

Neoadjuvant therapy for resectable and borderline resectable pancreatic cancer

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Abstract Neoadjuvant chemoradiation for resectable and borderline resectable pancreatic cancer has been widely investigated in the past two decades. Research demonstrates that this therapy may help improve surgical margins, reduce rates of lymph node positivity, allow for earlier initiation of systemic therapy, and select for patients with aggressive disease in whom surgery may not be warranted. This review presents the data for neoadjuvant chemoradiation in pancreatic cancer with a focus on resectable and borderline resectable disease.

Keywords Pancreatic cancer · Neoadjuvant therapy · Radiation therapy · Resectable · Borderline resectable

Introduction

Despite the dismal 5-year overall survival of <5 % for pancreatic cancer, resection offers the only hope for cure. Patients with resectable pancreatic tumors who undergo resection have a far superior survival compared to patients who do not undergo resection [1]. Unfortunately, only 15–20 % of patients will present with resectable or borderline resectable disease [2]. While the median survival of early-stage pancreatic cancer patients is approximately 20–24 months, the median survival for those with locally advanced (unresectable) disease is 9–15 months [2]. Given the importance of identifying patients in

whom surgical resection is possible, careful assessment of tumor involvement of the celiac, superior mesenteric, and hepatic arteries, along with accompanying veins, is paramount preoperatively (utilizing a pancreatic protocol CT) and intraoperatively. To be considered fully resectable, pancreatic masses should have no visible metastatic sites, clear fat planes around the key central arteries (celiac, superior mesenteric, and hepatic), and no evidence of abutment, distortion, or encasement of the portal vein or superior mesenteric vein [3].

While a TNM (tumor-node-metastasis) staging system has been developed for pancreatic cancer, a consensus guideline utilizing surgical resectability (Table 1) has been developed by a joint committee of the American Hepato-Pancreato-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), and the Society for the Surgery of the Alimentary Tract (SSAT) [3, 4]. These consensus guidelines specify that a patient with tumor abutment, but with $\leq 180^\circ$ involvement of the superior mesenteric, celiac, or hepatic arteries, is considered to be borderline resectable (Fig. 1) [3]. Katz and colleagues from the MD Anderson Hospital (MDAH) also include in this category patients in whom there is a clinical concern for nodal involvement or suspicion for metastatic disease by imaging, as well as patients with marginal performance status [5]. This is an important distinction as many of these patients would previously have been considered locally advanced and not appropriate for surgical resection. However, this subgroup of patients has been the subject of many retrospective and prospective analyses regarding the use of neoadjuvant therapy in the hope of sterilizing the operative bed and downstaging the pancreatic tumor to permit a curative resection.

The advantages of neoadjuvant chemotherapy or radiotherapy for pancreatic cancer include the ability to select patients who may either be chemo- or radio-responsive and may be downstaged by upfront therapy, or not operating on those who progress or clinically deteriorate during induction therapy. Also, surgeons may be better able to achieve an R0

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Table 1 The AHPBA/SSO/SSAT pre-treatment staging system of pancreatic adenocarcinoma [5]

Resectability status	Criteria	Median survival (months)
Resectable	No distant metastases No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or encasement Clear fat planes around the celiac axis, hepatic artery, and SMA	20–24
Borderline resectable	No distant metastases Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction GDA encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the celiac axis Tumor abutment of the SMA not to exceed $>180^\circ$ of the circumference of the vessel wall	Resected, ~20 Unresected, ~11
Locally advanced	Head: no distant metastases, SMA encasement exceeding $>180^\circ$ or any celiac axis abutment, unreconstructible SMA/portal vein occlusion/encasement, extensive hepatic artery involvement, aortic invasion or encasement Body: no distant metastases, SMA or celiac axis encasement $>180^\circ$, unreconstructible SMV/portal vein occlusion, aortic invasion Tail: no distant metastases, SMA or celiac axis encasement $>180^\circ$ All: metastases to lymph node beyond the field of resection	9–15
Metastatic	Any presence of distant metastases	4–6

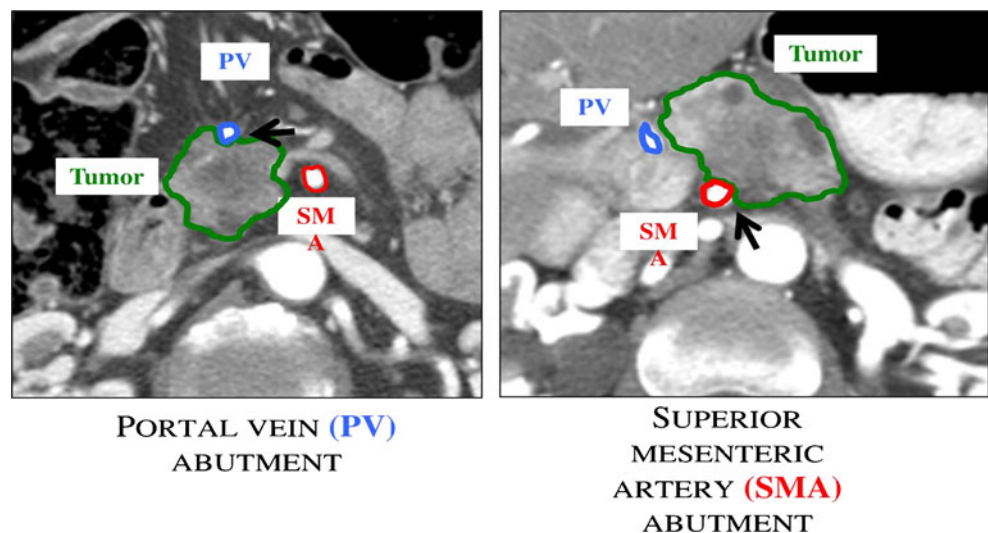
SMV superior mesenteric vein, SMA superior mesenteric artery, GDA gastroduodenal artery

resection with induction therapy. One study from MDAH showed that lymph node positivity was reduced to 38 % with induction chemoradiation, pathological complete response (pCR) rate was 1 %, and the rate of margin-negative resections was 89 % [6]. In comparison, the recently published long-term results of the US Intergroup/RTOG 9704 study of resectable pancreatic cancers treated with adjuvant chemoradiation demonstrated positive lymph nodes in 67 % of patients and an R0 resection rate of only 40 % [7]. Incorporating upfront therapy also increases the likelihood that patients will receive the needed chemotherapy and radiation therapy to treat microscopic disease, without any delays from post-operative recovery [8]. Specific benefits of the

incorporation of neoadjuvant radiation therapy include the ability to treat visible disease and target radiation to the vessel locations which qualified patients to be borderline resectable in the first place. It potentially targets an intact vascular supply for better oxygenation and may allow for smaller radiation portals. If surgery is not performed, it also allows for “definitive” local therapy in a timely fashion. The major critique of neoadjuvant therapy in pancreatic cancer is that it delays surgery and, thus, potentially eliminates a chance of cure in eligible patients.

Given the potential advantages of neoadjuvant treatment for pancreatic cancer, it has been increasingly utilized in the past two decades. Below, we review the data regarding neoadjuvant

Fig. 1 Examples of borderline resectable pancreatic cancer. *Left*, tumor abutment of the portal vein; *right*, tumor abutment of the superior mesenteric artery $<180^\circ$ circumference



therapy for potentially resectable and borderline resectable pancreatic cancer with a survey of prospective, retrospective, imaging, and pathological studies.

Predictors of response to therapy

Attention has been focused on the histopathologic response to induction therapy and subsequent patient outcomes. Tumor response has been graded according to one of three systems: Ishikawa, Evans criteria, and the College of American Pathologists (CAP); while the Ishikawa criteria are still implemented in Japan, the Evans and CAP criteria are the most widely used elsewhere [9–11]. The Ishikawa criteria grade response based on severely degenerative cancer cells (SDCCs), in which grade 1 is <33 % SDCCs, grade 2 is 33–66 % SDCCs, and grade 3 is ≥ 67 % SDCCs [9]. The Evans criteria grade response on a scale from I to IV by assessing the percentage of viable tumor cells in the post-treatment surgical specimen [10]. Increasing grade represents less viable tumor: grade I, no or little (<10 %) tumor cell destruction; grade IIa, 10–50 % tumor cell destruction; grade IIb, 50–90 % tumor cell destruction; grade III, few (<10 %) viable tumor cells; and grade IV, no viable tumor [10]. Similarly, the CAP system uses a four-tier system: grade 0, no viable residual tumor (pCR); grade 1, marked response (minimal residual tumor with single cells or cell groups); grade 2, moderate response (residual cancer outgrown by fibrosis); and grade 3, poor or no response [11].

Multiple studies have attempted to correlate patient outcomes with histological response following neoadjuvant therapy for resectable and borderline resectable pancreatic cancer. The great majority of these studies have been retrospective, and one is based on a prospective dataset [12–17]. The largest of these analyses was performed at MD Anderson by Zhao and colleagues who analyzed 442 patient specimens by the Evans criteria [12]. Patients had undergone neoadjuvant therapy (5-FU, gemcitabine, or chemoradiation) followed by pancreatic resection from 1995 to 2010 [10]. Post-treatment cancer specimens were identified as stage I (14 with ypT1 and 1 with ypT2 disease) and stage IIA disease (85 with ypT3 disease). Eleven cases (2.9 %) had a pCR. The study notes that the survival of patients with pCR to neoadjuvant therapy was significantly longer than those who had residual disease (ypT1–T3). While specific survival numbers are not provided in the published data, the Kaplan–Meier estimates suggest a disease-specific survival (DSS) of 100 % at 10 years for patients with a pCR following neoadjuvant therapy, whereas for stage I and IIA diseases following neoadjuvant therapy, DSS was approximately 70 % and 35 %, respectively. Such pathological responses probably reflect the biology of each patient's cancer.

Similar to the previous study, White and colleagues at Duke performed an analysis of 102 patients with potentially resectable tumors treated since 1994 with neoadjuvant chemoradiation (5-FU-based with 50.4 Gy of radiation), 54 (53 %) of whom underwent subsequent resection [13]. The pathological specimens were analyzed and scored according to the Evans criteria [10]. An impressive pathologic response was noted in which 73 % of patients had R0 resections, 70 % of patients had lymph node-negative resections, and 6 % had a pCR to neoadjuvant therapy. Tumor fibrosis was extensive in most specimens (76 %), and necrosis was noted in 1/3 of patients. There was no relationship between tumor necrosis and gross tumor size, initial resectability, or residual tumor load. An immunohistochemical analysis was also performed on the residual tumor specimens and revealed p53 overexpression in almost half of all specimens (44 %), and epidermal growth factor (EGFR) staining was present in 5 % of residual carcinomas. Survival was improved in patients with a small to moderate residual tumor load versus those with a large amount of residual tumor ($p=0.02$). The degree of fibrosis was not associated with survival, and tumor necrosis was associated with a worse survival ($p<0.02$).

Literature regarding treatment

Prospective trials

Neoadjuvant chemotherapy alone

Single-modality early-phase trials have primarily addressed the role of chemotherapy alone as neoadjuvant therapy for pancreatic cancer (Table 2) [18–21]. Four phase II studies have studied either gemcitabine alone or combination chemotherapy with gemcitabine [18–21]. The resection rate in this group of patients varies widely between 33 and 89 %, and the R0 resection rate is 75 %. Disease-free survival (DFS) ranges between 9.2 and 12 months, and overall survival (OS) in resected patients 18 months (range, 9.9 to 26.5 months). Palmer and colleagues compared gemcitabine alone versus gemcitabine+cisplatin as neoadjuvant therapy for resectable and borderline resectable patients [18]. The combination of gemcitabine and cisplatin led to an improved resection rate versus gemcitabine alone (70 % vs. 38 %, respectively), as well as an improved median overall survival (15.6 months vs. 9.9 months). One caveat to these studies is that the number of patients enrolled is low (range, 12–28).

Neoadjuvant radiation alone

A phase I trial studying carbon ion radiotherapy has been completed in Japan (Table 2) [22]. The authors investigated escalating doses of carbon ions from 30 to 36.8 Gy as

Table 2 Prospective single-modality therapy studies of neoadjuvant therapy for resectable and borderline resectable pancreatic cancer

Author (year)	Number of patients	Res/BR/Both (criteria)	Total RT	Frac dose	Chemo	Resection (%)	R0 (%)	Median OS (months)
Palmer (2007)	24	Both (Consensus)	NA	NA	Gem (1,000 mg/m ² weekly)	38	75	9.9 (1 year, 42 %)
	26	Both (Consensus)			Gem (1,000 mg/m ² weekly) +Cis (25 mg/m ²)	70	75	15.6 (1 year, 62 %)
Heinrich (2008)	28	Both (Consensus)	NA	NA	Gem (1,000 mg/m ² twice weekly) +Cis (50 mg/m ²)	89	80	26.5
Sahora (2011)	15	BR (Consensus)	NA	NA	Gem (900 mg/m ² weekly) +Ox (60 mg/m ²)	47	69	22 resected, 12 no surgery
Sahora (2011)	12	BR (Consensus)	NA	NA	Gem (900 mg/m ² weekly) +Tax (35 mg/m ²)	33	87	16 resected, 12 no surgery
Lee (2012)	18	BR (Consensus)	NA	NA	Gem (1,250 mg/m ² every 3 weeks)+Cap (950 mg/m ²)	61	82	16.6 (surgery 23.1, no surgery 13.2)
Shinoto (2012)	26	Res (Consensus)	30–36.8	Carbon ions	None	81	90	18.6 (1 year 69 %, 3 years 42 %, 5 years, 42 %)

Res resectable, BR borderline resectable, RT total radiation dose, Frac dose fractionated radiation dose, Gem gemcitabine, Cis cisplatin, Ox oxalipatin, Tax taxotere, Cap capecitabine, NA not applicable

neoadjuvant therapy for resectable pancreatic cancer. The resection rate was high (81 %) as was the R0 resection rate (90 %). In this select group of patients, local control was 100 %, DFS was 6.2 months (40 % 1-year DFS, 23 % 3- and 5-year DFS), and OS was 18.6 months (69 % at 1 year, 42 % at 3 and 5 years). In the subset of patients who underwent surgery, the 5-year survival was an impressive 52 %. Intriguingly, grade 3/4 toxicity was low at 8 %. Concurrent chemotherapy was not administered with the radiation. These exciting results suggest a role for further investigational trials on this subject with the caveat that the availability of this technology remains limited.

Induction chemotherapy prior to neoadjuvant chemoradiation

Induction chemotherapy prior to neoadjuvant chemoradiation has also been investigated (Table 3) [23–26]. Most of these trials have studied induction gemcitabine-based chemotherapy. Resection rates range from 18 to 71 % with induction chemotherapy, and R0 resection rates vary between 50 and 96 %. The largest of these studies was completed by Varadachary and colleagues and studied the use of gemcitabine and cisplatin prior to neoadjuvant chemoradiation with gemcitabine and 30 Gy of external beam radiation therapy (EBRT) [24]. In their 90-patient trial, a median DFS of 13.2 months and an OS of 17.4 months were observed. As with previously described data, the survival rate of resected patients was statistically greater than that of unresected patients (28.3 months vs. 10.5 months) in this series. Pipas and colleagues investigated the role of induction cetuximab, an epidermal growth factor receptor antibody, prior to neoadjuvant chemoradiation with gemcitabine [26]. They reported a

relatively high pathologic complete response rate (8 %) in the post-operative specimen, with similar survival results as seen in previous trials. However, EGFR receptor status was not predictive of response to therapy.

Neoadjuvant chemoradiation

Neoadjuvant chemoradiation has been extensively studied in prospective phase I and II clinical trials and prospective database studies (Table 4) [6, 17, 25, 27–41]. Gemcitabine and either 5-FU or capecitabine have been the primary chemotherapy used, while radiation doses have mostly been up to 50.4 Gy in 1.8 Gy/fraction, though some have used 30 to 36 Gy in 3 Gy/fraction. Because the standard definition of “borderline resectable” was not widely applied until the mid-2000s, trials initiated prior to this date may not have had the NCCN/Consensus guidelines used in their accrual. However, data from these trials are interpreted as closely as possible using the NCCN/Consensus definitions for resectability.

Evans and colleagues from MD Anderson Hospital published the results of their prospective phase II trial of neoadjuvant chemoradiation for resectable pancreatic cancer in 2008 [6]. Their treatment regimen consisted of concurrent weekly gemcitabine (400 mg/m²) and 30 Gy in ten fractions followed by five additional doses of weekly gemcitabine at the same dose. Of their 86 enrolled patients, 73 (85 %) underwent surgical resection, and 64 (74 %) had a successful pancreatectomy. The median survival of their entire cohort was 22.7 months, with a statistically better survival in patients who underwent pancreatectomy (34 months vs. 7 months, $p < 0.001$). This improved survival was dramatically demonstrated in the rates of 5-year survival: 36 % in resected patients versus 0 % in unresected patients. Progression-free survival

Table 3 Prospective studies of induction chemotherapy followed by neoadjuvant chemoradiation for resectable and borderline resectable pancreatic cancer

Author (year)	Number of patients	Res/BR/Both (criteria)	Total RT (field size)	Chemo	Resection (%)	R0 (%)	Median OS (months)
Pipas (2005)	24	Both (Lu (AJR))	50.4 (Large)	Docet (65 mg/m ²)+Gem (4,000 mg/m ² every 2 weeks) →Gem (50 mg/m ² twice weekly)+50.4	71	76	14 (all patients)
Varadhachary (2008)	90	Res (MDAH)	30 (Small)	Gem (750 mg/m ² every 2 weeks)+Cis (30 mg/m ²) →Gem (400 mg/m ² weekly)+30 Gy	66	96	17.4 (resected 28.3, unresected 10.5)
Landry (2010)	10	BR (Consensus)	50.4 (Small)	Gem (500 mg/m ² , weekly)	30	33	19.4 (resected 26.3), 1 year, 69 %
Leone (2012)	15	BR (Consensus)	50.4 (Small)	Gem (175 mg/m ² , four doses)+Cis (20 mg/m ²) →5-FU (CI, 225 mg/m ²)+50.4 Gy	18	50	13.4 (resected 26.3), 1 year, 62 %
Pipas (2012)	33	Both (Consensus)	54.0 (Large)	Gem (1,000 mg/m ²)+Ox (100 mg/m ²) →Gem (50 mg/m ² twice weekly)+50.4 Gy Cetuximab (400 mg/m ²) →Gem (50 mg/m ² twice weekly) + cetuximab (250 mg/m ²)+54 Gy	60	Res, 100; BR, 78	27.8 BR, 12.3 unresected 17.3 (24.3 resected, 10.0 unresected)

Res resectable, BR borderline resectable, RT total radiation dose, Frac dose fractionated radiation dose, Gem gemcitabine, Cis cisplatin, Ox oxaliplatin, Tax taxotere, Cap capecitabine, Small radiation field included gross tumor and involved nodes only, Large radiation field included gross tumor and prophylactic regional nodal treatment, Unsp unspecified

was 28.6 months in resected patients. Local recurrence was only 11 % in patients who underwent successful surgery. One unique finding from an earlier prospective database analysis from MD Anderson was the influence of intra-operative radiation therapy (IORT) [42]. They specifically identified that in 56 % of patients receiving IORT in their patient population, IORT did not provide a survival benefit, though no local recurrences were observed with the addition of IORT to full dose (50.4–54.0 Gy) EBRT.

A study by Landry and colleagues compares induction chemotherapy followed by neoadjuvant chemoradiation versus neoadjuvant chemoradiation alone [25]. Both borderline resectable and locally advanced patients were enrolled in this study. In this randomized trial, overall resection rate, R0 resections, DFS, and OS were higher in patients treated with neoadjuvant chemoradiation alone.

Surgical results from a summary of these trials in Table 6 show a median resectability rate of 57 % (range, 18 to 100 %) and a median R0 resection rate of 85 % (range, 33 to 100 %). DFS and OS vary widely as represented in Table 6. Reported 1-year DFS ranges from 42 to 59 % for resected patients, and 2-year DFS ranges from 33 to 43.7 %. Extended OS (>2 years) for patients with resectable disease ranges from 28 to 58 % in this collection of randomized trials [6, 27, 28, 33, 35]. Grade 3/4 toxicities range from 20 to 66 %, while reported surgical complications range from 0 to 50 %. Randomized prospective data is limited for neoadjuvant therapy in pancreatic cancer.

One factor that may result in differences between these trials is the varied implementation of adjuvant therapy. Due to the variety of agents and cycles used, it is difficult to reliably interpret data from these trials in their use of adjuvant therapy.

In general, prospective data appears to support the use of neoadjuvant therapy in resectable and borderline resectable tumors in identifying patients more likely to present with metastatic disease shortly after surgery and, hence, sparing them from significant surgical side effects. Overall and R0 resection rates appear to be favorable with relatively low surgical complications and reduced pancreatic leak rates [5]. Many surgeons agree that surgery following chemotherapy or chemoradiation for pancreatic cancer does not increase surgical morbidity if it is performed within a reasonable period (approximately 4–8 weeks) of the completion of radiation. While this data is extremely encouraging to consider the standardization of neoadjuvant chemoradiation in resectable and borderline resectable pancreatic cancer, a large randomized, prospective phase III clinical trial will be necessary to answer this question.

Retrospective data

Multiple retrospective series have been performed on the topic of neoadjuvant therapy for resectable pancreatic cancer

Table 4 Prospective trials utilizing neoadjuvant chemoradiation for resectable and borderline resectable pancreatic cancer

Author (year)	Number of patients	Res/BR/Both (criteria)	Total RT (field size)	Chemo	Resection (%)	R0 (%)	Median OS (months)
Yeung (1993)	8	Both (local disease)	50.4 (Small)	5-FU (CI, 1,000 mg/m ²)+ MMC (10 mg/m ²)	80		5 years, 16 % (resected 58 %, unresected 0 %)
Magnin (2003)	32	Both (Consensus)	45 Gy or split course 30 Gy (Large)	5-FU (CI, 650 mg/m ²)+ Cis (80 mg/m ²)	59	89	
Le Scodan (2009)	41	Res (Unsp)	50.4 (Small)	5-FU (CI, 300 mg/m ²)+ Cis (20 mg/m ²)	63	81	9.4 (resected 11.7, unresected 8.5, no surgery 5.7)
Staley (1996)	39	? (MDAH)	50.4/30 (Small)	5-FU (CI, 300 mg/m ²)	100	82	19
Spitz (1997)	91	Res (Führman et al.)	50.4/30 (Unsp)	5-FU (CI, 300 mg/m ²)	57	88	19.2 pre, 20.2 post, 7.2 no surgery
Mehta (2001)	15	BR	50.4	5-FU (CI, 250 mg/m ²)	60	100	30 resected vs. 8 unresected
Breslin (2001)	132	Both (MDAH)	45/50.4/30+IORT in 56 % (Unsp)	Most CI 5-FU, some Gem, Tax			21 (5 years, 23 %)
Piperdi (2010)	8	BR (MDAH)	50.4 (Large)	5-FU or Gem		100	Neoadjuvant+surgery 16.1 vs. surgery alone 14.0
Ammori (2003)	18	BR (Consensus)	50.4 Gy (Large)	Gem (300 to 700 mg/m ² weekly)	33		Resected 17.6, unresected 11.6
Joensuu (2004)	25	BR (MDAH)	50.4 (Small)	Gem (300 mg/m ² weekly)			25 (1 year 67 %, 2 years 55 %)
Evans (2008)	86	Res (MDAH)	30.0 (Large)	Gem (400 mg/m ² weekly)	74	89	22.7 (resected 34, unresected 7), 5 years, 27 % (resected 36 %, unresected 0 %)
Talamonti (2006)	20	Res (Consensus)	36 Gy (Small)	Gem (1,000 mg/m ² , three doses)	85	94	18 (resected 26, 2 years 61 %)
Marti (2008)	3	BR (Consensus)	50.4 (Large)	Gem (1,000 mg/m ² weekly)+Cis (30 mg/m ²)	100	100	13 (no difference between resected and unresected)
Landry (2010)	10	BR (Consensus)	50.4 (Small)	Gem (500 mg/m ² weekly)	30	33	19.4 (resected 26.3, 1 year 69 %)
	11		50.4 (Small)	Gem (175 mg/m ² twice weekly)+Cis (20 mg/m ²)→5-FU (CI, 225 mg/m ²)+50.4 Gy	18	50	13.4 (resected 26.3, 1 year, 62 %)
Pisters (2002)	36	Res (MDAH)	30 Gy EBRT+ 10/15 IORT (Large)	Paclitaxel (60 mg/m ²)	56	68	12 (3 year, 14 %), resected 19 (3 years, 28 %), no surgery 10 months
Lind (2008)	17	BR (Consensus)	50.4 (Small)	Cap (2,000 mg/m ²)+Ox (130 mg/m ²)	47		19 (4 years 24 %)
Turrini (2010)	34	Res (Consensus)	45.0 (Large)	Docetaxel (300 mg/m ²)	50		Resected 32 (5 years 41 %), overall 15.5 (5 years, 20.6 %)
Stokes (2011)	34	BR (MDAH)	50.4 (Small)	Cap (1 g AM, 2 g PM)	46	75	23.0 (resected)
Satoi (2012)	34	BR (Consensus)	50.4 (Small)	S-1 (Tegafur, CDDP, oteracil) 80 mg/m ²	88	93	NR

Res resectable, BR borderline resectable, RT total radiation dose, Gem gemcitabine, Cis cisplatin, Ox oxaliplatin, Tax taxotere, Cap capecitabine, Small radiation field included gross tumor and involved nodes only, Large radiation field included gross tumor and prophylactic regional nodal treatment, NR not reported

Table 5 Retrospective studies on neoadjuvant therapy for resectable and borderline resectable pancreatic cancer

Author	Number of patients	Res/BR/Both (criteria)	Total RT (field size)	Chemo	Resection (%)	R0 (%)	Median OS (months)
Calvo (2004)	15	BR (Unsp)	45.0 (Large)	Tegafur	60	77	10 (22 resected/7 unresected)
Brown (2008)	13	BR (Consensus)	50.4 (NR)	5-FU or Gem	100	85	Not reached
Satoi (2009)	19	BR (Consensus)	40.0 (Large)	Cis/5-FU or Gem	84	94 (combined R0/R1)	Not reached
Chun (2010)	74	BR (MDAH)	Unsp	Gem or 5-FU	46	59	23
McClaine (2010)	26	BR (MDAH)	(Only three patients)	5-FU or Gem	46	67	20.0 resected vs. 9.2 unresected
Kang (2012)	32	BR (Consensus)	45–50.4 (Small)	Gem	88	88	26.3
Patel (2011)	18	BR (MDAH/Consensus)	50.0 (Small)	GTX → 5-FU+RT	53	89	15.6
Takahashi (2011)	24	BR (Consensus)	Unsp	Unsp	33	71	15.7 (2 years 33 %)
Arvold (2012)	24	BR (Consensus)	50.4 (Unsp)	5-FU	33	79	35 month MS from surgery
Banugola (2012)	27	BR (MDAH/Lu)	50.4 (Unsp)	Gem-based	96 CRT, 35 chemo	96 CRT, 35 chemo	35 month MS from surgery
Estrella (2012)	240	Res (MDAH)	Unsp	5-FU or Gem-based CRT or with induction chemo	75	89	34 (1 year 91 %, 3 years 47 %)
Hossein (2012)	4	BR (Consensus)	None	FOLFIRINOX	95	100	1 year 100 %
Sho (2012)	64	Both (Consensus)	50–54 (Large)	Gem	95	92 (vs. 52 % no NA CRT)	28 (1 year 85.8 %, 2 years 59.4 %)

Res resectable, BR borderline resectable, RT total radiation dose, Frac dose fractionated radiation dose, Gem gemcitabine, Cis cisplatin, Ox oxaliplatin, Tax taxotere, Cap capecitabine, Small radiation field included gross tumor and involved nodes only, Large radiation field included gross tumor and prophylactic regional nodal treatment, Unsp unspecified, CRT chemoradiation therapy

Table 6 Ongoing prospective clinical trials with neoadjuvant chemotherapy alone in resectable and borderline resectable pancreatic cancer

Clinical trial number	Phase	Neoadjuvant investigational therapy	Location	Date opened
NCT01442974		Gem+Abraxane	Spain	January 2011
NCT01456585	I	Gem+CP-870,893	University of Pennsylvania	April 2012
NCT00892242	I	Zoledronic acid	Washington University (St. Louis)	December 2009
NCT01431794	I/II	LDE-225 (hedgehog inhibitor)+Gem	Johns Hopkins	September 2011
NCT01088789	II	Neoadjuvant GM-CSF secreting vaccine +/- cyclophosphamide	Johns Hopkins	April 2010
NCT01660711	II	FOLFIRINOX	University of Chicago	July 2012
NCT01298011	II	Gem+Abraxane	Celegene Corp (USA)	May 2011
NCT00733746	II	Gem+Tarevea	National Cancer Institute	April 2009
NCT01150630	II/III	Gem +/- Xeloda and epirubicin and cisplatin	Italy	May 2010
NCT00727441	III	Neoadjuvant GM-CSF secreting vaccine +/- cyclophosphamide	Johns Hopkins	July 2008
NCT01521702	III	Gem+oxaliplatin	France	December 2011
NCT01314027	III	Gem+oxaliplatin	Switzerland	September 2009

Gem gemcitabine, *FOLFIRINOX* combination chemotherapy of 5-FU, leucovorin, oxaliplatin, and irinotecan

[43–55]. Historically, retrospective studies have focused on locally advanced disease, but more recent data has included primarily resectable cancers. Most studies have included chemoradiation, but limited data on chemotherapy alone is also available [49, 54].

A review of 13 retrospective studies from 2004 to 2012 demonstrated that the majority of patients in whom neoadjuvant therapy was analyzed pertained primarily to borderline resectable disease (Table 5) [43–55]. As a whole, the median number of patients included in these studies was 22. Most patients received either 5-FU or gemcitabine-based therapy, and the most common radiation therapy regimen was to 50.4 Gy in 1.8-Gy fractions. The median resection rate following neoadjuvant therapy was 68 %; the median R0 rate was 89 % with a pCR rate of approximately 9 %. In a retrospective analysis by Barugola et al., the R0 rate was significantly in patients who received neoadjuvant chemoradiation versus chemotherapy alone (96 % vs. 35 %, respectively) [52]. Local control following chemoradiation ranged between 78 and 89 %.

Overall survival and disease-free survival were reported in most studies [43, 46–50, 52–55]. One-year DFS ranged from 51 to 88 %, while 1-year OS ranged from 85.8 to 100 %. Median OS for resected patients ranged from 15.3 to 35 months. In two studies, a statistically significant difference in overall survival was noted between resected and unresected patients following neoadjuvant therapy (median, 21 months vs. 8.1 months, respectively). Data from the largest of the retrospective analyses was completed by Estrella et al. and showed a survival benefit for neoadjuvant therapy versus adjuvant therapy for resectable disease (33.5 months vs. 26.4 months, $p=0.04$) [53].

Neoadjuvant therapy was also reported to be safe, though with grade 3/4 toxicity rates of 22 to 66 %. Surgical

complication rates ranged between 24 and 67 %. One study noted that neoadjuvant therapy led to decreased rates of pancreatic fistula and shorter hospital stays [55]. This is in contrast to Kang et al. who reported higher rates of second blood transfusions and longer hospital stays with neoadjuvant therapy [48].

Surveillance, Epidemiology, and End Results (SEER) databases allow for a review of patient charts as reported to a central database. Two SEER database analyses have been completed in the USA [56, 57].

The larger of these SEER studies was completed by Stessin in 2008 [56]. They identified patients treated from 1993 to 2003 with neoadjuvant radiation therapy for pancreatic cancer. They removed patients with stage III/IV disease to limit the contribution of unresectable disease. Of the 3,885 patients that met their initial criteria, 70 (2 %) were treated with neoadjuvant chemoradiation, 1,478 (38 %) had adjuvant radiation, and 2,337 (60 %) had no radiation as part of their treatment. The authors' major findings support an improved median survival of 23 months with adjuvant radiation versus a median survival of 14 months in patients without radiation (hazard ratio (HR) 0.55, $p<0.01$).

A more recent SEER database analysis was completed by Artinyan in 2011 and reviewed patients as part of the California Cancer Surveillance Program [57]. A comparative analysis was performed between patients treated with neoadjuvant therapy and those treated with adjuvant therapy. A far greater number of patients were included in the adjuvant therapy group (419 patients) than in the neoadjuvant therapy group (39 patients). As with the previous SEER database study, the overall survival was statistically greater for patients treated with neoadjuvant therapy (33.8 months vs. 19.0 months, $p=0.003$). When controlling for lymph node status, tumor extension, and the addition of radiation, neoadjuvant

chemotherapy was still associated with improved overall survival (HR for death 0.57, $p=0.013$).

A Japanese survey of pancreatic cancer patient outcomes in 146 institutions was performed and showed similar survival patterns as the aforementioned SEER database analyses [58]. While retrospective and difficult to control for the heterogeneity of cases, the SEER database analyses provide further hypothesis-generating data along with the previously noted retrospective analyses for the use of neoadjuvant therapy.

Meta-analyses of neoadjuvant therapy data

Given the substantial amount of data accumulated, predominantly in the last two decades, on the utilization of neoadjuvant therapy for pancreatic adenocarcinoma, it comes as no surprise that multiple meta-analyses have been published in an attempt to fully digest this data [59–62]. Laurence and colleagues reviewed 19 cohort studies conducted between 1985 and 2007 [59]. Studies were selected to include all categories of patients which included initially unresectable disease. The neoadjuvant chemoradiation schedule was predominantly comprised of 5-FU- or gemcitabine-based chemotherapy and radiation typically prescribed to a dose of 45–50.4 Gy in 1.8- to 2.0-Gy fractions. A total of 2,148 patients were included in this analysis: neoadjuvant chemoradiation was administered to 901 patients (469 of which went on to receive subsequent surgery) who were compared to 982 who did not receive neoadjuvant therapy (811 underwent resection). It should be noted that only 4 of the studies analyzed included resectable patients; the remaining 15 had unresectable and borderline resectable patients. The authors note that the survival of patients with initially unresectable disease is improved with the addition of neoadjuvant therapy but, unfortunately, do not separate the survival of borderline resectable patients in this analysis. This may be due to the great heterogeneity seen in patients treated during this time period and the various definitions of borderline (or potentially) resectable cancer utilized.

The largest meta-analysis we identified was published by Gillen in 2010 [61]. This study included phase I and II clinical trials, cohort studies, and retrospective case series. In all, they were able to compile patients from 78 prospective studies and 33 retrospective studies. Neoadjuvant chemotherapy was utilized in 96.4 % of these studies (mostly gemcitabine- (46 %) and 5-FU-based (54 %) treatments), and radiation therapy was used in 93.7 % of studies (most commonly between 45 and 50.4 Gy in 1.8-Gy fractions). Though their group included an array of patients, they were able to dichotomize patients into two groups: group 1, patients that were initially resectable, and group 2, initially unresectable disease. Imaging outcomes (by Response Evaluation Criteria in Solid Tumors (RECIST)), resectability, morbidity, toxicity, and survival were reported. Neoadjuvant therapy led to an imaging complete response (CR) in 3.9 % of patients, partial response (PR) in 29.1 %,

stable disease in 43.9 %, and progressive disease (PD) in 20.8 %. Overall grade 3/4 toxicity in 29.4 % of neoadjuvant therapy patients was evenly distributed between groups 1 and 2 (26.3 and 31.1 %, respectively). Resection was completed in 75.5 % of group 1 patients and 32.8 % of group 2 patients. In all resectable cases, however, R0 resections were accomplished in a vast majority of cases, with 82.1 % of group 1 and 79.2 % of group 2 patients. It should be noted that perioperative morbidity was higher in group 2 patients, 39.1 % versus 26.7 %, as was in-hospital mortality, 7.1 % versus 3.9 %. Overall survival was strongly correlated to resection. In group 1 patients, the median survival in resected patients was 23.3 months versus 8.4 months for those unresected. Similar results were seen in group 2 patients (20.4 months vs. 10.2 months). Though the data from meta-analyses can often be difficult to interpret given the heterogeneity of patients between trials as well as treatment differences that occur with time, this data strongly suggests that neoadjuvant therapy may not only help achieve margin-negative resections but also identify patients that may otherwise not benefit from upfront resection.

Imaging outcomes

Recently, multiple studies have sought to quantify imaging responses to neoadjuvant therapy for pancreatic cancer patients [63, 64]. Chuong and colleagues performed a small retrospective analysis of neoadjuvant gemcitabine, taxotere, and capecitabine, followed by radiation (50.4 Gy, predominantly intensity modulated radiation therapy (IMRT)) and 5-FU for borderline resectable pancreatic cancer patients [63]. The authors analyzed whether tumor response to neoadjuvant therapy was best assessed using one-, two-, or three-dimensional measurements on follow-up CT scans. Fourteen patients were included, and the results demonstrated that all measurement dimensions were concordant to one another, with even one-dimensional measurements of tumor response being equal to volumetric measurements. Further, the authors report that responses were equivalent whether utilizing the WHO, RECIST, or volumetric methods in all but one patient. All 14 patients in this analysis underwent surgical resection, with 12 (86 %) achieving an R0 resection and 2 (14 %) with microscopically positive margins.

A larger retrospective analysis was completed at the MD Anderson Cancer Center [64]. In this report, 129 patients with borderline resectable pancreatic cancer as defined by the AHPBA/SSO/SSAT or MD Anderson criteria were included. Patients underwent neoadjuvant therapy with one of two treatment regimens: (1) gemcitabine-based systemic chemotherapy followed by chemoradiation to 30 Gy in ten fractions or 50.4 Gy in 1.8-Gy fractions along with concurrent gemcitabine, 5-FU, or capecitabine; and (2) chemoradiation alone. A pre-

treatment CT scan with oral and intravenous contrast was performed, as was a post-neoadjuvant therapy CT scan. Response criteria followed the modified RECIST criteria: PD was identified as new metastatic foci or an increase in greatest dimension by $\geq 20\%$, a PR was defined as a decrease of $\geq 30\%$ in greatest dimension, CR was disappearance of the primary tumor, and stable disease (SD) was tumor growth $< 20\%$ or shrinkage $< 30\%$. This study demonstrated a lack of significant CR by imaging criteria [64]. Of the 122 patients assessed for response using the AHPBA/SSO/SSAT criteria, only 1 patient was downstaged, 98 patients remained the same (80%), and 23 patients had upstaging (19%). This does not imply that the tumor did not decrease in size, only that the consensus surgical stage was not altered by the treatment. Of the treated patients, only patients with a PR or SD underwent resection. The single patient with disease downstaging underwent resection, as did 82 of the 98 patients with SD (84%). RECIST response was not associated with a longer median overall survival, but surgically resected patients had a median overall survival of 33.0 months as opposed to 12.0 months in those that did not undergo resection. Further, an R0 resection was accomplished in 81/101 patients (80%) in whom metastatic disease was not observed following neoadjuvant therapy. The authors conclude that despite a lack of radiographic response in this patient population, aggressive resection should be attempted in borderline resectable patients following neoadjuvant therapy in the absence of locally progressive or metastatic disease.

The use of FDG-PET scanning is an area of active research in pancreatic cancer. This modality continues to be explored for its possible role in determining treatment response as retrospective analyses demonstrate that it may have clinical utility in identifying tumor response and potential resectability [65–69]. As a whole, these studies demonstrate improved survival and resectability in patients who achieve a PET response, defined as $\geq 50\%$ reduction in PET avidity. However, they are all limited by their small patient size and lack of a numerical SUV for universal implementation. Testing the use of PET scans in a large prospective trial will help determine the clinical accuracy of this imaging modality for pancreatic cancer.

Pathological correlation with patient outcome

While the rationale for neoadjuvant therapy in pancreatic cancer would suggest that most patients with localized, surgically resectable disease will be benefited, there is a small group of patients that does not benefit from this treatment modality. Histopathologic analyses have been performed to assess whether a subset of patients that will not benefit from this treatment may be identified. Further, predictive markers have also been studied to answer this question.

Limited studies exist regarding predictive markers of patient outcome in pre-treated patient samples. A study by Preis and colleagues from Dartmouth Medical Center studied pancreatic cancer patients treated with neoadjuvant gemcitabine-based chemoradiation followed by planned surgical resection [70]. They investigated the correlation of microRNA expression, as characterized by in situ hybridization and immunohistochemistry, and patient outcomes. They found that lower levels of miRNA10b expression correlated with an improved response to multimodality neoadjuvant therapy, an improved likelihood of surgical resection, delayed time to metastases, and increased survival. However, this study is limited by its small sample size (ten patients) uncommon use of this test, and needs to be reproduced in a prospective setting.

Data from Iacobuzio-Donohue and colleagues demonstrates that positive immunolabeling of DPC4 (deleted in pancreatic cancer) on rapid autopsy specimens may be more locally destructive tumors and less metastatic disease, whereas loss of DPC4 labeling was associated with a higher burden of metastatic disease and less locally advanced disease [71]. Further research on this topic will elucidate whether this marker may be used to prospectively consider intensification of radiation therapy for DPC4 wild-type cases and intensification of chemotherapy for DPC4 mutated cases, prior to surgical research for initially non-metastatic disease.

CA 19–9 is a sialylated Lewis A blood group antigen commonly associated, but not specific for, pancreatic tumors. It should be obtained in the preoperative setting with a normalized bilirubin, as well as in the post-operative setting to monitor for treatment response [8]. Katz et al. investigated the role of CA 19–9 in two phase II clinical trials for neoadjuvant therapy (gemcitabine-based chemoradiation) for surgically resectable patients [72]. In the pre-treatment setting, patients with a CA 19–9 in the normal range had a more favorable survival than those with an elevated CA 19–9 ($p=0.02$), though this was not maintained when evaluating only patients who underwent a pancreaticoduodenectomy ($p=0.08$). At re-staging, a CA 19–9 cutoff of 61 U/mL was proposed as the optimal cutoff value that maximized both sensitivity (72%) and specificity (69%) for completing all therapy. A decreased CA 19–9 between pre-treatment and re-staging was correlated with more favorable survival (25.7 months vs. 10.4 months, $p=0.01$), and these patients were more likely to undergo surgery (77% vs. 42%, $p=0.02$) [72]. There was no correlation between treatment effect in the surgical specimen and CA 19–9 change over the course of induction therapy. Further study is necessary prior to utilizing this marker in routine clinical selection of treatment options following induction therapy, but it is suggestive that CA 19–9 may help guide therapeutic strategies.

In an effort to better clarify which patients may need more aggressive therapy following surgery, the prognostic significance of lymphovascular invasion, perineural invasion (PNI),

Table 7 Ongoing prospective clinical trials with neoadjuvant chemoradiation in resectable and borderline resectable pancreatic cancer

Clinical trial number	Phase	Neoadjuvant investigational therapy	Location	Date opened
NCT01446458	I	FOLFIRINOX followed by SBRT (12 Gy×3 fractions)	Emory University	November 2011
NCT01068327	I	Gem+leucovorin+5-FU followed by SBRT (five fractions) with concurrent nelfinavir	University of Nebraska	November 2007
NCT01027221	I/II	Low-dose radiation (one fraction of 0.5, 2.0, or 5.0 Gy)	Germany	November 2009
NCT01458717	II	CRT (54 Gy+Gem), followed by surgery vs. surgery followed by adjuvant 54 Gy+Gem	Korea	November 2011
NCT01333332	II	CRT with Xeloda and standard fraction RT	University of Virginia	August 2010
NCT01397019	II	FOLFIRINOX followed by 50.4 Gy RT	Denmark	October 2011
NCT01661088	II	FOLFIRINOX followed by concurrent Gem+50.4 Gy RT	University of Michigan	June 2011
NCT01531712	II	Gem+oxaliplatin+Tarceva followed by Gem+Tarceva+ radiation (50.4 Gy)	Spain	July 2011
NCT01591733	II	FOLFIRINOX followed by 5 days of proton radiation (dose not specified)	Massachusetts General Hospital	May 2012
NCT01560949	II	FOLFIRINOX followed by concurrent Gem+50.4 Gy RT	MD Anderson	June 2012
NCT01470417	II	Abraxane+Gem followed by concurrent radiation (dose not specified) and chemotherapy (not specified)	University of Florida	October 2011
NCT01240304	II	Gem and radiation (7.0 Gy/fraction) alternating every 24 h for a total of ten treatments (total 35 Gy RT)	University of Arkansas	November 2010
NCT01677988	II	FOLFIRINOX→Xeloda+radiation (dose not specified)	Medical University of South Carolina	July 2012
NCT00456599	II	Gem+oxaliplatin+radiation (30 Gy in ten fractions)	University of Michigan	April 2007
NCT01389440	II	Gem+Tarceva followed by Gem+Tarceva+radiation (45 Gy)	Spain	May 2011
NCT01360593	II	Gem+Xeloda followed by SBRT (12 Gy×3 fractions)	University of Pittsburgh	July 2011
NCT00609336	II	Gem+Xeloda+oxaliplatin+Cisplatin+IMRT	University of Washington	January 2008
NCT00557492	II	Gem+Avastin+radiation (30 Gy in 10 fractions)	University of Pittsburgh	December 2006
NCT00763516	II	Xeloda+proton radiation (50.4 CGE)	University of Florida	September 2008
NCT01494155	II	Xeloda+hydroxychloroquine+proton radiation (five fractions)	Massachusetts General Hospital	December 2011
NCT01065870	II	Gem+Xeloda+docetaxel +/- radiation (50.4 Gy)	Columbia University	December 2009

CRT chemoradiation therapy, *RT* radiation therapy, *Gem* gemcitabine, *FOLFIRINOX* combination chemotherapy of 5-FU leucovorin, oxaliplatin, and irinotecan, *Gy* gray

and involvement of the portal vein or superior mesenteric vein has been investigated [73–76]. The work by Chatterjee and colleagues indicates that tumor invasion into lymphatic spaces was associated with a higher percentage of lymph node positivity but not in other clinical outcomes; tumor invasion into vasculature was associated with a worse DFS and OS than in patients with no lymphovascular invasion or lymphatic invasion alone [74]. In an extension of the same dataset, Chatterjee and colleagues presented data suggesting that the presence of intraneural and PNI in the surgical specimen correlated with a worse DFS and OS [73]. A similar outcome was described by Takahashi and colleagues who noted that nodal involvement and PNI in the surgical specimen portend a worse disease-free survival, but went on to note that PNI was associated with a statistically higher risk of recurrence within the abdominal cavity while nodal involvement was the single factor associated with an increased risk of distant recurrence [75]. Lastly, Wang and colleagues noted that histopathologic tumor involvement of the resected portal vein and superior mesenteric vein was associated with greater intraoperative blood loss,

larger tumor size, increased margin-positive resection, and a greater risk of local recurrence and distant metastasis [76]. In summary, PNI and vascular involvement may be associated with a worse outcome for pancreatic cancer patients and may warrant more aggressive therapy.

Current research protocols

Active areas of research on the use of neoadjuvant radiation in borderline resectable pancreatic cancer will likely focus on the use of FOLFIRINOX and stereotactic body radiation therapy (SBRT). Given the interest in FOLFIRINOX and the survival advantage seen in metastatic patients, it follows that many clinical trials will be applying this chemotherapy regimen in the neoadjuvant and adjuvant setting [77]. Stereotactic radiation therapy has gained active interest in the pancreatic cancer community, though its utility has primarily been limited to unresectable disease [78–83]. It follows that ongoing and upcoming protocols will implement SBRT in the treatment

of borderline tumors to further improve resectability and R0 resection rates. Additional concepts may focus on a radiation boost to the regions of vessel involvement to better facilitate margin-negative surgery. Tables 6 and 7 list the actively accruing clinical trials investigating neoadjuvant therapy in resectable and borderline resectable pancreatic cancer as identified in clinicaltrials.gov.

Summary

Resectable and borderline resectable pancreatic cancer patients are a group of patients in whom neoadjuvant radiation therapy may provide a significant benefit. It is important for the radiation oncologist to understand this data to best implement it not only into his or her own practice but also to make appropriate recommendations in the multi-disciplinary setting. As detailed in our review, the use of radiation therapy in this population may allow not only for resectability in the borderline setting but also an R0 resection, thus improving a patient's chance for cure. R0 resection rates may be improved with the addition of chemoradiation neoadjuvantly compared to chemotherapy alone in the setting of borderline resectable pancreatic cancers. Ongoing clinical trials will help define the role of specific chemotherapies and stereotactic body radiation therapy in the management of borderline resectable pancreatic cancer.

At this time, the standard of care for the utilization of neoadjuvant chemoradiation in the setting of a resectable or borderline resectable tumor involves between 1 and 3 cycles of chemotherapy prior to chemoradiation. For patients with a poor performance status or concern for early progression, gemcitabine alone is the most common first agent applied. However, if the patient has a better performance status, combination chemotherapy, usually GTX (gemcitabine-taxotere-Xeloda (capecitabine)) or FOLFIRINOX, may be considered prior to chemoradiation prior to chemoradiation. While combination chemotherapy may offer a stronger treatment regimen, it comes at a risk of significant grade 3/4 toxicities and should be used with caution [77].

If the patient does not develop metastatic disease during the application of initial chemotherapy, radiation therapy is subsequently administered with chemotherapy. A dose of 50 to 54 Gy may be delivered to the primary tumor and peripancreatic lymph nodes using conventional or three-dimensional conformal radiation beams. If using doses greater than 54 Gy, IMRT with image guidance is necessary. Ideally, this is to be done in a clinical trial. The Radiation Therapy Oncology Group is conducting a dose escalation study in which the primary tumor will receive 63 Gy for unresectable tumors. Active participation in this upcoming protocol is encouraged.

Finally, altered fractionation, including SBRT, may be used in the neoadjuvant setting. Inclusion in a clinical trial is the recommended scenario for using this method. Early data has delivered very high doses in a single fraction, though fractionation (typically five fractions) is gaining significant popularity [78–83]. Despite encouraging early data, long-term prospective validation is necessary before this may be considered the standard of care. With that said, the potential benefits to SBRT in terms of reduced toxicity, increased patient convenience, and reduced time to resection cannot be overlooked.

Conflict of interest Rachit Kumar declares that he has no conflicts of interest. Salma Jabbour declares that she has no conflicts of interest.

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