Review

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The role of systemic therapy in borderline resectable and locally advanced pancreatic ductal adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains a deadly disease, even in patients whose cancer is localized and non-metastatic. Surgical resection provides the only option for cure, but long-term survival rates remain dismal. For patients with borderline resectable (BR) disease who undergo upfront resection, many patients are either too unwell for subsequent adjuvant systemic therapy, develop recurrence soon after, or are found to have unresectable disease intra-operatively. There is increasing evidence for a neoadjuvant approach, using more conventional multi-agent chemotherapy regimens, which have demonstrated higher activity in the metastatic setting compared to single agents. For patients with locally advanced (LA) disease, which is unresectable by current definitions, there is mounting evidence that effective neoadjuvant systemic therapy is able to convert some patients' disease to a resectable state, offering the potential for long-term survival and cure. Herein we present a review of key trials focusing on prospective, randomized studies to provide high-level evidence supporting a neoadjuvant approach to both BR and LA PDAC. However, many knowledge gaps exist, such as the optimal neoadjuvant multi-agent chemotherapy regimen, the role of radiotherapy, and the safety and efficacy of adding immunotherapy to chemo/radiation therapy. Future challenges in determining the optimal approach to patients with BR or LA PDAC include not only overcoming the inherent difficulties in conducting complex, multidisciplinary, multicentre randomized trials in patients with a high-morbidity and mortality disease, but also trying to standardize disease definitions, treatment regimens, and outcome measures.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) incidence is increasing worldwide[1-4] and is associated with a high mortality rate owing to its aggressive biology and oftentimes late presentation. It is now the third leading cause of cancer-related death in the United States[3], expected to become the third leading cause in Canada[2], and the fourth leading cause in Europe[5]. Surgical resection currently remains the only option for cure, although rates remain dismal at < 4% at 10 years[6]. The spectrum of non-metastatic disease is currently classified as resectable, borderline resectable, and locally advanced disease, the latter is considered unresectable. In reality, these classifications represent a continuum and have evolved over time based on a combination of surgical expertise and high-quality imaging of disease involvement with nearby vasculature. Unfortunately, early pancreatic cancer is often asymptomatic, with only 15%-20% of patients presenting with resectable disease and approximately 30%-35% presenting with locoregional/vessel involvement that precludes upfront resection[7].

For patients with resectable or borderline resectable disease, the traditional treatment paradigm includes upfront resection followed by adjuvant systemic therapy, with regimens such as FOLFIRINOX (FFX)[8], gemcitabine with capecitabine[9], or gemcitabine alone[10]. However, 10%-20% of such patients are actually found to have unresectable disease at the time of surgery[11], and another 20% of patients are too unwell after resection to receive adjuvant systemic therapy[12], or develop metastatic recurrence soon after resection, thus causing iatrogenic morbidity without substantial benefit. As a result, there has been recent interest in using systemic therapy in the neoadjuvant setting for patients with localized disease, with the potential benefit of treating micrometastatic and measurable disease early, improving the R0 resection rate (R0: microscopically margin-negative resection), delivering systemic therapy to a higher number of patients, and avoiding non-therapeutic laparotomy in patients with aggressive disease biology. For patients with locally advanced unresectable disease, neoadjuvant systemic therapy has the potential to convert their disease to a resectable state. Conversely, there is the potential risk that the disease is not responsive to neoadjuvant systemic therapy, resulting in a delay to curative resection. Further, it will be important to identify how and when to optimally assess treatment response in the neoadjuvant setting for surgical planning. Ultimately, whether the aforementioned benefits outweigh this risk and result in longer survival and higher rates of cure has been under active investigation, particularly over the last decade.

In this article, we review the evidence behind the use of systemic therapy in the neoadjuvant setting for borderline resectable PDAC (BR-PDAC) and locally advanced PDAC (LA-PDAC) [Table 1].

BORDERLINE RESECTABLE DISEASE (BR-PDAC)

The National Comprehensive Cancer Network (NCCN) was the first to adopt the terminology "borderline resectable pancreatic ductal adenocarcinoma" in 2006 for patients identified to be at high risk of a margin-positive resection and for whom neoadjuvant treatment should be considered. In the most recent NCCN guidelines for pancreatic cancer (Version 1.2022) published in February 2022[22], BR-PDAC is defined by the following criteria, assessing the tumor's relation to both arterial and venous structures [Table 2]. In clinical practice, determination about resectability should be made by consensus at a multidisciplinary discussion, primarily by the surgeon involved in the case. The consensus and classification of the patient's disease have significant implications on the approach to treatment, such as the use of neoadjuvant treatment *vs.* upfront resection.

Table 1. Summary of trials presented in this review

Study	Year	Study phase	BR/LA definition	Treatment arms	No. of patients	mFollow-up (mo)	Primary outcome	mOS (mo)	Resection rate	R0 rate	R1 rate
Resectable and borderline resectable PDAC											
Versteijne[13] (PREOPANC)	2020, 2022	III RCT	DPCG	CRT (gem) → resection → adj gem Resection → adj gem	248 (120) (128)	59	OS (ITT)	15.7 14.3	61% 72%	41% 28%	16% 53%
Borderline resectable PDAC											
Jang[14]	2018	II/III RCT	NCCN	CRT (gem) → resection → adj gem Resection → CRT (gem) → adj gem	58 (27) (23)	NR	2-yr OS (ITT)	21 12	63% 78%	52% 26%	NR
Murphy[15]	2018	II	NCCN	FFX → CRT (cape) → resection	48	18[b]	R0 resection rate	37.7	67%	65%	NR
Ghaneh[16] (ESPAC-5F)[a]	2020	III	NCCN	GnP, FFX, or CRT (cape) → resection → adj Resection → adj	88 (56) (32)	12	Resection rate (ITT) R0/R1 resection rate	NR	55% 62%	23% 15%	NR
Borderline resectable and locally advanced PDAC											
Reni[17]	2018	II	NCCN	GnP + cisplatin + cape → resection GnP → resection	54 (26) (28)	31	R0/R1 resection rate	20.7 19.1	31% 32%	19% 14%	11% 7%
Locally Advanced PDAC											
Hammel[18] (LAP07)	2016	III RCT	UICC	Gem (+/- erlotinib) → CRT (cape) Gem (+/- erlotinib)	442 (133) (136)	34.3	OS (ITT)	15.2 16.5	4%	2%	0.5%
Murphy[19]	2019	II	NCCN	FFX + losartan → CRT (cape) → resection	49	17.1	R0 resection rate	31	69%	61%	NR
Philip[20] (LAPACT)	2020	II	AHPBA/SSO/SSAT	GnP → CRT (gem or cape) GnP → resection GnP	(18) 107 (17) (12)	25.4	Time to treatment failure (ITT)	18.8	16%	7%	9%
Kunzmann[21] (NEOLAP)	2021	II	NCCN	GnP → FFX → resection GnP → resection	168 (66) (64)	24.9	Surgical conversion rate (R0/R1; ITT)	20.7 18.5	43.9% 35.9%	30% 23%	NR

[a]Not yet published in full article format, [b]Of patients still alive at time of study completion; Statistically significant difference between the two treatment arms. PDAC: Pancreatic ductal adenocarcinoma; BR: borderline resectable; LA: locally advanced; RCT: randomized control trial; DPGC: Dutch Pancreatic Cancer Group; NCCN: National Comprehensive Cancer Network; UICC: International Union Against Cancer; AHPBA/SSO/SSAT: Americas Hepatopancreaticobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; adj: adjuvant; CRT: chemoradiation therapy; FFX: FOLFIRINOX; GnP: gemcitabine plus nab-paclitaxel; gem: gemcitabine; cape: capecitabine; mo: months; m: median; OS: overall survival; ITT: intention to treat; NR: not reported.

Table 2. NCCN (Version 1.2022) definition of borderline resectable pancreatic adenocarcinoma

Arterial	Venous
Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumor contact with the SMA of ≤ 180° • Solid tumor contact with variant arterial anatomy (ex. accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning Pancreatic body/tail: • Solid tumor contact with the CA of ≤ 180°	• Solid tumor contact with the SMV or PV of > 180°, contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the IVC

CHA: Common hepatic artery; CA: celiac axis; SMA: superior mesenteric artery; SMV: superior mesenteric vein; PV: portal vein; IVC: inferior vena cava.

Notably, since the NCCN definitions, a number of other groups have developed similar but slightly different definitions, such as the Americas Hepatopancreaticobiliary Association/ Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT)[23], MD Anderson Cancer Centre[24], and Intergroup Alliance[25]. In 2016 an international consensus was developed during the 20th meeting of the International Association of Pancreatology (IAP) in Sendai, Japan, and published in 2017[26]. This definition includes not only the same anatomic considerations as above (and specifying borderline resectable status by arterial or venous criteria), but also biological and conditional criteria. Specifically, if there are suspicious findings for extra-pancreatic disease or a CA19-9 > 500 units/mL, and if the patient's Eastern Cooperative Group (ECOG) performance status was 2 or greater, patients would be considered to have BR-PDAC. The International Study Group of Pancreatic Surgery (ISGPS) also published a consensus statement for BR-PDAC in 2014[27]. They support the 2013 NCCN imaging-based criteria for borderline resectability by using a specialized pancreatic CT protocol that includes the abdomen and pelvis, and that all cases should be discussed and managed by a multi-disciplinary team. Nonetheless, there still exists variation in the way that clinical trials have defined BR-PDAC when enrolling patients, and thus it remains critical to scrutinize the definition used when comparing studies and drawing conclusions from BR-PDAC trials.

Systemic therapy in BR-PDAC

In the early 2010s, multi-agent chemotherapy was demonstrated to have improved overall survival (OS) over gemcitabine alone in metastatic pancreatic adenocarcinoma, with regimens such as gemcitabine plus nab-paclitaxel (GnP)[28] and FFX[29] [Table 3]. Following this, multi-agent regimens started to be used neoadjuvantly for BR-PDAC in the absence of randomized data. A patient-level meta-analysis of neoadjuvant FFX systemic therapy (median 4-9 cycles given) for BR-PDAC was published in 2019 and found a median OS (mOS) of 22.2 months and a median progression-free survival (mPFS) of 18 months[30]. It analyzed data from 24 studies (313 patients), comprising 16 retrospective and 8 prospective studies of phase I-II trials and cohort studies, mostly reporting intention-to-treat (ITT) analyses. ITT analysis is critical as there are a significant number of enrolled patients who never received resection due to disease progression or unresectable disease at the time of surgery, and excluding these patients would lead to overestimates of OS. The resection rate was 67.8% with an R0 rate of 83.9%. The most common grade 3 adverse events (AEs) included: neutropenia (17.5%), diarrhea (11.1%), and fatigue (10.8%), with no deaths attributable to FFX. Most notably, there were no randomized control trials (RCTs) in this meta-analysis, and there was heterogeneity in the studies including variations in the FFX regimen, number of cycles administered, use of chemoradiation, and borderline resectability criteria as described above. Nonetheless, the body of evidence thus far suggests that neoadjuvant FFX has the potential to improve resection rates, R0 rates, and ultimately OS for patients with BR-PDAC.

Table 3. FOLFIRINOX and gemcitabine plus nab-Paclitaxel chemotherapy regimens for locally advanced unresectable or metastatic pancreatic adenocarcinoma

FOLFIRINOX (FFX)[a]	Gemcitabine plus nab-Paclitaxel (GnP)
• Oxaliplatin 85 mg/m^2 IV (over 2 h) on Day 1, then • Leucovorin 400 mg/m^2 IV (over 2 h) on Day 1, then after 30 min • Irinotecan 180 mg/m^2 IV concurrently with leucovorin (over 90 min), then • 5-Fluorouracil 400 mg/m^2 IV bolus on Day 1, then • 5-Fluorouracil 2400 mg/m^2 infusion (over 46 h) on Day 1	• Nab-Paclitaxel 125 mg/m^2 IV on Days 1, 8, and 15 • Gemcitabine 1000 mg/m^2 IV on Days 1, 8, and 15
To be repeated every 14 days (one cycle) until disease progression or toxicity; 12 cycles are recommended for patients who are responding	To be repeated every 28 days (one cycle) until disease progression or toxicity

[a]A modified FFX regimen (mFFX) uses a lower dose of irinotecan at 150 mg/m^2 and also omits the 5-fluorouracil bolus; FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin). IV: Intravenous.

Since the meta-analysis, a number of subsequent trials have been published to further investigate the role of neoadjuvant systemic therapy for BR-PDAC, especially given the lack of RCT data. A Korean phase II/III RCT by Jang *et al.* of neoadjuvant chemoradiation with gemcitabine (*n* = 27) *vs.* upfront resection (*n* = 23) followed by adjuvant chemoradiation in patients with BR-PDAC was published in 2018[14]. Both treatment arms also received four cycles of adjuvant gemcitabine. The primary outcome was 2-year OS by ITT analysis, and this trial is one of the first RCTs that demonstrated a survival benefit for a neoadjuvant approach for BR-PDAC. In the overall population of 50 patients, the mOS was 16mo, with a 2-year OS of 34%. However, patients who received neoadjuvant treatment had superior 2-year OS and mOS of 40.7% and 21 months, compared to those who underwent upfront resection (26.1% and 12 months). The R0 rate was also higher at 51.8% *vs.* 26.1%. These results were found at an interim analysis after 50% enrollment, and the study was terminated early due to the definite difference in mortality rate between the neoadjuvant and upfront resection groups.

Subsequently, a similar but larger phase III Dutch RCT named PREOPANC studied neoadjuvant chemoradiation therapy with gemcitabine (*n* = 120) *vs.* upfront resection (*n* = 128) in patients with either resectable PDAC (54%) or BR-PDAC (46%). Both treatment arms also included adjuvant gemcitabine after resection. The primary outcome was OS by ITT analysis. The initial report did not demonstrate a survival benefit with neoadjuvant chemoradiation[31], however, with a longer median follow-up of 59 months, a modest median survival advantage with neoadjuvant chemoradiation was found (15.7 *vs.* 14.3 months; HR = 0.73)[13]. This survival advantage was maintained in the subgroup of patients with BR-PDAC only (HR = 0.67). The 5-year OS in the overall population was 20.5% *vs.* 6.5%, suggesting that a subgroup of patients may have significantly longer-term responses to neoadjuvant treatment than the average patient. It is also notable that only 55/120 patients in the investigational arm, and 65/128 patients in the control arm completed their assigned treatment (at least one cycle of adjuvant gemcitabine), again highlighting the importance of ITT analyses in this population. Thirteen patients (11%) in the investigational arm also did not proceed to surgery after chemoradiation due to progression or unresectable/metastatic disease at the time of response evaluation. A significantly higher proportion of patients in the investigational arm also achieved an R0 resection compared to the group that had upfront resection (41% *vs.* 28%). A criticism of the study includes a higher proportion of ECOG 0 in the interventional arm (58% *vs.* 39%) suggestive of unequal randomization. Like the Jang *et al.* study, it remains to be determined how much of the benefit of neoadjuvant therapy can be attributed to chemotherapy *vs.* radiation, or if the benefit is the result of the combination as gemcitabine is a potent radiosensitizer[14]. Although both studies demonstrated a survival benefit, a significant difference was observed as early as one year in the Jang *et al.* study, whereas no survival benefit was seen up to 27 months of follow-up in PREOPANC[14]. This may be a result of the differences in sample size of the two trials. As mentioned previously, since the conception of these two trials, multi-agent chemotherapy has established superiority over gemcitabine alone in metastatic PDAC, such as GnP[28] and

FFX[29]. Thus neoadjuvant trials in patients with BR-PDAC using more active regimens should be studied, and indeed neoadjuvant FFX is being studied in the currently active PREOPANC-2 trial (NTR7292).

In support of multi-agent chemotherapy, a single-arm phase II trial by Murphy *et al.* assessed the role of neoadjuvant FFX for 8 cycles in 48 patients with BR-PDAC, with subsequent chemoradiation with capecitabine (either short course or long course, if there is persistent vascular involvement after chemotherapy)[15]. They found an R0 resection rate of 65% (31/48), with a mPFS of 14.7 months and mOS of 37.7 months[15]. The authors concluded that these outcomes were substantially better than historical controls when only adjuvant therapy was used. Furthermore, this strategy appears safe as there were no grade 3 toxicities exceeding 10% and no deaths from toxic effects. However, replication of these impressive results in a larger RCT will be necessary.

Yet another phase II trial by Reni *et al.* published in 2018 randomized 54 patients at a single center with either BR-PDAC or LA-PDAC to GnP with and without cisplatin and capecitabine[17]. The primary endpoint was the rate of R0 and R1 resection, though notably only 8/26 patients (31%) in the quadruple-agent arm and 9/28 (32%) in the GnP only arm actually underwent resection. The R0 rate was 5/8 and 4/9 patients respectively making it difficult to draw definitive conclusions. Furthermore, randomization between the two arms was uneven as the GnP only treatment arm had a higher proportion of Karnofsky performance status (KPS) in 90-100 patients (86% *vs.* 73%) and a higher proportion of BR-PDAC (54% *vs.* 38%). This uneven distribution of important prognostic factors would likely bias outcomes more favorably towards the GnP only arm. Interestingly, there were more grade 3-4 adverse events in the GnP only arm, suggesting that the addition of capecitabine and cisplatin did not significantly increase toxicity. Nonetheless, the authors conclude that further testing in a phase III trial is needed to determine if there is a benefit to adding cisplatin and capecitabine to GnP in the neoadjuvant setting. This study also highlights the difficulty and complexity of conducting and completing neoadjuvant studies in pancreatic cancer, as it requires the participation of multiple disciplines and stakeholders.

ESPAC-5F was a prospective phase II trial designed to compare upfront resection to neoadjuvant treatment with GnP, FFX, or chemoradiation with capecitabine (50.4 Gy/28 fr) in patients with BR-PDAC[16]. A total of 88 patients were randomized to the four arms and analyzed. The primary outcome was resection rate and R0/R1 (R1: microscopic margin-positive resection) resection rate by ITT, whereas OS and toxicity were secondary endpoints. While there was no significant difference in resection or R0 rate between upfront resections compared to neoadjuvant treatment, the one-year survival rate was significantly improved with neoadjuvant treatment (77% *vs.* 40%; HR = 0.27). It is important to note the low sample size and phase II nature of this study, and also that it has yet to be published in full article format.

In the Alliance for Clinical Trials in Oncology randomized phase II trial A021501 (NCT02839343) presented as an abstract at ASCO 2021, patients with BR-PDAC of the pancreatic head were randomized to neoadjuvant FFX without the 5FU bolus [Table 3] with or without subsequent stereotactic body radiation therapy (SBRT), prior to resection and adjuvant FFX. The primary endpoint was 18-month OS, and was found to be 67.9% without SBRT and 47.3% with SBRT[32,33]. Amongst those who underwent pancreatectomy, the 18-month OS was 93.1% and 78.9% respectively. While both treatment arms outperformed historical controls of 50% 18-month OS, these results suggest that the addition of SBRT did not improve survival. However, this was only a small study of 126 patients between both arms. This study has also yet to be published in full article format.

Ongoing systemic therapy trials in BR-PDAC

There are a multitude of ongoing trials to further study neoadjuvant therapy for BR-PDAC. As mentioned above, the PREOPANC-2 study (NTR7292) is a randomized phase III trial comparing OS (by ITT) between neoadjuvant FFX *vs.* neoadjuvant chemoradiation with gemcitabine in resectable and BR-PDAC. Another randomized phase II trial called PANDAS-PRODIGE 44 (NCT02676349) aims to compare neoadjuvant mFFX with or without chemoradiation with capecitabine for patients with BR-PDAC, with a primary outcome of R0 resection rate[34].

With numerous phase II and recent phase III RCT studies published in the last few years, data supporting neoadjuvant therapies is starting to emerge for BR-PDAC. At present, it is difficult to recommend a definitive strategy due to the significant heterogeneity amongst the studies, including the definition of BR-PDAC used, the inclusion of other risk groups of PDAC in the same study (i.e., resectable, locally advanced), the surgical skill of the cancer center, variations in the neoadjuvant chemotherapy regimen, the use of concurrent chemoradiation or radiation alone, and the outcome measures assessed (i.e., OS by ITT, per protocol, or other proxy measures such as R0 resection rates, relapse rates, and PFS). Accrual to high-quality prospective trials is encouraged to determine the most effective strategy for this population.

LOCALLY ADVANCED DISEASE (LA-PDAC)

Locally advanced PDAC is considered to be surgically unresectable. It is defined in the NCCN guidelines as follows [Table 4].

Systemic therapy in LA-PDAC

As discussed earlier in the BR-PDAC section, a phase II trial by Reni *et al.* randomized 54 patients at a single centre with either BR-PDAC or LA-PDAC to GnP with and without cisplatin and capecitabine[17]. This study was not powered sufficiently to draw conclusions about the superiority of either treatment arm with respect to the primary outcome of R0/R1 resection rates. Furthermore, this study did not analyze patients by resectability classification (ex. BR-PDAC or LA-PDAC), choosing to group both populations together in their analysis. While these two entities exist on a spectrum, they arose due to differences in resectability at the time of diagnosis, have different baseline risks for poor outcomes, and should be examined separately.

A systematic review and patient-level meta-analysis on neoadjuvant FFX for patients with LA-PDAC was published in 2016[35]. This review included studies up to July 2015, with a primary outcome of OS. Secondary endpoints included PFS, proportion of patients receiving radiation/chemoradiation, rates of grade 3 or 4 AEs, rates of surgical resection, and R0 resection rates. A total of 13 studies were included (689 patients), but only 315 patients had LA-PDAC and were eligible for patient-level meta-analysis of survival. The pooled mOS was 24.2 months, with a mPFS of 15 months. The grade 3 and 4 AE rate was approximately 60%, though no deaths were attributable to FFX toxicity. Radiotherapy was given after neoadjuvant FFX in 63.5% of patients, but there was no significant association found between radiotherapy and OS. The resection rate was approximately 26%, with an R0 resection rate of 78%. Criticisms of this meta-analysis include the fact that none of the included studies had randomization and the vast majority (11/13) were retrospective in nature, thus leading to potentially significant selection and sampling bias. Nonetheless, this study provided some evidence that neoadjuvant chemotherapy was able to convert a subset of patients with unresectable disease due to vessel involvement, to a state where an R0 resection was achievable. Unfortunately, the contributory role of radiotherapy to resectability was not determined. Achieving an R0 resection is important because it represents the only chance for long-term survival and cure, but high-level evidence of whether neoadjuvant systemic therapy followed by resection leads to

Table 4. NCCN (version 1.2022) definition of locally advanced pancreatic adenocarcinoma

Arterial	Venous
Pancreatic head/uncinate process: • Solid tumor contact > 180° with the SMA or CA Pancreatic body/tail: • Solid tumor contact of > 180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

CA: Celiac axis; SMA: superior mesenteric artery; SMV: superior mesenteric vein; PV: portal vein.

improved outcomes over continuing induction chemotherapy in patients with LA-PDAC is lacking and under active investigation. A number of prospective, randomized studies were conducted to fill this knowledge gap, and are presented below.

The phase III LAP07 RCT investigated whether adding chemoradiation to induction chemotherapy in patients with LA-PDAC increased survival[18]. A total of 442 patients were randomized to either gemcitabine alone (1000 mg/m²) or in combination with erlotinib (100 mg/day) for four months, the latter being an outdated multi-agent regimen by today's standard. Patients who had stable disease or disease response (61%; n = 269) were then randomized again to either chemoradiation with capecitabine (800 mg/m² with 54 Gy/30 fr) or to continue induction chemotherapy alone for an additional two months. After a median follow-up of 34.3 months, the mOS of patients receiving chemoradiation was no different from those who continued induction chemotherapy alone (15.2 months *vs.* 16.5 months; HR = 1.03; 95%CI: 0.79-1.34), and neither was mPFS. Likewise, the mOS for patients who received gemcitabine alone was no different than patients who received multi-agent systemic therapy with erlotinib (13.6 months *vs.* 11.9 months; HR = 1.19; 95%CI: 0.97-1.45), and again there was no difference in mPFS. The LAP07 authors concluded that there was no survival benefit from adding chemoradiation with capecitabine compared with continuing induction chemotherapy alone in patients with LA-PDAC, and that there was also no survival benefit from adding erlotinib to gemcitabine induction chemotherapy. This study supports the use of chemotherapy alone as a neoadjuvant treatment for LA-PDAC. Notably, 18/442 (4%) patients were able to undergo curative-intent resection, with the majority (11/18; 2% of the study population) achieving an R0 resection, 2/18 (< 1% of the study population) achieving an R1 resection, and the remainder with unknown resection outcome. The mOS for these 18 patients was 30.9 months, seemingly much longer than the mOS of 12.8 months in the overall population, further providing support for the goal of being able to achieve an R0 resection as a proxy for improved survival.

One of the first prospective studies using more standard multi-agent systemic therapy in patients with LA-PDAC as induction was the international phase II LAPACT trial. Patients received six cycles of GnP, and for those without disease progression, continued therapy as per investigator's choice: continued GnP, chemoradiation with capecitabine or gemcitabine, or surgical resection. The primary endpoint was time to treatment failure by ITT, which is defined as the time after the first dose of study therapy until disease progression, death by any cause, or the start of a non-protocol-defined anti-cancer therapy. Many patients were not able to complete induction (44/107; 41%), most commonly due to AEs (22/107; 21%). Of the 62/107 (58%) patients who completed induction chemotherapy, 47/107 (44%) patients continued onto investigator's choice treatment: 12/107 (11%) continued GnP, 18/107 (17%) received chemoradiation, and 17/107 (16%) underwent surgical resection with 7/107 achieving an R0 resection and the remaining 10/107 achieving an R1 resection. The median time to treatment failure was 9 months for the overall population, with a mPFS of 10.9 months, and a mOS of 18.8 months. There was no comparison of PFS or OS between the different investigators' choices. The disease control rate was 77.6% (83/107), with an overall response

rate of 33.6%. A criticism of this study includes the lack of a central review of imaging, and it was up to investigators to make determinations about whether patients' disease met protocol-defined criteria for LA-PDAC.

The more recent NEOLAP randomized phase II trial compared the conversion rate by ITT (from unresectable to R0/R1 resection status) of GnP *vs.* GnP followed by FFX as neoadjuvant treatment for LA-PDAC[21]. Patients were planned to receive two cycles of GnP, and those without progressive disease were then randomized to either continuing GnP for two more cycles or switching to four cycles of FFX as neoadjuvant chemotherapy (GnP-FFX). Of 168 patients, 38 (22.6%) did not meet the criteria for randomization, with 22 (13%) patients having disease progression. The disease control and surgical exploration rate for the remaining 130 randomized patients was 78% and 63% respectively in the GnP group (n = 64), and 68% and 64% in the GnP-FFX (n = 66) group respectively, though these differences between the groups were not statistically significant. The conversion rate from unresectable to R0/R1 resectable disease was 35.9% (23/64) in the GnP group and 43.9% (29/64) in the GnP-FFX group, but the difference was also not statistically significant. The mOS for the overall population was 17.1 months after a median follow-up of 24.9 months, and there was no statistically significant difference in mOS between the GnP and GnP-FFX groups (18.5 months *vs.* 20.7 months respectively). However, there was a significant difference in survival between those who underwent resection compared to those that did not (27.5 months *vs.* 13.9 months). The rate of grade 3 or higher AEs were similar between the two treatment groups at approximately 54%, with neutropenia, nausea/vomiting, and biliary obstruction as the most common AEs. The NEOLAP authors conclude that there is no added benefit of switching from GnP induction chemotherapy to FFX for LA-PDAC, but that resection is important and associated with long-term survival. This study does not answer the question of which GnP or FFX induction chemotherapy is superior for LA-PDAC, and further trials are required to answer this question. However, the resection rate of 36%-44% is significantly higher than the 4% reported in the LAP07 trial, consistent with the understanding that GnP and FFX are more active than gemcitabine alone in pancreatic cancer. This is significant as the criteria for LA-PDAC in NEOLAP allow some CA or SMA involvement in contrast to the criteria used in LAP07, which would make resection even more challenging. However, it is important to note that NEOLAP planned surgical exploration after chemotherapy, and is a phase II trial with a smaller sample size.

Another phase II study by Murphy *et al.* examined total neoadjuvant therapy in patients with LA-PDAC, mirroring the approach currently used in rectal cancer with both induction chemotherapy and chemoradiation therapy prior to planned resection[19]. A total of 49 patients who met NCCN guidelines for LA-PDAC were given FFX for up to 8 cycles with losartan (25 mg up-titrated to 50 mg daily), an angiotensin-receptor blocker (ARB), followed by either short-course chemoradiotherapy with capecitabine (25 Gy/5 fr; 825 mg/m^2) if they had resectable disease on re-evaluation, or long-course chemoradiotherapy with capecitabine or fluorouracil (50.4 Gy/28 fr with a vascular boost to 58.8 Gy; capecitabine 825 mg/m^2; 5-FU 225 mg/m^2/day) if they had persistent vascular involvement, with a primary outcome of R0 resection rate. The authors used losartan as anti-cancer therapy based on pre-clinical data demonstrating that ARB may enhance the delivery of chemotherapy to the tumor. Of 49 patients, 34 (69%) underwent resection. The R0 resection rate was 61% (30/49 patients). The mOS was 31 months and mPFS was 17.5 months. The authors conclude that neoadjuvant FFX and losartan combined with personalized chemoradiation can lead to high rates of R0 resection in patients with LA-PDAC and can prolong survival compared to historical controls. Criticisms of this study include lack of randomization, personalized treatment delivery (short *vs.* long course chemoradiation), and relatively small sample size. Thus, it is difficult to determine how much of the benefit seen is attributable to the FFX regimen itself, radiation therapy, and losartan.

Ongoing systemic therapy trials in LA-PDAC

As with BR-PDAC, randomized prospective LA-PDAC trials using current conventional chemotherapy regimens such as GnP and FFX are needed. NEOPAN (NCT02539537) is an ongoing randomized phase III trial of FFX for 12 cycles *vs.* gemcitabine alone for patients with LA-PDAC, with a primary outcome of PFS. This study will provide high-level evidence regarding the use of FFX in this patient population. LAPTOP (NCT04247165) is a phase I/II study investigating the safety and efficacy of combining dual immunotherapy (ex. Nivolumab and ipilimumab) with GnP followed by SBRT, hypothesizing that the combination of cytotoxic chemotherapy and radiation therapy will work synergistically with immunotherapy to lead to sustained responses. Overall, extensive studies of neoadjuvant immunotherapy in pancreatic cancer are still lacking.

There is also literature that the tumour microenvironment (TME), which consists of immunosuppressive cell types and the cytokines that recruit them, plays a critical role in the control of proliferation, metastasis, and evasion of immune surveillance in pancreatic adenocarcinoma[36]. Thus, the TME represents a potential therapeutic target for enhancing anti-tumour response of immune checkpoint blockade. An ongoing randomized phase III placebo-controlled trial (NCT03941093) aims to evaluate the efficacy of neoadjuvant targeted therapy with a monoclonal antibody to connective tissue growth factor (pamrevlumab)/placebo in combination with GnP or FFX prior to assessment for resection. Another novel agent, such as defactinib, a focal adhesion kinase (FAK) inhibitor is being studied in borderline resectable and locally advanced pancreatic adenocarcinoma (NCT04331041).

The role of radiation/chemoradiation therapy for patients with LA-PDAC will need to be further investigated. The most recent American Society for Radiation Oncology (ASTRO) guidelines currently have conditional recommendations based on low-quality evidence[37]. LAP07 did not show benefit to adding chemoradiation for either OS or PFS, but further research is needed to confirm or refute this finding as radiation techniques improve, and dosing and timing can be adjusted (ex. upfront radiation prior to induction chemotherapy in contrast to LAP07). Other outcome measures including local recurrence and complication rates due to local disease would be useful to better define the role of radiation.

Overall, evidence is emerging for the benefit of resection after systemic therapy for patients with LA-PDAC responsive to treatment. This represents a paradigm change, as these patients were traditionally thought to have unresectable disease and that systemic chemotherapy would be the mainstay of treatment. LAP07 and NEOLAP showed that patients who underwent curative-intent resection had longer survival time than those who did not, and LAPACT and NEOLAP showed that improved resection rates can be attained with current standard multi-agent chemotherapy.

CONCLUSION

The role of systemic therapy in patients with pancreatic adenocarcinoma has changed over time. For patients with BR-PDAC, a number of trials including phase III RCTs have demonstrated evidence that neoadjuvant treatment followed by resection leads to favorable outcomes compared to upfront resection followed by adjuvant therapy, by improving R0 resection rates, prolonging OS, and avoiding non-curative resections. For patients who present with LA-PDAC, whom by definition have unresectable disease, emerging evidence shows that a proportion of patients respond well to neoadjuvant systemic therapy and are able to be converted to a resectable state and may achieve an R0 resection and potential long-term survival. Multiple trials are underway that also include radiation and more conventional chemotherapy regimens to better characterize their benefits and risks for both BR-PDAC and LA-PDAC. There are also ongoing studies on the combination of immunotherapy with chemo/radiotherapy for patients with LA-

PDAC. Future challenges in determining the optimal approach to treating patients with BR-PDAC or LA-PDAC include not only overcoming the inherent difficulties in conducting complex, multidisciplinary, multicentre randomized trials in patients with a high-morbidity and mortality disease, but also trying to standardize disease definitions, treatment regimens, and outcome measures.

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