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REVIEW ARTICLE

Pancreatic Cancer: A Review of Current Treatment and Novel Therapies

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ABSTRACT

Pancreatic cancer is one of the leading causes for cancer-related deaths in the United States. Majority of patients present with unresectable or metastatic disease. For those that present with localized disease, a multidisciplinary approach is necessary to maximize survival and optimize outcomes. The quality and safety of surgery for pancreatic cancer have improved in recent years with increasing adoption of minimally invasive techniques and surgical adjuncts. Systemic chemotherapy has also evolved to impact survival. It is now increasingly being utilized in the neoadjuvant setting, often with concomitant radiation. Increased utilization of genomic testing in metastatic pancreatic cancer has led to better understanding of their biology, thereby allowing clinicians to consider potential targeted therapies. Similarly, targeted agents such as PARP inhibitors and immune checkpoint- inhibitors have emerged with promising results. In summary, pancreatic cancer remains a disease with poor long-term survival. However, recent developments have led to improved outcomes and have changed practice in the past decade. This review summarizes current practices in pancreatic cancer treatment and the milestones that brought us to where we are today, along with emerging therapies.

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Background

Pancreatic ductal adenocarcinoma (PDAC) is the third overall leading cause for cancer-related mortality in the US [1]. According to Surveillance, Epidemiology and End Result Program (SEER), roughly 57,600 new cases were diagnosed in 2020, resulting in 47,050 deaths [2]. The poor prognosis associated with this disease is attributable to its early systemic spread and aggressive local growth. Nearly 50–60% of patients present with distant metastatic disease, 25–30% with regional disease and only 10–15% of patients present with local disease [3]. Treatment and prognosis for patients with local or regional disease depend on resectability of the tumor. Incomplete resection (R2) is known to have a detrimental effect on survival, approaching those presenting with metastatic disease [4–6]. Therefore, the selection of patients eligible for complete and curative resection is crucial. However, the definition of resectability – easily resectable versus borderline resectable – has varied amongst surgeons which led to a degree of heterogeneity in earlier study populations undergoing resection [7]. Still today, definitions by expert panels differ slightly on what constitutes resectable disease (Table 1) [7, 8].

Although our understanding of this disease is still limited and overall prognosis poor, improvements in survival have been made in recent years. The quality of surgical care has improved, owing to increased expertise and the development of high-volume centers. More patients are candidates for resection owing to techniques that include arterial and venous resections and reconstruction. Minimally invasive surgery has found a role, with 15% of all pancreaticoduodenectomies being performed laparoscopically. Similarly, systemic therapy has evolved toward improved survival with growing interest in tumor genomics and targeted therapies. In this review, we will discuss the evidence behind current therapies along with novel treatments that are underway.

Surgical outcomes and adjuncts

Short term outcomes

The choice of surgery for pancreatic cancer depends on the location of the tumor in the pancreas. While tumors distal to the pancreatic head are usually amenable to a distal pancreatectomy, the majority of pancreas tumors, located in the head, require a pancreaticoduodenectomy for complete resection [5]. For the purpose of this review, we will focus on outcomes related to the classic pancreaticoduodenectomy.

Pancreaticoduodenectomy (PD) has evolved since its debut in 1889 by the Italian dr. Codivilla [9]. This complex procedure was not fully established until Dr. Whipple described it in his two-step approach for ampullary malignancies in a seminal article in 1935 [10]. However, perioperative mortality remained high for decades. Early reports of post-operative mortality were as high as 30-45% [11–13]. Today, mortality has vastly improved and is now at an acceptable 1-3% in

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Table 1. Criteria for resectability per the National Comprehensive Cancer Network (NCCN) and MD Anderson Cancer Center (MDACC) [7].

	Resectable		Borderline Resectable		Locally advanced	
	NCCN	MDACC	NCCN	MDACC	NCCN	MDACC
SMV/PV	No tumor contact or under <180° contact without irregularity	Patent	Tumor abutment ≥180° +/= vessel irregularity. Amenable to reconstruction	Short segment occlusion with suitable vessel above/below for reconstruction	Tumor involvement or occlusion that is not amenable to reconstruction	Occluded with no technical reconstructive option
SMA/hepatic artery	No contact	No contact, normal fatty plane	Tumor abutment <180° of circumference of vessel wall	Tumor abutment ≤180° of circumference of vessel wall	Tumor encasement ≥180° of circumference of vessel wall	Encased (≥180° vessel involvement)
CHA	No contact	No contact	Reconstructable, short-segment interface between tumor and vessel of any degree	Short segment encasement/abutment	Not reconstructable, or long-segment encasement	Encased and no reconstructive option

SMV: Superior mesenteric vein. PV: portal vein. CHA: Common hepatic artery.
NCCN: National Comprehensive Cancer Network. MDACC: MD Anderson Cancer Center.

high-volume centers [13–16]. Nevertheless, short-term morbidity remains a significant issue [11]. The incidence of pancreatic fistula has varied in published literature, related to lack of clear definition. Commonly quoted at 5-15%, this complication is now defined into grades A-C as per the international Study Group On Pancreatic Fistulas (ISGPF) [17]. Delayed gastric emptying (DGE) is another serious complication that affects approximately 20% of patients [18]. Similar to pancreatic fistulas, the International Study Group on Pancreatic Surgery has defined DGE according to severity into grades A-C [19]. Both surgical technique and patient-related factors have been investigated for association with DGE. Eisenberg et al found intra-abdominal fluid collections and smoking history to be associated with DGE in their retrospective series of 721 patients [18]. A meta-analysis by Hanna et al on surgical technique found antecolic position of the gastrojejunostomy limb as well as subtotal stomach preserving PD to be associated with lower incidence of DGE [20]. Overall, DGE after PD remains a challenging issue in need of further study. With the advent of high-volume centers, outcomes have improved, prompting a recent attempt to define outcome benchmarks for pancreaticoduodenectomies [21]. Sanchez-Vazquez et al [21] derived benchmark values from operative and peri-operative data from 2,375 pancreaticoduodenectomies performed at high-volume centers around the world. Among those proposed standards included operative time ≤ 7.5 hours, ≤ 30% of patients suffering Clavien-Dindo [22] grade ≥3 complications, in hospital mortality ≤1.6% and ≤9% readmission rate. These benchmarks represent a modern standard in surgical care for patients undergoing pancreaticoduodenectomy.

Oncologic outcomes

The only hope of curing pancreatic cancer involves a combination of complete resection and systemic multi-agent chemotherapy [23]. Surgical outcomes have improved in the past two decades, largely due to increased surgical expertise at higher volume centers [13, 15]. More patients are now considered for resection thanks to aggressive surgical techniques that include vascular resection and reconstruction [24]. The median 5-year survival after surgery in modern reports is around 20% [13, 23]. Some have reported higher survival rates of up to 30% with the latest multimodal therapy [25, 26]. Overall recurrence rate, however, remains high at 70-80% [27, 28]. Distant metastases after surgery are the main mode of disease recurrence with the liver being the most common site [27–29]. Many believe this to be due to micro-metastases present at time of surgery. This is driving current practice toward treating patients with neoadjuvant chemotherapy before surgery, regardless of resectability [30, 31]. More data are pending that will hopefully establish the true benefits, if any, of this approach in patients with resectable disease [32]. Those with borderline resectable and locally advanced disease should receive neoadjuvant treatment before considering surgery [33]. This approach has been reported to achieve more negative margin resection rates, as well as to convert few unresectable patients to resectable state.

Minimally invasive pancreaticoduodenectomy

The first report of a laparoscopic pancreaticoduodenectomy (LPD) was by Gagner and Pomp in 1994, although not for the indication of malignancy [34]. Initial concerns regarding the laparoscopic approach centered around a long learning curve, increased operative time and potentially, complication rate. However, as this method gained popularity, early retrospective reviews generally reported favorable outcomes. A review summary of all reported LPDs (n = 146) in 2009 reported overall mortality at 1.3%, 16% complication rate, and average blood loss of 143 mL albeit a relatively long median hospital stay of 18 days, and a high conversion rate to open surgery at 43% [35]. As experience with the procedure grew, indications expanded to include mesenteric vascular resections with reconstructions [36, 37]. The only randomized clinical trial performed to date, addressed perioperative outcomes in their study of 66 patients (34 LPD, 32 OPD) in 2018. Among their significant findings was a benefit of the laparoscopic approach in terms of length of stay (13.5 vs 17 days) and post-operative complication burden [38]. Two meta-analyses have since been published comparing LPD to open PD in 9,144 and 15,278 patients with pancreatic cancer respectively [39, 40]. They reported rates for surgical mortality and pancreatic fistulas as similar between the two approaches while R0 resections and harvested lymph nodes were significantly better in the LPD group in both studies. Overall survival and 5-year survival were found to be similar between these approaches which have been supported by other studies as well [39, 41–43].

Much like LPD, robotic pancreaticoduodenectomy (RPD) has mostly observational evidence to justify its use. A multi-institutional retrospective study by Zureikat and colleagues in 2016 compared perioperative outcomes from 211 RPDs and 817 OPDs [44]. Their findings included no difference in mortality, hospital stay or re-admission rate. RPD was associated with less blood loss, less rate of severe complications and longer operative time. A meta-analysis of 11 comparative studies by Chen and colleagues further supported lower overall complication rate for patient undergoing RPD compared to OPD as well as lower operative blood loss, rate of wound infections and earlier activity after surgery without a difference in mortality.

Not all reports on minimally invasive PD (MIPD) have been favorable. Adams and colleagues compared actual national outcomes of patients undergoing LPD/RPD and OPD utilizing data from the National Cancer Database (NCDB) [45]. Their findings showed that the majority of hospitals performing minimally invasive PDs were low-volume (<10 cases/2 years) and 30-day unadjusted mortality was 5.1% vs 3.1% for MIPD vs OPD, respectively [45]. Additionally, Nussbaum et al investigated whether minimally invasive PD was superior to OPD in terms of patients receiving adjuvant therapy earlier, a theoretic advantage of the minimally invasive technique. Utilizing NCDB data from 2010-2012 they found no difference in time to adjuvant therapy or overall use of adjuvant therapy between those undergoing MIPD and OPD [46]. Finally, the majority of available data has been from expert centers, limiting generalizability of reported outcomes. Nevertheless, enthusiasm for minimally invasive PD is growing, in 2012, approximately 15% of all PDs were being performed using minimally invasive techniques [46].

Adjuncts to surgery

Given the need to achieve clear surgical margins for acceptable oncologic outcomes, mesenteric and portal vein resections have been investigated in multiple studies [47–49]. Venous resections are often necessary in borderline resectable and locally advanced pancreatic cancer patients with vascular involvement, if a curative resection is to be achieved. Currently, approximately 4–20% of pancreaticoduodenectomies involve venous resections. Published data speaks to its safety in terms of short-term morbidity while incurring increased operating times and blood loss [13, 24, 49]. From an oncologic standpoint, similar overall survival after venous resections has been described when compared to traditional PD despite tumor invasion into the portal vein/mesenteric vein on pathology [48]. Involvement of adjacent arterial structures, such as the celiac axis (CA), common hepatic artery (CHA), and superior mesenteric artery (SMA) has traditionally constituted unresectable disease. However, data have been accumulating from expert centers on combined arterial resections, that speak to its feasibility in select cases [49]. In the case of bulky pancreatic body tumors, the celiac axis can be resected either with or without reconstruction with acceptable outcomes [50]. In fact, available data suggests that achieving an R0 resection impacts survival more than the extent of resection [49, 50]. Chua et al, in their systematic review of all reports on vascular resections, found median overall and 3-year survival in patients undergoing combined venous and arterial resections to be 18 months and 13%, respectively. For optimal outcomes, vascular resections should be performed by surgeons at high-volume centers with experience in performing these procedures.

Irreversible electroporation (IRE), or Nanoknife ablation, is a non-thermal ablative technique that creates high voltage, short pulse electrical fields that induces local cellular apoptosis via micro-pores formed in the cell membrane [51]. This method is emerging as a potential palliative option in unresectable, locally advanced PDAC given its ability to cause tumor destruction without compromising adjacent vessels or bile ducts [52, 53]. A pilot study by Martin et al enrolled 27 patients with unresectable locally advanced pancreatic cancer and performed either resection of the primary tumor with IRE (NanoKnife®) margin accentuation (n = 8) or IRE alone (n = 19). Their findings at 3 months follow-up were consistent with complete tumor destruction in all patients without local recurrence, one patient (3.7%) died within that time and 33% morbidity was described [52]. Other authors have reported improved outcomes when used as an adjunct to PD as well [54]. We currently await the results of a randomized clinical trial that will compare survival of patients with stage 3 unresectable pancreatic cancer randomized to either FOLFIRINOX or FOLFIRINOX and IRE (NCT03899636).

Chemotherapy

Palliative chemotherapy for unresectable and metastatic PDAC patients

Patients with locally advanced or metastatic PDAC are generally considered non-curative and managed with palliative intent. Several trials have showed systemic chemotherapy improves overall survival in this setting. FOLFIRINOX was evaluated in the PRODIGE 4-ACCORD11 trial, comparing standard dose gemcitabine to FOLFIRINOX (5-Fluorouracil, Folinic acid, Irinotecan and Oxaliplatin) in patients with advanced PDAC. This phase 3, multicenter trial randomized 342 patients showed a median overall survival (mOS) benefit of 11.1 months vs. 6.8 months in favor of FOLFIRINOX [55]. In another phase 3 trial (MPACT), 861 patients were randomized to either nab-paclitaxel and gemcitabine (Gem-nabP) or gemcitabine alone [56]. mOS was superior in the Gem-nabP group (8.5 months vs 6.7 months) as well as progression-free survival (5.5 vs 3.7 months). There is no randomized head-to-head comparison of FOLFIRINOX and Gem-nabP, both are considered reasonable first-line treatments for unresectable PDAC. In clinical practice, FOLFIRINOX is generally reserved for fit patients whereas Gem-nabP is preserved for patients with mediocre performance, comorbidities or old age. There is evidence from retrospective data that FOLFIRINOX could improve OS, but causes more toxicity in vulnerable population [57]. Therefore, gemcitabine monotherapy or FOLFOX are considered reasonable treatments for PDAC patients with poorer performance status (ECOG ≥2). After progression on first-line gemcitabine-based therapy, nanoliposomal irinotecan in combination with 5FU compared to 5FU alone was shown in the NAPOLI-1 study to have survival advantage of a mOS of 6.1 months vs 4.2 months) in PDAC patients [58]. Now this combination is standard second-line therapy. About 5% of PDAC patients harbor germline BRCA mutations. Given the role of synthetic lethality and PARP inhibition in patients with DNA damage response (DDR) pathway aberrations, the POLO trial was conducted to investigate the efficacy of Olaparib (a PARP Inhibitor) as switch maintenance therapy in PDAC patients with germline BRCA mutations [59]. Based on the significant mPFS advantage and QOL results (7.4 months vs. 3.8 months, HR 0.53), Olaparib maintenance is now approved for BRCA mutated PDAC patients. In the randomized phase 2 SEQUENCE study, standard gem-nabP (Days 1,8 15) followed by mFOLFOX (on day 29 of 6 weeks cycles) compared to standard gem-nabP, was studied in 153 metastatic PDAC patients [60]. Results were intriguing with mOS 13.7 months vs 9.4 months, however grade 3 cytopenias were higher in the experimental arm. Patients receiving nab-P/Gem-mFOLFOX showed a significantly higher 12-month (55.3% vs. 35.4%), and 24- month (22.4% vs. 7.6%) survival. This could be a potential first-line option in metastatic PDAC treatment.

Adjuvant chemotherapy

Adjuvant chemotherapy after curative intent surgery in PDAC is evolving. Despite the survival benefit from singe agent adjuvant therapy with 5FU (ESPAC-1) or Gemcitabine (ESPAC-3, CONKO 001) [59–61], two most recent trials dictating current practice are the ESPAC-4 and PRODIGE 24 [61, 62]. The ESPAC-4 found gemcitabine/capecitabine combination to provide better OS (28 vs 25.5 months) compared to gemcitabine monotherapy in their trial of 732 patients [61]. PRODIGE 24 was a large multi-national phase 3 trial comparing modified FOLFIRINOX regimen (reduced irinotecan and no bolus 5-FU) to gemcitabine in the adjuvant setting [62]. The results showed improved mOS (54.4 months vs 35 months) in favor of mFOLFIRINOX. As expected, more toxicity was associated with mFOLFIRINOX. Modified FOLFIRINOX for 24 weeks remains the standard of care for good performance patients after surgical resection. Gemcitabine with or without Capecitabine is an option for those unable to tolerate mFOLFIRINOX.

Neoadjuvant therapy

Neoadjuvant chemotherapy offers several theoretical benefits over adjuvant chemotherapy. Those include the ability to address possible micro-metastases present at surgery by reaching target tissues more effectively, given intact perfusion of the tumor. Additionally, it has been shown to be better tolerated than adjuvant chemotherapy in other cancers, resulting in improved completion rates [63, 64]. The high rate of margin positivity with resection of borderline resectable tumors (36%-64%) and subsequent worse survival has driven research on neoadjuvant therapies [65]. In recent years, multiple trials have been conducted on patients with borderline resectable/locally advanced PDAC25 [33, 66–70], and resectable cancers [71–76]. A summary on the most recent trials on resectability, ability to achieve R0 resection and survival is listed in Table 2. In regards to resectable cancer, Lutfi et al evaluated data from the National Cancer Database on early stage PDAC patients (AJCC stage I/II) that underwent resection and received any type and timing of chemotherapy vs those who received no chemotherapy [77]. Their findings showed early stage patients had better survival with neoadjuvant-, adjuvant chemotherapy or both compared to surgery alone. A meta-analysis by Versteijne et al, including 3,484 patients with resectable and borderline resectable disease receiving any type neoadjuvant chemotherapy with/without radiation therapy, found a modest OS benefit for those undergoing neoadjuvant treatment (18.8 vs 14.8 months) despite lower resection rates in the neoadjuvant treatment group (66% vs 81.3%) [78]. Their results support that a subgroup of patients with local PDAC will develop aggressive disease progression and have no benefit from resection. Neoadjuvant treatment is thus emerging as a screening tool for PDAC patient who are truly localized and therefore benefits from surgical resection. Nevertheless, the role for chemotherapy in the neoadjuvant setting is still undefined. Larger, randomized trials are needed to compare the best regimens and further define the benefit in each clinical setting. Current NCCN guidelines recommend considering neoadjuvant treatment for borderline/locally advanced disease and preferred agents are

Table 2. Recent trials on neoadjuvant chemotherapy, resectability and outcomes.

Study	Design	Local stage	Chemotherapy	n	Resectability	R0 rate	Median OS (months)
McKenzie 2013	Phase 2 trial	Res	Gem/nP	25	80.0%	95%	NA
O'Reilly 2014	Phase 2 trial	Res	Gem/oxaliplatin	38	71.0%	74%	27.2
Sliesoraitis 2014	Phase 2 trial	Res/BR	Gem/nP vs surgery	32 (10 vs 22)	80% vs 100%	60% vs 77%	NA
Ielpo 2016	Phase 2 trial	Res/BR	Gem/nP	25	68.0%	100%	21
Katz 2016	Phase 1/2 trial	BR	mFOLFIRINOX	22	68.0%	93%	21.7
Okada 2017	Phase 1 trial	BR	Gem/nP	10	80.0%	70%	NA
Tsai 2018	Phase 2 trial	Res/BR	5-FU or gemcitabine-based chemotherapy, depending on molecular profiling	130	82.0%	81%	38
Reni 2018	Phase 2/3 trial	BR/LA	Gem/nP vs Gem/nP/cis/cap	54 (28 vs 26)	32% vs 31%		NA
Murphy 2018	Phase 2 trial	BR	FOLFIRINOX + CRT	48	66.6%	97%	37.7
De Marsh 2018	Phase 2 trial	Res	FOLFIRINOX	21	81.0%	94%	34
Wei 2019	Phase 2 trial	Res	Gem/erlotinib	114	73.0%	81%	21.3
Barbour 2020	Phase 2 trial	Res	Gem/nP	42	71.4%	86%	23.5
Sohal 2020	Phase 2 trial	Res	FOLFIRINOX vs Gem/nP	55 vs 47	73% vs 70%	85% vs 85%	22.4 vs 23.6

Abbreviations: Gem = gemcitabine, nP = nab-paclitaxel, CRT = chemoradiation therapy, OS = overall survival, Res: resectable, BR: borderline resectable.

FOLFIRINOXor Gemcitabine in combination with nab-paclitaxel [8]. A large, randomized phase III trial involving 352 patients is active recruiting to investigate perioperative versus adjuvant chemotherapy for resectable PDAC patients (NCT04340141)

Radiation

Adjuvant radiation

Adjuvant radiation therapy (RT) is widely utilized despite inconsistent evidence behind its efficacy. The GITSG study in 1985 was the first randomized study conducted to compare adjuvant chemoradiation (40 Gy in a split course with weekly bolus of 5-FU) to observation in 43 (22 vs 21) patients with negative margins after PDAC resection [79]. Their results showed an overall survival benefit with CRT (median 20 months vs 11 months), however the trial closed early due to poor accrual (intended to accrue 100 patients). CRT thus became the new standard in adjuvant treatment. However, multiple randomized trials conducted after this challenged the survival benefit of CRT in the adjuvant setting [80–83]. The ESPAC-1 trial, although highly criticized, went so far as to find chemoradiation detrimental to survival [81]. We await the results of the ongoing RTOG 0848 (NCT01013649) trial that will hopefully add valuable data on whether the addition of radiation to chemotherapy is truly beneficial in the adjuvant setting of PDAC. Currently, the role for adjuvant chemoradiotherapy is unclear and we recommend evaluating patients for clinical trials. The current American Society of Radiation Oncology (ASTRO) guidelines recommend utilizing conventional fractionated adjuvant RT in the setting of high-risk tumor features, such as positive lymph nodes or margin positivity [84].

Neoadjuvant radiation

Similar to chemotherapy, neoadjuvant radiation has its theoretical advantages. Given the high morbidity after PDAC surgery and early systemic recurrence, logic dictates increased efficacy of the neoadjuvant approach to radiation. Since the 1980s, researchers have only managed to find a modest benefit with neoadjuvant radiation. Most of these trials have been small and many aimed at establishing safety and feasibility of the treatments. Administered with either 5-FU or gemcitabine as radiosensitizers, its ability to improve local control and survival have been modest, both in resectable disease [85–88] and borderline resectable/locally advanced [89–91]. The 2018 PREOPANC-1 study provided better evidence for neoadjuvant chemoradiation in borderline resectable patients. They randomized 246 patients with borderline resectable PDAC into either neoadjuvant gemcitabine + 36 Gy radiation administered between 2 cycles of gemcitabine or upfront surgery with both groups receiving adjuvant chemotherapy. Although fewer patients in the chemoradiation arm underwent resection (62% vs 72%), they achieved significantly better R0 resection rate (65% vs 31%), disease-free survival (median 11.2 vs 7.9 months) and overall survival (median 17.1 vs 13.3 months) [31]. The benefits of neoadjuvant chemoradiation have additionally been supported in a 2018 meta-analysis and patient data from the surveillance, epidemiology, and end results (SEER) registry [78, 92].

In the 2019 American Society for Radiation Oncology guidelines, conventionally fractionated RT or SBRT is recommended with moderate evidence in borderline/locally advanced PDAC [84]. However, there is low evidence to recommend RT in high-risk patients in the adjuvant setting or in unresectable patients.

Stratifying patients for adjuvant and neoadjuvant therapy in PDAC and tools for early detection of recurrence

We strongly encourage PDAC patients to participate in available clinical trials. Outside clinical trials, we routinely consider neoadjuvant chemotherapy for patients with resectable PDAC (resectable and borderline). In PDAC patients with high risk for recurrence (bulky tumors, lymph node positive, aggressive pathological features), we consider neoadjuvant chemotherapy and chemoradiation (total neoadjuvant therapy, TNT) approach. Based on emergent data and in our experience, we believe this approach will select "truly localized" PDAC patients and avoid a highly invasive procedure that will otherwise be futile. This approach also decreases the rate of disease recurrence based on emerging data. Stratification of localized PDAC patients for risk of relapse is key factor in adjuvant vs neoadjuvant therapy. Several

factors such as tumor size, lymph node status, pathological features such as poorly differentiated histology, lymphovascular/perineural invasion, high CA 19-9 levels (>500), were historically used as biomarkers for recurrence risk stratification. Recently, more sophisticated biomarkers such as circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) have been studied [93, 94]. Recent advances in ctDNA technology could be a prognostic tool for early recurrence detection after surgery and chemotherapy [95]. In a recent study, using a personalized and tumor-informed multiplex PCR assay (Signatera™), in a cohort of 93 localized PDAC patients with multimodality therapy, ctDNA positivity correlated with patient survival outcomes more strongly than CA19-9 [96].

Metastasis directed treatment

Resection

Metastatic disease is the most common initial presentation of PDAC [3]. For those who undergo curative resection, over 70% will have disease recurrence, most commonly at distant sites such as the liver, lungs, peritoneum [27]. Although surgical resection is thought to be contraindicated in metastatic disease, expert centers around the world have attempted resection in highly selected patients with varying results. The largest published series on resection of PDAC metastases was reported by Hackert et al. [97] They resected both liver (n = 85) and inter-aortocaval lymph node (ILN, n = 43) metastases in 128 patients between 2001 and 2014. Their median survival after resection was 12.3 months, with an actual 5-year survival of 5.9% and 7.0% after liver and ILN resection, respectively. A marginal improvement over palliative chemotherapy alone [55]. Adams et al. retrospectively examined liver resections at 41 centers in France for non-colorectal, non-endocrine metastases, of which 41 patients were of pancreatic exocrine origin [98]. They reported 20% 5-year survival for this subset of patients after liver resection. Additionally, a retrospective German study reported outcomes from 29 patients after synchronous resection of liver, peritoneum- or aortocaval lymph node metastases during pancreatic resections for PDAC [99]. Ten of their patients had liver metastases, 11 lymph nodes and the rest peritoneal nodules. Their estimated median and 1-year survival was 13.8 months and 58.9%, respectively. There are those that have found no benefit to resection of PDAC metastases [100]. Gleisner et al. reported similar survival in patients undergoing palliative bypass and liver resection of pancreatic or biliary cancers (5.9 months vs 5.6 months) [100]. Perhaps the only scenario where resection of PDAC metastases has been consistently found to be beneficial is in the setting of lung metastases. Isolated metachronous lung metastases in PDAC are well known to incur better prognosis compared to other recurrence sites [27]. Furthermore, their resection in select cases has been associated with improved survival in multiple retrospective series [101, 102]. With the exception of lung metastases, survival after resection of metastatic disease varies and higher level of evidence is required to make recommendations. Resecting PDAC metastases is currently not routinely performed but can be considered in a trial setting.

Hepatic artery infusion therapy

Hepatic arterial infusion (HAI) therapy involves placing a catheter into the hepatic arterial vasculature (via gastroduodenal artery) supplying the liver and infusing chemotherapy directly into the liver. The benefits of HAI manifest in lower systemic toxicity and higher gradient of chemotherapy in the liver using certain agents [101]. The benefits of HAI therapy in the setting of liver metastases from colorectal cancer have long been recognized [102]. A few small studies have been conducted with HAI utilized as adjuvant treatment [103–105] as well as for metastatic PDAC [106]. They all have shown benefits to some extent. The non-randomized trial by Wang et al. compared 43 patients receiving adjuvant 2 cycles HAI chemotherapy followed by 4 cycles systemic chemotherapy (both consisting of 5-FU and gemcitabine) to 44 patients receiving adjuvant systemic gemcitabine + 5-FU alone [105]. Although 5-year disease-free probability was the same for both groups, the HAI group had significantly better 5-year overall survival probability (hazard ratio (HR) 0.60) and hepatic metastases-free survival (HR 0.50). Ohigashi et al and Beger et al described 53% 3-year survival and 54% 4-year survival, respectively, with the use of HAI chemotherapy in the adjuvant setting [103, 104]. Another small study by Tajima et al on patients with hepatic recurrence after resection showed a response rate in 6 out of 7 patients (85%) [106]. There is currently a phase 2 trial ongoing using floxuridine-based HAI chemotherapy for patients with liver metastases after PDAC resection (NCT03856658).

Immuno- and targeted systemic therapy

Over the last decade, there has been a paradigm shift in PDAC therapeutics development. Next-generation sequencing technology and bioinformatics lead to discovery of driver mutations and aberrant pathways in PDAC. This process led to the identification of novel targets and there by therapeutics. Innovative targeted therapies, based on genomic results could potentially improve survival and quality of life in PDAC patients [107]. PDAC patients with somatic/germ line mutations in DNA Damage Repair (DDR) pathway (BRCA 1,2, PALB2) homologous recombination repair (HRR) genes (ATM, BAP1, BARD1, BLM, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, RAD50, RAD51, RAD51C, and RTEL1) would comprise about 25% of PDAC patients. Recent meta-analysis involving six studies, with 21,842 PDAC patients, revealed that whole genome/whole exome sequencing allows the detection of greater proportion of patients with HRD (24–44%) compared to gene level hotspot/targeted NGS (14.5–16.5%). Prevalence of germline and somatic HRD mutations include BRCA1: 0.9%, BRCA2: 3.5%, PALB2: 0.2%, ATM: 2.2%, CHEK2: 0.3%, FANC: 0.5%, RAD51: 0.0%, and ATR: 0.1% [108]. Detection of DDR pathway deficiency, in other words "BRCAness" in PDAC is important, as these patients, not only respond to platinum-based

therapy, but also would benefit from PARP inhibitors, such as Olaparib [105]. For comprehensive coverage of this topic and for a list of the ongoing clinical trial, please refer to an excellent review by Dalmasso et al. [109]

Other major target for therapy in PDAC is KRAS, as it is mutated in about 95% of patients. KRAS codon 12 mutations are more common and constitute about 71%. These alterations include G12D (42%), G12V (32%), G12R (15%), G12C (1.5%), G12A (0.4%) and G12S(0.1%) [110]. There is great momentum in KRAS-targeted therapeutics. In phase I/II trial, Sotorasib in heavily pretreated PDAC patients harboring KRAS G12C mutation revealed clinically meaningful benefit and safety (ORR 21.1% and DCR of 84.2%, mPFS of 4 months and mOS of 7 months) [111]. Another G12C inhibitor Adagrasib showed the response rate of 50% and mPFS of 6.6 months (n = 10) in PDAC patients harboring G12C mutation [112]. A phase I/II trial evaluated a KRAS G12D targeting RNAi released over 4 months from a small biodegradable tumor implant. Results were encouraging with a median OS of 15 months [113]. Continued efforts at investigating KRAS as a therapeutic target are underway (NCT03608631, NCT01676259). Leidner et al. recently reported a single patient experience, who had a significant response (72% reduction of targeted tumor) after a single infusion of T cells that had been genetically engineered to clonally express two allogeneic HLA-C*08:02–restricted T-cell receptors (TCRs) targeting mutant KRAS G12D in tumor cells [114]. This response continues to last for over 6 months. A list of major ongoing trials targeting KRAS can be seen in Table 3.

Historically, PDAC did not show any response to immunotherapy. This is most likely due to immunosuppressive tumor microenvironment (TME). About 2% of PDAC patients have mismatch repair deficiency (dMMR) and/or microsatellite instability (MSI-H). Based on results from KEYNOTE 158 study, Pembrolizumab has tumor agnostic approval for treatment in advanced cancer patients with MSI-H status. In this study, 22 patients with metastatic PDAC with dMMR and/or MSI-H were studied. Responses were encouraging (one complete response, ORR 18% and median duration of response 13.4 months) [115]. Since PDAC is considered immunologically "cold", there are some studies focusing on making tumors immunologically active by activating innate lymphocytes or creating inflammatory response in TME and there by bringing in cytotoxic T cells. Recently, Selvanesan et al injected non-disease-causing listeria bacteria carrying a gene encoding for tetanus toxin into mice model of pancreatic cancer. The tetanus toxin-induced memory T cells, which activated cytotoxic T cells in TME, which led to 80% decrease in tumor size, when then they added low dose Gemcitabine [116]. Several clinical trials are investigating the role of chemo immunotherapy in PDAC. We are investigating the role of AZD 0171 (anti LIF1 monoclonal antibody- LIF1 an immune suppressor in TME in pancreatic cancer), durvalumab (PDL-1 inhibitor) in combination with Gemcitabine and Nab-paclitaxel in an open label phase II study (NCT04999969). Several immunological surrogate response markers such as tumor mutation burden (TMB), PDL-1, T cell response signatures are being investigated. Since germ line DDR gene mutations induces genomic instability and causes high TMB, PDAC patients with certain DDR mutations could benefit from immunotherapy. Hosein and colleagues conducted a small study with 12 PDAC patient harboring germ line HRD genetic mutations, which include *BRCA1, BRCA2*, *RAD51C*, *RAD51D*, and *ATM*, who failed on platinum-based chemotherapy and PARP inhibitors. They were treated with ipilimumab and Nivolumab for 4 cycles followed by Nivolumab. ORR was 42% and DCR of 58%. Complete response was observed in four patients (2 with *BRCA1*, 1 with *BRCA2*, 1 with *RAD51C*), partial response was observed in one (with *BRCA1*. 3 out 4 patients with CR discontinued treatment after 2 years [117].

Next-generation sequencing (NGS) testing also has advantage of identifying genomic tumor drivers and targeted therapies. One such target is tropomyosin receptor kinase (TRK). Even though incidence of TRK fusions are rare in PDAC (about 0.5%), TRK Inhibitors such Larotrectinib and Entrectinib are now being used in the setting of PDAC as second-line therapy based on phase I and case series experience [118, 119]. A comprehensive list of early phase clinical trials involving targeted therapies is shown in Table 3.

Table 3. List of selected early phase clinical trials involving targeted therapies in PDAC.

Target	Drug	Trial Phase	NCT Number
KRAS	TCR-T (G12V)	I	NCT04146298
	Exosomes (G12D)	I	NCT03608631
	LY3537982 (G12C)*	I	NCT04956640
	Anti-KRAS G12V mTCR PBL	I	NCT03190941
	anti-KRAS G12D mTCR PBL	I	NCT03745326
	MRTX849 **	II	NCT03785249
	ELI-002 ***	I	NCT04853017
CDKN2A	SY 5609 (CDK7)	I	NCT04247126
	Palbociclib (CDK 4/6) ***	I	NCT03065062
BRCA 1 or 2	Olaparib + pembrolizumab Vs Olaparib Alone	II	NCT04548752
BRCA1, 2, PALB2	Adjuvant Olaparib Vs Placebo (APOLLO Trial)	II	NCT04858334
ATM	ATR inhibitors		
PIK3CA	Taselisib (MATCH)	II	NCT02465060
ROS1	Crizotinib (MATCH)	II	NCT02465060
BRAF	Dabrafenib/trametinib	II	NCT02465060
ERBB2	T-DXd	II	NCT04482309
CTNNB1	Tegavivint	II	NCT04851119
NF1	Trametinib (MATCH)	II	NCT02465060
FGFR1	Trametinib (MATCH)	II	NCT02465060
TP53	SGT53+ GEM + NabP	II	NCT02340117

*Being studied in combination with other compounds Abemaciclib, Erlotinb, Pembrolizumab, Temuterkib, LY3295668, Cetuximab, TNO155.
**Being studied in combination with Pembrolizumab, Cetuximab, Afatinib.
*** ELI-002 2P (Amph modified KRAS peptides, Amph-G12D and Amph-G12R admixed with admixed Amph-CpG-7909) will be evaluated, with plans to transition to the ELI-002 7P drug product containing all 7 Amph-Peptides (G12D, G12R, G12V, G12A, G12C, G12S, G13D) in future clinical trials.
**** Being studied in combination with PI3K/mTOR Inhibitor Gedatolisib.
MATCH – Molecular Analysis for Therapy Choice clinical Trial.
T-DXd- Trastuzumab Deruxtecan.
GEM- Gemcitabine, NabP- Nanoliposomal Albumin Bound Paclitaxel.

Discussion

In this overview of pancreatic cancer treatments, we have reviewed the latest developments in surgical and medical

therapeutics for PDAC. Treatment options depend on the extent of disease at presentation. While those with resectable tumors at presentation have traditionally undergone surgery first, a paradigm shift is moving toward neoadjuvant chemotherapy first with emerging evidence in favor of total neoadjuvant treatment (chemotherapy followed by chemoradiation). Surgical options now include both minimally invasive approaches in select centers where experience has accumulated. Those with borderline resectable disease will benefit from neoadjuvant chemotherapy and chemoradiation. Provided a favorable response, these patients can undergo surgery although a more extensive resection to include vascular structures is often necessary to achieve an R0 resection. Patients with locally advanced or metastatic disease on presentation should undergo definitive chemotherapy with FOLFIRINOX, gem-nabP or gemcitabine + capecitabine +/- radiation. If patients respond to a sufficient degree, resection can be considered. For those with distant metastases, intra-abdominal metastases should generally not undergo resection unless in a trial setting while metachronous isolated lung metastases can be resected with favorable outcomes. For PDAC patients with isolated liver metastases, hepatic artery infusion pump is currently under investigation. Targeted therapeutics in PDAC are under investigation with the help of next-generation sequencing that allows genomic mapping of tumor cells for the identification of treatment targets. Currently, PARP inhibitors are utilized for tumors with DDR deficiency, agents targeting certain KRAS mutations have been shown to be efficacious in select patients as well as TRK inhibitors. Immunotherapy is currently utilized in the small cohort of PDAC patients with dMMR and/or high microsatellite instability (MSI-H) and multiple studies are ongoing on combination immuno- and chemotherapy.

Conclusion

In summary, pancreatic cancer remains a disease with dismal outcomes and benefits from new treatments have been modest so far. Nevertheless, outcomes continue to improve, and exciting new treatment avenues have opened in the last few years. Optimal care of patients with PDAC should be delivered with multidisciplinary input.

Disclosure statement

The authors have no conflicts of interest or financial ties to disclose.

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