Current status and future perspective of neoadjuvant therapy in locally advanced and borderline resectable pancreatic adenocarcinoma: a narrative review

Jaewon Hyung[1], Sang Soo Lee[2], Dae Wook Hwang[3], Jin-hong Park[4], Kyu-pyo Kim[1], Changhoon Yoo[1]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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Correspondence to: Changhoon Yoo, MD, PhD. Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 8 Olympic-ro, 43-gil, Songpa-gu, Seoul 05505, Republic of Korea. Email: yooc@amc.seoul.kr.

Background and Objective: The concept of neoadjuvant approach for patients with locally advanced pancreatic cancer (LAPC) has been evolving with the advancement in therapeutic modalities. In this narrative review, we aimed to discuss the updates and future perspectives on the treatment of LAPC.

Methods: We discussed the recent literature and up-to-date evidence along with the future perspectives for the treatment of LAPC using the neoadjuvant approach. Reviewed literatures were searched by systematic search of PubMed and Google Scholar, including articles published in English between January 1st, 2013, and October 31st, 2021.

Key Content and Findings: We aimed to review the efficacy outcomes of modern-era chemotherapy regimens and chemoradiation therapy for LAPC based on the results of up-to-date clinical trials and pivotal observational studies. Moreover, we aimed to discuss the role of conversion surgery and studies on the prediction of resectability after neoadjuvant therapy along with the necessity of adjuvant therapy for patients who have received neoadjuvant systemic treatments. Finally, we have addressed several unanswered questions regarding the optimal management of patients with LAPC and determined the future directions by introducing some ongoing trials.

Conclusions: Current chemotherapy and chemoradiation therapy has improved clinical outcomes and the conversion surgery rate in patients with LAPC. Future randomized clinical trials and biomarker studies are needed to provide better evidence that can aid in the selection of optimal treatment modalities for individual patients.

Keywords: Locally advanced pancreatic cancer (LAPC); neoadjuvant therapy; preoperative therapy; conversion surgery; pancreatic ductal adenocarcinoma (PDAC)

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly fatal malignant neoplasm arising from the exocrine pancreas. It is the second leading cause of cancer death in the United States, and the 5-year survival rate at the time of diagnosis is only 10% (1-3). PDAC can be classified

Table 1 Classification of pancreatic cancer according to the National Comprehensive Cancer Network resectability criteria (4)

Resectability	Arterial	Venous
Resectable	No arterial contact of the tumor including CA, SMA, and CHA	(I) No venous contact of the tumor including SMV and PV; (II) contact with SMV or PV but ≤180° without distorting the vein contour
Borderline resectable	Pancreatic head or uncinate process tumor: (I) contact with the SMA ≤180°; (II) contact with the CHA but no extension to CA or to the bifurcation of the hepatic artery, allowing safe and complete resection and reconstruction; (III) contact with variant artery Pancreatic body or tail tumor: (I) contact with the CA ≤180°; (II) contact with the CA more than 180° but no involvement of the aorta and with intact and uninvolved gastroduodenal artery, which allows the modified Appleby procedure (some panel members of the NCCN prefer these criteria to be in the locally advanced)	(I) Contact with the SMV or PV more than 180°; (II) contact with the SMV or PV ≤180° and contour irregularity of the vein or venous thrombosis with suitable vessel proximal and distal to the site of involvement enough for safe and complete resection and reconstruction; (III) contact with the IVC
Locally advanced	Pancreatic head or uncinate process tumor: contact with the SMA or CA more than 180° Pancreatic body or tail tumor: (I) contact with the SMA or CA of more than 180°; (II) contact with the CA and aortic involvement	Unreconstructable SMV or PV due to tumor involvement or occlusion by the tumor itself or bland thrombus

CA, celiac artery; SMA, superior mesenteric artery; CHA, common hepatic artery; SMV, superior mesenteric vein; PV, portal vein; IVC, inferior vena cava; NCCN, National Comprehensive Cancer Network.

according to its resectability, evaluated using multi-phase dynamic contrast-enhanced computed tomography (CT). The resectability criteria suggested by the National Comprehensive Cancer Network is widely accepted for PDAC resectability status evaluation (*Table 1*) (4,5). In brief, a normal tissue plane between the tumor and vessels indicates a resectable disease, contact with the adjacent artery (>180°) or unreconstructable superior mesenteric vein or portal vein involvement indicates a locally advanced disease, and contact with the adjacent artery (≤180°) or venous involvement, which can be surgically resected and reconstructed, indicates a borderline resectable disease. Only few patients with PDAC are diagnosed with resectable disease and may undergo surgical resection, which is the only curative treatment modality for patients with PDAC (6).

For borderline resectable pancreatic cancer (BRPC), neoadjuvant treatment followed by surgical resection is the standard treatment (4). Neoadjuvant therapy is aimed at achieving a higher R0 resection rate, which is well correlated with better survival outcomes (7-9). Neoadjuvant therapy allows the early treatment of micrometastasis, and unnecessary surgery is avoided in patients with unfavorable biology who does not respond to the neoadjuvant therapy (7). The application of modern chemotherapeutic regimens approved for the treatment of metastatic PDAC has strengthened the use of the neoadjuvant approach in patients with BRPC with higher response rates and longer survival outcomes (10-12). The regimens include a combination of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX) and gemcitabine plus nab-paclitaxel (GA), which were developed for the treatment of metastatic disease (13-18).

For selected patients with locally advanced pancreatic cancer (LAPC), accounting for one-third of all patients with PDAC, the standard first-line treatment is systemic chemotherapy with additional locoregional radiotherapy in selected patients (4). The clinical outcomes of LAPC treated with old-fashioned chemotherapy and chemoradiotherapy (CRT) were extremely poor, with a median overall survival (OS) of approximately 12 months (19). Regarding BRPC, the application of modern-era regimens for the treatment of patients with LAPC has also improved clinical outcomes and increased the surgery conversion rate (11,12). The use of the neoadjuvant approach for the management of patients with LAPC has been increasingly investigated, with a higher proportion of patients with LAPC undergoing conversion surgery (11,12). Recently, several well-written

Table 2 Literature search strategy

Items	Specifications
Date of search	November 1st, 2021
Database searched	PubMed and Google Scholar
Search terms used	PubMed: (I) locally advanced pancreatic cancer OR borderline resectable pancreatic cancer; (II) pancreatic cancer AND neoadjuvant; (III) pancreatic cancer
	Google Scholar: (I) neoadjuvant therapy for locally advanced pancreatic cancer; (II) neoadjuvant therapy for borderline resectable pancreatic cancer
Timeframe	Between January 1st 2013 and October 31st 2021
Inclusion and exclusion criteria	Inclusion criteria—(I) Articles language: English; (II) Article type: literature reviews and original studies including prospective clinical trials and observational studies of locally advanced and borderline resectable pancreatic cancer
	Exclusion criteria—(I) Articles language: non-English; (II) Article type: case studies and case series
Selection process	Jaewon Hyung did the study selection and reviewed by Changhoon Yoo
Additional considerations	None

review articles have discussed updates of neoadjuvant treatments for BRPC, LAPC and resectable PDAC (11,12,20). In this review, we will discuss recent updates of neoadjuvant approach focusing on LAPC and how FOLFIRINOX and GA regimen have improved outcomes of LAPC patients. Also, we will discuss the role of CRT in modern era chemotherapeutic regimens when compared to conventional chemotherapies. Moreover, we will discuss conversion surgery and adjuvant therapy options for LAPC patients following neoadjuvant treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-166/rc) (21).

Methods

We have reviewed the recent literature and up-to-date evidence to discuss current perspective of neoadjuvant approach for LAPC and BRPC. Reviewed literatures were searched by systematic search of PubMed and Google Scholar, including articles published in English between January 1st, 2013, and October 31st, 2021 on November 1st, 2021. The search terms used included locally advanced pancreatic cancer or borderline resectable pancreatic cancer, pancreatic cancer AND neoadjuvant and pancreatic cancer for PubMed search and neoadjuvant therapy for locally advanced pancreatic cancer and neoadjuvant therapy for borderline resectable pancreatic cancer for Google Scholar (*Table 2*). Review articles and original research articles including prospective trials and observational studies of locally advanced and borderline resectable pancreatic cancer written in English were included in the review. Non-English articles and case reports and case series were excluded.

Neoadjuvant chemotherapy

The efficacy of FOLFIRINOX as treatment for BRPC and LAPC has been widely investigated. A systematic review of 13 studies including 689 patients with BRPC and LAPC treated with neoadjuvant FOLFIRINOX showed a median OS of 10–32.7 months (22). A Korean phase 2 clinical trial of 44 patients with BRPC treated with neoadjuvant modified FOLFIRINOX followed by surgery and adjuvant gemcitabine showed an objective response rate (ORR) of 34.1%, a resection rate of 61.4% (R0 resection in 81.5%), and a median OS of 24.7 months (23). Similar results were reported in several retrospective studies on patients with BRPC treated with neoadjuvant FOLFIRINOX, with resection rates ranging from 41.7% to 87% (24,25).

The conversion surgery rate and survival outcomes of patients of LAPC treated with FOLFIRINOX were lower than those of patients with BRPC (22,26). In a systematic review, only 91 patients among 325 patients with LAPC underwent conversion surgery (resection rate: 28%, R0

resection rate: 74%) (22). Another systematic review of 14 studies involving 365 patients with LAPC showed similar outcomes, with a median OS of 8.9–25.0 months, a pooled resection rate of 28%, and an R0 resection rate of 77% (26). Other observational studies showed a resection rate of 19–60.8% among patients with LAPC treated with FOLFIRINOX (24,27-30). A previous analysis of 22 patients with LAPC treated with FOLFIRINOX reported an ORR of 27.3%, and resection was performed only in 5 (22.7%) patients who underwent additional CRT after receiving FOLFIRINOX as neoadjuvant treatment (27).

The efficacy of gemcitabine-based chemotherapy regimens for the treatment of patients with LAPC was also broadly investigated (*Table 3*). In a phase 3 study comparing the efficacy of gemcitabine plus S-1 and gemcitabine or S-1 monotherapy in 834 patients with LAPC or metastatic PDAC, no significant differences were observed in the survival outcomes between groups; moreover, a higher incidence of gastrointestinal and hematologic toxicity was documented in the combination arm (33). On the other hand, in a pooled analysis comparing the efficacy and safety of gemcitabine plus S-1 and gemcitabine alone in patients with PDAC, patients with LAPC treated with gemcitabine plus S-1 had significantly longer survival than those treated with gemcitabine alone, with median OS times of 16.4 months and 11.8 months, respectively (P=0.0220) (46). In a phase 1B trial of nab-paclitaxel, gemcitabine, capecitabine, and cisplatin in 24 patients with BRPC or LAPC, the ORR was 67%, with a resection rate of 25% (R0 resection rate 50%) and median OS of 18.1 months (34).

Recently, the evaluation of the GA regimen used for the treatment of LAPC showed comparable outcomes to those of FOLFIRINOX (*Table 3*). A phase 2 LAPACT trial evaluated the efficacy of neoadjuvant GA administered in six cycles to 107 patients with LAPC and showed an ORR of 33.6% and a median OS of 18.8 months, although conversion surgery was performed in only 27 patients (resection rate: 25.2%) (32). Another phase 2 trial evaluated the efficacy of adding S-1 to the GA regimen for the treatment of patients with BRPC and arterial contact (35). In 47 patients who received six cycles of GA plus S-1 regimen, the ORR was 46%, with an R0 resection rate of 86% and a median OS of 41.0 months (35).

Several studies comparing the outcomes of patients treated with FOLFIRINOX and GA have shown similar outcomes for the treatment of LAPC. A phase 2 trial compared the efficacy of sequential chemotherapy with two cycles of GA followed by four cycles of FOLFIRINOX and that of six cycles of the GA regimen for the treatment of LAPC or BRPC (31). Among the 130 patients, no significant difference was observed between groups in terms of resection rate (35.9% *vs.* 43.9%, P=0.38) and median OS (18.2 *vs.* 20.7 months, P=0.53), with similar toxicity profiles (31). Previous retrospective studies comparing the efficacy of GA and FOLFIRINOX as treatment for LAPC have shown similar clinical outcomes (47-49). In a study including 147 patients with LAPC treated with either GA (60 patients) or FOLFIRINOX (87 patients), the resection rates were 16.7% (R0 resection rate: 88.9%) and 16.1% (R0 resection rate: 88.9%), and no significant difference was found in terms of median OS (15.7 *vs.* 16.7 months, P=0.7) (49). However, there is lack of robust clinical trial data comparing the two regimens as treatment for LAPC.

Neoadjuvant chemoradiotherapy

There are relatively more randomized clinical trial data indicating the use of CRT as treatment for BRPC or LAPC than the trials which used chemotherapy alone (*Table 3*). In a phase 2/3 study, the efficacy of neoadjuvant CRT [total radiation therapy (RT) dose: 54 Gy] combined with weekly administration of intravenous gemcitabine (400 mg/m^2) within a 6-week period followed by surgical resection was compared to that of upfront surgery and adjuvant CRT according to the same schedule for the treatment of patients with BRPC (43). The neoadjuvant therapy group showed a significantly higher R0 resection rate (51.8% *vs.* 26.1%, P=0.004) and better OS outcomes than the upfront surgery group, with a hazard ratio (HR) at 2 years of 1.495 (P=0.028) (43). In addition, the phase 3 PREOPANC trial compared the efficacy of neoadjuvant gemcitabine-based CRT followed by surgery and additional postoperative gemcitabine and that of upfront surgery followed by 6 cycles of adjuvant gemcitabine for the treatment of BRPC and resectable PDAC (45). Among the 246 patients included, 133 were diagnosed with BRPC; the study failed to meet its primary endpoint with a median OS HR of 0.78 (P=0.096), although the follow-up data reported at the 2021 ASCO annual meeting showed better outcomes in the neoadjuvant arm than in the upfront surgery arm (HR: 0.72, P=0.025) (45,50). A subgroup analysis of 33 patients with BRPC showed significantly better R0 resection rate (79% *vs.* 13%, P<0.001) and survival (median OS: 17.6 *vs.* 13.2 months, P=0.029) in the neoadjuvant arm than in the upfront surgery arm (45).

However, the benefit of adding RT to neoadjuvant

Table 3 Summary of prospective clinical trial results of neoadjuvant therapy for locally advanced pancreatic cancer and borderline resectable pancreatic cancer

Phase	Condition	Intervention	Primary endpoint	No. of patients	ORR	Resection rate	R0 resection rate	Median OS (months)	Toxicity	Reference
Chemotherapy										
Phase 2	LAPC	Arm A: GA; Arm B: GA followed by FOLFIRINOX	Surgery conversion rate	Total 130 (Arm A: 64; Arm B: 66)	Arm A: 22%; Arm B: 17%	Arm A: 35.9%; Arm B: 43.9%; (P=0.38)	Arm A: 65%; Arm B: 63%	Arm A: 18.5; Arm B: 20.7; (P=0.53)	AE grade 3–4—Arm A: 55%; Arm B: 53%	Kunzmann *et al.* (31)
Phase 2	LAPC	GA	Time to treatment failure	107	33.60%	16%	43.80%	18.8	Neutropenia grade 3–4: 33%	Philip *et al.* (32)
Phase 3	LAPC and MPC	Arm A: Gemcitabine; Arm B: S-1; Arm C: Gemcitabine + S-1	Overall survival	834 (202 LAPC patients, 24.3%)	Arm A: 13.3%; Arm B: 21%; Arm C: 29.3%	–	–	Arm A: 8.8; Arm B: 9.7; Arm C: 10.1	–	Ueno *et al.* (33)
Phase 1B	BRPC and LAPC	Nab-paclitaxel + Gemcitabine + Cisplatin + Capecitabine	RP2D of nab-paclitaxel	24 (18 LAPC patients, 75%)	67%	25%	50%	18.1	AE grade 3–4: 67%	Reni *et al.* (34)
Phase 2	BRPC	FOLFIRINOX followed by adjuvant gemcitabine	1-year PFS	44	34.10%	61.40%	81.50%	24.7	Neutropenia grade 3–4: 54.5%	Yoo *et al.* (23)
Phase 2	BRPC	GA + S-1	OS	47	43%	96%	87%	41.0	AE grade 3–4: 30%	Kondo *et al.* (35)
Chemoradiation therapy										
Phase 2	LAPC	Gemcitabine 5 cycles + SBRT	1-year local PFS	20	–	–	–	11.8	–	Mahadevan *et al.* (36)
Phase 2	LAPC	Gemcitabine + Capecitabine followed by Arm A: Gemcitabine + RT Arm B: capecitabine + RT	9-month PFS >50%	Total 74 (Arm A: 38; Arm B: 36)	Arm A: 19%; Arm B: 23%	Arm A: 7.9%; Arm B: 13.9%	–	Arm A: 13.4; Arm B: 15.2; (P=0.012)	AE grade 3–4—Arm A: 37%; Arm B: 12%	Mukherjee *et al.* (37)
Phase 2	LAPC	Gemcitabine followed by SBRT	Toxicity	49	–	8.20%	100%	22.2	AE grade 2–4—Acute: 2%; Late: 11%	Herman *et al.* (38)
Phase 3	LAPC	Gemcitabine ± erlotinib followed by Arm A: CRT with Capecitabine Arm B: continue chemotherapy	Overall survival	269 randomized for arms A and B (Arm A: 133; Arm B: 136)	Arm A: 19%; Arm B: 23%	Arm A: 6%; Arm B: 2.9%	100% in both	Arm A: 15.2; Arm B: 16.5; (P=0.83)	AE grade 3–4—Arm A: 27%; Arm B: 29.3%	Hammel *et al.* (39)
Phase 2	LAPC	FOLFIRINOX 8 cycles followed by CRT (capecitabine) + losartan	R0 resection rate	49	51%	69%	88%	33	AE grade 3–4: 51%	Murphy *et al.* (40)
Phase 2	BRPC	FOLFIRINOX followed by hypofractionated *vs.* conventional CRT according to FOLFIRINOX response	R0 resection rate	48	–	65%	97%	37.7	–	Murphy *et al.* (41)
Phase 1	BRPC	FOLFIRINOX followed by CRT	Feasibility and safety	22	27%	68%	93%	21.7	AE grade 3–4: 64%	Katz *et al.* (42)
Phase 2/3	BRPC	Arm A: neoadjuvant gemcitabine + RT; Arm B: surgery followed by gemcitabine + RT	2 years OS	Total 50 (Arm A: 27; Arm B: 23)	–	–	Arm A: 51.8%; Arm B: 26.1%; (P=0.004)	2-year OS of Arm B: HR 1.97, P=0.028	-	Jang *et al.* (43)
Phase 1	BRPC	GA 2 cycles followed by CRT with GA	Safety	38	63.20%	63.20%	96%	–	–	Takahashi *et al.* (44)
Phase 3	RPC and BRPC	Arm A: gemcitabine + RT followed by surgery; Arm B: surgery followed by gemcitabine	Overall survival	Total 246—Arm A: 119 (55% BRPC); Arm B: 127 (53% BRPC)	–	Arm A: 61%; Arm B: 72%; (P=0.085)	Arm A: 71%; Arm B: 40%; (P<0.001)	Arm A: 16.0; Arm B: 14.3; (P=0.096)	AE grade 3–4—Arm A: 52%; Arm B: 41%; (P=0.096)	Versteijne *et al.* (45)

ORR, objective response rate; OS, overall survival; LAPC, locally advanced pancreatic cancer; BRPC, borderline resectable pancreatic cancer; GA, gemcitabine plus nab-paclitaxel; FOLFIRINOX, 5-fluorouracil and leucovorin plus irinotecan and oxaliplatin; AE, adverse event; RT, radiation therapy; SBRT, stereotactic body radiation therapy; PFS, progression-free survival; CRT, chemoradiation therapy; RP2D, recommended phase 2 dose.

chemotherapy in the era of modern chemotherapy is unclear in the treatment of BRPC in terms of resection rate and survival outcomes. A phase 1 study on the efficacy of two cycles of GA followed by CRT with concurrent GA regimen proved the feasibility and safety of this regimen; the resection rate was 63.2% (R0 resection rate: 96%) (44). The feasibility and safety of FOLFIRINOX followed by CRT in patients with BRPC was also demonstrated in a phase 1 trial, although the outcomes were like those reported in the Korean phase 2 trial on neoadjuvant FOLFIRINOX alone as treatment for BRPC (23,51). The recently reported phase 2 trial failed to prove the efficacy of additional RT after FOLFIRINOX as neoadjuvant therapy for BRPC (42). The primary endpoint of the study was an 18-month OS rate of >50% compared to that of the historical cohort, and the patients were either treated with eight cycles of neoadjuvant modified FOLFIRINOX (mFOLFIRINOX) followed by surgery and adjuvant modified 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX) (70 patients) or seven cycles of neoadjuvant mFOLFIRINOX followed by hypofractionated RT or stereotactic body RT (SBRT) and surgical resection with adjuvant mFOLFOX (56 patients) (42). The neoadjuvant mFOLFIRINOX group had an 18-month OS rate of 66.4%, with a resection rate of 49% and preoperative Common Terminology Criteria for Adverse Event (CTCAE) grade of 3–4 in 64% patients, while the neoadjuvant mFOLFIRINOX + RT group had an 18-month OS of 47.3%, with a resection rate of 35% and a CTCAE grade of 3–4 in 57% patients (42). On the contrary, a phase 2 trial including 48 patients with BRPC treated with FOLFIRINOX followed by individualized CRT demonstrated promising outcomes (41). According to the FOLFIRINOX response, patients who showed resolution of vascular involvement received a short-course CRT (25 Gy/five fractions, proton), while those with persistent involvement received conventional CRT. Overall, the resection rate was 65%, with a R0 resection rate of 97% and median OS of 37.7 months (41).

For selected patients with LAPC, sequential CRT may be administered to patients after induction systemic chemotherapy or upfront RT or CRT may be administered to patients who are not suitable for induction chemotherapy (4). However, CRT after old-fashioned chemotherapy regimens failed to show better efficacy outcomes than modern chemotherapy regimens alone in several trials (*Table 3*). In a phase 2 study of 20 patients with LAPC treated with SBRT and five cycles of gemcitabine, the median OS was only 11.8 months (36). Another phase 2 trial of gemcitabine plus SBRT treatment including 49 patients with LAPC showed similar results, with a median OS of 13.9 months, and conversion surgery was performed in 4 patients (38). The phase 3 LAP07 trial compared the efficacy of additional CRT after induction chemotherapy and that of chemotherapy alone with gemcitabine-based therapy in patients with LAPC (39). A total of 449 patients received induction gemcitabine with or without erlotinib for 4 months, and patients exhibiting disease control and good performances were randomized to receive either CRT with capecitabine or 2 months of additional chemotherapy (39). Among the 269 patients randomized to receive either CRT or chemotherapy; no significant difference was observed between the CRT and chemotherapy in terms of the median OS (15.2 *vs.* 16.5 months, P=0.83) (39). In the phase 2 SCALOP trial, 74 patients with LAPC were treated with six cycles of neoadjuvant gemcitabine plus capecitabine followed by either gemcitabine plus RT or capecitabine plus RT (37). The median OS was better in patients who received RT with capecitabine than in patients who received gemcitabine (15.2 *vs.* 13.4 months, P=0.012); moreover, the results of long-term follow-up showed a longer median OS in patients treated with capecitabine-based RT than in those treated with gemcitabine-based RT (17.6 *vs.* 14.6 months) (37,52).

A recent phase 2 trial showed promising results of additional CRT (50.4 Gy) with capecitabine after eight cycles of neoadjuvant FOLFIRINOX in 49 patients with LAPC along with losartan; the resection rate was 69% (R0 resection rate: 88%), with a median OS of 33 months (40). RT can be administered to patients with LAPC who are not suitable to undergo surgical resection after receiving first-line chemotherapy. An observational study of 119 patients with LAPC treated with induction chemotherapy (mostly FOLFIRINOX) followed by ablative RT (biologically active dose: 98 Gy) with concurrent fluoropyrimidine reported a median OS of 26.8 months, with a 2-year locoregional progression rate of 32.8% (53).

However, existing randomized trials have reported insufficient information on the efficacy of RT in patients with LAPC. An ongoing randomized phase 2 trial (SABER: NCT04986930) comparing the efficacy of modified FOLFIRINOX + SBRT and that of mFOLFIRINOX as treatment for LAPC will provide a high level of evidence to determine whether RT has clinical relevance in the era of modern chemotherapy regimens as treatment for LAPC. The efficacy of SBRT during the earlier clinical course (first four cycles of mFOLFIRINOX) is being evaluated in this trial.

Conversion surgery and adjuvant therapy after neoadjuvant therapy

Current evidence suggests that surgical resection after neoadjuvant therapy in patients with LAPC is strongly associated with better survival outcomes. An observational study compared the survival outcomes in 293 patients with LAPC exhibiting disease control after receiving FOLFIRINOX who underwent and did not undergo surgery; in terms of OS after surgery and a propensity score matched HR of 0.344 (P<0.01) was reported (54). Another observational study also proved the benefit of surgical resection after neoadjuvant therapy in patients with BRPC and LAPC. Among patients who received surgery, there was no significant difference of clinical outcomes between patients with BRPC and LAPC in terms of OS (median OS 15.0 *vs.* 14.5 months, P=0.7) (54). An observational study of 135 patients with BRPC and LAPC who underwent conversion surgery after neoadjuvant chemotherapy showed promising outcomes, with a median OS of 29.7 and comparable safety in terms of postoperative complications (55).

It is challenging to predict resectability based on imaging studies after neoadjuvant therapy, and many studies have reported that the radiological appearance after neoadjuvant therapy does not reflect the patient's response to therapy (56,57). An observational study of 188 PDAC patients who underwent surgery, the R0 resection rate was 92% among 40 patients with LAPC or BRPC who received neoadjuvant FOLFIRINOX despite the fact that 28 patients were still BRPC or LAPC by post-FOLFIRINOX imaging (58). In several studies, decrease or normalization of serum carbohydrate antigen (CA) 19-9 levels after neoadjuvant therapy was associated with better clinical outcomes (59-62). Surgical resection should be strongly considered for patients with LAPC without radiological progression after neoadjuvant therapy, especially in those with a good performance status and decreased CA 19-9 level (63). However, there are currently no established predictor of surgical resectability in patients with LAPC who have received neoadjuvant therapy (62). Several prognostic factors associated with better survival outcomes have been proposed, including CA 19-9, small baseline and post-treatment tumor size, and duration of neoadjuvant chemotherapy of longer than six cycles (62,64-67). Recently, a single center retrospective study showed that reduction of the tumor metabolic activity following neoadjuvant chemotherapy estimated by 18F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)-CT was associated with improved survival outcomes for patients with BRPC or LAPC (68).

The role of adjuvant therapy in patients with LAPC who have undergone conversion surgery after neoadjuvant therapy is not well established (69). A large observational study including 2,016 patients who received neoadjuvant therapy and underwent surgical resection evaluated clinical outcomes according to the status of adjuvant chemotherapy with propensity score matching; adjuvant chemotherapy was associated with better OS than no adjuvant chemotherapy (median OS: 29.4 *vs.* 24.9 months, P<0.001), irrespective of the pathological nodal status and margin status (70). On the contrary, an observational study of patients who underwent conversion surgery after at least two cycles of FOLFIRINOX showed no difference in OS rates according to the adjuvant chemotherapy status (HR: 0.99, P=0.93), although adjuvant chemotherapy seemed to improve the outcomes of patients with pathological regional lymph node involvement (HR for OS: 0.41, P=0.004) (71). Both studies did not exclusively include patients with LAPC; hence, more prospective studies are needed to determine the benefit of adjuvant therapy and optimal regimen in patients with LAPC patients who have undergone conversion surgery.

Future directions

The application of modern-era chemotherapy regimens including FOLFIRINOX and GA and addition of CRT has improved survival outcomes and the conversion surgery rate in patients with LAPC. *Figure 1* provides a summary our suggestion regarding the treatment flow for initially diagnosed patients with LAPC. However, several questions remain unanswered, and more robust randomized clinical trials data are needed. An optimal chemotherapy regimen should be established along with the role of additional CRT. Clinical trials should investigate the appropriate biomarkers to appropriately select high-risk patients who will benefit from additional CRT. In addition, the predictive biomarkers for surgical resectability after neoadjuvant therapy should be determined. Subsequently, additional studies should be conducted to investigate the role of adjuvant therapy after conversion surgery. The ongoing clinical trials registered at clinicaltrials.gov are listed in *Table 4*. Besides chemoradiation and surgical therapies, several studies also suggest the role of non-pharmacological management including exercise prescriptions and nutritional support, although high-quality evidence showing the efficacy of such

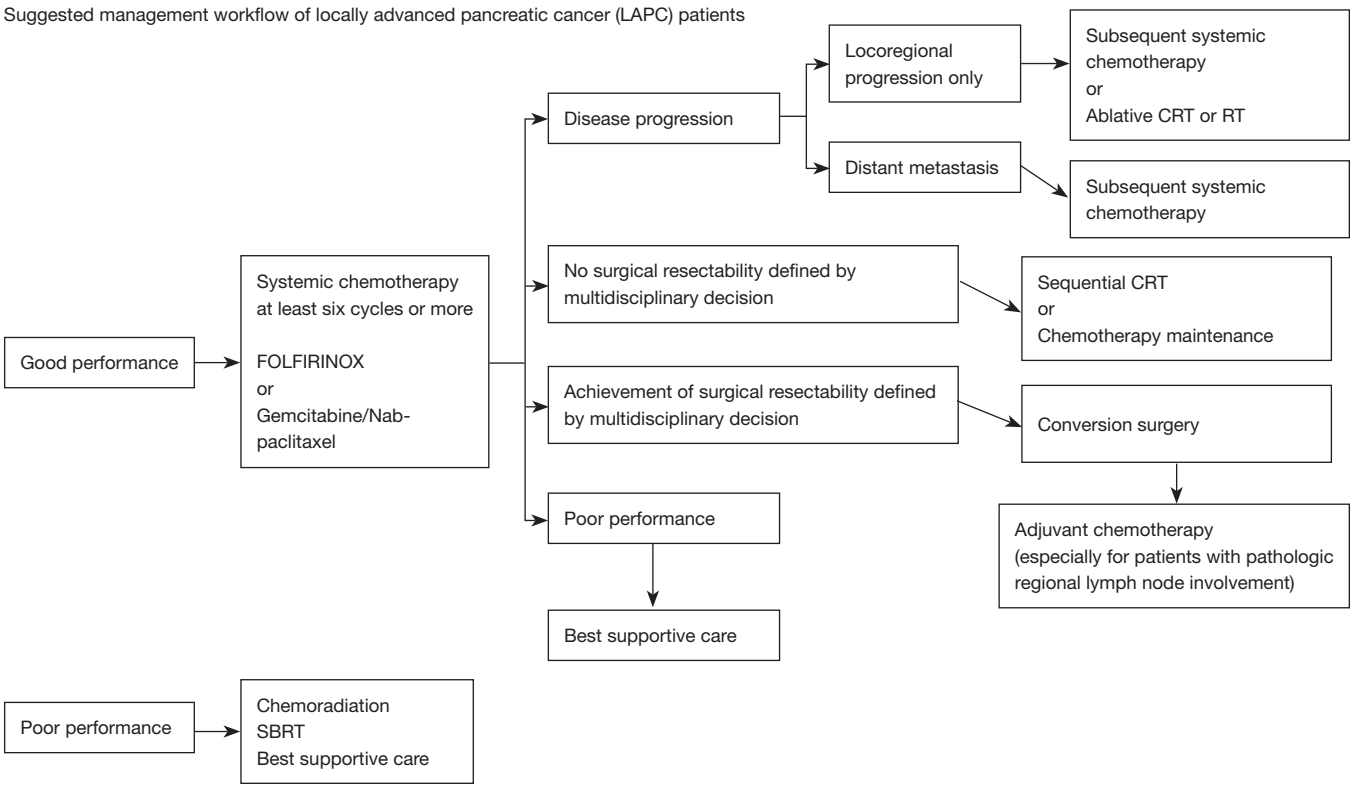

Figure 1 Suggested treatment flow for patients initially diagnosed with locally advanced pancreatic cancer. Patients eligible for intensive regimen should undergo induction chemotherapy with either FOLFIRINOX or gemcitabine plus nab-paclitaxel for at least six cycles. Patients exhibiting response and achieving resectability should undergo conversion surgery or may receive surgery after additional chemoradiation. Resectability is evaluated by multidisciplinary discussion including surgeon, radiologist, radiation oncologist and medical oncologist based on patients clinical status and follow-up imaging study results. Patients with substantial decrease or normalized serum carbohydrate antigen 19-9 levels after induction chemotherapy may be more actively considered for surgery than other patients. Patients exhibiting disease control without resectability may be treated with sequential chemoradiation therapy, preferably capecitabine based, or continue systemic chemotherapy. After additional chemoradiation or maintenance chemotherapy, conversion surgery should be strongly considered for patients without definite disease progression. For patients with disease progression, subsequent systemic treatment may be given if performance status allows. Ablative RT may be considered for patients with locoregional progression only. Adjuvant chemotherapy may be administered following curative resection, especially for patients with pathological regional lymph node involvement. FOLFIRINOX, a combination of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; SBRT, stereotactic body radiation therapy; RT, radiation therapy; CRT, chemoradiation therapy.

interventions still lacking, and further investigations are warranted (72-75).

Moreover, precision medicine should be introduced to help select the optimal therapeutic modalities for patients with LAPC (7). Studies to investigate molecular and immune biomarkers should be performed to predict the efficacy of preoperative treatment and clinical outcomes. In a previous retrospective study of 49 patients with LAPC who received neoadjuvant therapy followed by surgery, loss of SMAD4 protein was associated with poor survival outcomes (76). In a phase 2 clinical trial of neoadjuvant mFOLFIRINOX and sequential CRT combined with losartan in patients with LAPC, the serum transforming growth factor ß and thrombospondin 1 levels significantly decreased after administration of neoadjuvant therapy compared to those at baseline (40). Systemic inflammatory and immune biomarkers, including low fibrinogen to albumin ratio, lower peripheral monocytes, and higher $CD69^{+}$ gamma delta T cells levels at baseline, have been shown to be associated with better survival outcomes

Table 4 Ongoing prospective clinical trials on the treatment of locally advanced pancreatic cancer

Clinicaltrial.gov	Condition	Intervention	Phase	Completion
NCT01821729	LAPC	FOLFIRINOX + losartan followed by proton beam RT with capecitabine	Phase 2	September 2021
NCT02128100	LAPC	FOLFIRINOX followed by SBRT	Phase 2	May 2025
NCT02578732	LAPC	FOLFOX + nab-paclitaxel	Phase 2	December 2021
NCT02635971	LAPC	GEMOX *vs.* IA GEMOX	Phase 2	December 2022
NCT03138720	BRPC and LAPC	Nab-paclitaxel + GEMCIS + paricalcitol	Phase 2	March 2022
NCT03158779	LAPC	FOLFIRINOX or GA followed by SBRT	Phase 2	March 2022
NCT03523312	LAPC	Induction chemotherapy (FOLFIRINOX or GA) followed by ablative RT with capecitabine	Phase 2	April 2023
NCT03815461	LAPC	Nab-paclitaxel + S-1	Phase 2	October 2023
NCT03861702	LAPC	FOLFOX + nal-irinotecan	Phase 2	March 2023
NCT03885219	LAPC	Nab-paclitaxel + S-1	Phase 2	April 2022
NCT04089150	BRPC and LAPC	GA or FOLFIRINOX *vs.* GA or FOLFIRINOX + SBRT followed by adjuvant GEMCAP or FOLFIRINOX	Phase 2	August 2023
NCT04481204	Non-metastatic PDAC	Bayesian platform: Gemcitabine, GA, GemCis or FOLFIRINOX 3–6 months ± RT	Phase 2	April 2025
NCT04539808	Non-metastatic PDAC	FOLFIRINOX (switch to GA if progression or toxicity) followed by CRT with capecitabine + losartan	Phase 2	October 2025
NCT04570943	LAPC	Sequential GA and FOLFIRINOX followed by SBRT	Phase 2	October 2026
NCT04986930	LAPC	FOLFIRINOX *vs.* FOLFIRINOX + SBRT	Phase 2	August 2024
NCT02024009	LAPC	GA *vs.* GA followed by CCRT (capecitabine) *vs.* GA followed by CRT (capecitabine) + nelfinavir	Phase 2	August 2020
NCT01827553	LAPC	Induction chemotherapy followed by CRT with gemcitabine *vs.* chemotherapy only (FOLFIRINOX or gemcitabine)	Phase 3	April 2022
NCT01926197	LAPC	FOLFIRINOX *vs.* FOLFIRINOX + SBRT	Phase 3	September 2022
NCT03257033	LAPC	Nab-paclitaxel and gemcitabine + RT followed by IA gemcitabine *vs.* nab-paclitaxel and gemcitabine	Phase 3	September 2023
NCT03941093	LAPC	Pamrevlumab + chemotherapy *vs.* chemotherapy (FOLFIRINOX or gemcitabine + nab-paclitaxel)	Phase 3	December 2023
NCT03983057	BRPC and LAPC	FOLFIRINOX *vs.* FOLFIRINOX + anti-PD1	Phase 3	April 2024
NCT04617821	BRPC and LAPC	Gemcitabine plus nab-paclitaxel *vs.* FOLFIRINOX	Phase 3	September 2023
NCT03899636	LAPC	FOLFIRINOX *vs.* FOLFIRINOX + IRE with Nanoknife	Phase 3	December 2023

LAPC, locally advanced pancreatic cancer; BRPC, borderline resectable pancreatic cancer; FOLFIRINOX, a combination of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; RT, radiation therapy; SBRT, stereotactic body radiation therapy; FOLFOX, a combination of 5-fluorouracil, leucovorin, and oxaliplatin; GEMOX, gemcitabine plus oxaliplatin; GEMCIS, gemcitabine plus cisplatin; GA, gemcitabine plus nab-paclitaxel; GEMCAP, gemcitabine plus capecitabine; CRT, chemoradiation therapy; PDAC, pancreatic ductal adenocarcinoma; IRE, irreversible electroporation; IA, intra-arterial.

in patients with BRPC and LAPC (23,77). Recently, a biomarker study of patients with resectable pancreatic cancer showed that a circulating tumor DNA (ctDNA) detected at baseline and postoperative peripheral blood samples were associated with poor survival outcomes, and all patients with postoperative ctDNA positive results had

recurrence (78). The serial measurement of ctDNA during treatment along with tumor molecular profiling using next-generation sequencing techniques may help determine the novel biomarkers for LAPC. Although the use of targeted agents and immunotherapies is suggested for the treatment of patients with LAPC, only a few options are available, including pembrolizumab and olaparib, with minimal efficacy for patients with PDAC (79,80).

In conclusion, modern-era chemotherapeutics, including FOLFIRINOX and GA, and additional CRT have markedly improved the clinical outcomes of BRPC and LAPC patients. Particularly, the number of LAPC patients receiving conversion surgery which was provided for only a small proportion of patients is growing along with the application of FOLFIRINOX and GA.

However, there are limitations in the current practice as large randomized trials aimed at identifying the best treatment options for this patient group are ongoing. Hence, future clinical trials will improve the management of patients with LAPC. Molecular and immunologic biomarker studies are also warranted to determine whether precision medicine should be applied.

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