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The Multidisciplinary Approach to Localized Pancreatic Adenocarcinoma

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Opinion statement

Pancreatic adenocarcinoma 2030 (PCa) is predicted to be the second leading cause of cancer death in USA by 2030. To date, attempts at early detection have been unsuccessful. Therapies for resectable PCa include surgery followed by adjuvant chemotherapy with or without radiotherapy. Unfortunately, most patients with PCa present with advanced disease and thus only 20% of patients are potentially resectable upon presentation. Improved surgical techniques along with adjuvant combination chemotherapy have improved outcomes for patients with resectable disease. The optimal treatment approach for borderline resectable and locally advanced unresectable PCa has not yet been defined. Despite significant advances in the palliative treatment of PCa, long-term survival of early stage disease continues to be sobering. The key to improving outcomes for this largely fatal disease is to identify multidisciplinary therapeutic interventions including surgical, medical, and radiation techniques tailored to the patient and their disease characteristics. The neoadjuvant approach provides an in vivo platform to test novel treatment options to help us understand tumor biology and surrounding microenvironment, which may ultimately help us achieve the goal of improvement in long-term survival. While the neoadjuvant approach remains popular as a way to optimally select patients that might benefit most from surgery, randomized trials utilizing adjuvant and neoadjuvant novel therapies hold the key to truly personalizing the ideal treatment strategy for localized PCa.

Introduction

Pancreatic adenocarcinoma (PCa) is the fourth leading cause of death in USA with over 53,670 new cases and 80% mortality in 2017 [1]. The majority of the patients present with locally advanced unresectable and metastatic disease, with only approximately 20% of patients presenting with potentially resectable disease. Surgical resection is the only curative therapy for potentially resectable PCa but prognosis and long-term survival is poor even with complete surgical resection. Systemic chemotherapy provided after surgery (adjuvant therapy) has shown to improve overall survival after surgical resection, but the benefit is limited with a 5-year survival between 20 and 30%. Advancements in imaging and endoscopic ultrasound techniques have improved the ability to detect and more accurately stage the disease. Patients with resectable PCa are typically offered surgery followed adjuvant systemic therapy with or without radiotherapy. For the patients with unresectable disease combination therapy with chemotherapy and radiotherapy (chemo RT) is a standard of care with palliative intent and median survival of 8–12 months [2, 3]. In this article, the current multidisciplinary approach for the management of localized PCa is reviewed with focus on resectable and borderline resectable PCa.

Diagnosis and staging

Proper selection for the surgical resection of PCa is paramount in the current era of multidisciplinary management of PCa. High-resolution computerized tomography (CT) with dual phase contrast enhancement is the most acceptable imaging modality to determine staging and potential resectability of PCa. Endoscopic ultrasound (EUS) guided biopsy has become the preferred method of obtaining histologic confirmation. A meta-analysis looking at the success of EUS guided fine needle aspiration revealed a sensitivity and specificity of 92 and 96%, respectively [4]. It is reasonable to repeat EUS-FNA if the first attempt does not yield a diagnosis. For tumors beyond the reach of EUS, a percutaneous CT-guided biopsy approach is reasonable. If those attempts are unsuccessful then a surgical biopsy may be necessary. The preferred staging system for pancreatic adenocarcinoma of the tumor, node, metastasis (TNM) system of the combined American Joint Committee on Cancer (AJCC) considers isolated venous invasion as T3 disease (locally advanced but potentially resectable), while arterial invasion is deemed unresectable (T4 disease) [5]. Based on recent advances in surgical techniques and cross sectional imaging, the term borderline resectable disease has been introduced and many groups have proposed definitions for borderline resectable disease. According to National Comprehensive Cancer Center (NCCN) guidelines, borderline resectable PCa includes tumor that display the following: (1) head/uncinate tumor in contact with common hepatic artery (CHA) without extension to celiac or hepatic artery bifurcation, or in contact with superior mesenteric artery (SMA) < 180 degrees, or in contact with superior mesenteric vein (SMV) or portal vein (PV) > 180 degrees, or in contact with inferior vena cava; or (2) body and tail tumor in contact with celiac axis (CA) < 180 degree (Fig. 1). This radiographic determination is associated with a high-likelihood of positive (R1) surgical margin. Thus, patients with borderline resectable disease are generally offered preoperative (neoadjuvant) therapy prior to surgical resection. A multidisciplinary tumor board discussion at a high-volume center is vital in such cases to determine the role for and timing of perioperative therapy.

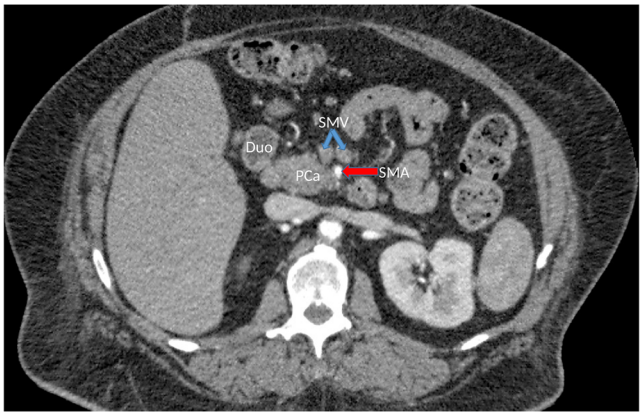

Fig. 1. Arterial phase computed tomography of abdomen exhibits a borderline resectable pancreatic adenocarcinoma. Tumor abuts with < 180 degree involvement. *Duo* duodenum, *PCa* for pancreatic cancer pancreatic adenocarcinoma (head of pancreas), *SMA* superior mesenteric artery, *SMV* superior mesenteric vein.

Role of adjuvant therapy

Even with recent advances in surgical techniques and diagnostic imaging, the prognosis and long-term survival of PCa remains dismal secondary to presence of micro metastatic disease at the time of presentation. Various versions of adjuvant systemic therapy have been shown to improve long-term survival. 5-fluorouracil (5-FU) has been one of the most extensively studied agents in the treatment of PCa with the first study to demonstrate a benefit from adjuvant therapy conducted by the Gastrointestinal Tumor Study Group (GITSG). This study showed an improved overall survival with adjuvant combined radiation and 5-FU (cheomRT) as compared to observation (2-year survival 42 vs 15%; $P = 0.03$) [6]. A trend towards the benefit of adjuvant 5-FU based chemoRT as compared to observation was seen in EORTC 40891 trial with non-statistically significant improvement in median overall survival (mOS) (24.5 vs 19 months; $P = 0.21$) [7].

Adjuvant chemotherapy and chemoRT were further studied in European Study Group for Pancreatic Cancer (ESPAC) 1 trial. In the ESPAC-1 trial, 289 patients were randomized to either receive 5-FU based chemotherapy, 5-FU based chemoRT, both treatments or observation following surgical resection. Results were analyzed in a two by two-factorial design and showed a survival benefit with adjuvant chemotherapy. For the chemotherapy comparison, OS was 20.1 months with adjuvant chemotherapy as compared to 15.5 months ($P = 0.009$) with no chemotherapy [8]. On the other hand, chemoRT was associated with a mOS of 15.9 months as compared to 17.9 months with no chemo RT ($P = 0.05$). The lack of benefit and inferior outcome from chemoRT was thought to be secondary to the lack of radiation quality control, use of split dose radiotherapy delivery techniques, and allowing clinicians to use back-ground chemotherapy and radiation. A meta-analysis of major clinical trials was performed and failed to show any significant benefit from adjuvant chemoRT (HR = 1.09, CI 089–1.32, $P = 0.43$). It did confirm a 25% reduction in risk of death with chemotherapy with HR of 0.75 (CI 0.64–0.9, $P = 0.001$).

Subgroup analysis suggested a trend towards benefit of chemoRT in patients with positive resection margins (R1) [9]. Radiation Therapy Oncology Group (RTOG) 9704 tried to optimize the use of chemotherapy with radiation. In this trial, 451 patients with resected PCa were randomized to adjuvant systemic chemotherapy (gemcitabine vs 5-FU) for 3 weeks followed by 5-FU-based chemoRT and then three more months of chemotherapy with the previously used agent. The mOS was 20.5 months for gemcitabine versus 16.9 months for 5-FU ($P = 0.09$) [10]. Adjuvant chemoRT is commonly utilized in the USA, although the absolute benefit of this approach remains in question. RTOG 0848 is an ongoing phase III trial in which post-operative head of the pancreas cancer patients receive 5 months of investigator's choice of adjuvant chemotherapy (i.e., gemcitabine, 5-FU, or gemcitabine/capecitabine) and are then subsequently randomized to receive 5-FU based chemoRT or one more month of chemotherapy (with omission of chemoRT) (NCT01013649). This critically important study will definitively define the role of adjuvant chemoRT.

Initial adjuvant chemotherapy trials exclusively utilized 5-FU; however, given the activity of gemcitabine in the advanced setting, studying this drug in the adjuvant setting was a logical next step [11]. The European CONKO-001 trial was an adjuvant study that included 368 patients with resected PCa (T1-4, N0-1) who were randomized to 6 months of gemcitabine or observation [12]. Adjuvant gemcitabine was associated with improvement in median disease free survival (DFS) (13.4 vs 6.9 months, $P < 0.001$) and statistically significant but modest improvement in mOS (22.8 vs 20.2 months, $P = 0.01$) [13]. The ESPAC3 trial was designed to compare 5-FU or gemcitabine as adjuvant therapy for resected PCa [14]. This trial demonstrated no difference in mOS between gemcitabine and 5-FU (23.6 vs 23 months, $P = 0.39$). Although gemcitabine and 5-FU were comparable in efficacy endpoints, gemcitabine seemed better tolerated with reduced rate of treatment-related serious adverse events (14 vs 7%, $P < 0.001$). In an ad hoc analysis of ESPAC3 data, survival was no different for patients who received adjuvant chemotherapy before 8 weeks post-operatively as compared to patients who started chemotherapy between 8 and 12 weeks. However, completion of 6 cycles of chemotherapy was an independent prognostic factor with a mOS of 28 months as compared to 14.6 months for patient who received 1–5 cycles of therapy (HR = 0.516, $P < 0.001$) [15]. Based on ESPAC-3 and RTOG 9704, gemcitabine may be the preferred systemic adjuvant agent due to the better toxicity profile, while 5-FU remains a reasonable alternative.

Until recently, gemcitabine with or without radiation remained the best adjuvant treatment option for patients with resected PCa. However, several ongoing adjuvant clinical trials are testing multi-agent combination therapy that is effective in the metastatic setting. The recently published ESPAC4 trial compared the combination of gemcitabine and capecitabine to gemcitabine alone for resected PCa [16••]. The vast majority of patients in both arms of this trial had microscopically positive margin (R1, 60%) and lymph node positive disease (80%). At median follow-up of 43.2 months, mOS was 25.5 months with gemcitabine as compared to 28.8 months in the gemcitabine and capecitabine combination arm (HR 0 · 82, $P = 0 \cdot 032$). A trend towards improvement in the estimated 5-year overall survival was seen in the combination arm 28.8% (CI 22.9–35.2) as compared to gemcitabine alone 16 · 3% (CI 10.2–23.7, $P = 0.032$). Combination therapy was associated with statistically higher

rate of grade 3–4 diarrhea (5 vs 2%t), hand foot syndrome (7 vs 0%), and neutropenia (38 vs 24%). Based on the ESPAC4 data, the combination of gemcitabine and capecitabine is now considered the new standard of care for the adjuvant systemic treatment of PCa (see Table 1 for landmark adjuvant trials). The APACT trial (NCT01964430) is testing gemcitabine with or without nab-paclitaxel and the PRODIGE 24/ACCORD 24 trial (NCT01526135) is comparing gemcitabine versus FOLFIRINOX in the adjuvant setting. The results of these completed trials are anxiously awaited.

Neoadjuvant therapy

Rationale and challenges of neoadjuvant therapy

Despite the noted advancements, 5-year survival rates for patients with PCa who undergo curative therapy remain suboptimal at 20–30%. The complications of surgery and post-operative recovery may delay or preclude the initiation of systemic therapy. In fact, approximately 30–40% of otherwise eligible patients fail to receive any systemic adjuvant therapy. This could be overcome through the use of neoadjuvant therapy [19]. Given that a large number of patients relapse quickly after surgical resection, neoadjuvant therapy offers an opportunity to deliver systemic therapy earlier in the disease course and prior to

Table 1. Landmark adjuvant randomized trials

Trial	Phase	*N*	Treatment	Primary endpoint	Results	*P* value
GITSG [6]	III	43	• Chemo RT with 5-Fu • Observation	Median OS	20 vs 11 mo	0.03
EORTC [7]	III	218	• Chemo RT with 5-Fu • Oservation	Median OS	24.5 vs 19 mo	0.02
ESPAC 1 [8]	III	289	• Chemo RT ≥ Chemotherapy • Chemo RT alone • Chemotherapy alone • Observation	Median OS	Chemo vs no chemo, 20.1 vs 15.5 mo ChemoRT vs no chemoRT, 15.9 vs 17.9 mo	0.009 0.05
CONKO-001 [13]	III	368	• gem • Observation	DFS	13.4 vs 6.9 mo	< 0.001
RTOG 9704 [17]	III	451	• gem before and after chemo RT • 5-Fu before and after chemo RT	Median OS	20.5 vs 16.9 mo	0.09
ESPAC-3 [14]	III	1088	• gem • 5-Fu	Median OS	23.6 vs 23 mo	0.39
JASPAC [18]	III	385	• S1 • gem	2 year OS	70 vs 53%	< 0.0001

Table 1. (Continued)

Trial	Phase	*N*	Treatment	Primary endpoint	Results	*P* value
ESPAC-4 [16••]	III	730	• gem + capecitabine • gem	Median OS	28 vs 25.5 mo	0.032

5-Fu 5-flurouracil, *Chemo RT* chemoradiation, *gem* for Gemcitabine *OS* overall survival, *DFS* disease-free survival, *PFS* progression-free survival, *Mo* months, *CONKO* Charite´ Onkologie trial, *EORTC* European Organization for Research and Treatment of Cancer, *ESPAC* European Study Group for Pancreatic Cancer, *GITSG* Gastrointestinal Tumor Study Group, *JASPAC* Japan Adjuvant Study Group of Pancreatic Cancer, *RTOG* Radiation Therapy Oncology Group

the systemic stress of surgical recovery. Neoadjuvant therapy may also aid in identifying patients who are more likely to benefit from surgery by helping to select those with a disease biology that is amenable to local management. Those that demonstrate metastatic disease during a course of neoadjuvant treatment would have never benefitted from a surgery-first approach. Neoadjuvant therapy also provides an opportunity for tumor downstaging which can allow for resection in a patient who was considered borderline resectable or even unresectable [20, 21]. Finally, incorporation of novel agents in the neoadjuvant setting offers a scientific opportunity to better understand PCa molecular and microenvironment interactions by allowing pre and post-operative tissue sampling. This approach also offers a ripe opportunity to study a myriad of correlatives, including the microenvironment (immune composition, stroma) and epigenetic changes of the tumor.

While neoadjuvant therapy can be safely delivered without negatively influencing perioperative morbidity and mortality, it has not yet demonstrated an improvement in OS. There are several potential hurdles in designing and conducting neoadjuvant clinical trials. First, patient selection can be a challenge in terms of deciding whether to include only up-front resectable patients or whether to also include borderline resectable patients. Additionally, despite well-established definitions, patient resectability can vary by institution and is not consistently standardized. Tissue acquisition for neoadjuvant treatment planning is occasionally difficult and potentially rate limiting. Finally, there remains a cultural unease for some surgeons to risk progression and "jeopardize" the chance for a potentially curative surgery. While this actually serves as a biologic determinant of surgical appropriateness, it is a clinical bias that nonetheless persists.

Available clinical data

To date, there are no published randomized phase 3 trials demonstrating a survival benefit for neoadjuvant therapy in resectable or borderline resectable PCa. However, a number of non-randomized studies have provided consistent data on the safety and feasibility of this approach in this patient population (Table 2). While all of these studies suffer from inherent selection bias, the overall approach continues to be endorsed by consensus guidelines and professional organizations [3, 40]. Several neoadjuvant approaches have been tested, but the ideal regimen has yet to be identified. Most utilized 5-Fu or gemcitabine-based neoadjuvant regiment with or without radiation [41].

Table 2. Selected ($n > 50$) prospective and retrospective neoadjuvant therapy trials in pancreatic adenocarcinoma

Author	N	Treatment	Resection rate	Median OS resected (mo)	Median OS not resected (mo)
Prospective					
Hoffman 1998 [22]	53 (R)	5Fu + Mitomycin + EBRT	ORR = 45% R0 = 32%	15.7	9.7
Snady 2000 [23]	68 (UR)	5-FU + Streptozocin + Cis + EBRT	ORR = 29% R0 = 28%	32	21
Moutardier 2004 [24]	61 (R)	5-FU + Cis + EBRT	ORR = 65% R0 = 60%	26.6	13
Palmer 2007 [25]	50 (R)	Gem vs Gem + Cis	ORR = 38% (Gem) 70%(Gem + Cis) R0 = 75%	28.4	Not reported
Evans 2008 [26]	86 (R)	Gem + EBRT	ORR = 74% R0 = 66%	34	7
Varadhachary 2008 [27]	90 (R)	Gem + Cis ≥ Gem + RT	ORR = 58% R0 = 56%	31	10.5
Bjerregaard 2009 [28]	63 (UR)	UFT + Folinic acid + RT	ORR = 17% R0 = 17%	48	8.8
Golcher 2014 [29]	73 (R)	Gem + Cis + EBRT ≥ Sx vs primary Sx	R0 = 48 vs 50%	18.9 vs 25	Not reported
Barbour 2015 [30•]	42 (R)	Gem + Abraxane (2 cycles) ≥ Sx ≥ 4 more cycles if resected	ORR =73% R0 = 50%	Not reported	Not reported
Retrospective					
Arvold 2012 [31]	46 (UR) 24 (BR)	5-FU or capecitabine + EBRT	ORR = 20% R0=79%	19.4	13.2
Sho 2013 [32] 22,766,692	61 (R)	Gem + EBRT	R0=92%	28	Not reported
Strobel 2012 [33]	257 (LA)	(5FU, Gem, or cetuximab-based) CRT or chemotherapy	ORR = 46.7 R0=30%	24.6	9
Takahasi 2013 [34]	188 (R) 80 (BR)	Gem + EBRT	R ORR = 87% (R) R0 = 99% (R) BR ORR = 54% (BR) R0 = 98% (BR)	All cases 5-yr. survival *R* = 57% BR = 34%	Not reported
Rose 2014 [35]	64 (BR)	Gem + docetaxel	ORR = 48% R0 = 87%	Not reached	15.4
Blazer 2015 [36]	18 (BR)	FOLFIRINOX then RT	ORR = 51%	Not reported	Not reported

Table 2. (Continued)

Author	*N*	Treatment	Resection rate	Median OS resected (mo)	Median OS not resected (mo)
	25 (LA)		R0 = 86.4%		
Marthey 2015 [37]	77 (LA)	FOLFIRINOX then RT	ORR = 36% R0 = 89%	24.9	15.9
Mellon 2015 [38]	110 (BR) 49 (LA)	FOLFIRINOX ($n = 23$), Gem + docetaxel + capecitabine ($n = 94$), Gem ($n = 28$), or Gem/abraxane ($n = 8$), then SBRT	ORR = 38% R0 = 96%	34.2	14
Sadot 2015 [39]	101 (LA)	FOLFIRINOX then CRT	ORR = 31% R0 = 55%	Not reached	Not reported

5-Fu fluorouracil, *Gem* gemcitabine, *Cis* cisplatin, *RT* radiation therapy, *EBRT* external beam radiation therapy, *CRT* chemoradiotherapy, *FOLFIRINOX* 5-fluorouracil, oxaliplatin, irinotecan, *R* resectable, *BR* borderline resectable, *UR* unresectable, *LA* locally advanced, *R0* margin negative resection, *ORR* overall response rate, *Sx* surgery, *mo* months

PCa neoadjuvant treatment protocols started incorporating gemcitabine-based combination therapy after the data from Burris and colleagues on beneficial role of gemcitabine in metastatic PCa [11]. One of these phase 2 trials from MD Anderson Cancer Center (MDACC) included 86 patients with potentially resectable PCa and delivered weekly gemcitabine for 7 weeks along with concomitant radiation therapy (30 Gy in 10 fractions over 2 weeks) [26]. This trial reported a resection rate of 74% (64/86) and OS of 22.7 months for all patients. However, mOS was 34 months for the patients who were able to undergo resection. Unfortunately, 57% (37/86) of patients who underwent resection still developed recurrent disease with liver mets being the most common organ involved. Based on these results, trials started incorporating more systemic therapy to mitigate the metastatic burden. Another study at MDACC evaluated 90 patients with resectable PCa treated with gemcitabine and cisplatin every 2 weeks for four doses followed by gemcitabine-based chemoRT. Of the 79 patients who finished therapy, 52 (66%) were able to undergo resection with mOS of 31 months [27]. In another phase 2 trial, 38 patients with resectable PCa underwent gemcitabine and oxaliplatin-based neoadjuvant therapy followed by surgery followed by additional adjuvant chemotherapy. In this trial, 27 of 38 patients (71%) underwent resection and the majority (23/27) were able to finish all planned therapy. The median overall survival for this group was 27.2 months [42].

The feasibility of neoadjuvant therapy has been studied in borderline resectable and locally advanced unresectable PCa (LAPC) although several of these early phase trials also included resectable patients. One of these phase 2 studies evaluated 68 patients with resectable or borderline resectable PCa and delivered 2 cycles of gemcitabine and oxaliplatin chemotherapy concurrent with radiation. A total of 61 patients were able to finish therapy, and 43 patients (63%) were able to undergo resection. The mOS was 27.1 months for patients who were able to undergo resection and 18.2 months for all patients [43].

Most recently, the use of more contemporary combination therapies (i.e., FOLFIRINOX [leucovorin, 5-FU, irinotecan, oxaliplatin] and GNA [gemcitabine, nab-paclitaxel]) have been explored in the neoadjuvant setting. In the published Massachusetts General Hospital experience, 22 patients with LAPC underwent neoadjuvant chemotherapy with FOLFIRINOX followed by 5-FU-based chemoRT. Five out of 22 (23%) underwent successful R0 resections [44]. In a French multicenter prospective observation cohort, 77 patients with LAPC were treated with FOLFIRINOX until progression or toxicity. A median of 6 cycles were given and 28 out of 77 (36%) patients underwent surgical resection with mOS of 24.9 months [37]. In a meta-analysis of 13 studies with 253 borderline resectable and LAPC who were treated with FOLFIRINOX with and without radiotherapy, 43% of patients were able to undergo resection. The rate of R0 resection was 63.5% in borderline resectable disease [45]. Although this approach may hold the potential to convert unresectable to resectable disease, the toxicity demonstrated was not insignificant with cumulative rate of 24–75% of grade 3 and 4 toxicities and most common toxicities were neutropenia and diarrhea. Several other centers have reported single institution retrospective data with neoadjuvant FOLFIRINOX that is summarized in Table 2.

It is clear that the neoadjuvant approach for the delivery of chemotherapy is feasible. The resection rate is variable due to the differences in the chemotherapy regimen used and based on initial resectability status. The

Table 3. Select upcoming studies of interest

Trial	Phase	Treatment	End point
NEOPAC (NCT01521702)	3	Neoadjuvant Gem/oxaliplatin plus adjuvant Gem in resectable PCa	PFS
NEOPA (NCT01900327)	3	Sequential neoadjuvant CRT followed by curative surgery vs primary surgery alone for resectable PCa	3-yr survival
NCT01458717	3	Neoadjuvant CRT in borderline resectable PCa	2-yr survival
NorPACT-1 (NCT02919787)	3	Neoadjuvant vs adjuvant chemotherapy in resectable PCa	OS at 1 yr
NCT02172976	3	Randomized multicenter phase II/III study with adjuvant Gem vs neoadjuvant/adjuvant FOLFIRINOX for resectable PCa	Median OS
S1505 (NCT02562716)	2	Perioperative mFOLFIRINOX vs Gem/nab-paclitaxel as therapy for resectable PCa	OS
NCT03199144	2	Neoadjuvant Gem + abraxane with stereotactic radiotherapy	OS at 3 yrs
NCT02241551	2	Neoadjuvant chemotheraphy (Gem and nab-paclitaxel vs mFOLFIRINOX) and sterotatic body radiation therapy for borderline resectable PCa	Safety and PCR and R0 resection rate
NCT02717091	2	Neoadjuvant FOLFIRINOX or nab-paclitaxel with Gem for borderline resectable PCa	R0 resection rate
PANDAS-PRODIGE 44 (NCT02676349)	2	Neoadjuvant mFolfirinox with or without preoperative concomitant CRT in patients with borderline resectable pancreatic carcinoma	R0 resection rate
NCT02305186	1/2	CRT with or without pembrolizumab in resectable and borderline resectable PCa	Safety and number of tumor infiltrating lymphocytes

Gem gemcitabine, *FOLFIRINOX* 5-fluorouracil, oxaliplatin, irinotecan, *FOLFOX* 5-fluorouracil, oxaliplatin, *PCa* pancreatic carcinoma, *CRT* chemo-radiotherapy, *PFS* progression-free survival, *OS* overall survival, *PCR* pathologic complete response, *R0* margin negative resection

initial trials reported resection rate of 50–70% for the patients with resectable disease and 5–30% for the patients who had LAPC at the time enrollment [46]. In a restrospective analysis MDACC which included 160 patients with borderline resectable PCa, 41% underwent surgery and 94% had R0 resection. Median overall survival was 40 months for the patients who underwent surgery as compared to 13 months ($P < 0.001$) for patients who did not undergo surgery [47]. Another meta-analysis included 536 patients from 14 phase 2 clinical trials who were divided into two groups: resectable (group A) and borderline resectable or LAPC (group B). After neoadjuvant therapy, 31.6% patients in group B were deemed to be resectable as compared to 65.8% in group A. Median overall survival was similar in both the groups who were able to undergo resection (22 months in-group A vs 23 months in group B). One of the largest meta-analysis by Gillen and colleagues included 111 studies [48]. The most common neoadjuvant or preoperative regimens were gemcitabine, 5-FU, mitomycin, and platinum

compounds. Neoadjuvant radiotherapy was applied in 93.7% of the studies with doses ranging from 24 to 63 Gy. The resection rate was 73.6% for patients with resectable disease with R0 resection rate of 82%. The mOS in this group was 23.3 months (range 12–54 months) with 2-year survival of 47%. Among the patients with borderline resectable or LAPC disease, the resection rate was 33.2% with R0 resection rate of 79%. The mOS was 20.5 months (range 9–62 months) with a 2-year survival of 50%. Similar to all other studies, it was noted that approximately one third of patients initially deemed borderline resectable or LAPC were able to undergo resection with comparable survival to initially resectable patients. The authors conclude that all initially unresectable patients should be considered for neoadjuvant treatment with a repeat evaluation for surgery after therapy. Due to the heterogeneity of data, no standard regimen could be determined.

Role of neoadjuvant therapy in locally advanced PCa

Based on the this data, most of the institutions and guidelines recommend neoadjuvant multi-agent chemotherapy approach for the patients with borderline resectable and locally advanced disease, noting that resection rates for patients with LAPC are only 5–30%. The optimal treatment approach for LAPC patients who responded or have stable disease at the end of induction chemotherapy has not been determined and most of the guidelines recommend continued chemotherapy versus chemoradiotherapy for this patient population [49, 50]. Importantly, the role of consolidation chemo RT was prospectively evaluated in LAP07 trial in which 442 patients with LAPC were randomly assigned to chemotherapy with gemcitabine versus gemcitabine + erlotinib in 2 × 2 factorial design. At the end of 4 months, patients without systemic progression underwent a second randomization to continued chemotherapy versus chemo RT. While the clinical benefit of erlotinib in this patient population was not significant, chemo RT was associated with decreased local progression (32 vs 46%, $P = 0.03$) but failed to show any survival benefit (mOS of 13.6 vs 11.9 months, HR, 1.19; $P = 0.09$) [51]. Thus, the role of consolidation chemoRT after demonstrated disease stability on systemic chemotherapy in patients with LAPC appears associated with improved local, but not overall, disease control. Patients who have progressive disease after induction chemotherapy are treated similarly to those with stage IV disease.

Final thoughts

In absence of the prospective studies with upfront surgery as control arm, it is difficult to determine whether the neoadjuvant approach represents an actual benefit or whether upfront surgery would achieve similar outcome in resectable PCa. A potential confounder in determining the magnitude of benefit of neoadjuvant therapy for achieving an R0 resection is the improving surgical techniques, specifically the ability of the surgeon to perform vascular reconstruction. Additionally, the lack of standard radiographic indicators to determine response to neoadjuvant therapy further complicates the neoadjuvant approach. In a single institution analysis from MDACC, 122 borderline resectable patients were treated with variety of neoadjuvant strategies and15 patients had a partial response, 84 had stable disease, and 23 were thought to have

progressive disease based on standard Response Evaluation Criteria in Solid Tumors (RECIST). Although only one patient was thought to have resectable disease, 85 (66%) were taken for pancreatectomy and 81 achieved R0 resection. Median OS was 33 months for patients who underwent surgery that was not associated with a RECIST response (P-0.78) [52]. This data suggests that radiographic downstaging after neoadjuvant treatment should not dictate surgical resectability, and such candidates should undergo further surgical exploration in absence of documented metastatic disease.

In the end, the totality of data supports the feasibility of neoadjuvant therapy and potential benefit in a subset of patients with PCa. In the setting of borderline resectable and LAPC, even in the absence of a prospective trial, academic institutions and national practice and professional guidelines support a neoadjuvant therapy approach aimed to achieve R0 resection. In the setting of initially resectable disease, use of neoadjuvant therapy remains controversial at this time. The modest benefit of adjuvant therapy after surgery and nearly one third of the patient not able to receive adjuvant therapy due to complications of the surgery makes neoadjuvant approach attractive even in the resectable patient population. Several randomized, controlled trials are now ongoing with more contemporary systemic regimens and will hopefully provide further direction regarding this approach (see Table 3). Until further data become available, multidisciplinary management at high-volume centers with an individualized approach to patients should be the standard.

Future directions

The optimal multidisciplinary modalities, sequence, and timing of treatments are all yet to be defined. Incorporation of multi-agent chemotherapy regimens with FOLFIRINOX and gemcitabine combination in neoadjuvant setting is one of the most active areas of the research with several ongoing trials (Table 3). The key to improving outcomes for this recalcitrant disease involves optimizing the most effective therapy for the individual patient at the onset. This involves more investigation into defining and treating the molecular subtypes of PCa inclusive of the stromal elements and immune microenvironment surrounding the tumor.

While a complete inventory of ongoing investigations into potential PCa vulnerabilities is beyond the scope of this review, there are several lines of inquiry that are categorically representative of work in this field. About 90% of PCa tumors harbor a mutation of the oncogene *KRAS* resulting it its constitutive activation. Unfortunately, despite decades of efforts, there are no currently effective therapies that target this mutation. However, new approaches are on the horizon such as siG2 LODER, which is miniature biodegradable polymeric matrix containing small-interfering RNAs for the mutated KRAS oncogene, KRASG12D (siG12D), with potential antitumor activity and immunotherapy aimed to identify the mutant KRAS protein as a neoantigen (NCT01676259). Loss of function of several tumor suppressor genes such as TP53, p16/CDKN2A, and SMAD4 have been documented with silencing of the tumor suppressor gene CDKN1A due to mutation or deletion has been shown in more than 50% of PCa patients. A highly potent CKD4/6 inhibitor to target the CDKN1A has shown preclinical activity in PCa and is being tested in early phase studies in metastatic setting (NCT01783171) [53].

Approximately 5–10% of patient's harbor a germline mutation in the BRCA1, BRCA2, and PALB2 genes. It has been shown that a certain number of patients with chromosomal instability in the BRCA gene show exceptional sensitivity to platinum agents [54]. Whether patients with germline mutation in this gene would benefit from platinum-based neoadjuvant or adjuvant therapy is unknown at this time. The stromal component of PCa is known to affect tumorigenesis, angiogenesis, therapy resistance, and possibly the metastatic spread of tumor cells [55]. Therefore, targeting the tumor stroma, in combination with chemotherapy, is a promising approach. A trial is currently ongoing investigating the role of PEGPH20, a PEGylated form of recombinant human hyaluronidase, along with chemotherapy in advanced PCa (NCT02715804). Incorporation of these approaches in select-targeted patient populations could be rapidly tested in the neoadjuvant or adjuvant setting once proof of principle has been garnered from studies in metastatic disease.

Somatic or germline mutation of the DNA mismatch repair (MMR) genes is known in about 5% of patients with PCas. The programmed cell death 1 (PD-1) antibody, pembrolizumab, was recently approved for any malignancy with a deficient MMR or microsatellite high (MSI-H) genotype. This offers an exciting opportunity to further explore immunotherapy for this disease. Unfortunately, single agent PD-1 and cytotoxic T lymphocyte-associated protein 4 (CTLA4) directed therapy has failed to show any activity in the metastatic setting for PCa [56•, 57•]. Several PD-1 and programmed cell death ligand (PDL-1) inhibitors in combination with other immune targets are being tested in the salvage and neoadjuvant settings. It is unclear at this time if neoadjuvant immunotherapy, for those with MMR deficiency, can improve outcomes, obviate the need for chemotherapy, or even obviate the need for surgery. There are several ongoing studies evaluating this approach (NCT02451982). Although vaccine studies have failed to show any meaningful benefit in the adjuvant and metastatic setting, this approach is being further explored in the neoadjuvant setting. Additionally, multiple attempts to augment the killer T cell function and overcome simultaneous immune suppression in this disease are ongoing. Some examples of this approach include combining immune checkpoint inhibitors with vaccines, MEK inhibition, dual, or triple immunotherapy (PD-1 and CTLA-4) axis modulation and radiation/chemotherapy to overcome immunoediting. The PCa Action Network (PANCAN) will provide invaluable information on personalized treatments for PCa by providing innovative trials through their Precision Promise Clinical Trials Network that initially focuses on DNA repair, pancreatic stroma/microenviroment, and immune-oncology interventions [58••].

Conclusion

The field of PCa remains challenging with few cures still dependent upon surgical resection and early metastatic spread evading detection. Perioperative multidisciplinary management of patients at high-volume centers is a critical component of optimizing outcomes. Systemic chemotherapy improves outcomes beyond surgical resection alone with a neoadjuvant approach offering an opportunity to ensure patients are appropriately selected for a local surgical intervention. New treatments on the horizon offer tremendous hope for

targeted patient populations with perioperative exploration of such treatments providing a potential new window of opportunity.

Compliance with Ethical Standards

Conflict of Interest

Hiral D. Parekh declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
2. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst. 1988;80:751–5.
3. Network NCC. Pancreatic Adenocarcinoma, Version 2.2017.
4. Chen J, Yang R, Lu Y, Xia Y, Zhou H. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. J Cancer Res Clin Oncol. 2012;138:1433–41.
5. Tamm EP, Balachandran A, Bhosale PR, et al. Imaging of pancreatic adenocarcinoma: update on staging/resectability. Radiol Clin N Am. 2012;50:407–28.
6. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg. 1985;120:899–903.
7. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230:776–82.discussion 782-774
8. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet. 2001;358:1576–85.
9. Stocken DD, Büchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005;92:1372–81.
10. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299:1019–26.
11. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15:2403–13.
12. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297:267–77.
13. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310:1473–81.
14. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a

randomized controlled trial. JAMA. 2010;304:1073–81.
15. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol. 2014;32:504–12.
16.•• Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017;389:1011–24.
Changed Standard of care for adjuvant therapy.
17. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18:1319–26.
18. Uesaka K, Boku N, Fukutomi A, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388:248–57.
19. Abbott DE, Baker MS, Talamonti MS. Neoadjuvant therapy for pancreatic cancer: a current review. J Surg Oncol. 2010;101:315–20.
20. Ferrone CR, Brennan MF, Gonen M, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. J Gastrointest Surg. 2008;12:701–6.
21. Assifi MM, Lu X, Eibl G, Reber HA, Li G, Hines OJ. Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials. Surgery. 2011;150:466–73.
22. Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an eastern cooperative oncology group study. J Clin Oncol. 1998;16:317–23.
23. Snady H, Bruckner H, Cooperman A, Paradiso J, Kiefer L. Survival advantage of combined chemoradiotherapy compared with resection as the initial treatment of patients with regional pancreatic carcinoma. An outcomes trial. Cancer. 2000;89:314–27.
24. Moutardier V, Magnin V, Turrini O, et al. Assessment of pathologic response after preoperative chemoradiotherapy and surgery in pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys. 2004;60:437–43.
25. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol. 2007;14:2088–96.
26. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26:3496–502.
27. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol. 2008;26:3487–95.
28. Bjerregaard JK, Mortensen MB, Jensen HA, et al. Long-term results of concurrent radiotherapy and UFT in patients with locally advanced pancreatic cancer. Radiother Oncol. 2009;92:226–30.
29. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer: results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015;191:7–16.
30.• Barbour AORN, Chandrasegaram MD, Chua YJ, Kench J, Samra JS, Pavlakis N, et al. A multicenter, phase ii trial of preoperative gemcitabine and nab-paclitaxel for resectable pancreas cancer: the AGITG GAP study. ASCO Meeting Abstracts. J Clin Oncol. 2015;33:41152015.
Neoadjvuant phase 2 trial with Gemcitabine/Abraxane.
31. Arvold ND, Ryan DP, Niemierko A, et al. Long-term outcomes of neoadjuvant chemotherapy before chemoradiation for locally advanced pancreatic cancer. Cancer. 2012;118:3026–35.
32. Sho M, Akahori T, Tanaka T, et al. Pathological and clinical impact of neoadjuvant chemoradiotherapy using full-dose gemcitabine and concurrent radiation for resectable pancreatic cancer. J Hepatobiliary Pancreat Sci. 2013;20:197–205.
33. Strobel O, Berens V, Hinz U, et al. Resection after neoadjuvant therapy for locally advanced, "unresectable" pancreatic cancer. Surgery. 2012;152:S33–42.
34. Takahashi H, Ohigashi H, Gotoh K, et al. Preoperative gemcitabine-based chemoradiation therapy for resectable and borderline resectable pancreatic cancer. Ann Surg. 2013;258:1040–50.
35. Rose JB, Rocha FG, Alseidi A, et al. Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. Ann Surg Oncol. 2014;21:1530–7.
36. Blazer M, Wu C, Goldberg RM, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol. 2015;22:1153–9.
37. Marthey L, Sa-Cunha A, Blanc JF, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015;22:295–301.
38. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol. 2015;54:979–85.

39. Sadot E, Doussot A, O'Reilly EM, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol. 2015;22:3512–21.
40. Khorana AA, Mangu PB, Berlin J, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34:2541–56.
41. Hoffman JP, Weese JL, Solin LJ, et al. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. Am J Surg. 1995;169:71–7.discussion 77-78
42. O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. Ann Surg. 2014;260:142–8.
43. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer. 2013;119:2692–700.
44. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital cancer center experience. Oncologist. 2013;18:543–8.
45. Petrelli F, Coinu A, Borgonovo K, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas. 2015;44:515–21.
46. Tang K, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Pancreatology. 2016;16:28–37.
47. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg. 2008;206:833–46.discussion 846-838
48. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7:e1000267.
49. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, Unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34:2654–68.
50. NCCN clinical practice guidelines in oncology Pa, V 3.2017, 2017.
51. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. JAMA. 2016;315:1844–53.
52. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer. 2012;118:5749–56.
53. Franco J, Witkiewicz AK, Knudsen ES. CDK4/6 inhibitors have potent activity in combination with pathway selective therapeutic agents in models of pancreatic cancer. Oncotarget. 2014;5:6512–25.
54. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015;518:495–501.
55. Erkan M, Hausmann S, Michalski CW, et al. The role of stroma in pancreatic cancer: diagnostic and therapeutic implications. Nat Rev Gastroenterol Hepatol. 2012;9:454–67.
56.• Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010;33:828–33.
Negative single agent sutdy for CTLA-4 agent, ipilimumab.
57.• Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65.
No role of single agent PD1 therapy in pancreatic cancer.
58.•• PrecisionPromise Clinical Trials Network https://www.pancan.org/research/precision-promise/Up and coming for metastatic pancreatic cancer, see text for details.