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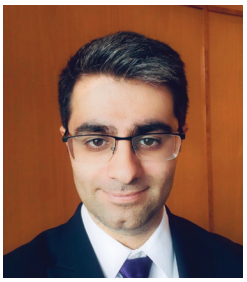

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An Evolving Paradigm in Borderline Resectable and Locally Advanced Pancreatic Cancer: Current Strategies and Opportunities for the Future

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Introduction

Pancreatic ductal adenocarcinoma (PDAC), a cancer of the gastrointestinal tract, has been increasing in incidence, with an estimated doubling worldwide over the past two decades.[1] Despite increases in awareness and innovations in genomics and drug discovery, 5-year survival remains low, at only 10%. This is in part owing to the majority of patients being diagnosed at the advanced stage of the disease, in addition to chemotherapy recalcitrant disease.[2]

Surgical resection is necessary for a potential cure, however, this is only possible for the 10% of patients who present with resectable disease and potentially for those with borderline resectable disease.[3] Locally advanced pancreatic cancer accounts for approximately 30% of those with PDAC and most of those patients are often precluded from curative intent surgery due to major vascular invasion and local infiltration into peri-pancreatic soft tissue. In cases of locally advanced disease, induction chemotherapy is often used, identifying the subgroup of patients more suited for local treatments and those who may later develop metastases. The treatment regimens used for patients with locally advanced PDAC are often extrapolated from trials involving patients with metastatic disease. In some cases, responses to neoadjuvant therapy have allowed for surgical resection, albeit these aggressive resections were associated with significant morbidity.[4]

There is growing interest in identifying the optimal neoadjuvant treatment for patients with borderline resectable pancreatic cancer (BRPC) and locally advanced PDAC (LAPC) in an effort to improve outcomes. Here we review therapeutic strategies for borderline resectable and locally advanced PDAC, with a focus on novel systemic therapy regimens, chemoradiation, and different radiation modalities.

All in the Definition

The definition of “resectability” has been subject to intense debate and remains variable. The National Comprehensive Cancer Network (NCCN) definitions for resectable, borderline resectable, and locally advanced disease are based on arterial and venous involvement; namely, the superior mesenteric artery, celiac axis artery (CAA), common hepatic artery (CHA), superior mesenteric vein, and portal vein (PV) (**Figure 1**).

Evolving surgical techniques have improved resectability in what was previously classified as BRPC. There is also considerable ambiguity on what constitutes borderline resectability, because patients that have LAPC are defined as having BRPC or vice versa.[5,6] In general, patients with BRPC must have <180% abutment of the superior mesenteric artery (SMA), short-segment or small contact with CHA or CAA, whereas patients with LAPC have more than a 180-degree involvement of the SMA. Other guidelines include the MD Anderson Classification (MDACC) and International Association of Pancreatology (IAP), with a slight variance in the CAA, CHA, superior mesenteric vein (SMV), and PV involvement; however, if no

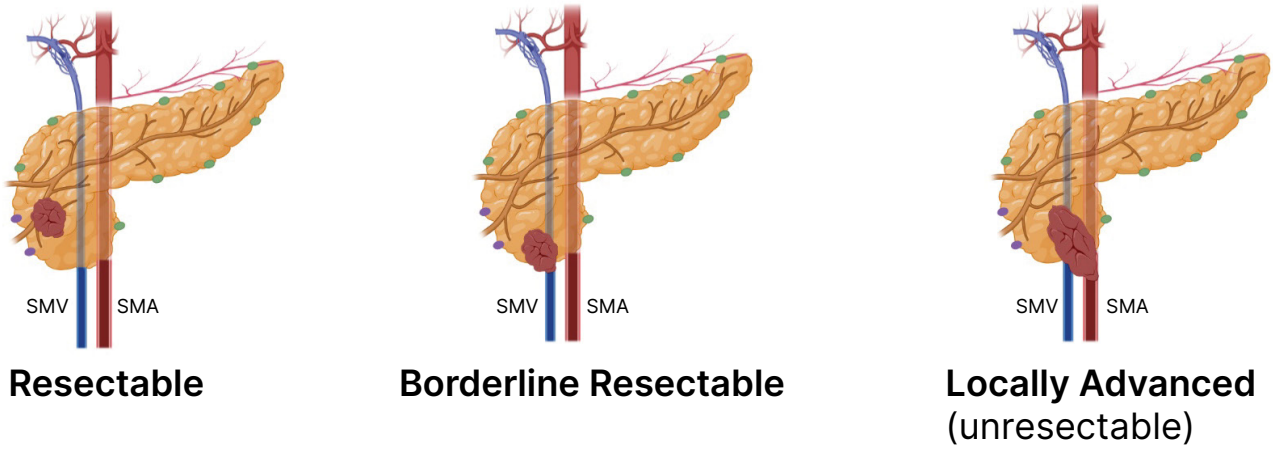

Figure 1. Illustration of resectable, borderline resectable, and locally advanced (unresectable) pancreatic cancers. The figure demonstrates definition based on involvement of the superior mesenteric vein (SMV) or superior mesenteric artery (SMA); *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

reconstructive options or >180 degree vessel involvement or involvement of the duodenum is noted, an LAPC classification is given.[7] Whenever possible, decisions on the treatment of patients with BRPC/LAPC should be made in a multidisciplinary setting involving experienced hepatobiliary surgeons, radiation oncologists, and medical oncologists.[8]

Borderline Resectable Pancreatic Cancer

The optimal treatment approach for patients with BRPC is not yet defined. Based on the currently available evidence, guidelines generally recommend neoadjuvant intent chemotherapy (NAC). The rationale used by clinicians in offering NAC is to increase margin negative (R0) resection rates, to identify patients with rapidly progressive disease who can be spared futile surgery, and to optimize the chance of perioperative therapy, particularly considering that prolonged post-surgical recovery may impede the timely initiation of adjuvant therapy. There is also the potential to improve overall survival (OS) by treating micrometastatic disease. It should be noted that some trials include patients with resectable, BRPC, or LAPC disease, which also adds complexity in interpreting this data.

Optimizing Induction Systemic Therapy Approaches in BRPC

Table 1 provides a summary of recent studies on BRPC. One of the largest phase III multicentre studies to assess the role of neoadjuvant chemoradiation in patients with resectable pancreatic cancer and BRPC was the Dutch PREOPANC trial.[9] In this trial, patients were randomized to receive neoadjuvant gemcitabine with gemcitabine-based radiation (36 Gy in 15 fractions) then 2 weekly doses of gemcitabine followed by surgery and adjuvant gemcitabine for 4 cycles compared to upfront surgery and adjuvant gemcitabine for 6 cycles. An updated analysis published in 2022 demonstrated a difference in the median OS of 1.4 months (15.7 months vs. 14.3 months) favouring the neoadjuvant chemoradiation group despite a hazard ratio (HR) of 0.73. The 5-year OS was higher at 20.5% in the neoadjuvant group compared to 6.5% in the upfront surgery arm. Subgroup analysis of patients with BRPC favoured neoadjuvant chemoradiation. This trial enrolled patients between 2013 and 2017, and since then, the standard of care for adjuvant therapy has changed to include combination regimens. Thus, further trials are required using these newer regimens. It is notable that over half of the patients who participated in this trial were above the age of 65 years and had a World Health Organization (WHO) performance status of 1 or 2. Therefore, this regimen remains applicable in more frail or elderly patients who may be unfit for standard of care adjuvant chemotherapy.

The phase II multicentre ESPAC5 trial compared upfront surgery with three different neoadjuvant treatment arms and included 90 patients with BRPC.[10] These treatment arms included neoadjuvant gemcitabine/capecitabine

Trial Name	Phase	Population	Intervention	Control	Primary Outcome	Sample Size	Region
Neoadjuvant chemotherapy alone							
Prep-02/ JASP05	II/III	BRPC	NAC (gemcitabine + S1) followed by surgery	Upfront surgery	Overall survival	360	South Korea, Japan
NUPAT-01	II	BRPC	NAC (FOLFIRINOX) followed by surgery	NAC (G/N) followed by surgery	R0 resection rate	51	Japan
ESPAC-5	III	BRPC	NAC (FOLFIRINOX or gemcitabine + capecitabine or N-CRT) followed by surgery	Upfront surgery	Recruitment rate and resection rate	90	United Kingdom, Germany
NEOLAP-AIO-PAK-0113	II	LAPC	NAC (FOLFIRINOX)	NAC (G/N)	Surgical conversion rate	130	Germany
Neoadjuvant radiation alone or after neoadjuvant chemotherapy							
A021501	II	BRPC	NAC + Radiation	NAC	Overall survival	126	USA
LAPC-1	II	LAPC	FOLFIRINOX + SBRT	FOLFIRINOX	Overall survival	50	Netherlands
SMART	II	LAPC	Ablative MRI guided radiation	N/A	Gastrointestinal toxicity (secondary endpoint of overall survival)	133	USA, Israel
Neoadjuvant chemoradiotherapy							
LAP07	III	BRPC or LAPC	NAC (gemcitabine) + N-CRT (capecitabine)	NAC (gemcitabine)	Overall survival	449	France
NCT01458717 Trial	II/III	BRPC	N-CRT followed by surgery	Surgery alone	R0 resection rate	58	South Korea
JCOG1106	II	LAPC	NAC (S1) followed by N-CRT	NAC (gemcitabine) followed by N-CRT	Overall survival	100	Japan
JCOG1407	II	LAPC	NAC (FOLFIRINOX)	NAC (gemcitabine + Nab-paclitaxel)	Overall survival	126	Japan

Trial Name	Phase	Population	Intervention	Control	Primary Outcome	Sample Size	Region
JASPAC05	II	BRPC	N-CRT (S1)	N/A	R0 resection rate	50	Japan
CONKO-007	III	BRPC or LAPC	NAC (FOLFIRINOX) + N-CRT	NAC	Tumour resectability	180	Germany
PREOPANC-1	III	Resectable pancreatic cancer or BRPC	N-CRT(gemcitabine) then surgery	Surgery followed by adjuvant gemcitabine	Overall survival	246	Netherlands
NCT01591733	II	BRPC	NAC (FOLFIRINOX) + N-CRT (capecitabine)	N/A	R0 resection rate	48	USA
PREOPANC-2	III	BRPC	N-CRT (gemcitabine) followed by surgery followed by adjuvant gemcitabine	NAC (FOLFIRINOX) followed by surgery	Overall survival	375	Netherlands
Ascott et al.	II	BRPC	N-CRT (nab-paclitaxel)	N-CRT (5-FU or gemcitabine)	Toxicity (secondary endpoint local failure and conversion to resectability)	50	USA
T2212	II	LAPC	NAC (GOFL) + N-CRT (gemcitabine)	NAC (FOLFIRINOX) + N-CRT (gemcitabine)	Progression free survival	55	Taiwan

Table 1. Summary of recent studies informing care of patients with borderline resectable pancreatic cancer/locally advanced pancreatic cancer; *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

Abbreviations: BRPC: Borderline resectable pancreatic cancer; **LAPC:** locally advanced pancreatic cancer; **SOC:** Standard of Care chemotherapy; **USA:** United States of America; **NAC:** Neoadjuvant chemotherapy; **N-CRT:** neoadjuvant chemoradiotherapy

for two cycles, neoadjuvant FOLFIRINOX for 4 cycles, or neoadjuvant chemoradiation (N-CRT) with capecitabine for 5 weeks. All patients who had surgery received adjuvant therapy at the discretion of the treating oncologist. The primary outcomes of the trial were patient recruitment and surgical resection. A 1-year disease-free survival of 33% was noted in the surgery alone arm compared to a 1-year disease-free survival of 59% with neoadjuvant therapies (compiled data). The trial reported that the 1-year OS rate was 39% for immediate surgery compared to 78% with gemcitabine/capecitabine, 84% for those who received FOLFIRINOX and 60% for those who underwent chemoradiation. These differences in 1-year OS were significant (p=0.0028). However, there were no significant differences in R0 resection rates between neoadjuvant chemotherapy and N-CRT. It should be noted that adjuvant gemcitabine was the standard of care regimen at the time of trial design, however, newer standard of care regimens became available near the end of the trial. The results of the ESPAC5 trial demonstrated that NAC or N-CRT resulted in a higher proportion of patients alive at 1 year compared to those who underwent upfront surgery and adjuvant treatment alone. This feasibility trial has demonstrated that neoadjuvant treatment is feasible and possibly effective in the treatment of patients with BRPC, however long-term outcomes have yet to be published.

The recently reported PREOPANC-2 trial was a large phase III trial that involved 375 patients with both BRPC and resectable PDAC that was conducted across 19 centres in the Netherlands.[11] Patients were randomized to 8 cycles of FOLFIRINOX followed by surgery without adjuvant therapy or neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions in cycle 2) followed by surgery then 4 cycles of adjuvant gemcitabine. The trial reported a median OS of 21.9 months in the neoadjuvant FOLFIRINOX arm compared to a median OS of 21.3 months in the chemoradiation arm (HR 0.87, p=0.28). Resection rates were also comparable, at 77% with FOLFIRINOX and 75% with chemoradiation. It is important to note that adjuvant single agent gemcitabine is typically not used unless patients are unfit for combination regimens, thus, the applicability of the chemoradiation arm remains unclear.

Smaller studies have been conducted to compare modern chemotherapy regimens in BRPC. Yamaguchi and colleagues reported results from the phase II NUPAT-01 study that included 51 patients with BRPC. Patients received either FOLFIRINOX for 4 cycles or gemcitabine/nab-paclitaxel for 2 cycles, however, there was no surgery alone arm.[12] In this trial, 15.7% of patients did not undergo surgery. Intention-to-treat analysis demonstrated a 3-year OS of 54.7% and a 5-year OS of 36.6%. In addition, the FOLFIRINOX group demonstrated an improved invasive disease-free survival (iDFS), (p=0.044).. No significant OS difference was observed between the two groups.

Other agents have been used outside of North America for the treatment of pancreatic cancer, such as S-1, which has been used in Asian countries. The Japanese Prep-02/JSAP05 phase II/III trial examined the role of 2 cycles of preoperative gemcitabine combined with S-1 compared to upfront surgery in 364 patients with resectable pancreatic cancers and BRPC[13]. All patients received adjuvant S-1 for 6 months if they had curative resections. The interim results of this trial were presented at the American Society of Clinical Oncology (ASCO) 2019 meeting. The findings demonstrated a median OS of 36.7 months in those who received NAC compared to 26.6 months in those who underwent up-front surgery. The R0 resection rates were similar between the two groups.[14] A recent phase II trial conducted in Japan by Kondo *et al*. assessed the use of 6 cycles of gemcitabine, nab-paclitaxel, and S-1 as NAC for BRPC. This single arm study of 47 patients demonstrated an impressive 86% R0 resection rate with a median OS of 41 months.[15] A subsequent JASPAC05 single arm Japanese phase II trial was conducted in which 41 patients with BRPC received S-1 with concurrent radiotherapy (50.4 Gy in 28 fractions) and then surgery. The R0 resection rate was 63% with a 2-year median OS of 30.8 months.[16]

Can Radiation Augment Responses?

The role of adding radiation after initial induction chemotherapy for BRPC has been explored in a number of studies. Murphy and colleagues reported results from a phase II single centre study of 48 patients with BRPC who received an upfront induction of FOLFIRINOX for 8 cycles. If resolution of vascular involvement was observed, short course chemoradiation (5 Gy x 5 with protons) was administered. If vascular involvement remained, patients underwent long-course chemoradiation (50.4 Gy

in 28 fractions with vascular margin given 58.8 Gy in 28 fractions) with 5-fluorouracil or capecitabine. Results from this small study appeared promising, with an R0 resection observed in 31 patients (65%) and a 2-year OS of 72%.[17]

In a phase II/III trial that was conducted at several Korean centres, Jang *et al*. assessed the role of N-CRT (54 Gy EBRT) with gemcitabine versus upfront surgery and subsequent chemoradiation in patients with BRPC.[18] This study was terminated early owing to a statistically significant benefit of neoadjuvant treatment, at which time 50 patients were accrued out of a planned 110 patients. In the intention to treat (ITT) analysis, the 2-year OS was 41% in the neoadjuvant group compared to 26% in the upfront surgery group. The median OS was significantly longer in the N-CRT arm (21 months) vs. surgery and subsequent CRT (12 months).[19] Of note, this was a small study with 50 enrolled patients, which had provided the impetus for further trials assessing the use of N-CRT as opposed to adjuvant CRT.

Stereotactic body radiation therapy (SBRT) has been touted as being able to deliver a higher biological effective dose (BED) in a shorter time frame. Early small studies of SBRT in BRPC have been reported to allow approximately 50% of patients to proceed to surgical resection.[20,21] Given these results, SBRT was investigated in the larger Alliance A021501 phase II trial. In this trial, 126 patients with BRPC were randomized to 8 cycles of preoperative FOLFIRINOX or to 7 cycles of FOLFIRINOX followed by SBRT (33–40 Gy in 5 fractions) or to hypofractionated image-guided radiation (25 Gy in 5 fractions).[19] If disease progression was not observed, patients underwent surgical resection. With a primary endpoint of 18-month OS, the trial was powered to compare the 18-month OS with a historical reference of 50% survival at 18 months, rather than comparing between the two arms. At the interim analysis, only 33% of patients had an R0 resection in arm 2 (combination arm), thus, this arm was closed early. Patient accrual continued for arm 1 (FOLFIRINOX alone). The findings indicated an 18-month OS of 66.7% in the chemotherapy alone arm compared to 47.3% in the radiation arm. It should be noted that the median carbohydrate antigen 19-9 level was higher in the radiation arm (a median of 260 in the radiation arm compared to a median of 167 in the chemotherapy arm). A lower percentage of patients in the radiation arm underwent surgical resection (35%) compared to 49% after FOLFIRINOX alone, which may have impacted the primary endpoint. This is also thought to potentially reflect the heterogeneity of enrolling centres, which may not all have been high volume pancreatic cancer centres. Overall, this study solidified the role of FOLFIRINOX as a neoadjuvant treatment regimen in BRPC.

Locally Advanced Pancreatic Cancer

Table 1 provides a summary of recent studies on LAPC. FOLFIRINOX remains the most commonly used treatment regimen for patients with LAPC, despite the lack of randomized prospective phase III data. The JCOG1407 study compared FOLFIRINOX with gemcitabine/nab-paclitaxel in 126 patients with LAPC.[22] This trial reported a higher efficacy compared to historical numbers with gemcitabine alone, with a 1-year OS of 77.4% and 82.5% in the FOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively. The median PFS was 11.2 months and 9.4 months in the FOLFIRINOX and gemcitabine/nab-paclitaxel arms, respectively. In a patient-level meta-analysis, Suker and colleagues examined 13 studies which included a total of 355 patients with LAPC. The percentage of patients who also went on to receive radiotherapy ranged from 31% to 100%.[23] Overall, FOLFIRINOX appeared to have a longer median OS compared to gemcitabine.

Other gemcitabine-based regimens have been studied. Kunzmann and colleagues reported results from the NEOLAP-AIO-PAK-0113 phase II trial that included patients with LAPC, in which patients received 2 cycles of gemcitabine and nab-paclitaxel. If no evidence of disease progression was observed, patients would then be randomized to an additional 2 cycles of gemcitabine/nab-paclitaxel or to 4 cycles of FOLFIRINOX. No difference was observed in the primary endpoint of surgical conversion rate (complete macroscopic tumour resection), at 35.9% in the gemcitabine/nab-paclitaxel group vs. 43.9% in the sequential FOLFIRINOX group (p=0.38). No significant differences in overall survival were noted between the two strategies (median OS of 18.5 months vs. 20.7 months respectively, p=0.53).[24] Gemcitabine alone is typically not used given the low conversion rates to resectability. It is reserved for patients who would not otherwise tolerate combination chemotherapy.

Additional combination chemotherapeutic regimens outside of FOLFIRINOX and gemcitabine have also been investigated. Arscott and colleagues recruited 50 patients with BRPC

and LAPC. Of these, 28 patients received concurrent nab-paclitaxel with radiation (52.5 Gy total) and 22 patients received standard chemoradiation (54.5 Gy total).[25] Toxicity was a primary endpoint, with toxicities being similar between the two groups. A higher proportion of patients (9 of 28; 32%) went on to surgery in the nab-paclitaxel arm compared to the standard chemoradiation (3 of 22; 14%). The Taiwan Cooperative Oncology Group T2212 trial used gemcitabine, oxaliplatin, 5-FU/leucovorin (GOFL) or FOLFIRINOX as the induction regimen, then patients underwent 5-FU or gemcitabine-based chemoradiation (5040 cGy/28 fractions).[26] No differences in PFS or OS were observed between these two arms.

Role of Radiation in LAPC

Similar to BRPC, the addition of radiation to chemotherapy has also been studied. The goal of radiation therapy in these circumstances is to achieve local control. In a rapid autopsy series of patients with stage III and IV PDAC, 30% of them died from locally destructive disease, namely tumour infiltration to nearby structures.[27] Clinically, this manifests as epigastric and back pain, gastric outlet obstruction, bleeding, and obstructive jaundice. Local control through radiation therapy is meant to prevent these types of complications and to improve outcomes.

In the LAP-07 trial, patients with LAPC were initially randomized to either gemcitabine alone or gemcitabine with erlotinib for four cycles.[28] If no evidence of progression was observed after induction chemotherapy, patients were randomized to either chemoradiotherapy with capecitabine (54 Gy of EBRT with capecitabine at 1600 mg/m^2 per day) or an additional 2 months of gemcitabine alone. The primary endpoint was OS. The trial was stopped early (accrual reached 442 out of a planned 820 patients) owing to futility at the interim analysis in which no difference with chemoradiotherapy was found (or with erlotinib use). The ITT analysis demonstrated no difference in OS between induction chemotherapy regimens (median OS of 13.6 months with gemcitabine alone and 11.9 months with gemcitabine/erlotinib; HR 1.19). An ITT analysis of the second randomization comparing chemoradiation with chemotherapy also showed no difference in OS (15.2 months and 16.5 months respectively; HR 1.03). Some radiation deviations were noted (18% of patients experienced major deviations, 50% of patients experienced minor deviations), although this did not appear to impact survival outcomes.

This concept of chemoradiation post induction chemotherapy was further studied in the CONKO-007 phase III trial in which patients with LAPC received 3 months of induction chemotherapy with either FOLFIRINOX or single agent gemcitabine. If no progression was observed, patients were then randomized to continue chemotherapy for an additional 3 months or to receive chemoradiation (50.4 Gy) with gemcitabine. The primary endpoint was OS, but was later changed to R0 resection rate due to slow patient accrual. Over the course of 8 years, 525 patients were enrolled, of which 335 were randomized. Among the 122 patients who underwent surgery, R0 resection rate was higher in the chemoradiation arm at 69% vs. 50% in the gemcitabine alone arm. However, no statistically significant difference was noted when comparing R0 resection rates among all randomized patients (25% in the chemoradiation arm vs. 18% in the gemcitabine alone arm, p=0.11). No differences in PFS or OS were observed.[29]

The JCOG1106 phase II trial published by Ioka *et al*. included patients with LAPC and assessed the role of upfront chemoradiation compared to induction chemotherapy followed by radiation. Patients in arm A received chemoradiotherapy with S-1, whereas patients in arm B received gemcitabine for 12 weeks followed by radiotherapy with S-1. The results of this trial were reported to favour chemoradiotherapy alone. The 2 year median OS was longer in arm A vs arm B (36.9% vs 18.9%, respectively),[30] although single agent gemcitabine is now rarely used in this setting.

Novel Radiation Techniques in LAPC

Newer technologies, such as SBRT, have facilitated the precise delivery of high dose radiation to treat LAPC. Early small studies have demonstrated high local control rates with SBRT ranging from 89%–100%.[31–33] Intensity modulated radiation therapy (IMRT) and image guided techniques have been explored to allow dose escalation in certain areas of the tumour to maximize the treatment effect and minimize toxicities. Rudra and colleagues employed adaptive magnetic resonance imaging-guided radiation therapy, including conventional fractionation, hypofractionation, and SBRT, to treat 44 patients with unresectable LAPC.[34] Patients who received high-dose

radiation were found to have a longer 2-year OS compared to those who received standard doses (49% vs. 30%, respectively, p=0.03). In another study, Krishnan *et al*. reviewed the outcomes of 200 patients with LAPC who were treated with induction chemotherapy followed by chemoradiation in which 24% of them received dose-escalated IMRT.[35] Those who received a BED >70 Gy had a longer OS (median of 17.8 months vs. 15 months, p=0.03), with no significant differences in toxicity observed.

Crane and colleagues used high-dose hypofractionated radiation (98 Gy BED) to treat 119 patients with LAPC in a single centre cohort study after a median of 4 months of induction chemotherapy.[36] The 2-year OS, from the time of ablative radiation, was 38%, and the median OS from diagnosis was 26.8 months. Locoregional failure occurred in 32.8% of patients at the two-year mark. Given these promising results, further studies using ablative radiation therapy in patients with LAPC are warranted.

A number of novel radiation-based therapies are currently being employed in the treatment of BRPC/LAPC. These include electrochemotherapy, proton and carbon ion radiation, and electroporation. A few small phase I/II trials have assessed these novel treatments, and more trials are needed to clarify their role in patients with BRPC/LAPC.

Emerging Role of Cancer Vaccines

There is much excitement in the realm of cancer vaccines, with the promise of impacting the immunologically "cold" tumour microenvironment in PDAC. Early favourable results with a personalized neoantigen vaccine in the resectable PDAC setting with long-term survivors has now led to a prospective phase III trial, for which we eagerly await results.[37]

The phase I/II LAPC-2 trial recruited 38 patients with LAPC who had received induction chemotherapy with FOLFIRINOX.[38] They were then treated with SBRT (40 Gy) and 6 biweekly vaccinations of heat-killed myobacterium (IMM 101). There were 13 grade 3 events and one grade 5 event, which were not related to the IMM-101 vaccination. The median OS was 19 months, and 21% of patients were able to undergo resection.

One of the largest trials to date in BRPC or LAPC was the HyperAcute-Pancreas-Immunotherapy (HAPa) phase III study.[39] This vaccine was made of allogeneic pancreatic cancer cells expressing the murine alpha(1,3) GT gene, with the goal of increasing immunogenicity. Patients with BRPC or LAPC received upfront FOLFIRINOX or gemcitabine/nab-paclitaxel followed by either HAPa immunotherapy or chemoradiation. There was no significant difference in the median OS (14.9 months vs 14.3 months, respectively), progression free survival, or grade 3 adverse events. There was also no difference in terms of conversion to resectability.

Conclusions and Future Directions

Treatment of patients with BRPC and LAPC continues to evolve owing to advancements in drug discovery, surgical procedures, and radiation techniques. A number of active clinical trials are currently underway to optimize systemic therapy regimens and to elucidate the role of radiation in this setting (**Table 2**). Novel radiation techniques, including proton radiotherapy, cyberknife, and ultrasound, are under investigation. The addition of immunotherapy in the neoadjuvant setting is also being explored. Taken together, these novel approaches and emerging techniques hold substantial promise to improve survival outcomes in patients with BRPC and LAPC.

Registration ID	Phase	Population	Intervention	Control	Primary outcome	Expected sample size	Region
NCT02676349	II RCT	BRPC	NAC (FOLFIRINOX) + CRT	NAC (FOLFIRINOX)	R0 resection rate	130	France
NCT05634564	II single arm open label	BRPC	Gemcitabine + tislelizumab + nab paclitaxel + radiation	N/A	Overall response rate	62	China
NCT05083247 (STEREOPAC)	II RCT	BRPC	NAC (FOLFIRINOX) x 8 cycles	NAC (FOLFIRINX) x 6 cycles followed by SBRT	Disease free survival and R0 resection rate	256	Belgium
NCT05415917	II open label	Resectable or LAPC or BRPC	NAC followed by surgery gemcitabine + capecitabine	NAC followed by surgery and observation	Safety	75	USA
NCT03777462	II	BRPC	N-CRT	NAC alone	Overall survival	150	China
NCT03983057	III	BRPC or LAPC	NAC (FOLFIRINOX) + PD-1 antibody	NAC (FOLFORINOX)	Progression free survival	830	China
NCT03563248	II	BRPC or LAPC	NAC + losartan + nivolumab + SBRT	NAC + SBRT	R0 resection rate	168	USA
NCT04390399	II open label	LAPC or metastatic pancreatic cancer	SOC Chemotherapy + aldoxorubicin + PD-L1 therapy	SOC chemotherapy	Progression free survival	328	USA
NCT02598349	II	BRPC or LAPC	N-CRT (proton radiotherapy)	N/A	Overall survival	60	USA
NCT03377491	III	LAPC	N-CRT (Tumour treating fields + chemotherapy)	SOC chemotherapy	Overall survival	556	Multicentre (Multiple Countries)
NCT02539537 (NEOPAN)	III	LAPC	FOLFIRINOX	Gemcitabine	Progression free survival	171	France
NCT03899636	III	LAPC	FOLFIRINOX + Irreversible electroporation (Nanoknife)	FOLFIRINOX	Overall survival	528	USA
NCT04986930 (SABER)	II	LAPC	NAC (FOLFIRINOX) + SBRT	NAC (FOLFIRINOX)	Overall survival	92	South Korea

Registration ID	Phase	Population	Intervention	Control	Primary outcome	Expected sample size	Region
NCT03941093 (LAPIS)	III	LAPC	NAC + pamrevlumab	NAC	Overall survival	284	Multicentre (Multiple Countries)
NCT04617821	III	BRPC	NAC (mFOLFIRINOX)	NAC (gemcitabine + Nab-paclitaxel)	Overall survival	300	China
NCT03257033	III	LAPC	NAC + radiation followed by Intra-arterial gemcitabine	NAC + radiation	Overall survival	320	USA, Belgium
NCT05466799	II	LAPC	FOLFIRINOX+ Oncosil™	FOLFIRINOX	Safety + Local disease control rate	80	Belgium, Italy, Spain, United Kingdom
NCT04821284	I/II	LAPC or metastatic pancreatic cancer	SOC chemotherapy + sonoporation	SOC chemotherapy	Progression free survival	120	USA, Norway
NCT01585805	I/II	LAPC or metastatic pancreatic cancer	Gemcitabine + cispatin + veliparib	Gemcitabine + cispatin	Optimal dose + response rate	107	USA, Canada, Israel
NCT05851924	II	BRPC/LAPC	NALIRIFOX + ablative radiation therapy	N/A	Event free survival	60	USA
NCT04570943 (GABRINOX-ART)	II	LAPC	NAC (G/N) followed by FOLFIRINOX followed by MRI guided radiotherapy	N/A	Progression Free Survival	103	France
NCT05825066	II	BRPC/LAPC	NAC	N/A	R0 resection rate	64	USA
NCT02839343	II	BRPC	NAC + radiation	NAC	Overall survival	126	USA, Canada

Table 2. Ongoing Phase II/III trials in patients with borderline resectable pancreatic cancer or locally advanced pancreatic cancer with >60 patients; *courtesy of Arman Zereshkian, MD and Erica S. Tsang, MD*

Abbreviations: BRPC: Borderline resectable pancreatic cancer, **LAPC:** locally advanced pancreatic cancer, **SOC:** Standard of Care chemotherapy, **USA:** United States of America, **NAC:** Neoadjuvant chemotherapy, **N-CRT:** neoadjuvant chemoradiotherapy

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