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Review

Neoadjuvant therapy in pancreatic cancer: the emerging standard of care

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ABSTRACT

Pancreatic adenocarcinoma is a rapidly lethal disease process for which, surgical resection is currently the only potential curative treatment. In order to maximize the number of patients able to undergo resection and to maximize the outcome of the procedure itself, extensive research has been completed on potential neoadjuvant therapies for pancreatic cancer. Several sources have confirmed that neoadjuvant therapy can improve the oncologic quality of resection in borderline pancreatic cancer patients and even potentially convert those with locally advanced disease. This article reviews the pros and cons of neoadjuvant therapy in pancreatic cancer, the definitions of resectable, borderline resectable, and locally advanced pancreatic cancer, and the significant studies and current recommendations for the use of neoadjuvant treatment with radiation, chemotherapy, chemoradiation, and/or targeted therapies.

KEYWORDS: pancreatic cancer, chemotherapy, ductal adenocarcinoma, neoadjuvant therapy, radiation therapy, chemoradiation therapy, target therapy, FOLFIRINOX, nab-paclitaxel

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INTRODUCTION

Each year, there are more than 45,000 new cases of pancreatic cancer diagnosed in the United States. Those diagnosed with pancreatic cancer unfortunately make up the 4th most common cause of cancer-related deaths in the US, with greater than 35,000 deaths annually. The current five-year survival rate is a dismal 3% for all stages combined. To this day, surgical resection of the primary tumor and regional lymph nodes still remains the only potential chance for cure. At the time of diagnosis, only 15-20% of patients are potential surgical candidates. Those who undergo curative resection increase their five-year survival rates to only 15-20%, most of who eventually succumb to the disease with either locoregional recurrence or metastatic spread [1-3].

Surgical resection alone has been proven ineffectual on multiple occasions at greatly improving the survival rates in pancreatic cancer. Several studies investigating various adjuvant options including, gemcitabine, fluorouracil (5-FU), and erlotinib have shown slightly improved survival times. Regine *et al.* observed an increase in median survival from 16.9 to 20.5 months ($p = 0.001$) after the addition of gemcitabine to their baseline fluorouracil-based adjuvant chemoradiation regimen [4]. Both Ueno *et al.* and Oettle *et al.* noted

improved disease-free survival of 11.4 vs. 5.0 months ($p = 0.01$) and 13.4 vs. 6.9 months ($p < 0.001$), respectively, when pancreatic cancer patients were treated with gemcitabine vs. observation only post-resection [5, 6]. A review of 3 European randomized controlled trials, European Study Group for Pancreatic Cancer (ESPAC)-1, 1 plus, and 3, revealed the median survival with adjuvant 5-FU therapy was improved when compared to that of resection alone (23.2 vs. 16.8 months, respectively; $p = 0.003$) [7]. Another phase III trial published by Moore *et al.* illustrated both slightly improved overall survival (6.24 vs. 5.91 months; $p = 0.038$) and progression-free survival (3.75 vs. 3.55 months; $p = 0.004$) when erlotinib was added to gemcitabine adjuvant therapy [8].

Considering the minor increase in survival times found with previously studied therapies, additional efforts are being made to discover more effective treatment options. One area of increased controversy and focus is the debate over whether neoadjuvant therapy is more beneficial than adjuvant therapy and which neoadjuvant therapy provides the highest survival benefit. This article reviews the rationales, current data and information on various neoadjuvant therapies in pancreatic cancer, revealing its journey towards being the treatment standard of care.

Definitions of resectable, borderline resectable, and locally advanced disease

Before being able to understand and select the most appropriate treatment for pancreatic cancer patients, one has to consider the exact definitions of resectable, borderline resectable, locally advanced, and metastatic disease. Unfortunately, there are many accepted definitions of these classifications and they are not all the same. In turn, this makes being able to compare studies even more difficult than it already is at baseline. Certainly, the specific interpretation being used in a specific study is information that would need to be taken into consideration when attempting to apply the findings of such study to the care of individual pancreatic cancer patients. There are many slight variations of the definitions; however, there are 3 main census descriptions that practitioners use to group their patients into. Census categorizations exist from MD Anderson, the National Comprehensive Cancer Network (NCCN), and the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/ Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT). Of course, there is agreement that the presence of any distant metastases places the patient into the metastatic pancreatic cancer category. Table 1 depicts the slight differences between the other definitions chosen by each institution [9-11]. Throughout the study of pancreatic cancer therapeutics, the category within which the study population falls should be made clear.

Pros and cons

The theoretical benefits and thus, the impetus to study neoadjuvant therapies in pancreatic cancer are undeniable. Following a complete resection and adjuvant therapy, the risk for systemic recurrence is still > 70%. This elevated recurrence rate is thought to be due to the presence of micrometastatic disease in the lymph nodes, liver, peritoneum, and/or lungs at the time of diagnosis [4]. Prompt initiation of neoadjuvant therapy allows for immediate focus on micro-and macroscopic disease control and potential cure. Otherwise, there is an assured delay of > 2 months between the time of diagnosis and the initiation of standard postoperative adjuvant therapy. Additionally, a larger proportion of patients may receive the treatment, and the treatment itself may be better tolerated and completed as intended when given in the neoadjuvant setting. Postoperatively, many patients experience surgical complications, a prolonged recovery period, decreased performance statuses, comorbidities, or early disease recurrence, and will thus be rendered unable to start or complete the appropriate adjuvant treatment regimens. Finally, neoadjuvant therapy has the potential to greatly improve the surgical resection procedure by decreasing the intraoperative tumor spillage and by reducing the risk of tumoral infiltration of regional lymph nodes and resection margins in the surgical specimen [12].

Similar to the potential positives, there are, however, many potential negatives with the use of neoadjuvant therapy that continue to make its use

Table 1. Criteria for resectability.

	Resectable	Borderline resectable	Locally advanced
MD Anderson	~ No extension and clear fat planes between the tumor and the SMA, celiac axis, and hepatic artery ~ SMV and PV are patent	~ Tumor abutment ≤ 180° of the circumference of the SMA ~ Short-segment encasement/abutment of the common hepatic artery ~ Short-segment occlusion of SMV or PV with suitable vessel above and below	~ SMA encased > 180° ~ Celiac axis or hepatic artery encased with no technical option for reconstruction ~ SMV or PV occluded with no technical option for reconstruction
NCCN	~ No extension and clear fat planes between the tumor and the SMA, celiac axis, and hepatic artery ~ No SMV or PV abutment, distortion, tumor thrombus, or venous encasement	~ Tumor abutment ≤ 180° of the circumference of the SMA ~ 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 ~ Involvement of the SMV or PV showing tumor abutment with or without impingement and narrowing of the lumen, encasement without encasement of nearby arteries, or short-segment occlusion with suitable vessel proximal and distal to the involvement, allowing for reconstruction	Tumors of the head: ~ SMA encased > 180° ~ Any celiac abutment ~ Aortic invasion or encasement ~ Unreconstructible SMV or PV occlusion Tumors of the body: ~ SMA or celiac encasement > 180° ~ Aortic invasion ~ Unreconstructible SMV or PV occlusion Tumors of the tail: ~ SMA or celiac encasement > 180°
AHPBA/SSO/SSAT	~ No extension and clear fat planes between the tumor and the SMA, celiac axis, and hepatic artery ~ No extension and clear fat planes between the tumor and the SMV and PV	~ Tumor abutment < 180° of the circumference of the SMA ~ Uninvolved celiac axis ~ Short-segment encasement or abutment of the common hepatic artery that is amenable to reconstruction ~ Abutment, encasement, or occlusion of a short segment of the SMV or PV	~ Tumor abutment or encasement > 180° or thrombosis of the SMA ~ Abutment or encasement of the celiac axis ~ Occlusion, thrombosis, or encasement extending several cm of the SMV or PV

Abbreviations: AHPBA/SSO/SSAT, Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/ Society for Surgery of the Alimentary Tract; cm, centimeters; GDA, gastroduodenal artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

in pancreatic cancer controversial. Perhaps most notable, it is thought that neoadjuvant therapy will greatly increase the morbidity and mortality of the resection operation or that the disease may metastasize or become unresectable during the course of preoperative therapy, thus preventing the only potentially curative treatment of resection. However, current literature on the effects of neoadjuvant therapy in pancreatic cancer suggests these concerns have minimal merit. Heinrich *et al.* completed a phase II trial investigating the effects of gemcitabine and cisplatin neoadjuvant therapy. Of 24 patients, the treatment induced a histologic response in 54% and cytopathic effects in 83% of them. There was also a significant decrease in the standard uptake values (SUV) on FDG PET/CT

with the treatment. Along with these indications of positive therapy response, they also found less frequent pancreaticoduodenectomy (PD) complications requiring invasive treatments than in those completed without neoadjuvant therapy, no in-hospital and 30-day mortalities, and only 1 pancreatic fistula [13]. Takahashi *et al.* further substantiated Heinrich's findings with their study of 58 pancreatic cancer patients. Following completion of their preoperative gemcitabine-based chemoradiation therapy (CRT), they found no difference in intraoperative and postoperative variables between the group that received the CRT and those that did not, including the operation time, need for intraoperative transfusions, length of postoperative in-hospital stay, minor complications, or postoperative day on which adjuvant chemotherapy was able to be initiated. They did, however, report a decrease in the incidence of clinically significant pancreatic fistulas following PD if the patient received preoperative CRT (11% vs. 37%) [14]. Similarly, Cheng *et al.* noted a significantly lower pancreatic leak (10.1% vs. 43.3%; $p < 0.001$) and intra-abdominal abscess rate (8.8% vs. 20.9%; $p < 0.03$) when they studied the impact of a 5-FU-based neoadjuvant treatment regimen vs. a PD first treatment regimen in 146 patients [15]. In the study of 506 borderline resectable or locally advanced pancreatic cancer cases (NCCN census), 174 of whom initially received neoadjuvant therapy and 469 who proceeded to PD first, Epelboym *et al*. found that neoadjuvant therapy led to slightly increased intraoperative blood loss (1.5 vs. 1 L; $p < 0.001$) and longer operative time (524 vs. 412 min; $p < 0.001$). They also found the preoperative therapy generated no increased overall morbidity (49.7% vs. 48.9%; $p = 0.901$), major morbidity (24.5% vs. 24.9%; $p = 0.941$), pancreatic fistula occurrence (4.2% vs. 5.5%; $p = 0.547$), or reoperation rates (11.9% vs. 7.7%; $p = 0.137$) [16].

There are a few more recent studies and reviews that complete head-to-head comparisons of neoadjuvant and adjuvant therapy in the treatment of pancreatic cancer. Barugola *et al*. retrospectively reviewed a prospective database of 41 initially locally advanced or borderline resectable patients (AHPBA census) who received neoadjuvant therapy and 362 patients who underwent upfront surgery without neoadjuvant therapy. They found those who had completed neoadjuvant therapy had significantly lower T stages ($p < 0.0001$), decreased incidence of nodal involvement ($p < 0.0001$), and increased rates of R0 resections (70.7% vs. 59.7%; $p < 0.0001$). All these factors have been described to independently predict survival in various studies. However, Barugola *et al*. did not find a difference in the median survival time between the group that received neoadjuvant therapy and those that did not (35 months vs. 27 months; $p = 0.74$) [17]. Artinyan *et al*. did note a significant difference in the survival rates of those who received preoperative vs. postoperative therapy. In a group of 458 resectable and borderline resectable patients, they found a median survival of 31.1 months for those who received neoadjuvant therapy vs. 19.0 months for those who received only adjuvant therapy ($p = 0.018$) [18]. Gillen *et al*. completed a huge systematic review and meta-analysis of response to neoadjuvant therapy in pancreatic cancer. They found 73.6% of patients initially determined to be resectable were able to be resected after neoadjuvant therapy, which was similar to the 78-96% of initially determined resectable patients who were able to be resected without neoadjuvant therapy. The median survival of 23.3 months for resectable cancer patients who received neoadjuvant therapy was also comparable to the 20.1-23.6 month range observed for those who went straight to surgery. Thirty-three point two percent of non-resectable pancreatic cancer patients were also able to undergo resection, and this led to a 20.5-month median survival, which was again comparable to the survival rates of the initially resectable patients who were able to undergo resection first [19].

Finally, multiple studies have documented disease progression while patients are completing neoadjuvant regimens, rendering them unable to undergo the resection operation. Evans *et al*. completed a phase II trial of 86 patients and found that 13 of them had disease progression or status decline while attempting to complete their preoperative therapy of gemcitabine chemoradiation. However, just as stated in the many other trials noting similar findings, Evans *et al*. do not acknowledge this finding as a negative one. They believe the treatment time period accurately

identifies those who are likely to achieve a survival benefit from surgery and prevents those unlikely to benefit from undergoing such a morbid operation [20].

Radiation

Throughout the several decades of investigation into the neoadjuvant treatment of pancreatic cancer patients, few studies have focused on treatment with solely radiation therapy. However, there are multiple occasions when proof of its benefit has been made. Through use of the Surveillance, Epidemiology, and End Results (SEER) registry database, Stessin *et al*. reviewed the cases of 190 patients between 1994-2003 who had received neoadjuvant radiation therapy (RT). They found a statistically significant improvement in median survival time from 12 months, with no RT, to 17 months, with adjuvant RT, to 23 months, with neoadjuvant RT ($p < 0.01$). They theorized that those who received preoperative vs. postoperative RT had improved efficacy of the RT and thus better survival due to the improved oxygenation of undissected tissues [21]. Pingpank *et al*. from Fox Chase also found an increased survival in 53 patients who received neoadjuvant therapy compared to 47 patients who did not ($p = 0.02$). This improved survival was attributed to the decreased frequency of margin positivity in the neoadjuvant group (7.5% had more than 1 positive margin vs. 44.7% of those without neoadjuvant therapy; $p < 0.001$) [22].

Focusing on the potential added benefits of RT used as a definitive therapy, the Gastrointestinal Tumor Study Group (GITSG) studied a population of 43 patients with locally unresectable pancreatic adenocarcinoma in 1988. Comparing the two groups of treatment with streptozocin, mitomycin, and 5-FU (SMF) to treatment with RT combined with 5-FU, followed by the SMF regimen, this randomized trial revealed an improved median survival time of 42 weeks vs. 32 weeks when the patients were treated with the added RT ($p < 0.02$). No conversions to resectability were identified [23]. Similarly, the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) published encouraging results from their phase II and III studies of 181 patients with locally unresectable pancreatic cancer. After an initial 3 months of various chemotherapy (CT) regimens, those without disease progression were divided into a continued CT only group or a chemoradiation therapy (CRT) group. The group with the additional RT displayed both a longer progression-free survival (PFS) (10.8 vs. 7.4 months, respectively; $p = 0.005$) and a longer median overall survival (OS) time (15.0 vs. 11.7 months, respectively; $p = 0.0009$). Again, no conversions to resectability were listed [24].

On perhaps a slightly less important yet very interesting point, several studies have reported findings suggesting that preoperative RT can improve the outcomes of the PD procedure. Cho *et al*. completed a very large American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) study showing that weight loss, increased median operative time, and vascular reconstruction were all more common in the neoadjuvant RT group ($p < 0.001$). However, mortality and morbidity were not worsened and the median hospital stay was shorter ($p = 0.005$) [25]. Ishikawa *et al*. demonstrated a decrease in the minor pancreatic fistula rate, a common surgical complication of a PD, with the use of preoperative RT (0% vs. 17%; $p < 0.05$). They postulated that preoperative RT decreased the leak rate by impairing the pancreatic exocrine function and by inducing fibrosis in the gland, thus improving the ability of the utilized suture to effectively secure and oversew the remaining pancreatic tissue [26]. All major studies detailed in this section are briefly outlined in Table 2.

Chemotherapy

A few concerns over the neoadjuvant use of RT have led to the desire to use and study the preoperative use of CT only in pancreatic cancer. Most patients do not die due to local tumor burden in the pancreas but they usually succumb to the metastatic disease involving the liver and peritoneum. Therefore, some feel the neoadjuvant treatment focus should be on systemic disease control rather than on localized radiation therapy. Concurrent use of CT and RT is also felt to limit the potential intensity of CT administered because of the effect of the RT on the patients. Thus, some believe the focus could and should remain on maximizing the efficacy of systemic therapy with the preoperative use of standalone CT [27].

Table 2. Reviewed neoadjuvant trials.

Study	Institution	Pts	CT	RT	Resectability	Median OS	R0 Resections
Stessin *et al.* [21]	Weill Cornell Medical College	190		varied	Resectable	23.0 mo(s)	
Pingpank *et al.* [22]	Fox Chase	53	varied	50.4 Gy	Resectable and borderline resectable		50.9%
GITSG [23]	GITSG	43	streptozocin; mitomycin; 5-FU	54 Gy	Locally unresectable	42.0 wk(s)	
Huguet *et al.* [24]	GERCOR	181	varied	varied	Locally unresectable	15.0 mo(s)	
Heinrich *et al.* [13]	Swiss HPB-Center	28	gemcitabine; cisplatin		Resectable	26.5 mo(s)	80.0%
Palmer *et al.* [29]	United Kingdom	50	gemcitabine; cisplatin		Resectable	15.6 mo(s)	75.0%
Lee *et al.* [67]	Korean	43	gemcitabine; apecitabine		Borderline resectable or locally unresectable	23.1 mo(s)	82.3%
Sahora *et al.* [31]	Austrian	25	gemcitabine; docetaxel		Borderline resectable or locally unresectable	16.0 mo(s)	87.0%
Sahora *et al.* [32]	Austrian	33	gemcitabine; oxaliplatin		Borderline resectable or locally unresectable	22.0 mo(s)	69.0%
Rose *et al.* [68]	Virginia Mason Medical Center	31	gemcitabine; docetaxel	50.4 Gy	Borderline resectable		87.0%
Isacoff *et al.* [27]	SWOG	50	5-FU; leucovorin; mitomycin; dipyridamole		Locally unresectable	13.8 mo(s)	100.0%
Kim *et al.* [36]	US Multi-Institutional	68	gemcitabine; oxaliplatin	30 Gy	Respectable or borderline resectable	34.6 mo(s)	84.0%
Katz *et al.* [37]	MD Anderson	194	gemcitabine, 5-FU, or capecitabine	30-50.4 Gy	Respectable or borderline resectable	35.6 mo(s)	
Brown *et al.* [38]	Fox Chase	13	varied	50.4 Gy	Borderline resectable	15.0 mo(s)	85.0%

Table 2 continued..

Stokes *et al.* [39]	University of Virginia	34	capecitabine	50.4 Gy	Borderline resectable	23.0 mo(s)	88.0%
Cho *et al.* [40]	Korean	30	gemcitabine; cisplatin or capecitabine	45-58.4 Gy	Borderline resectable	45.0 mo(s)	

*All listed values for median OS and R0 resections are representative of the published results for patients who were resectable or converted to resectability with treatment and underwent the operation.
Abbreviations: 5-FU, 5-fluorouracil; CT, chemotherapy; GERCOR, Groupe Cooperateur Multidisciplinaire en Oncologie; GITSG, Gastrointestinal Tumor Study Group; Gy, gray; mo(s), month(s); OS, overall survival; Pts, patients; RT, radiation therapy; SWOG, Southwestern Oncology Group; wk(s), week(s).

As mentioned previously, Heinrich *et al*. was able to demonstrate some significant findings in their 2008 study of neoadjuvant gemcitabine and cisplatin in resectable pancreatic adenocarcinoma patients. Among other findings, they documented some level of histologic response in 54% and cytopathic effects in 83% of their patients. They had an 80% R0 resection (resection with microscopic tumor margin clearance) rate and commented that the treatment was well tolerated and did not impair the resectability of the tumor. The treatment plus resection also led to a median survival of 26.5 months [13, 28]. Palmer *et al*. also completed a neoadjuvant randomized phase II study comparing treatment with gemcitabine alone vs. gemcitabine plus cisplatin. Of 50 potentially resectable patients, 38% of those receiving gemcitabine only were able to undergo resection, and 70% receiving the combination CT were able to undergo resection. Either therapy option appeared to improve survival; however, the combination CT seemed to be the best by allowing for a high proportion of R0 and node-negative resections [29].

In the study of locally advanced pancreatic adenocarcinoma (NCCN census), Lee *et al*. reviewed 43 eligible patients who underwent treatment regimens consisting of gemcitabine and capecitabine. They documented an 18.6% response rate, which allowed 17 patients (11 borderline resectable and 6 locally unresectable at presentation; 39.5%) to undergo resection, 14 of whom (82.3%) had an R0 resection. For those who were able to undergo the resection, the treatment helped lead to a 23.1 month median overall survival time period [30]. Sahora *et al*. also studied patients with locally advanced pancreatic cancer (AHPBA census) in two separate studies. One examined the preoperative use of gemcitabine and docetaxel (NeoGemTax), and the other reviewed the preoperative use of gemcitabine and oxaliplatin (NeoGemOx). NeoGemTax was studied in 25 patients, 8 of whom (32%) were able to undergo resection. Seven of the 8 (4 borderline resectable and 4 unresectable at presentation; 87%) had an R0 resection, and with resection, NeoGemTax gave patients a median overall survival of 16 months [31]. Similarly, NeoGemOx was reviewed in 33 patients. Thirteen of these 33 patients (2 potentially resectable and 11 borderline resectable at presentation; 39%) were able to have curative resection, and 9 of the 13 (69%) had an R0 resection. With this treatment and resection, the median overall survival was 22 months [32]. In their study of 64 borderline resectable pancreatic cancer patients (AHPBA census), Rose *et al*. found that 28 of 31 patients (87%) who were able to complete their extended gemcitabine-based neoadjuvant chemotherapy regimen and resection were able to successfully have R0 resections [33]. Finally, Isacoff *et al*. completed a phase II trial of a 4-drug CT regimen in locally unresectable pancreatic cancer patients in the SWOG S9700 trial. Fifty patients were recruited to undergo the therapy regimen, including 5-FU, leucovorin, mitomycin, and dipyridamole. Results showed a 26% objective response rate, 6 of whom converted to resectability and were able to undergo R0 resections. The median survival was 13.8 months [27]. All major studies detailed in this section are outlined in Table 2.

Chemoradiation

Various CRT options have been studied more than any other potential neoadjuvant therapy for pancreatic cancer over the past several decades. While in the process of ensuring the appropriate use of a prognostic nomogram for pancreatic cancer, White *et al*. showed that even though those who received CRT in their study were more likely to have locally advanced tumors on initial staging than those who did not receive CRT, they also seemed to be in better condition at the time of resection. The authors found those patients who received preoperative CRT had smaller tumors (average tumor diameter 2.3 vs. 3.1 cm; $p < 0.05$), were less likely to have T3 tumors (54% vs. 80%; $p < 0.01$), were less likely to have positive lymph nodes (29% vs. 58%; $p < 0.01$), and had fewer positive lymph nodes (average 4 vs. 1.9 lymph nodes; $p < 0.01$). Thus, the preoperative CRT patients presented with a much-improved picture at the time of resection [34]. Interestingly, another study from Abbott *et al*. revealed that, not only does neoadjuvant CRT improve overall survival of the patients, but it actually turns out to be the most cost-effective route of treating pancreatic cancer patients. Overall, a surgery-first approach costs an average of $46,830/patient and yielded a survival of 8.7 quality-adjusted life-months (QALMs), while 164 patients who underwent the neoadjuvant CRT approach accrued average costs of $36,583/patient and yielded a survival of 18.8 QALMs [35].

Many studies have focused on the ability of neoadjuvant therapies to improve the rate and quality of R0 resections for pancreatic cancer. In a multi-institutional phase II study, Kim *et al*. studied the preoperative use of full-dose gemcitabine, oxaliplatin, and RT in 68 patients (23 potentially resectable, 39 borderline resectable, and 6 locally unresectable at presentation; NCCN census). This treatment regimen led to a R0 resection in 84% of those who underwent surgery (n = 36/43) and a median survival of 34.6 months in those same patients. This showed a huge improvement in survival over the 10.9 months for those who did not undergo resection or the 27.1 months for those who underwent any resection [36]. MD Anderson completed a study of 147 patients (106 potentially resectable and 41 borderline resectable at presentation; MDACC census) who were given neoadjuvant CRT with concurrent gemcitabine or 5-FU. Again, those who received preoperative CRT showed a statistically significant smaller median tumor diameter ($p = 0.03$) and a smaller percentage of lymph node positivity ($p < 0.001$) over those who went straight to surgery. The group found that those who received preoperative CRT also had longer SMA margin distances, and those who received the CRT and had longer SMA margin distances were associated with a longer PFS ($p = 0.003$) and local progression-free survival (LPFS) ($p = 0.01$). The SMA margin is key because it is the margin most frequently found to be positive for cancer cells following resection. Any treatment that increases that margin increases the chances for an R0 resection [37].

A paper from Fox Chase retrospectively studied the impact of preoperative CRT and standalone chemotherapy (CT) in 13 patients with borderline resectable pancreatic cancer (NCCN census). They were able to achieve an 85% R0 resection rate following their more aggressive treatment regimens, which is much improved over other R0 resection rates for those patients who progress to surgery first [38]. Stokes *et al*. also completed a review of borderline resectable pancreatic cancer patients (MDACC census) who received capecitabine-based preoperative CRT. Of 34 patients, 22 (55%) completed the designated therapy, and 16 (40%) of these underwent resection. Eighty-eight percent of these originally borderline patients were able to get an R0 resection and illustrated similar survival to patients with initially resectable pancreatic tumor burden [39]. Cho *et al*. similarly describe a statistically significant lower recurrence rate (50% vs. 81.6%; $p = 0.028$) and improved overall survival time (45.0 vs. 23.5 mo; $p = 0.045$) in their study of borderline resectable pancreatic cancer patients who received neoadjuvant gemcitabine-based CRT vs. no CRT [40]. All studies described in this section are outlined in Table 2.

Targeted therapies

Even with the best alternative adjuvant or neoadjuvant treatment, pancreatic cancer has still

proven to be one of the most resilient and difficult to treat cancers in existence. For this reason, focus has recently been turned to potential targeted therapies in the field of pancreatic cancer therapeutic research. However, all the studies, save one, have yet to find a significant benefit from the addition of these various agents. As mentioned previously, Moore's phase III trial of gemcitabine plus erlotinib compared with gemcitabine alone has been the only study to show a meaningful and acceptable impact from the addition of a targeted agent. In 569 patients, the epidermal growth factor receptor (EGFR) inhibitor provided an increased one-year (23% vs. 17%, respectively; $p = 0.023$) and overall (6.24 vs. 5.91 months, respectively; $p = 0.038$) survival advantage when used as an addition to the definitive therapy treatment regimen. With this slight but significant improvement, these results, together with the finding that erlotinib only minimally worsened the patient-experienced drug toxicity, allowed erlotinib to become a U.S. Food and Drug Administration (FDA)-approved advanced pancreatic cancer therapy option [8]. As with erlotinib, the study of most targeted therapies in pancreatic cancer has been directed towards the use of these agents in the definitive treatment realm, and not in a neoadjuvant setting.

A few studies examining the impact of adding cetuximab, a monoclonal antibody that blocks the EGFR, have reported conflicting results. Pipas *et al*. reported very positive findings. In their study of 33 patients (4 potentially resectable, 23 borderline resectable, and 6 locally unresectable; AHPBA census) who underwent neoadjuvant therapy with cetuximab, gemcitabine, and intensity-modulated radiotherapy (IMRT), 10 patients had a partial response, 20 had stable disease, and 3 patients had disease progression. Twenty-five patients (76%), 3 of whom converted from unresectable, were able to have tumor resections, and 23 of these patients (92%) had complete R0 resections. The median OS was 24.3 months in the resected patients. With frequent but manageable toxicities, Pipas *et al*. felt the substantially active treatment regimen was a viable therapy choice [41]. However, Fensterer *et al*. and Philip *et al*. also completed trials involving the use of cetuximab and found less encouraging results. Fensterer *et al*. studied 73 previously resected patients in their phase II trial on the use of gemcitabine and cetuximab without RT. They found a median disease-free survival (DFS) of 10.0 months and a median OS of 22.4 months. They felt the addition of cetuximab did not seem to improve survival at all after their comparison with the CONKO-001 trial on gemcitabine only that showed a DFS of 13.4 months and an OS of 21.7 months [42, 43]. Philip *et al*. also completed a large phase III trial, the Southwest Oncology Group-Directed Intergroup Trial S0205, on 745 metastatic or locally unresectable patients. Again, no added benefit was seen from the addition of cetuximab to gemcitabine (OS 6.3 months for the gemcitabine plus cetuximab group vs. 5.9 months for the gemcitabine plus placebo group) [44].

Several projects investigating the potential benefit of agents targeting vascular endothelial growth factor (VEGF) as a definitive therapeutic option have also been completed without very encouraging findings. Kindler *et al*. completed both a phase II and phase III trial of bevacizumab plus gemcitabine therapy for metastatic or locally unresectable pancreatic cancer patients. In their initial study of 52 patients, they had 11 patients (21%) with partial responses, 24 (46%) with stable disease, and 13 (25%) with progressive disease. The median PFS was 5.4 months, and the median OS was 8.8 months. No conversions to resectability were mentioned [45]. Their follow-up phase III trial studied 602 patients in the Cancer and Leukemia Group B (CALGB) 80303 trial. They had similar median PFSs (3.8 months for the gemcitabine plus bevacizumab group vs. 2.9 months for the gemcitabine plus placebo group) and median OSs (5.8 months for the combination group vs. 5.9 months for the gemcitabine group) in their group comparisons. The objective response rates (ORRs) were also similar with no conversions to resectability, so they concluded the addition of bevacizumab is not beneficial to pancreatic cancer patients [46]. Kindler *et al*. also attempted a phase III trial on the use of axitinib, an inhibitor of VEGF receptors 1, 2, and 3, and found similar results. Of 632 patients, the median OS was 8.5 months for the gemcitabine plus axitinib group and 8.3 months for the gemcitabine plus placebo group. The addition of axitinib showed no improved survival benefit [47].

Additional targeted regimens have attempted the use of interferon α-2b (IFNα-2b) to supplement traditional pancreatic cancer treatments. Picozzi *et al*. published the results of their phase II trial (ACOSOG trial Z05031) on the use of cisplatin, 5-FU, and IFNα-2b-based CRT. In 89 post-resection patients, the median DFS was 14.1 months, and the median OS was 25.4 months. However, they reported that 95% of the patients experienced grade 3 or 4 acute toxicity with the regimen. Therefore, they concluded that this is a very active regimen in the treatment of pancreatic cancer; however, future use would require multiple modifications to decrease the associated toxic effects [48, 49].

FOLFIRINOX

FOLFIRINOX is a chemotherapy regimen composed of folinic acid (leucovorin), 5-FU, irinotecan, and oxaliplatin. It was originally created and marketed for use in metastatic colorectal cancer. However since 2010, FOLFIRINOX is used by many as the first-line therapy option for patients with advanced pancreatic cancer with good performance statuses. Initially, 5-FU was used as the primary CT choice for pancreatic cancer and then gemcitabine was proven to provide patients with an increased survival and quality-of-life advantage. For many years and still in some circumstances, gemcitabine-based treatments are seen as the true first-line treatment option; however in 2010, Conroy *et al*. published his landmark paper from the PRODIGE4/ACCORD11 study (Partenariat de Recherche en Oncologie Digestive 4/Actions Concerteesdans les Cancers Colo-Rectaux et Digestifs 11) which showed FOLFIRINOX to be superior to gemcitabine in the treatment of metastatic pancreatic cancer. They studied 342 patients with Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 or 1 with pancreatic cancer. One group received FOLFIRINOX while the others received standard gemcitabine dosing. The objective response rate (ORR) was 31.6% for the FOLFIRINOX group and 9.4% for the gemcitabine group ($p < 0.001$). The median PFS (6.4 vs. 3.3 months, respectively; $p < 0.001$) and the median OS (11.1 vs. 6.8 months, respectively; $p < 0.001$) were all far superior in the FOLFIRINOX vs. the gemcitabine group. FOLFIRINOX was shown to cause increased adverse events compared to gemcitabine, such as neutropenia, thrombocytopenia, diarrhea, and alopecia. However, they still found a significant increase in time until a definitive deterioration in observed quality of life in the FOLFIRINOX vs. the gemcitabine group. Therefore, Conroy *et al*. suggested FOLFIRINOX be used as the new first-line treatment for metastatic pancreatic cancer in those under 71 years of age with good performance statuses, no cardiac ischemia, and good bilirubin levels [50].

Before and after the phase III trial, multiple studies investigating the safety and response rate of FOLFIRINOX had been completed. Conroy *et al*. published a study of 46 patients with advanced pancreatic cancer (11 locally unresectable and 35 metastatic) treated with FOLFIRINOX. They illustrated a 26% overall response rate and a 4% complete response rate. Median PFS was 8.2 months and median OS was 10.2 months. No conversion rate was listed [51]. Tinchon *et al*. also put out a small paper on the safety of FOLFIRINOX in their patient population of borderline resectable pancreatic cancer patients. Of 2 patients, they found a partial remission in 4, stable disease in 6, and progressive disease in 2 of the patients. Resection was able to be performed in 10 of the 12 patients. They concluded FOLFIRINOX was safe and efficacious in this patient population, as long as they had adequate performance scores and liver function. They commented that prior biliary stenting should not exclude patients from the effective treatment regimen, given their experience of 0 cases of cholangitis [52].

Hosein *et al*. then followed Conroy's study with a FOLFIRINOX project focused more on the treatment of patients with locally advanced pancreatic cancer. They studied 18 patients (4 borderline resectable and 14 locally unresectable at presentation; AHPBA census) with a median age of 57.5 years and all with good ECOG status scores. Seven of the 18 (39%) were found to be resectable radiologically after treatment. Five had R0 resections, 1 had an R1 resection (resection with microscopic tumor infiltration at the margins), and 1 was unresectable at the time of laparotomy. After additional combined CRT, 3 of

the remaining 11 patients went on to have R0 resections. Thus, the overall R0 resection rate with FOLFIRINOX was 44% [53]. Faris *et al*. from Massachusetts General Hospital also published a review of their institution's experience with FOLFIRINOX treatment in metastatic and locally unresectable pancreatic cancer patients (NCCN census). Out of 22 patients, they discovered an overall response rate (ORR) of 27.3%, with a median PFS of 11.7 months. Five of the 22 patients (23%) converted and were able to have R0 resections following treatment with FOLFIRINOX and CRT [54]. Peddi *et al*. had similar conclusions in their multi-institutional review of their FOLFIRINOX use. Sixty-one patients (4 borderline resectable, 19 locally unresectable, and 38 metastatic; AHPBA census) with a median age of 58 years and a mixture of metastatic and non-metastatic disease were examined. Overall, one patient had a complete response, 9 had a partial response, 19 had a stable response, and 11 had disease progression. The 4 patients who initially had borderline resectable disease were all able to undergo resection, as well as 4 of the 19 patients (21.1%) with locally advanced disease who also received RT following their FOLFIRINOX treatments. The median PFS was 7.5 months, and the median OS was 13.5 months [55]. Finally, Boone *et al*. published a paper of their FOLFIRINOX experience at the University of Pittsburgh in 25 borderline resectable and locally unresectable pancreatic cancer patients (AHPBA census). They found an R0 resection rate of 33% for patients with either borderline resectable or locally unresectable disease treated with FOLFIRINOX ± stereotactic body radiation therapy (SBRT) [56].

Secondary to the perceived efficacy of FOLFIRINOX in pancreatic cancer patients, continued studies of its application for both neoadjuvant and adjuvant therapy are being carried out. Christians *et al*. from MD Anderson recently published their experience of neoadjuvant FOLFIRINOX in 18 borderline resectable patients. Fifteen patients were able to complete therapy, and 12 of the 15 were able to undergo resection, all with R0 resections. Only 2 patients were node positive. There were no in-hospital or 30-day mortalities and no pancreatic leaks or reoperations. Overall, neoadjuvant therapy with FOLFIRINOX followed by CRT was felt to be safe and led to favorable resection rates [57]. James *et al*. studied a modified version of FOLFIRINOX in locally advanced and metastatic patients and found there was a 29.0% response rate, and 46% of the locally advanced patients were able to undergo resection in the interim analysis of their project [58]. Blazer *et al*. also studied neoadjuvant modified FOLFIRINOX in 20 borderline resectable and 23 locally unresectable patients. They had a 53.8% overall resection rate and 45.0% of those patients were from the locally advanced subset. The R0 resection rate was 85.7%, and the median PFS was 18.4 months ($p < 0.001$) [59].

Nab-paclitaxel

Another extremely active CT regimen that deserves attention is nab-paclitaxel. Nab-paclitaxel (abraxane) is a nanoparticle, albumin-bound formulation of paclitaxel that was initially FDA approved for the treatment of breast and lung cancers. However, it has been found to be advantageous in the treatment of pancreatic cancer as well [60]. Frese *et al*. first showed that nab-paclitaxel increases the intratumoral gemcitabine level by decreasing the activity of cytidine deaminase, the primary metabolizing enzyme of gemcitabine [61]. Alvarez *et al*. was also one of several to show the effectiveness of nab-paclitaxel in stromal disruption in pancreatic cancer. Following treatment, they were able to document a marked decrease in the tumor stiffness measured by endoscopic ultrasound (EUS) elastography. Of 10 potentially resectable and borderline resectable (NCCN census) patients, 1 had a complete response, 6 had major pathological responses, 1 had a partial response, and 2 patients did not respond. Ninety-two percent of the patients were able to have R0 resections [62].

Von Hoff *et al*. recently completed the most convincing set of trials reviewing the impact and potential use of nab-paclitaxel in metastatic pancreatic cancer. In their phase I and II trials, they found that the dose-limiting toxicities (DLTs) were sepsis and neutropenia. However,

at their maximum-tolerated dose (MTD), the nab-paclitaxel plus gemcitabine combination produced encouraging results. The ORR was 48%, the median PFS was 7.9 months, and the OS was 12.2 months. There were no listed conversions to resectablility; however, they felt the results were very promising and required further attention in their phase III study [63]. Not to as great the extent as in their phase II study results, but they still found an improvement in the median PFS (5.5 vs. 3.7 months, respectively; $p < 0.0001$) and the median OS (8.5 vs. 6.7 months, respectively; $p < 0.0001$) in the gemcitabine plus nab-paclitaxel vs. gemcitabine only groups. Serious adverse events occurred with equal frequency in both groups. The nab-paclitaxel group reported slightly increased frequencies of neutropenia, leukopenia, fatigue, and peripheral neuropathy. They felt the addition of nab-paclitaxel was superior to single-agent gemcitabine, and the added side effects were generally minor and reversible [64]. The FDA agency has subsequently, recently, approved nab-paclitaxel plus gemcitabine as a potential first-line therapy option for advanced pancreatic cancer patients.

Following the publication of Von Hoff's initial trials including nab-paclitaxel, several others have reviewed the use of this agent in one way or another without much success. Ko *et al*. completed a phase I trial in metastatic pancreatic cancer patients with the use of nab-paclitaxel, gemcitabine, and capecitabine. Although well tolerated, they found there was only modest antitumor activity with this regimen. Of 14 patients, only 2 (14.3%) demonstrated an objective response, and the median OS was 7.5 months. Taking these results into consideration, they felt the regimen did not warrant further review [65]. Hosein *et al*. did seem to find use for nab-paclitaxel as a single-agent therapy for second-line treatment in a very select few advanced pancreatic cancer patients. In 19 patients who had progressive disease on gemcitabine-based therapy, they tried treatment with nab-paclitaxel. They found a median PFS of 1.7 months and OS of 7.3 months. One patient was found to have a partial response, and 6 had stable disease. Again, they felt their study showed only modest activity of this agent with its benefits being shown in very few patients [66].

DISCUSSION

Pancreatic cancer has proven on countless occasions to be a highly lethal cancer due to its late diagnosis and its drug resistant nature. Because the only potential for cure is surgical resection yet, a majority of patients present when they are already unresectable, a lot of research focus has been directed towards potential neoadjuvant therapies in an attempt to move patients into that resectable category.

For those patients with metastatic disease, the initial undisputed step is to start them on definitive chemotherapy. The more recently accepted standard of care for locally advanced patients is to begin neoadjuvant therapy and reevaluate with the hope of converting the tumor to a resectable state. The exact sequence and course of treatment for both borderline resectable and potentially resectable patients is more controversial. As with the treatment of locally advanced tumors, the trend towards neoadjuvant therapy first seems to be the emerging trend for borderline resectable tumors; however, the data for resectable tumors is too contradictory to change the current practice of surgery first. Those who support neoadjuvant treatment believe this approach provides immediate treatment to control micrometastatic disease, sets up the best conditions under which to perform tumor resection, and selects out those patients with occult or aggressive metastatic disease who would not benefit from a potentially morbid resection procedure anyway. Knowledge on which option provides the best outcome when compared head-to-head is still lacking. Studies have shown survival statuses are improved with R0 resections, negative lymph nodes, and treatment with some sort of additional therapy. In those with preoperative radiologically resectable, borderline resectable or even locally advanced disease, neoadjuvant therapy can ensure increased resected margin widths and an increased proportion of patients with completed R0 resections. Neoadjuvant therapy can limit the percentage of patients with lymph node positivity. Simply from its preoperatively administered nature, it can ensure the patient completes the intended therapeutic regimen, instead of being unable to receive adjuvant therapy secondary to unforeseen surgical complications or morbidities.

Several studies have shown that neoadjuvant RT alone or CT alone provide benefit in both achieving R0 resections and prolonging overall survival in the neoadjuvant setting. The study by Stessin *et al*. showed a distinct survival advantage when preoperative RT alone was utilized in the treatment of resectable pancreatic cancer patients [21]. As one example, the phase II study by Heinrich *et al*. showed that the preoperative CT regimen of gemcitabine and cisplatin allowed patients to have an increased median DFS and OS [13]. However, a strong base of phase III trials supporting the phase II trial results showing the benefits of CT only is thus far lacking. Certain specific variations of each, RT and CT, have proven beneficial; however, combining the two options has revealed potentially even better results. Katz *et al*. found that even with a variety of different CRT regimens, all those who received some form of CRT had a benefit. Those who received CRT had wider resection margins, lower recurrence rates, and longer PFSs [37]. GITSG was able to show that CRT, with SMF as the CT regimen, provided an increased median OS when compared to the CT regimen alone [23].

A few of the healthcare providers involved in treating pancreatic cancer patients have been resistant to use neoadjuvant CRT because they believe the added toxicity of the RT limits the intensity of the CT that can be given. They believe the focus should be on maximizing the CT as the disease is considered to be micrometastatic already, and it is most commonly the metastatic spread of the disease that ends up taking the patient's life. One viable solution is inductive CT followed by CRT, and hopefully curative resection, in patients whose disease remains stable or shows a response to the induction CT. In the GERCOR studies, Huguet *et al*. showed that this approach appeared advantageous with resultant improved PFS, OS, and R0 resection rates [24].

The investigation that has been directed at discovering potentially beneficial targeted therapies for pancreatic cancer has thus far been largely disappointing. Until this point in time, erlotinib has been the only drug to show its even slight survival advantage consistently [8]. Other agents targeting EGFR, VEGF, and other proteins significant in various carcinogenic pathways have all been shown to not be beneficial. There has been no successful investigation of their potential use as neoadjuvant agents, to date. However, the focus on these agents is still very strong in the pancreatic cancer research field, and thus the potential to discover more active therapeutic agents is certainly present. Table 3 lists a sample

Table 3. Sample of ongoing trials involving targeted therapy in pancreatic cancer.

Sponsor	Collaborator	Therapy	Disease status	Trial status	NCTID
Comprehensive Cancer Center of Wake Forest University	NCI	CPI-613; modified FOLFIRINOX	Metastatic	Recruiting	NCT01835041
Andrew Ko	Infinity Pharmaceuticals, Inc.	IPI-926; FOLFIRINOX	Locally advanced or metastatic	Ongoing, not recruiting	NCT01383538
NCI		AZD6244; erlotinib	Locally advanced or metastatic	Ongoing, not recruiting	NCT01222689
PhilogenS.p.A.		L19IL2; gemcitabine	Locally advanced or metastatic	Recruiting	NCT01198522

Abbreviations: AZD6244 (solumetinib), a MEK1 and 2 kinase inhibitor; CPI-613, a mitochondrial metabolism inhibitor; IPI-926, a Hedgehog pathway inhibitor; L19IL2, monoclonal antibody-cytokine fusion protein; NCI, National Cancer Institute; NCTID, National Clinical Trial Identification.

of the many ongoing studies reviewing the use of targeted agents in the treatment of pancreatic cancer [www.clinicaltrials.gov].

Most of the more recent encouraging findings have arisen from the studies on the more active CT agents of FOLFIRINOX and nab-paclitaxel. The PRODIGE 4/ACCORD 11 study launched FOLFIRINOX into the position of first-line therapy for advanced pancreatic cancer, instead of gemcitabine-based treatments. They were able to show a several-month improvement in overall survival when patients were treated with FOLFIRINOX instead of gemcitabine. However, it was also noted that patients experienced more adverse effects from the more active regimen [50]. Therefore, FOLFIRNOX is now recommended as the initial treatment choice for advanced pancreatic cancer in patients with good performance statuses. Multiple studies have since expanded the application of FOLFIRINOX beyond only definitive therapy for metastatic cancer patients to neoadjuvant therapy for potentially resectable, borderline resectable, and locally unresectable patients. Blazer *et al*. demonstrated its potential significant effects in their study of borderline resectable and locally unresectable patients. They had a greatly improved overall resection rate and resultant PFS, with improved adverse effects due to their modified FOLFIRINOX regimen [59]. As an alternate choice for those unable to tolerate FOLFIRINOX, nab-paclitaxel has recently emerged as a less-toxic, still very active treatment option. Von Hoff *et al*. published findings from their phase III trial showing an improved OS with the use of the nab-paclitaxel + gemcitabine combination versus gemcitabine alone. They found that this CT regimen had slightly increased, yet reversible, associated toxicities [64]. Although it is difficult to directly compare the primary end points of two separate studies, the median OS time from their phase III trial did not match the OSs encountered in their phase I or II trials, and it is not as long as that found by Conroy *et al*. in his study of FOLFIRINOX. Both nab-paclitaxel plus gemcitabine or simply a modified FOLFIRINOX regimen, likely with the aid of granulocyte colony-stimulating factor (GCSF), appear to be great alternatives for those who are slightly older, with worse performance statuses, and who cannot tolerate standard FOLFIRINOX dosing.

CONCLUSION

In conclusion, pancreatic cancer is an extremely lethal disease that deserves a significant amount of attention being paid to potential treatment avenues. Neoadjuvant therapy is becoming the standard of care for borderline resectable patients. Locally advanced patients benefit from neoadjuvant therapy and reevaluation to check for conversion to resectability. Those with resectable disease are likely to benefit from preoperative treatment as well because it ensures the best chances of a R0 resection, lymph node negativity, and the best chances to complete the intended multimodality therapy before undergoing the morbid PD procedure; however, the evidence to change the current standard of practice in this area is not yet conclusive.

CT and RT both appear beneficial in the neoadjuvant setting when administered individually; however when given together, their resultant survival benefits appear to increase. Therefore, one viable treatment model is to begin with induction CT followed by concurrent CRT, using FOLFIRINOX, a gemcitabine-based regimen, or nab-paclitaxel, and then followed with surgery to maximize resectability and long-term survival. Even with the research support noted in this paper, this treatment strategy still requires further validation in ongoing and future clinical trials.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to note.

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