the effects of SBRT in the context of 5-FU/capecitabine with or without zoledronic acid (clinical trial: NCT03073785). Additional studies have evaluated the role of non-chemotherapeutic radiosensitizers to improve the efficacy and limit the toxicity of radiation. This includes our phase I trial evaluating the use of nelfinavir as a radiosensitizing agent given in conjunction with SBRT therapy for the treatment of borderline or unresectable pancreatic cancer.[50] Therefore, as new chemotherapeutic regimens are designed and implemented, the role of radiation therapy for the treatment of pancreatic cancer will need to be constantly re-evaluated as the evidence for the use of radiation therapy becomes outdated. In fact, several of the landmark trials for the use of radiation therapy in pancreatic cancer could be considered suboptimal already, because they are based on outdated chemotherapeutic regimens, specifically regimens utilizing 5-FU or gemcitabine as single agents.

With poor prognosis and locally advanced or metastatic disease common at the time of patient presentation, the role of radiation therapy in pancreatic cancer can be difficult to discern. As our understanding of this disease advances, it is likely that the role for radiation therapy will continue to expand, as the evidence currently suggests a clear role for radiation therapy to suppress local and regional disease progression. However, the true efficacy of radiation therapy in the context of pancreatic cancer is still being elucidated, as many of the previous clinical trials have used different total radiation doses given in variable fractionation schemes with various adjunct therapies resulting in highly variable outcomes. In particular, the role of conventionally fractionated radiation therapy versus SBRT will need to be further evaluated, as there has not been a prospective study providing a direct comparison to date. In addition, some groups have started evaluating the use of intensity-modulated radiation therapy with dose painting further adding to the complexity, and necessitating further study.

Comparing SBRT and conventionally fractionated radiation therapy, SBRT has a smaller treatment field, but receives a higher dose. This allows for substantial dose to the tumor, but without proper alignment could cause a high dose of radiation to be directed at normal tissue. Therefore, a major concern with the use of SBRT in the treatment of pancreatic cancer is the risk of GI toxicity. In fact, in our study, GI bleed-

TABLE 3 Toxicity in CFRT clinical trials

	Acute			Late		
Study (ref. no)	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Rich *et al.*, 2004[7]			49/109 (45%)			5/100 (5%)
Ko *et al.*, 2007[28]			4/25 (16%)[H]			
Chauffert *et al.*, 2008[12]			36/55 (65.5%)			32/41 (78.1%)
Evans *et al.*, 2008[4]			37/86 (43%)[H] 32/86 (37.2%)[C] 30/86 (34.9%)[G]			
Loehrer *et al.*, 2011[20]			28/34 (82.4%)			
Katz *et al.*, 2011[73]			25/28 (89%)			
Crane *et al.*, 2011[52]		32%[G]	10%[G] 13%[H]			
Regine *et al.*, 2009 and 2011[53,54]			58% with Gem 9% with 5-FU		18.6–21%	
Cetin *et al.*, 2013[74]	11/11 (100%)[H] 11/11 (100%)[NH]		6/11 (55%)[H] 6/11 (55%)[NH]			
Kim *et al.*, 2013[75]			39/71 (54.9%)[H] 34/71 (47.9%)[NH]			
Van Buren *et al.*, 2013[76]			21/59 (35.6%)			
Mukherjee 2013 and Hurt 2017[55,56]			4/34 (12%) Cap-CRT 14/38 (37%) Gem-CRT			
Golcher *et al.*, 2015[6]			10/29 (34.5%)			
Hammel *et al.*, 2016[13]			4/103 (3.9%)[H] 24/104 (23.1%)[NH]			
Katz *et al.*, 2016[5]			9/21 (43%)			

[C], Constitutional toxicities only; [G], gastrointestinal toxicities only; [H], hematological toxicities only; [NH], non-hematological toxicity. CFRT, conventionally fractionated radiation therapy.

ing was a late toxicity seen after SBRT. The mechanism for this toxicity is not fully understood. Regardless, careful attention must be focused on limiting GI dose and complying with GI constraints. Furthermore, two patients developed pseudoaneurysms after treatment with SBRT in our study, suggesting a potential effect of SBRT on the vasculature.[50]

A second concern with the tighter field in SBRT is the possibility for increased local recurrence or nearby lymph node spread, as conventionally fractionated radiation therapy innately covers a larger field and contains a higher number of in-field lymph nodes. However, the evidence suggests this is not the case, as multiple studies have shown equivalent 1-year local control with SBRT compared with conventional fractionation regimens. A previous retrospective study by our group reviewed the patterns of local recurrence in pancreatic cancer treated with SBRT that showed 26.1% of patients failed within field and 15.9% of patients failed out of field, suggesting that the coverage field was sufficiently large with sufficient coverage of nearby lymph nodes.[79] Furthermore, these data suggest that SBRT provides adequate coverage of lymph nodes despite having a smaller field, which hints that limiting lymph node coverage in pancreatic cancer might be acceptable. However, the evidence supporting this conclusion thus far is circumstantial, and formal evaluation, including randomized studies, is required.

Although the post-hoc comparisons of SBRT versus conventional radiation therapy appear to favor SBRT, there are still challenges to using SBRT for pancreatic cancer. The two main constraints that need to be considered are the movement of the tumor and nearby normal structures that occurs with respiration, and the radiosensitivity of the adjacent gastrointestinal tract, including the stomach, duodenum, and jejunum, as the toxicities associated with radiation of the pancreas largely involve the gastrointestinal system. We carried out a secondary analysis of our phase I trial to assess relationships between dosimetric parameters and histopathologic/clinical duodenal toxicities. Our study showed that duodenal histological damage correlates with mean duodenal dose, V20–V35, and PTV mean and maximum doses.[81] These constraints need to be constantly balanced with the need for complete tumor coverage to maximize the therapeutic benefit, while attempting to minimize the toxicities. Additionally, our phase I SBRT trial exposed a potential toxicity to blood vessels, as two patients developed pseudoaneurysms and subsequent GI bleeds after SBRT for pancreatic cancer.[50] This highlights the need for additional evaluation and the possible need for dose constraints for nearby major vascular structures. We also quantified renal function after pancreatic SBRT. We found that V5 ≥210 cm^3 was associated with a post-SBRT glomerular filtration rate decline of >23 mL/min/1.73 cm^2. If V5 is

TABLE 4 Local control and overall survival in stereotactic body radiation therapy clinical trials

	Study design					Outcomes			
Study (ref. no)	Phase (no. patients)	Type of Tx	Surgery	Dose (Gy)/fractions	Chemo	1 year LC %	mOS (months)	Conclusions	PMID
Koong *et al.*, 2004[35]	I (15)	Definitive	2/15	15, 20, 25/1	± Various	100% (25 Gy)	11	No comparison	15001240
Koong *et al.*, 2005[57]	II (16)	Definitive	0/16	45 Gy IMRT/25 + 25 Gy SRS/1	5-FU[C]	94%	8.25	No comparison	16168826
Hoyer *et al.*, 2005[58]	II (22)	Definitive	0/22	45/3	Gemcitabine (at relapse)	57%	5.7	No comparison	15990186
Schellenberg *et al.*, 2008[36]	II (16)	Definitive	4/16	25/1	Gemcitabine[C]	81%	11.4	No comparison	18395362
Chang *et al.*, 2009[37]	Retro (77)	Definitive/ salvage	0/77	25/1 Cyberknife ± EBRT	Gemcitabine-based regimens	84%	11	No comparison	19117351
Mahadevan *et al.*, 2010[40]	Retro (36)	Definitive	0/36	24–36/3	Gemcitabine[P]	78%	14.3	No comparison	20171803
Polistina *et al.*, 2010[39]	Prospective (23)	Neoadjuvant	2/23	30/3	Gemcitabine[I,C]	–	10.6	No comparison	20224860
Didolkar *et al.*, 2010[60]	Retro (85)	Adjuvant Definitive	14/85	15–30/3	Gemcitabine[P]	91.7%	18.6	No comparison	20839073
Mahadevan *et al.*, 2011[43]	Retro (39)	Definitive	0/39	24–36/3	Gemcitabine[I,C]	85%	20	No comparison	21658854
Rwigema *et al.*, 2011[61]	Retro (71)	Adjuvant/ definitive/ salvage	28/71	18–25/1–3	Various[I,P]	48.5%	10.3	No comparison	20308870
Schellenberg *et al.*, 2011[59]	II (20)	Definitive	0/20	25/1	Gemcitabine[I,C,P]	94%	11.8	No comparison	21549517
Goyal *et al.*, 2012[62]	Prospective (20)	Definitive	0/20	22–30/1–3	Various	65%	14.4	No comparison	21937061
Kim *et al.*, 2013[63]	Retro (26)	Definitive	0/26	24/1, 30–36/3	+/– Various [I,P]	41.2%	7.6	No comparison	24131503
Chuong *et al.*, 2013[41]	Retro (73)	Neoadjuvant/ definitive	32/73	35–50/5	Gemzar, taxotere, and xeloda [I]	81%	15 (LAPC) 16.4 (BRPC)	No comparison	23562768
Rajagopalan *et al.*, 2013[77]	Retro (12)	Neoadjuvant	12/12	24/1 or 36/3	Various [I]	–	47.2	No comparison	24175982
Tozzi *et al.*, 2013[42]	Prospective (30)	Definitive/ salvage	9/30	45/6 or 36/6	Gemcitabine-based[I,P]	75%	11	No comparison	23799996
Gurka *et al.*, 2013[64]	Prospective DB (10)	Definitive	0	25/5	Gemcitabine[C]	60%	12.2	No comparison	23452509

(Continues)

TABLE 4 (Continued)

Study (ref. no)	Study design					Outcomes			PMID
	Phase (no. patients)	Type of Tx	Surgery	Dose (Gy)/fractions	Chemo	1 year LC %	mOS (months)	Conclusions	
Pollom *et al.*, 2014[44]	Retro (167)	Definitive	0	25/1 or 25–45/5	±Various [I,P]	90.5%[S] 89.3%[M]	13.6	Multifraction SBRT had decreased toxicity and equivalent LC *vs* single fraction	25585785
Hong *et al.*, 2014 NCT00438256[65]	I/II (48)	Neoadjuvant	37/48	25/5	Capecitabine[C], Gemcitabine [P]	83.8%	17	No comparison	24867540
Mellon *et al.*, 2015[49]	Retro (159)	Neoadjuvant/ Definitive	56/110 of BRPC, 6/49 of LAPC	IMRT 28–30 paint up to 50 Gy/5	Various [I]	78% (without resection)	19.2 (BRPC) 15.0 (LAPC)	No comparison	25734581
Lin *et al.*, 2015[66]	Retro series (41)	Definitive	0/41	35–45/5	±mFOLFOX or gemcitabine[C]	~80%	20 (SBRT)	No comparison	25629569
Song *et al.*, 2015[67]	Retro (59)	Definitive	0	35-50/3-8	±Various	90.8%	12.5	No comparison	26109866
Su *et al.*, 2015[78]	Retro (25)	Definitive	0	30-36/3 or 40–48/4	±Various	–	9.0	No comparison	26185389
Moningi *et al.*, 2015[45]	Retro (88)	Neoadjuvant/ Definitive	19/88	25-33/5	±Various	61%	14.4 (BRPC) 18.4 (LAPC)	No comparison	25564157
Herman *et al.*, 2015 NCT01146054[46]	II (49)	Definitive	4/49	33/5	Gemcitabine[C]	78%	13.9	No comparison	25538019
Comito *et al.*, 2017[68]	II (42)	Definitive	0	45/6	Various[I], Gemcitabine[P]	>90%	13	No comparison	27311310
Gurka *et al.*, 2017[69]	Prospective DB (38)	Definitive	0	25-30/5	Various[C,P]	79%	14.3	No comparison	25171298
Murphy *et al.*, 2018 NCT01591733[70]	II (48)	Neoadjuvant	32/48	25/5	FOLFIRINOX [I] Capecitabine[C] or 5-FU[C]	94%	37.7	No comparison	29800971
Lin *et al.*, 2019 NCT01068327[50]	I (39)	Neoadjuvant	12/39	25–40/5	Gemcitabine, leucovorin, 5-FU[I]; Nelfinavir[C]	85%	14.4	No comparison	30825970
Holyoake *et al.*, 2016 NCT02308722[80]	I (recruiting)	Neoadjuvant	–	30, 32.5, or 35/5	Various	Ongoing			27619800
Roach NCT02950025	II (5)		0	≥50 Gy/5	Various	Terminated (low accrual)	–		–

Chemotherapy codes: BRPC, borderline resectable PC; C, concurrent; I, induction; LAPC, locally advanced PC; LC, local control; M, maintenance; P, postsurgery/adjuvant. IMRT, intensity-modulated radiation therapy; Retro, retrospective; SBRT, stereotactic body radiation therapy; mOS, median overall survival.

TABLE 5 Toxicity in stereotactic body radiation therapy clinical trials

	Acute			Late		
Study (ref. no.)	Grade 1	Grade 2	Grade ≥3	Grade 1	Grade 2	Grade ≥3
Koong *et al.*, 2004[35]	2/15 (13%)	3/15 (20%)	0/15 (0%)			
Koong *et al.*, 2005[57]	7/16 (43.75%)	4/16 (25%)	2/16 (12.5%)			
Hoyer *et al.*, 2005[58]	14/18 (78%)					
Schellenberg *et al.*, 2008[36]		2/16 (13%)[G]	1/16 (6%)[G]		5/16 (31.25%)	2/16 (13%)
Chang *et al.*, 2009[37]	4/77 (5%)				3/77 (4%)	7/77 (9%)
Mahadevan *et al.*, 2010[40]	15/36 (42%)	9/36 (25%)	5/36 (14%)			
Polistina *et al.*, 2010[39]	0/23 (0%)				0/23 (0%)	
Didolkar *et al.*, 2010[60]			19/85 (22.3%)[G]			
Mahadevan *et al.*, 2011[43]	22/39 (56%)	9/39 (23%)	0/39 (0%)			3/39 (9%)
Rwigema *et al.*, 2011[61]	17/71 (24%)	8/71 (11.3%)	3/71 (4.2%)	3/71 (4.2%)	0%	0%
Schellenberg *et al.*, 2011[59]		3/20 (15%)	0/20 (0%)			1/20 (5%)
Goyal *et al.*, 2012[62]	2/19 (11%)		3/19 (16%)			
Kim *et al.*, 2013[63]			0%			
Chuong *et al.*, 2013[41]			0/73 (0%)			5.3%
Rajagopalan *et al.*, 2013[77]			0/12 (0%)			
Tozzi *et al.*, 2013[42]	5/30 (17%)[G]	3/30 (10%)[G]	0/30 (0%)			
Gurka *et al.*, 2013[64]	10/10 Present before treatment and acutely post-RT		0/10 (0%)	6/10 (60%)	0/10 (0%)	0/10 (0%)
Pollom *et al.*, 2014[44]					10/76 (13.2%)[S] 2/91 (2.2%)[M]	9/76(11.8%)[S] 6/91(6.6%)[M]
Hong *et al.*, 2014[65]			2/35 (4.1%)			
Mellon *et al.*, 2015[49]			11/159 (7%)			
Lin *et al.*, 2015[66]			0%			
Song *et al.*, 2015[67]	36/59 (61%)		1/59 (1.7%)			
Su *et al.*, 2015[78]	5/25 (20%)[G]	1/25 (4%)[G]	0/25 (0%)[G]			
Moningi *et al.*, 2015[45]	3/88 (3.4%)				5/88 (5.7%)	
Herman *et al.* 2015[46]	1/49 (2%)[G]				5/47 (11%)[G]	
Comito *et al.*, 2017[68]	21/42 (50%)		0/42 (0%)		2/42 (4%)	0/42 (0%)
Gurka *et al.*, 2017[69]			2/38 (5.3%)		3/38 (7.9%)	3/38 (7.9%)
Murphy *et al.*, 2018[70]			9/48 (19%)			
Lin *et al.*, 2019[50]		16/39 (41%)				4/39 (10%)

[C], Constitutional toxicities only; [G], gastrointestinal toxicities only; [H], hematological toxicities only; [M], multi-fraction [NH], non-hematological toxicity; [S], single fraction; RT, radiotherapy.

kept to <210 cm^3, the median glomerular filtration rate decline was just 11.8 mL/min/1.73 cm^2.[82]

Finally, there remains some controversy regarding the efficacy of radiation therapy overall for the treatment of pancreatic cancer. There is continued debate over the ideal patient population and tumor characteristics that lend themselves toward improved outcomes with the addition of radiation therapy to the treatment regimen. Additionally, the combined effects of radiation therapy with specific chemotherapeutic regimens remains poorly understood. The different chemoradiation regimens used in different trials makes interpreting and extrapolating these results for real-time patient treatment decisions difficult. The role for radiation therapy is likely to expand in the future as chemotherapeutic regimens continue to improve and are better able to control disseminated/metastatic disease, thereby increasing the number of patients that are likely to benefit from adjuvant radiation therapy. Therefore, identifying the most efficacious and least toxic radiation therapy regimens for the treatment of pancreatic cancer will be of great importance moving forward.

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CONFLICT OF INTEREST

The authors declare that they have read the article and there are no competing interests.

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