Neoadjuvant Therapy for Pancreatic Cancer: A Current Review

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The optimal therapy for pancreatic cancer continues to evolve. Neoadjuvant chemoradiation is a key component of current treatment regimens, and evaluation of previous treatment options will help guide future trials. Here the authors present a review of the current literature with discussion of future directions.


**BACKGROUND**

Pancreas cancer remains a dire diagnosis accompanied by an unacceptably high mortality. Annually, 37,000 patients are diagnosed with pancreatic cancer, and without significant advances nearly all will die of their disease [1]. For many years, a minority of pancreas cancer patients were considered to have (potentially) resectable disease and proceeded to exploratory and/or definitive surgical therapy, while those with advanced locoregional or systemic disease were offered a variety of chemotherapeutic treatment options. This process has become incrementally refined with significant advancements made in pre-operative imaging (increasingly discriminating three-dimensional imaging and endoscopic ultrasound), diagnostic maneuvers (laparoscopy) and systemic treatment options. However the most recent, and perhaps promising, focus has been on neoadjuvant therapy for pancreatic cancer patients.

Surgery remains the mainstay of curative therapy for resectable pancreas cancer. Recent studies have demonstrated that surgery at high volume centers results in 18- and 42-month median survival for patients with and without nodal disease respectively, while survival is effected by neither extent of lymph node dissection nor by resection type (e.g., standard vs. pylorus preserving) [2,3]. In fact, surgeon and hospital volume have a higher impact on survival after pancreaticoduodenectomy (PD) than other identifiable operative strategies, illustrating that expertise and experience are more critical than type of resection [4]. As such, it has become clear that advances in survival will primarily result from progress in non-surgical therapy [5]. This was demonstrated in 2004 by Neoptolemous et al. [6] who described a survival benefit for patients with resected pancreatic cancer undergoing post-operative chemotherapy, though the addition of post-operative radiation therapy remains controversial. The approximate 15–20% long-term survival rate for resected pancreatic cancer certainly seems insufficient and necessitates further advances.

The rationale for neoadjuvant therapy in pancreatic cancer is multi-fold. Preoperative chemoradiation or radiation may theoretically downstage disease by (1) sterilizing peripheral extent of tumor infiltration, resulting in fewer R1 margin-positive resections, (2) decreasing tumor volume such that borderline-resectable disease may become more easily resectable, and (3) minimizing regional nodal disease/tumor burden such that locoregional recurrence is reduced. Furthermore, patients who receive neoadjuvant therapy are more likely to complete their full course of chemotherapy and radiation when compared to patients given post-operative chemoradiation; between 21% and 30% of patients undergoing PD may not complete adjuvant chemoradiation due to post-operative morbidity or patient refusal [7–9]. Additionally, chemoradiation administered to undissected, well-oxygenated tissue may maximize any cytotoxic benefit gained from treatment. Lastly, and perhaps most importantly, patients who exhibit disease progression during their neoadjuvant therapy self-select themselves as poor responders who are least likely to gain benefit from resection and may forego the morbidity of pancreatic resection. Each of these clinical justifications is relevant in pancreatic cancer, as the aggressive and unforgiving nature of this disease leaves little margin for mismanagement or over/under treating.

Here we examine the data regarding the current feasibility and efficacy of neoadjuvant chemotherapy and radiation therapy for patients with pancreas cancer. We will explore the utility of neoadjuvant therapy for patients who are potentially resectable based on initial imaging studies or considered borderline resectable based on extent of local vascular involvement. Though some past evidence suggests that neoadjuvant therapy does not affect overall survival, the evolution of chemotherapeutic options and concordant administration of guided radiotherapy holds promise as a critical component in progress towards curative treatment of pancreas cancer.

**EXISTING DATA**

During the past decade, chemotherapeutic components of adjuvant (as well as neoadjuvant) treatment for resected/resectable pancreatic cancer have shifted. Traditional regimens were 5-FU based, and studies evaluating the utility of dose variable chemoradiation therapy demonstrated clear benefits of post-operative 5-FU while the benefits of radiation therapy were less apparent [7,8,10]. Recently gemcitabine, a cytosine analogue that results in DNA chain termination following its metabolism and incorporation, has been added to treatment arms of chemoradiation showing promising results. The current standard of care includes neoadjuvant gemcitabine-based chemoradiation with the goal of attaining optimal resectability in patients considered potentially resectable. A phase III trial of neoadjuvant chemoradiation with gemcitabine and cisplatin (GEMCIS) compared to surgery alone randomized patients with borderline resectable pancreas cancer to neoadjuvant chemoradiation followed by surgery alone. The results were recently published in 2010 and demonstrated a statistically significant improvement in progression-free survival (PFS) and overall survival (OS) favoring the neoadjuvant arm [11]. This drug continues to be

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evaluated in both pre- and post-operative regimens in association with radiotherapy. Data about the combined efficacy of gemcitabine-based chemoradiation continue to be determined. This evolution in chemotherapeutic strategy has led to gemcitabine largely supplanting 5-FU as the initial chemotherapeutic agent utilized to treat pancreas cancer at major cancer centers.

**Resectable Disease**

Patients with clinically localized disease who undergo successful resection and on pathologic review are found to have clear resection margins (R0) and no evidence of nodal metastases have a relatively favorable prognosis compared to patients with either margin-positive resections (R1 or R2) or nodal and regional disease [12]. Thus, those patients with limited disease found on non-invasive imaging are those most likely to survive, with a corollary that these patients are most likely to benefit further from advances in neoadjuvant therapies. There is a growing body of literature examining neoadjuvant strategies in this selected subgroup of patients who by definition have no imaging evidence of nodal disease, disruption of local planes or extension of tumor outside the pancreas. Figure 1 highlights select studies demonstrating the evolution of specific treatment regimens in potentially resectable patients [13–17].

In 1997, Spitz et al. [9] reported the MD Anderson Cancer Center experience providing pre-operative 5-FU-based chemoradiation to patients with potentially resectable tumors based on high quality imaging and comparing outcomes with those receiving post-operative combined modality therapy. Of the 91 patients in the neoadjuvant therapy cohort, 26% exhibited disease progression during therapy and were not offered operative intervention. Of the remaining 67 patients, 41 were treated according to study protocol (chemoradiation followed by resection). Median survival in this cohort was 19.2 months compared to 22 months in the post-operative adjuvant cohort, despite post-operative therapy patients more frequently having a microscopically positive margin and positive regional lymph nodes on final histologic examination. This lack of survival benefit in the neoadjuvant cohort may be explained by bias in their selection criteria; to be included in this treatment arm, patients were required to have histologically proven pancreatic adenocarcinoma and a hypodense mass in the pancreatic head; those without CT evidence of a mass or biopsy proven pancreas cancer were given post-operative chemoradiation. Because the two treatment arms were neither matched nor randomized, it is difficult to derive definitive conclusions regarding efficacy from these data. Certainly, the study did confirm the feasibility and safety of a neoadjuvant approach. Of note, this study also detailed the high GI toxicity of standard 5.5-week radiation therapy (32% of patients required hospital admission) and the better tolerated 2 weeks, rapid fractionation that evolved from this finding.

Lowy [20], in his recent review of adjuvant and neoadjuvant therapy for pancreatic cancer, outlines twelve studies published between 1993 and 2006 that evaluate a variety of pre-operative chemoradiation regimens. As noted, early studies were largely 5-FU based, with or without mitomycin-C, while more recent investigations either added (or replaced 5-FU with) gemcitabine. Radiation schema usually delivered between 30 and 50.4 Gy with fairly wide treatment fields including prophylactic regional nodal radiation. Primary outcomes reported include percent of patients resected following neoadjuvant therapy (range 38–85%) and median survival (range 12–36 months). No correlation between dose of pre-operative radiation and resectability or survival has been demonstrated, nor was the addition of mitomycin-C to chemotherapeutic regimens related to increased survival. It is noteworthy that two of the three studies that added cisplatin to their 5-FU-based neoadjuvant therapy demonstrated survival at the higher end of the 12-study range (23 and 27 months) [15,16]. Furthermore, the use of gemcitabine in the pre-operative protocol of three studies was associated with 20-, 26-, and 34-month median survival, again much longer survival than most 5-FU-based reports [18,19,21]. Talamonti et al. [19] reported 20 patients in a multi-center trial utilizing 36 Gy of limited field radiation and full dose gemcitabine (1000 mg/m²). This trial reported an 85% resectability

![Comparison of resectability and median survival for patients with (pre-treatment) resectable pancreas adenocarcinoma treated with neoadjuvant chemoradiation. Number in parenthesis under study author indicates dose of radiation therapy in (Gy); †Denotes gemcitabine based neoadjuvant regimes (*) includes a cohort of initially unresectable patients.](image)
rate and a median survival of 26 months. These data are consistent with earlier Phase I trials and animal models which demonstrate that gemcitabine is an excellent radiosensitizer (when compared to 5-FU) and that its use may portend increased survival for patients who are operative candidates.

A large series from the MD Anderson Cancer Center expanded on these outcomes using gemcitabine-based neoadjuvant chemoradiation. In 2008, Evans et al. [18] described the administration of gemcitabine (7 weeks, 400 mg/m²) and rapid-fraction radiation therapy (30 Gy over 2 weeks) in patients with resectable pancreas cancer. While 26% of patients exhibited either disease progression or were deemed unresectable at surgery, a full 74% of patients underwent successful resection. Median survival for these patients was 34 months compared to only 7 months for patients who had unresectable disease. This substantial median survival compares very favorably to nearly all other neoadjuvant regimes, demonstrating the best median survival for patients undergoing neoadjuvant therapy for resectable pancreas cancer.

Varadhachary et al. [22] reported outcomes in a cohort of patients who received four additional doses of gemcitabine–cisplatin in addition to the standard pre-operative gemcitabine and rapid fractionation, 30 Gy radiation therapy (gemcitabine 400 mg/m² pre-operatively, 750 mg/m² post-operatively with cisplatin 30 mg/m²). This extra treatment period did not adversely affect tumor progression, though patients did require more durable biliary decompression. In the 88% of patients who completed chemo-chemoradiation, 66% underwent resection. The median survival in resected patients was 31 months versus only 10.5 months in the unresected group. The authors’ conclusions, when comparing median survival to the similar cohort described by Evans et al. (34 months) [18], were that the addition of gemcitabine–cisplatin to gemcitabine-based neoadjuvant chemoradiation was not efficacious in extending survival.

The omission of radiation therapy and the accentuation of neoadjuvant chemotherapy is a novel strategy with recent support [23]. Heinrich et al. demonstrated the feasibility of delivering gemcitabine with cis-platinum and no radiation therapy in a recent phase II trial. The regimen was well tolerated, graded histologic tumor responses were comparable to chemoradiation protocols, and there was no added surgical morbidity. This strategy of neoadjuvant chemotherapy alone for resectable pancreas cancers is under investigation in a current American College of Surgeons Oncology Group clinical trial.

In examining these data on neoadjuvant therapy for resectable pancreas cancer on the whole, it is important to note that there are no randomized, prospective trials evaluating either 5-FU or gemcitabine-based chemoradiation in a neoadjuvant setting. Despite this shortcoming, many researchers have noted a median survival that exceeds traditionally recognized survival for operable pancreas cancer and this should serve as the paradigm on which further clinical trials are based.

**Borderline Resectable and Locally Advanced Disease**

A recent consensus conference with representation from the Society of Surgical Oncology, the American Society of Clinical Oncology and the American Hepato-Pancreatico-Biliary Association attempted to define reproducible and clinically relevant criteria to better categorize resection classifications for non-metastatic pancreatic cancers [24]. These classifications are listed below and are crucial if the efficacy for neoadjuvant strategies is to be carefully assessed and determined based on extent of disease.

(1) Tumors considered localized and resectable should demonstrate the following:

(a) No distant metastases.  
(b) No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement.

(c) Clear fat planes around the celiac axis, hepatic artery, and SMA (see Fig. 2).

Fig. 2. Localized and potentially resectable pancreatic cancer based on lack of major vessels involvement.

(2) Tumors considered borderline resectable include the following:

(a) No distant metastases.  
(b) 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.  
(c) Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.  
(d) Tumor abutment of the SMA not to exceed 180° of the circumference of the vessel wall (see Fig. 3).

Despite the attempt to strictly classify a tumor as “borderline resectable” or “locally advanced,” there continue to be significant challenges in uniformly determining exactly which “box” an
individual tumor should be placed in. Can intra-operative, much less radiographic, determination of SMA abatement versus encasement be made consistently between each surgeon and institution? Do all surgeons interpret “significant” PV or SMV impingement the same way? These semantic issues not only make individual operative decision making a substantial challenge, but most certainly make standardized study and assessment of data very difficult. It is with this caveat in mind that we discuss the existing data regarding neoadjuvant therapy for borderline-resectable pancreatic cancer.

Most studies that address neoadjuvant chemoradiation for borderline resectable or locally advanced tumors prior to 2005 include patients who have visceral vessel abutment or encasement (again a vague distinction for study purposes) with relatively low subsequent resection rates ranging from 1% to 29% [16, 25, 26]. In these reports, there was significant variability in treatment regimens, at times including the use of some or all of the following agents: EBRT, 5-FU, streptozotocin, cisplatin, mitomycin-C, leucovorin, and dipyridamole. Utilizing a variety of pre-operative chemoradiation strategies, median survival ranged from 10% to 32% depending on patient cohort and inclusion criteria used [27–31] (Fig. 4).

There are a number of more recent studies that have helped to refine our understanding of optimal neoadjuvant treatment strategies for borderline resectable disease. Two studies from Japan highlight their experience with pre-operative chemoradiation for borderline resectable pancreas cancer. In the first, 32 patients with <50% of SMA encasement and no cavernous transformation or thrombosis of the SMV–portal vein confluence were treated with EBRT (40 Gy) and either 5-FU/cisplatin or gemcitabine (GEM; 400 mg/m²) based chemotherapy [32]. Twenty-four of the 32 patients underwent definitive resection, with median survival of 26 months and 20 months for 5-FU/cisplatin and GEM treatment strategies, respectively (P = NS). A caveat in interpreting this study is in the lack of clarity in the study arm, as patients may either belong to “resectable” or “borderline resectable” by expert consensus criteria highlighted above. The second study from the same group retrospectively examined 68 patients with pancreatic adenocarcinoma who were initially found to have extra-pancreatic disease (T3/4 by AJCC staging) or borderline disease by previous NCCN criteria [33]. Utilizing the same neoadjuvant regimen described in their previous study (40 Gy EBRT with 5-FU/cisplatin or GEM at 400 mg/m²), 35 patients (19 potentially resectable and 16 locally advanced) received preoperative chemoradiation without adjuvant therapy. Following neoadjuvant therapy, 79% of patients underwent surgical resection. Median survival was 24.5 months in the resected group in the neoadjuvant arm compared to 18.5 months in a historical control surgery alone group.

A retrospective review from MD Anderson, published in 2008, details the preoperative classification, administration of therapy and subsequent response (with or without the addition of surgery) in 160 patients [34]. Many were deemed to have borderline resectable disease (proximity/abutment/encasement of visceral vessels—Group A). However, the authors submitted that two additional subsets of patients exist; those with questionable metastatic disease (Group B) and those who display either a suboptimal performance status or have prohibitive medical comorbidities and who are not initially surgical candidates (Group C). All 160 patients received either chemotherapy, chemoradiation or both. This primarily consisted of either 50.4 or 30 Gy of EBRT with radiosensitizing doses of either 5-FU, paclitaxel, gemcitabine, or capecitabine. Resection rates following neoadjuvant therapy were 38%, 50%, and 38% in Groups A, B, and C, respectively. Furthermore, resected patients in Groups A, B, and C exhibited 40/29/39-month median survivals compared with 15/12/13-month median survivals for unresected patients. This important study certainly does not demonstrate a clear benefit of one treatment regimen versus another, but does clearly make two salient points. Firstly, patients with stringent definition of borderline resectable disease who respond to neoadjuvant therapy and undergo definitive surgical therapy have a significant survival advantage compared to patients with unresectable disease. Secondly, and perhaps more provocatively, there are further subsets of patients, not encompassed by traditional AJCC criteria, who may equally benefit from a trial of neoadjuvant chemotherapy. Further studies will need to be done to validate these findings, but the notion of expanding the indications for neoadjuvant therapy for this disease warrants further investigation.

Fig. 4. Comparative resectability rates and median survival for patients with initially deemed borderline-resectable or locally advanced pancreas cancer treated with neoadjuvant chemoradiation; ∗ indicates the gemcitabine-based treatment cohort exhibited 20-month median survival; ∗∗ indicates median survival for the cohort inclusive of both potentially resectable and borderline resectable patients.

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It is fairly apparent that the optimal management of borderline resectable disease is less clearly defined as is that of resectable disease, evidenced by both relatively fewer studies addressing the issue as well as the wider variability in treatment regimens and outcomes. Most importantly, the lack of consistency in defining study participants makes interpretation particularly dangerous. Certainly, as treatment strategies become more disease-stage specific, efficacious, tolerable, and consistent, better data will exist to guide ongoing management. Many high volume centers will now accept radiographic findings of a borderline resectable tumor as an indication for a neoadjuvant treatment strategy based on the possible survival benefits versus a primary surgical approach for these patients. There does not yet exist consensus agreement as to the optimal treatment schema for neoadjuvant therapy in borderline resectable disease, though most investigators would now agree on a gemcitabine-based regimen.

Unresectable Disease

There is a paucity of data regarding the use of neoadjuvant chemoradiation in clearly unresectable, non-metastatic pancreatic cancer. Wilkowski et al. [35] described the use of gemcitabine (300 mg/m²) and 5-FU along with EBRT (45 Gy) in patients with primary inoperable pancreatic cancer that occasionally led to resection, but close examination of inclusion criteria demonstrate that many patients who underwent resection may have more appropriately been labeled borderline resectable. To this end, it would be impossible to make evidence-based recommendations regarding administration of chemoradiation with intent of curative resection in patients with truly unresectable disease (metastatic or not). These patients would most optimally be served by clinical trials with new agents or combinations of existing therapies.

Non-Adenocarcinoma Pancreas Cancer

Most studies discussed herein contain whole or subset analysis of pancreatic adenocarcinoma alone, though it is possible that some data are confounded by the inclusion of distal bile duct tumors, duodenal adenocarcinoma, ampullary neoplasms, or neuroendocrine tumors, all with significantly variable tumor biology and prognoses. Furthermore, the focus of this review is pancreas adenocarcinoma rather than mucinous or neuroendocrine neoplasms, whether malignant or pre-malignant, and the role of neoadjuvant therapy in these disease processes remains poorly defined.

DISCUSSION

The process of drug development, understanding optimal treatment choices and paradigms as well as appropriate patient selection are evolving issues that need to be addressed when discussing neoadjuvant therapy for pancreas cancer. Undoubtedly (or at least hopefully), we are at the beginning of a road that will eventually lead to effective therapies for patients with not just early stage pancreas cancer, but for those with locally advanced (or even metastatic) disease at the time of presentation.

The undeniable truths are: (a) even the most optimistic results from existing data demonstrate survival rates in months, rather than years, (b) there are no randomized studies, leading to level 1 data, that exist to guide our management decisions, and (c) tumor biology continues to trump any advancement in traditional or biologic therapeutics. There is perhaps room for cautious optimism, however. For patients with resectable disease, gemcitabine-based neoadjuvant chemoradiation appears to be well tolerated and associated with longer survival than 5-FU-based chemoradiation. Abbreviations and modifications of radiation delivery have been investigated and appear to offer a reduction in complications and improved tolerability. Outcome studies have recognized that patients at high volume centers have fewer peri-operative deaths and complications. All of these factors, and others, should continue to improve the care of pancreas cancer patients as more efficacious care is developed and delivered.

REFERENCES


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