REVIEW ARTICLE

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Essential updates 2019/2020: Multimodal treatment of localized pancreatic adenocarcinoma: Current topics and updates in survival outcomes and prognostic factors

Hiroyuki Kato [iD] | Akihiko Horiguchi [iD] | Masahiro Ito | Yukio Asano |
Satoshi Arakawa

Department of Gastroenterological Surgery, Bantane Hospital, Fujita Health University School of Medicine, Nagoya, Aichi, Japan

Correspondence
Akihiko Horiguchi, Department of Gastroenterological Surgery, Fujita Health University School of Medicine, Bantane Hospital, Nagoya, Japan.
Email: akihori@fujita-hu.ac.jp

Abstract

Overall survival of patients with localized pancreatic ductal adenocarcinoma (PDAC) is extremely poor. Therefore, the establishment of multimodal treatment strategies is indispensable for PDAC patients because surgical treatment alone could not contribute to the improvement of survival. In this review article, we focus on the current topics and advancement of the treatments for localized PDAC including resectable, borderline resectable, and locally advanced PDAC in accordance with the articles mainly published from 2019 to 2020. Reviewing the articles, the recent progress of multimodal treatments notably improves the prognosis of patients with localized PDAC. For resectable PDAC, neoadjuvant chemo or chemoradiation therapy, rather than upfront surgery, plays a key role, especially in patients with a large tumor, poor performance status, high tumor marker levels, peripancreatic lymph nodes metastasis, or neural invasion suspected on preoperative imaging. For borderline resectable PDAC, neoadjuvant treatments followed by surgery is a desirable approach, and maintenance of immunonutritional status during the treatments are also important. For locally advanced disease, conversion surgery has a central role in improving a survival outcome; however, its indication should be standardized.

KEYWORDS
conversion surgery, localized pancreatic adenocarcinoma, neoadjuvant treatment

1 | INTRODUCTION

Overall survival (OS) in patients with pancreatic ductal adenocarcinoma (PDAC) is extremely unfavorable compared to other gastrointestinal cancers.[1] PDAC has been regarded as a systemic disease at the time of diagnosis since some patients already have occult metastasis before the initiation of treatment.[2,3] Therefore, multimodal treatment strategies for PDAC patients are essential at the time of diagnosis because surgical treatment alone does not contribute to improved survival. These strategies have recently improved the poor prognosis of patients with PDAC due to significant advances in anti-cancer therapies and surgical techniques.[4–6] In this review article, we focus on recently published treatments and guidelines for localized PDAC including resectable, borderline resectable, and locally advanced disease, and further discuss the outcomes of advanced surgical techniques, such as portal vein (PV) resection, resection of the celiac axis (CA) and other major arteries, superior mesenteric artery (SMA) nerve plexus dissection, as well as extent of lymphadenectomy.

2 | TREATMENT GUIDELINES FOR LOCALIZED PDAC AND THEIR EVOLUTION

Surgical resection is the only potentially curative treatment for localized PDAC; however, only 10%-20% of patients have curatively resectable disease after careful staging before treatment is initiated.[7] According to the Japan Pancreas Society, which hosts a nationwide pancreatic cancer registry, historical 5-year survival (5YS) rates for PDAC patients undergoing pancreatectomy have been miserable: 10.9% from 1981 to 1990, 13.7% from 1991 to 2000, and 18.8% from 2000 to 2007.[8] To improve this disastrous prognosis and standardize treatment strategy, various PDAC treatment guidelines have been proposed by the National Comprehensive Cancer Network (NCCN),[9] European Society for Medical Oncology (ESMO),[7] International Study Group of Pancreatic Surgery (ISGPS),[10] American Society of Clinical Oncology (ASCO),[11] Japan Pancreas Society (JPS),[12] and others.[13–15] Among these guidelines, those from the NCCN have been most accepted by clinicians and surgeons who treat PDAC around the world. The difference between the 2017[16] and 2020 version 1[17] NCCN guidelines and comparison with the updated JPS 2019 guidelines are summarized in Table 1.

In terms of resectability criteria, tumor contact with the first jejunal SMA branch or most proximal draining jejunal branch into the superior mesenteric vein (SMV) was regarded as unresectable in the NCCN 2017 guidelines; however, in NCCN 2020 version 1, these descriptions were removed and the importance of frozen section biopsy of the pancreatic neck and bile duct at the time of surgery was added into the surgical technique section.

Regarding adjuvant chemotherapy after surgical resection, modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) is recommended as the preferred adjuvant chemotherapy in fit patients (Eastern Cooperative Oncology Group [ECOG] performance status [PS] 0–1) who underwent R0 or R1 resection. This recommendation is based on a randomized control study (RCT) conducted by Conroy et al[18] that showed a median OS of 54.4 months in the modified FOLFIRINOX group and 35.0 months in the gemcitabine group (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.48-0.86; $P = .003$). These are the most favorable OS data reported for adjuvant treatment of resected PDAC to date. In frail patients (PS 2–3), the combination of gemcitabine and capecitabine is an alternative option to modified FOLFIRINOX.

The NCCN 2020 version 1 guidelines highly recommend tumor/somatic gene profiling for patients with locally advanced or metastatic disease who are candidates for anti-cancer therapy to identify various fusion genes (ALK, NRG1, NTRK, ROS1), mutations (BRAF, BRCA1/2, HER2, KRAS, PALB2), mismatch repair (MMR) deficiency, and high microsatellite instability (MSI-H) via immunohistochemistry (IHC), polymerase chain reaction (PCR), or next-generation sequencing (NGS). Although testing of tumor tissue is preferred, cell-free DNA testing can be considered if tumor testing is not feasible. Based on the profiling results, immune check point inhibitors or other specific regimens can be used alternatively or even as first-line therapy for frail patients.

3 | RESECTABILITY CRITERIA AND CORRESPONDING OPTIMAL TREATMENT STRATEGIES

Various criteria defining resectability status of PDAC have been proposed. PDAC without distant metastasis has been categorized as resectable, borderline resectable, and locally advanced, which was previously referred to as unresectable or initially unresectable.[16,19] Resectability status depends on the degree of soft tissue contact with major adjacent arteries and veins such as the SMA, common hepatic artery (CHA), CA, PV, and SMV. In 2017, the International Association of Pancreatology (IAP) acknowledged that resectability should not be defined based on these anatomic factors, but rather on biological and conditional dimensions.[20] The main biological factor considered is serum carbohydrate antigen (CA) 19-9 level (cutoff, 500 units/mL). The main conditional factor is PS.[1-4] In this section, we explain recent updates in treatment options, prognosis, and indicators influencing treatment outcomes according to resectability status.

3.1 | Recent updates in treatment, survival, and prognostic factors for resectable PDAC

According to NCCN 2019,[21] resectable PDAC (RPDAC) is defined as a tumor without adjacent arterial (CA, SMA, and CHA) contact and without venous (SMV or PV) contact or ≤180° contact without vein contour irregularity. For the treatment of RPDAC, surgical resection without neoadjuvant chemotherapy (upfront surgery) is planned unless there are high-risk features including highly elevated CA 19-9 level, large primary tumor, large regional lymph nodes, excessive weight loss, and extreme pain. If these high-risk features are not present, neoadjuvant treatment is only recommended in the context of a clinical trial (Table 1). In the meantime, the results of the PREP-02/JSAP-05 randomized controlled trial (RCT) comparing neoadjuvant chemotherapy with gemcitabine and S1 (NAC-GS) to upfront surgery in patients with PDAC undergoing planned resection have been reported.[22] From January 2013 to January 2016, 362 eligible patients were enrolled in 57 Japanese centers (NAC-GS, 182; upfront surgery, 180). Median OS was 36.7 months in the NAC-GS group and 26.6 months in the upfront surgery group (HR 0.72, $P = .015$), demonstrating a significant survival benefit for NAC-GS. Therefore, the JPS clinical practice guidelines for pancreatic cancer suggest NAC-GS as neoadjuvant treatment for RPDAC. Nevertheless, the use of NAC-GS for tumors without high-risk features remains under discussion.

Regarding prognosis of RPDAC, reported survival rates used to be extremely poor compared to other gastrointestinal cancers. According to the pancreatic cancer registry of Japan, from 1981 to

TABLE 1 Differences between the 2017 and 2020 version 1 National Comprehensive Cancer Network guidelines and comparison with 2019 Japanese Pancreatic Society guidelines

Categories	Points of difference	NCCN 2017	NCCN 2020 version 1	Guideline 2019 from JPS
Resectability status	Revision of Terms	"Unresectable"	"Locally advanced"	UR-LA
	Definition of LAPC (arterial factor)	"Solid tumor contact with the first jejunal SMA branch" was categorized as unresectable	Removed	There is no description regarding tumor contact with the first jejunal SMA branch and most proximal draining jejunal branch into the SMV. Resectability criteria are defined according to the JPS 7th edition
	Definition of LAPC located in head/process (venous factor)	"Solid tumor contact with most proximal draining jejunal branch into SMV" was categorized as unresectable	Removed	
	Definition of LAPC located in body and tail (venous factor)	Tumor with "Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) " was categorized as unresectable	Removed	
Neoadjuvant treatment	Resectable PDAC	There is limited evidence to recommend specific neoadjuvant regimens. Only recommended in a clinical trial unless there are high-risk features (i.e. very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain)	Same	Combined therapy for Gemcitabine and S1 are suggested
	Borderline resectable PDAC	There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation	Same	There is limited evidence to recommend specific neoadjuvant regimens
	LAPC	1) FOLFIRINOX ± subsequent chemoradiation 2) Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation 3) Gemcitabine+cisplatin (≥2–6 cycles) followed by chemoradiation (reserved for patients with BRCA1/BRCA2 or other DNA repair mutations)	1) FOLFIRINOX or mFOLFIRINOX ± subsequent chemoradiation 2) Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation 3) Only for known BRCA1/2 or PALB2 mutations: FOLFIRINOX or mFOLFIRINOX or Gemcitabine + cisplatin (≥2–6 cycles) ± subsequent chemoradiation	Gemcitabine alone, S1 alone, FORFIRINOX and Gemcitabine + albumin-bound paclitaxel
Surgical technique	Consideration of frozen section analysis of the pancreatic neck and bile duct	No description	To avoid cautery artifact that may confound the frozen section, assess the pancreatic neck and bile duct at time of surgery by frozen section approximately 5 mm from the transection margin. If tumor is located within 5 mm of margins, consider further excision of the pancreas and bile duct to ensure at least 5 mm of clearance.	No description

(Continues)

TABLE 1 (Continued)

Categories	Points of difference	NCCN 2017	NCCN 2020 version 1	Guideline 2019 from JPS
	Management of neck lesions	No description	Cancers in the pancreas neck are located anterior to the superior mesenteric vessels and portal vein. Depending on the extent of involvement, a pancreaticoduodenectomy extending to the left of the SMV (extended pancreaticoduodenectomy), a distal pancreatectomy extending to the right of the SMV (extended distal pancreatectomy), or a total pancreatectomy may be required to obtain an R0 resection.	No description
Adjuvant therapy	Recommendation of regimen after resection	First-line therapy Gemcitabine (category 1) 5-FU/leucovorin (category 1) Gemcitabine + capecitabine (category 1)	Modified FOLFIRINOX for fit patients Gemcitabine and capecitabine as alternative	S1 monotherapy

Abbreviations: FORFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; JPS, Japanese Pancreatic Society; LAPC, locally advanced pancreatic cancer; NCCN, national comprehensive cancer network; PDAC, pancreatic ductal adenocarcinoma; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; UR-LA, unresectable-locally advanced.

2007, 5YS was only 30.2% in Union for International Cancer Control (UICC) 7th edition stage IIA patients and 13.3% in stage IIB patients.[8] Moreover, Strobel et al reported that median survival time (MST) in 937 patients who underwent upfront surgery was 22.1 months and the actual 5YS was 17.0%; however, patients with pN0R0 disease had a 38.2% 5YS and patients with exclusively favorable factors had >50% 5YS.[23] Therefore, indications for surgical resection were considered to be further restricted by tumor markers, preoperative imaging, and patient background. Thus, researchers conducted survival analyses and found additional prognostic factors in RPDAC patients who underwent upfront surgery that might contribute to showing the legitimacy of upfront surgery and identifying patients who benefit from resection.[23–26]

We searched for relevant articles regarding a prognostic factor of RPDAC patients with upfront surgery in the PubMed database and summarized the retrieved articles published from January 2019 to present in which patient prognosis (MST or 5YS) was reported.[22,24,25,27–36] This summary is shown in Table 2. Among these articles, Sugimoto et al[27] retrospectively analyzed 192 anatomically resectable PDAC patients who underwent upfront surgery and found that MST in patients with and without nerve plexus invasion on preoperative computed tomography (CT) was 19.7 and 38.5 months, respectively. Nakamura et al[24] analyzed 153 RPDAC patients who underwent upfront surgery and found an MST of 26.4 months overall. They also reported that pancreatic head tumor (odds ratio [OR] 1.97, P = .015), preoperative CA 19-9 level >100 U/mL (OR 1.92, P = .0009), and tumor size >20 mm (OR 1.50, P = .038) were significant independent predictive preoperative risk factors for unfavorable prognosis; 5YS was 60.7%, 21.5%, and 0% in patients

with zero, one or two, and three risk factors, respectively. Kim et al[28] analyzed 139 RPDAC patients who underwent upfront surgery and found that MST in patients with CA 19-9 level <93 and ≥93 U/mL were 28 and 21 months, respectively. Regarding conditional factors of RPDAC, Kato et al[37] retrospectively reviewed 157 RPDAC patients who underwent upfront surgery and reported that MST of the overall cohort was 40 months; PS ≥2 (HR 2.47, P = .014) and lymph node metastasis suspected by imaging (HR 1.55, P = .003) were significant independent predictors of poor prognosis. Kawai et al[29] retrospectively analyzed 102 patients with resectable body/tail PDAC and found that MST among resectable, resectable with SV (splenic vein) invasion, and resectable with SA (splenic artery) invasion was 80.6, 23.4, and 15.1 months, respectively, suggesting that SA invasion is a notably unfavorable prognostic factor.

Even in RPDAC, surgeons may encounter cancer-positive abdominal washing cytology. Tsuchida et al[30] analyzed 1970 patients who underwent upfront surgery using data from the Japan Pancreatic Cancer Registry and showed that when stratified by stage of disease, MST in patients with cancer-positive cytology (T1, 16.0 months; T2, 18.0 months; and T3, 14.7 months) was significantly less favorable compared to patients with negative cytology (T1, 56.1 months; T2, 28.3 months; and T3, 21.3 months). Taken together, these high-risk features (elevated CA 19-9 level, PS ≥2, large tumor size, suspected peripancreatic lymph node metastasis, peripancreatic neural invasion, body/tail tumor invading the splenic vessels [Figure 1], and cancer-positive abdominal washing cytology) are essential to exclude the RPDAC patients with occult metastasis, as surgical resection itself might interfere with systemic chemo- or chemoradiotherapy, resulting in a

TABLE 2 Current update of the survival outcomes and significant prognostic factor of RPDAC (January 2019 to October 2020)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST and/or 5YS)
Sugimoto M et al[27]	2019	Japan	2006-2015	Retrospective study	Upfront surgery	192 anatomically RPDAC	Extrapancreatic nerve plexus invasion on CT (NPF)	MST of patients with and without nerve plexus invasion on CT: 19.7 vs 38.5 months
Nakamura T et al[24]	2020	Japan	2001-2015	Retrospective study	Upfront surgery	153 RPDAC patients	Pancreatic head tumor, preoperative CA19-9 > 100 U/mL and tumor size > 20 mm (NPF)	MST of total cases: 26.4 months
Kim JK et al[28]	2020	USA	2007-2015	Retrospective study	Upfront surgery	139 RPDAC patients	CA19-9 > 93U/ml (NPF)	MST for CA 19-9 < 93 and ≥93: 28 months vs 21 months, respectively.
Kato Y et al[25]	2019	Japan	2001-2017	Retrospective study	Upfront surgery	157 RPDAC patients	Performance status ≥2, lymph node metastasis on imaging (NPF)	MST: 40months in total cases
Unno M et al[22]	2019	Japan	2013-2016	Randomised control study	NAC-GS or upfront surgery	182 to NAC-GS and 182 to upfront surgery	NAC-GS (PPF)	MST of NAC-GS group and upfront surgery group: 36.7 months vs 26.6 months
Kawai M et al[29]	2020	Japan	2003-2018	Retrospective study	Upfront surgery	102 RPDAC of pancreatic body/ tail	Splenic artery invasion (NPF)	MST of RPDAC, RPDAC with SV invasion and RPDAC with SA: 80.6, 23.4, and 15.1 months
Tsuchida H et al[30]	2019	Japan	2008-2012	Retrospetive study using the data from the Pancreatic Cancer Registry in Japan	Upfront surgery	1,970 patients who underwent tumor resection	Cancer positive in peritoneal washing cytology (NPF)	MST of T1 with cytology negative, T2 with cytology negative and T3 with cytology negative: 56.1, 28.3, and 21.3 months
Takeuchi T et al.[31]	2019	Japan	2005-2015	Retrospective study	NCRT (Gem vs GS) followed by resection	36 RPDAC who received NCRT-Gem (n = 15) and NCRT-GS (n = 21) followed by resection	No description	5YS of GS-CRT group: 55.6% 5YS of Gem-CRT group: 47.6%
Baugh KA et al[33]	2019	USA	2004-2014	Retrospective study using NCDB	Upfront surgery	4404 patients with clinical stage I PDAC treated with upfront resection	True stage I (PPF)	5YS of true stage I disease: 42.9% 5YS of disease clinically understaged: 16.6%

(Continues)

TABLE 2 (Continued)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST and/or 5YS)
Vega EA et al[34]	2020	USA	2010-2016	Retrospective study using NCDB	Surgical resection for RPDAC (stage IA and IB UICC 7th)	4785 PDAC patients (Stage1A: n = 688, Stage1B: n = 4197)	preoperative chemotherapy (PPF)	MST: 26.6 months in total cases MST: 20.0months in no chemotherapy MST: 32.9 months in both pre and postoperative chemotherapy
Takahashi H et al[35]	2020	Japan	2002-2017	Retrospective study	gemcitabine-based CRT followed by surgery	133 RPDAC patients with CA19-9 < 120	normalization of CA19-9 after NCRT (PPF)	5YS: 64% in the 133 RPDAC patients with CA19-9 < 120, 5-ys: 55% in the 56 RPDAC patients with CA19-9 > 120, and its normalization after NCRT, 5YS: 25% in the 75 RPDAC patients with CA19-9 is >120, and no normalization after NCRT
Chawla A et al[36]	2020	USA	2004-2015	Retrospective study using NCDB	Upfront surgery	7729 RPDAC with upfront resection	NA	MST: 26.5 months

Abbreviations: 5-ys, 5-year survival; CA19-9, carbohydrate antigen 19-9; Gem, gemcitabine; GS, gemcitabine+S1; NCDB, National Cancer Data Base; NCRT, neoadjuvant chemoradiotherapy; NPF, negative prognostic factor; OS, overall survival; PPF, positive prognostic factor; RPDAC, resectable pancreatic ductal adenocarcinoma; SA, splenic artery; SV, splenic vein; USA, United States of America.

poor surgical outcome. However, most of these articles regarding RPDAC and its treatment were retrospective studies; future prospective studies are needed to reveal the true prognosis of patients with RPDAC.

3.2 | Recent updates in treatment, survival, and prognostic factors for borderline resectable PDAC

In 2001, Mehta et al[38] reported treatment outcomes in 15 PDAC patients with tumors involving the PV, SMV, or a major artery and referred to this subset of tumors as marginally resectable. Thereafter, the NCCN adopted the term borderline resectable PDAC (BRPDAC) in 2006 to describe localized PDAC and has since modified the concept.[9,16,39–41] In NCCN 2020,[17] BRPDAC of the pancreatic head was defined as: (a) solid tumor contact with the CHA without extension to the CA or hepatic artery bifurcation that allows for safe and complete resection and reconstruction; (b) solid tumor contact with the SMA of ≤180°; (c) solid tumor contact with variant arterial anatomy including an accessory right hepatic artery (RHA), replaced RHA, etc.; (d) solid tumor contact with the SMV or PV of >180°, contact of ≤180° with vein contour irregularity or thrombosis but with suitable vessel proximal and distal to the site of involvement that allows for safe and complete resection and vein reconstruction; and (e) solid tumor contact with the inferior vena cava (IVC). BRPDAC of the pancreatic body/tail was also defined as (a) solid tumor contact with the CA of ≤180°; (b) solid tumor contact with the CA of >180° without involvement of the aorta and with an intact and uninvolved gastroduodenal artery; and (c) unreconstructible SMV/PV due to tumor involvement or occlusion (which can be due to tumor or bland thrombus).

The actual prognosis of BRPDAC had been poor until recently. Previously, Kato et al[42] analyzed 624 BRPDAC patients from 2002 to 2007 using data from the Japanese Society of Pancreatic Surgery (JSPS) and reported that overall 3YS, 5YS, and MST were 16.1%, 9.9%, and 12.6 months, respectively. The respective outcomes were 22.8%, 12.5%, and 13.6 months in resected patients, and 4.4%, 0%, and 8.8 months in unresected patients. However, advances in multimodal treatment have provided improvement. In 2019, Nagakawa et al[43] analyzed 884 patients with BRPDAC from 2011 to 2013 based on data from the JSPS and found that MST in patients treated with neoadjuvant therapy followed by resection was significantly better than that in patients who underwent upfront surgery (29.8 vs 21.5 months, $P = .001$). These MSTs are considerably better than those reported by Kato et al.[42] Neoadjuvant chemo- or chemoradiotherapy has been widely accepted to improve survival in BRPDAC patients and the NCCN guidelines have been modified accordingly.

Despite this wide acceptance, the supporting evidence remains limited. In 2018, a prospective RCT showed a survival benefit for neoadjuvant chemoradiotherapy (NCRT) compared to upfront surgery. In intention-to-treat analysis, the 1YS, 2YS, and MST in 27 BRPDAC patients treated with gemcitabine-based NCRT (74.1%, 40.7%, and 21 months, respectively) were significantly higher than those in the upfront surgery group (47.8%, 26.1%, and 12 months, respectively).[44] In other BRPDAC studies, prolonged survival was associated with neoadjuvant treatment (NAT), however, most of these were retrospective in nature.[36,43,45–48] The one conducted by Kurahara et al[46] reported favorable prognosis (MST, 53.7 months) in BRPDAC patients who could complete NAT using gemcitabine or S-1 based chemo or chemoradiotherapy followed by surgical resection. Medrano et al[45] observed an MST of 45 months in 121 BRPDAC patients who received FOLFIRINOX induction treatment followed by surgical resection. Chawla et al[36] compared patients who received NAT (n = 890) with those who underwent upfront surgery followed by adjuvant treatment (n = 1092) using data from
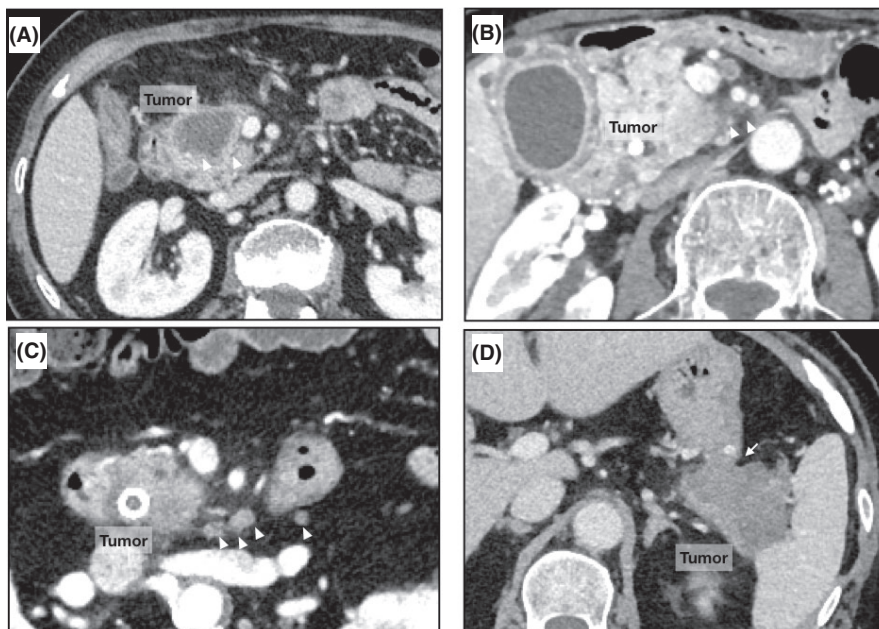
FIGURE 1 Typical preoperative CT images of resectable PDAC with high-risk futures. A, The 34-mm large tumor located in the pancreatic head (white arrows). B, The 20-mm tumor located in the uncinate process with suspected invasion into the SMA neural plexus (white arrow heads). C, 18-mm tumor located in pancreatic head with peripancreatic lymnodes swollen. D, The 40-mm pancreatic tail tumor with peripheral splenic artery and gastric invasion (white arrow)

the National Cancer Database of the United States and found that MST was significantly superior in the NAT group compared to the upfront surgery/adjuvant treatment group (25.7 vs 19.6 months, $P < .0001$). Takeda et al[47] analyzed prognosis in 108 BRPDAC patients who received NAC followed by resection (initial regimen, nab-paclitaxel/gemcitabine in 106 and gemcitabine alone in two); MST in patients with tumors located in the body/tail and head were 33.2 and 31.1 months, respectively. Therefore, NAT for patients with BRPDAC appears promising, but further prospective studies are needed.

In addition to being prognostic factors, biological and conditional markers are considered crucial in determining BRPDAC surgical outcomes. CA19-9 level during preoperative treatment has been shown to predict postoperative outcomes.[35,49–53] Barnes et al[54] analyzed 185 BPRDAC patients who received NCRT (FOLFIRINOX or gemcitabine with nab-paclitaxel) and reported an MST of 46 months in patients whom normalization of CA19-9 level was achieved after the completion of NCRT. Takahashi et al reported 25% and 34% 5YS in 143 anatomical BRPDAC patients and the 94 resected BRPDAC patients. Moreover, when anatomical RPDAC with pre-NCRT CA19-9 level >120 U/mL was defined as biological BRPDAC, prognosis of patients without CA19-9 normalization was obviously worse (32% 5YS; n = 55), being recognized as anatomical BRPDAC in the NCRT strategy.[35]

Several articles focusing on various conditional factors have been recently published.[55–57] There is no doubt that ECOG PS ≥2 is a poor prognostic factor in BRPDAC patients.[20,25,56,58] In addition, Kubo et al analyzed 119 BRPDAC patients who received NCRT and found that MST was significantly longer in patients with post-NCRT neutrophil-to-lymphocyte ratio (NLR) <3 compared to those with post-NCRT NLR >3 (45 vs 22 months, P = .040; HR 2.24).[55] Kawai et al retrospectively examined 67 BRPDAC patients who received NAC followed by pancreatectomy and found an MST of 37.1 months in the patients whose post-neoadjuvant treatment lymphocyte-to-monocyte ratio (LMR) was >3.0 (n = 39); however, in patients whose post-treatment LMR was <3.0 (n = 26), MST was only 14.9 months. Patient prognosis and the various prognostic factors mentioned above are summarized in Table 3. Based on these studies, it appears that the prognosis of BRPDAC has improved due to the efficacy of multimodal treatment, including NAC and NCRT followed by surgery, especially in patients who achieve a good tumor oncological response and maintain immuno-nutritional status.

3.3 | Recent updates in treatment, survival, and prognostic factors for locally advanced pancreatic cancer (initially unresectable PDAC)

In locally advanced pancreatic cancer (LAPC), previously referred to as initially unresectable PDAC, prognosis and surgical outcomes had been extremely poor due to severe major vessel invasion.[59–61] NCCN 2020 version 1 defines LAPC as contact with the SMA >180°

and/or CA >180° in tumors of the pancreatic head/uncinate process, or as contact with the SMA or CA >180° or aortic involvement in tumors of the pancreatic body/tail. In addition, any tumor with an unreconstructible SMV/PV is regarded as LAPC.[9] Since this subset of tumor is considered surgically unresectable due to local involvement of the SMA, CA, and PV, current guidelines recommend multidisciplinary approaches including genetic profiling and MSI, MMR, and germline testing of available tumor tissue.[9]

Guidelines for LAPC patients who respond favorably to neoadjuvant treatment have been adapted to include curative-intent pancreatectomy. Gemenetzis et al[62] reported significantly longer MST in LAPC patients who underwent surgical resection than in those who did not (35.3 vs 16.3 months) and better PS, smaller median tumor size, and lower median CA 19-9 level were recognized as favorable prognostic factors. Surgical resection for LAPC during multimodal treatment is referred to as "conversion surgery" (CS).[63,64] However, the role of CS in LAPC and patients who benefit from it have not been completely addressed. Satoi et al[19] reported significantly favorable OS following initial neoadjuvant treatment, especially in patients who received non-surgical anti-cancer treatment for >240 days, and noted that type of chemotherapy and length of chemo- or chemoradiotherapy were associated with outcome. In addition, from 2019 to 2020, numerous researchers investigated prognoses in patients with LAPC, focusing on biological markers,[65,66] conditional markers,[67] and type of induction chemo- or chemoradiotherapy as prognostic markers,[31,68–71] as well as benefit of surgical resection,[62,72–74] as shown in Table 4. Serum CA19-9 level before surgery and/or induction chemotherapy and its reduction are considered essential for predicting prognosis in patients with LAPC, similar to patients with BRPDAC and RPDAC.[63,66,74,75] Among these articles, the review article by Satoi et al[63] proposed the algorithm for CS, and CS could be indicated after staging laparoscopy when CA19-9 level was less than 100U/mL after the multimodal therapies. In addition, serum carcinoembryonic antigen (CEA) level is also regarded as a crucial predictor that influences the outcome of CS. Kato et al[65] retrospectively analyzed 72 LAPC patients who underwent CS under the pretext of favorable local tumor control and CA19-9 reduction during NCRT and concluded that elevated CEA level, particularly >7.2 ng/mL, should still be recognized as a sign of systemic disease due to its prediction of poor prognosis. Furthermore, maintenance of patient condition from initiation of induction treatment to surgery is also crucial. Naumann et al[67] reported that loss of subcutaneous fat (SCT) >10% and reduction in skeletal muscle mass >5% during NCRT are significant predictors of worse prognosis in LAPC patients. MST was 24.9 months in patients with <10% loss of SCF, whereas its was 14.4 months in those who lost >10%. Specific induction chemotherapy regimen may be one of the most important prognostic factors for LAPC patients. Murphy et al[68] conducted a phase II study using FOLFIRINOX + losartan + RT followed by surgery and reported an overall MST of 31.4 months in all 49 LAPC patients; in the 34 patients who underwent resection, MST was 33.0 months, an obviously better prognosis. Maggino et al reported that completion of FOLFIRINOX and surgical resection were the most influential

TABLE 3 Updates in survival outcomes and prognostic factors of borderline resectable pancreatic ductal adenocarcinoma (2019 to October 2020)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Nagakawa Y et al[43]	2019	Japan	2011-2013	Retrospective study using data from JSPS	Upfront surgery, NAC and NCRT followed by surgery	884 BRPDAC patients	Neoadjuvant treatment (PPF)	MST of NAT group and upfront surgery group: 25.7 vs 19.0 months
Medrano J et al[45]	2020	France	2011-2018	Retrospective study	FOLFIRINOX induction therapy followed by surgery	121 BRPDAC patients	CA 19-9 < 500 U/mL, no regional lymph node metastasis (PPF)	MST: 45 months in the 121 BRPDAC patients who received FOLFIRINOX induction treatment
Kurahara H et al[46]	2019	Japan	2010-2014	Retrospective study	NAT followed by resection vs upfront surgery followed by adjuvant therapy	BRPDAC with NAT (n = 58) Upfront surgery (n = 107)	NAT followed by resection (PPF)	MST of NAT group: 22.0 months; MST of upfront surgery group: 16.7 months; MST of resection after NAT: 53.7 months
Chawla A et al[36]	2020	USA	2004-2015	Retrospective study using NCDB	NAT followed by resection vs upfront surgery followed by adjuvant therapy	BRPDAC with NAT (n = 890); BRPDAC with adjuvant alone (n = 1092)	NAT (PPF)	MST of NAT: 25.7 months; MST of adjuvant alone: 19.6 months
Takeda T et al[47]	2020	Japan	2015-2019	Retrospective study	NAC followed by resection (initial regimen, nab-paclitaxel/gem in 106 and gem alone in 2)	108 BRPDAC patients	Tumor location	MST of Pbt BRPDAC: 33.2 months; MST of Ph BRPDAC: 31.1 months
Barnes CA et al[54]	2019	USA	2009-2017	Retrospective study	NCRT followed by surgery (FOLFIRINOX or gem with nab-paclitaxel)	185 BRPDAC patients	Completion of the protocol (NCRT followed by surgery), CA19-9 normalization (PPF)	MST: 20 months in total; MST: 31 months in resected patients; MST: 13 months in unresected patients; MST: 46 months in patients with normalization of CA19-9 after completion of NCRT
Anger F et al[52]	2020	Germany and Netherlands	2003-2017	Retrospective study	Upfront surgery	Anatomically BRPDAC (n = 30); biological BRPDAC (n = 62)	CA19-9 > 500U/mL (NPF)	MST: 15 months in anatomically BR; MST: 12 months in biological BR
Takahashi H et al[35]	2020	Japan	2002-2017	Retrospective study	Gem-based NCRT followed by surgery	Anatomically BRPDAC (n = 143 in total and n = 94 with resection)	Initial CA19-9 > 120U/mL (NPF), CA19-9 normalization (PPF)	5YS: 34% in anatomically BRPDAC patients with resection

(Continues)

TABLE 3 (Continued)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Kubo H et al[55]	2020	Japan	2009-2017	Retrospective study	NCRT followed by surgery	119 BRPDAC patients	post-NACRT NLR <3 (PPF)	MST: 22.0 months in post-NCRT NLR > 3 MST: 45.0 months in post-NCRT NLR <3
Javed AA et al[56]	2019	USA	2013-2016	Retrospective study	NAT followed by resection	151 BRPDAC patients	ECOG-performance status	MST: 28.8 months in resected (n = 96) MST: 14.5 months in non-resected (n = 55) Median disease-free survival: 13.4 months in 96 resected cases
Kawai M et al[56]	2020	Japan	2010-2016	Retrospective study	Neoadjuvant treatment followed by resection or upfront surgery	67 BRPDAC patients with NAC followed by pancreatectomy	post-neoadjuvant LMR > 3.0 (PPF)	MST: 31.7 months in 39 BRPDAC patients whose post-neoadjuvant LMR was >3.0; MST: 14.9 months in 26 patients whose LMR was <3.0
Imamura T et al[48]	2020	Japan	2012-2018	Retrospective study	NAT followed by surgery	63 BRPDAC patients	Abutment to the J3A or MCA (NPF)	5YS: 21.5% in with abutment of the SMA branches; 5YS: 82.3% in without abutment

5YS, 5-year survival; BRPDAC, borderline resectable pancreatic ductal adenocarcinoma; CA19-9, carbohydrate antigen 19-9; FOLFIRINOX, 5-fluorouracil+leucovorin+irinotecan+oxaliplatin; Gem, gemcitabine; GS, gencitabine+S1; J3A, jejunal artery (3rd branch); JSPS, Japanese Society of Pancreatic Surgery; LMR, lymphocyte-to-monocyte ratio; MCA, middle colic artery; MST, median survival time; NAC, neoadjuvant chemotherapy; NAT, neoadjuvant therapy; NCDB, National Cancer Database; NCRT, neoadjuvant chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; NPF, negative prognostic factor; OS, overall survival; PPF, positive prognostic factor; SA, splenic artery; SMA, superior mesenteric artery; SV, splenic vein; USA, United States of America.

TABLE 4 Current update of the survival outcomes and significant prognostic factor of LAPC (January 2019 to October 2020)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Kato H et al[65]	2020	Japan	2005-2017	Retrospective study	NCRT followed by surgery	72 LAPC who underwent conversion surgery	Preoperative CEA > 7.2 ng/ml (NPF)	MST after surgery: 24.0 months (CEA < 7.2) MST after surgery: 8.0 months (CEA ≥ 7.2)
Gemenetzis G et al[62]	2019	USA	2013-2017	Retrospective study	NCRT followed by resection	415 LAPC patients	Surgical resection (PPF)	MST: 35.3 months (resected) MST: 16.3 months (non-resected) P < 0.001
Takeuchi T et al[31]	2019	Japan	2008-2012	Retrospective study	G-CRT or GS-CRT followed by resection	41 LAPC patients	GS-CRT (PPF)	MST after initial treatment: 36.0 months (GS-CRT) MST after initial treatment: 18.1 months (G-CRT)
Yoo C et al[72]	2019	Republic of Korea	2005-2017	Retrospective study	CS after NAC or upfront surgery	70 LAPC patients	CS after NAC (PPF)	MST: 26.6months (CS after NAC) MST: 17.1months (Upfront surgery), P = 0.001
Murphy JE et al[68]	2019	USA	2013-2018	PhaseII study	FORFIRINOX + losartan + RT followed by surgery	49 LAPC patients	Total neoadjuvant therapy with FOLFIRINOX, losartan, (PPF)	MST: 31.4 months in overall patients MST: 33.0 months in 34 patients with resection
Rangelova E et al[73]	2019	Sweden	2010-2017	Retrospective study	FORFIRINOX followed by surgery	132 LAPC patients	Surgical resection (PPF)	MST: 21.8 months
Byun Y et al[69]	2019	Republic of Korea	2011-2017	Retrospective study	FORFIRINOX	135 LAPC patients	Surgical resection (PPF)	MST: 21.0 months (in total) MST: not applicable [19] MST: 19.0 months [115]
Heger U et al[66]	2019	Germany	2001-2017	Retrospective study	FORFIRINOX or GEM followed by surgery	235 LAPC patients	CA19-9 reduction (<91.8U/ml) (PPF)	MST: 23.0 months in 165 resected patients
Klaiber U et al[74]	2019	Germany	2006-2017	Retrospective study	FORFIRINOX followed by surgery	280 initially unresectable PDAC patients with resection	preoperative CA 19–9 levels, lymph node involvement, and vascular involvement (NPF)	MST: 19.0 months in 280 resected patients
Naumann P et al[67]	2019	Germany	No description	Retrospective study	NCRT followed by surgery	141 LAPC patients	10% loss of subcutaneous fat, 5% reduction in skeletal muscle area (NPF)	MST: 24.0 months in 33 resected patients

(Continues)

prognostic factors, with MST reaching 41.8 months in 33 LAPC patients after receiving FOLFIRINOX and resection. Taken together, these updates suggest that the effectiveness of FOLFIRINOX is promising for not only borderline resectable and RPDAC, but also LAPC. Moreover, CS is considered to be indicated after the adequate continuation of multimodal treatments (>240 days at least) in the following situation: (a) CA19-9 < 100 u/mL and CEA < 7 ng/mL, (b) PS:0 or 1, (c) no deterioration of nutritional status, (d) favorable tumor response for treatment based on the response evaluation criteria in solid tumors (RECIST): partial response or stable disease.

4 | ADVANCES IN SURGICAL PROCEDURES

The major obstacle to R0 resection of PDAC is the proximity of adjacent major blood vessels such as the PV, SMA, CHA, and CA. Combined resection of these vessels, particularly the SMA, CHA, and CA, is considered challenging and vessel reconstructability depends on the skill of the individual surgeon. In this section, we focus on updates in advanced surgical procedures for localized PDAC that aim to achieve R0 resection and prolong patient survival.

4.1 | PV resection

The feasibility of en bloc PV resection (PVR) and reconstruction during curative-intent pancreatoduodenectomy (PD) has been discussed for more than 3 decades.[76–81] A recent review from France concluded that PVR is recommended if possible in the presence of limited lateral or circumferential involvement without venous occlusion and in the absence of arterial contact with the CA and SMA.[82] Moreover, neoadjuvant treatment has been recommended in cases of planned PVR since it improves the rate of R0 resection and survival. Since pathological tumor invasion of the PV has been recognized as an indicator of dismal prognosis,[83] PVR could play an important role in achieving radical resection in PDAC patients with true PV invasion. Kishi et al[84] suggested that PVR is required only when the tumor is in clear contact with the PV and cannot be detached during surgery. In patients without pathological PV invasion, they found that the rate of R0 resection (66% vs 73%, P = .337) and MST (32.4 vs 32.1 months, P = .780) were not significantly different between 64 PDAC patients who underwent PVR and 64 matched patients who did not. However, Teramura et al[85] reported that accurately determining PV invasion is difficult when based only on morphological features visualized on preoperative CT. Oba et al[86] compared en bloc resection of the soft tissue around the confluence of the PV and SV and the right half of the SMA plexus with combined standard PD and PVR and found an improved rate of R0 resection (80% vs 66.1%, P = 0.014) and MST (32 vs 21 months, P = .004) in the former, suggesting its clinical feasibility. Furthermore, neoadjuvant treatment may change any tumor contact with the PV because of its anti-cancer effect. Josseanchiun et al[87] retrospectively analyzed 84

TABLE 4 (Continued)

Author	Year	Country	Type of study	Patient collection	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Maggino L et al[70]	2019	Italy	Retrospective study	2013-2015	NAC or NCRT followed by surgery	365 LAPC patients	Chemotherapy completion, FORFIRINOX and surgical resection (PPF)	MST: 41.8 months in 33 resected LAPC patients
Napolitano F et al[71]	2019	Italy	Retrospective study	2014-2019	FORFIRINOX or Gemcitabine NabPaclitaxel	59 LAPC patients	Surgical resection (PPF)	MST: 96 weeks in FORFIRINOX group MST: 62.6 weeks in Gem + NabPaclitaxel group

Abbreviations: CA19-9, carbohydrate antigen 19-9; CS, conversion surgery; FORFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; G-CRT, gemcitabine-based chemoradiation therapy; GEM, gemcitabine; GS-CRT, gemcitabine plus S1-based CRT; LAPC, locally advanced pancreatic cancer; MST, median survival time; NAC, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; NPF, negative prognostic factor; PPF, positive prognostic factor; RT, radiation therapy; USA, United States of America.

PDAC patients who underwent NCRT followed by pancreatectomy with PVR and showed that patients with a PV patency ratio >0.6 (n = 45) had a significantly lower incidence of pathological PV invasion, better response to CRT, and improved rates of R0 resection and survival (3YS, 65%; 5YS, 60%). In their study, radical regional PD with PVR was also employed. Surgical outcome and prognosis of patients with PVR are summarized in Table 5.[80,81,84,86–89] Based on these updates, the combination of NCRT and radical regional PD with PVR might increase the ability to achieve a more radical resection and result in prolonged survival; however, future prospective studies are needed to determine which patients benefit from PVR.

4.2 | Combined arterial resection

Radical pancreatectomy with arterial resection (AR) in localized PDAC remains controversial. Even though this operation is not recommended as a standard procedure, complete tumor removal achieved via AR may provide the only opportunity for long-term survival in selected patients. Sonohara et al[90] retrospectively analyzed 44 PDAC patients who underwent AR involving the HA (21 patients, 48%), CA (12 patients, 27%), and SMA (four patients, 9%) and found median recurrence-free survival (RFS) and OS times of 7.4 and 11.0 months, respectively. Furthermore, considering advancements in surgical techniques and multimodal therapy with newly developed preoperative regimens, they analyzed a subgroup of 22 patients from 2010 and found improved median RFS and OS times of 19.0 and 60.0 months, respectively. Yang et al[91] analyzed outcomes in 14 PDAC patients who underwent pancreatectomy with AR (PD, 11 patients; total pancreatectomy, three patients) and reported an MST of 30 months. In 2020, Bachellier et al[92] reported a study assessing the safety and outcomes of the largest cohort of pancreatectomy with AR for localized PDAC (n = 118), showing that the overall mortality and morbidity were 5.1% and 41.5%, respectively, and the median overall survival after resection was 13.7 months after surgery. Moreover, they suggested that R0 resection and the absence of venous invasion are favorable predictors for long-term outcomes .

Nevertheless, in a retrospective review, Oba et al[93] reported that operative mortality rates after AR for PDAC range from 0% to 13%, with morbidity rates ranging between 9.8% and 54%. Therefore, pancreatectomy with AR should be performed at high-volume centers to reduce morbidity and mortality.

Surgical outcome and prognosis of patients with AR are summarized in Table 5. According to these articles, the results of AR might be acceptable in terms of survival and postoperative mortality, provided the procedure is performed in a high-volume center. However, further study is warranted.

4.3 | Other advanced surgical procedures

Several other surgical procedures may contribute to improved survival in patients with localized PDAC. The mesenteric approach is an artery-first approach during PD reported by Nakao et al[94,95] that aims to achieve radical resection of the tumor and connective tissue surrounding the SMV and SMA. In this procedure, the approach from the infracolic mesenterium to the mesenteric root is commonly employed, and Kocher's maneuver is performed last, just before retrieval of the specimen. This procedure is based on the philosophy that a non-touching isolation technique might avoid intraoperative spread of cancer cells and potentiate the R0 resection rate by completely dissecting the peripancreatic tissues such as the SMA plexus and regional lymph nodes. Hirono et al[96] reported a low incidence of local recurrence and a significant survival advantage in R- and BRPDAC patients who underwent PD using the mesenteric approach compared to standard PD. Currently, a multicenter RCT (MAPLE-PD) to compare surgical outcomes between the mesenteric and conventional approaches is underway.[97]

Distal pancreatectomy with CA resection (DP-CAR), also referred to as the "modified Appleby" procedure, is often indicated for advanced pancreatic body/tail tumors.[98,99] This technique was originally adapted for advanced gastric cancer, but also offers the possibility for radical removal of tumors located in the body/tail of the pancreas that involve the CA or CHA. Recent reports have shown that DP-CAR for PDAC is relatively safe and effective, with reported mortality rates ranging between 0% and 14% and MST ranging from 16 to 35 months.[100–104] The most recent large multi-institutional retrospective study (n = 194) reported an acceptable MST of 19.0 months and 9.5% mortality at 90 days.[105] Moreover, 90-day mortality was significantly lower in patients treated at high-volume centers.

Dissection of the SMA nerve plexus to enhance operative curability for localized PDAC is an important topic,[106–108] as it seems to be necessary for complete clearance of tumor invading the SMA nerve plexus; however, it often induces refractory postoperative diarrhea, which interferes with adjuvant treatment. However, Kondo et al[109] reported the utility of PD with circumferential dissection of the SMA lymph nodes and complete preservation of the SMA plexus in preventing severe postoperative diarrhea. Nagakawa et al[110] reported the superiority of PD based on the nervous and fibrous tissue (NFT) structures around the SMA, compared to simple hemi-SMA nerve plexus dissection, as evidenced by improved MST (49.6 vs 23.6 months, P = .01) and rate of R0 (93.6% vs 65.0%, P < .01). Meanwhile, in 2020, Yamada et al[111] reported the results of the first RCT to evaluate right-half dissection of the SMA nerve plexus for localized PDAC, which found no differences in the incidence of local or systemic recurrence and comparable MSTs (37.9 vs 34.6 months, P = .77) between the hemi-dissection and total preservation groups. Thus, based on these studies, dissection of SMA nerve plexus and peri-SMA connective tissue including lymph nodes should be distinguished, and the impact of prophylactic right-half dissection of the SMA nerve plexus remains still controversial in patients with RPDAC.

Regarding lymph node dissection during pancreatectomy for PDAC, the American Joint Committee on Cancer (AJCC) 8th edition and ISGPS have defined the regional lymph nodes and peripancreatic

TABLE 5 Updates in advanced surgical procedures (2019 to October 2020)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Josseanchiun W et al[87]	2019	Japan	2005-2017	Retrospective study	NCRT followed by PD with PVR	84 PDAC patients with PV resection	PV patency ratio >0.6 after CRT (PPF)	5YS: 60% in patients with PV patency ratio <0.6 after CRT
Oba A et al[86]	2020	Japan	2005-2016	Retrospective study	PD with PVR	268 PDAC patients	Regional pancreatoduodenectomy (PPF)	Median RFS and OS after RPD were 17 and 32 months, respectively, compared with 11 and 21 months after SPD
Kishi Y et al[84]	2020	Japan	2002-2016	Retrospective study	PD with PVR	500 PDAC patients	CA19-9 > 200U/mL(NPF), postoperative adjuvant chemotherapy (PPF), extrapancreatic nerve plexus invasion (NPF), nodal metastasis (NPF), R1 resection (NPF)	MST of patients with PVR (−) and pathological PV invasion (−): 32.4 months, MST of patients with PVR (+) and pathological invasion (−): 32.1 months, $P=0.780$)
Honda M et al[80]	2020	Japan	2011-2018	Retrospective study	PD with PVR	110 patients with standard PVR and 10 patients with resection of second jejunal vein	Pancreaticoduodenectomy with J2VR for PDAC can be safely performed with a satisfactory overall survival rate	MST: 1.9 years and 4.2 years ($P=0.651$)
Terasaki F et al[88]	2019	Japan	2001-2017	Retrospective study	PD with PVR	97 who underwent end-to-end anastomosis and 25 (20.5%) had an interposition graft using the right external iliac vein	Preoperative albumin <3.5ng/mL (NPF), postoperative adjuvant chemotherapy (PPF)	5YS: 13.7% in the group with end-to-PV anastomosis 5YS: 10.0% in the group with anastomosis using interposition graft
Prakash LR et al[81]	2019	USA	2003-2015	Retrospective study	PD with PVR	127 PDAC patients	Cancer invasion into the lumen of PV/SMV (NPF)	MST: 30 months in patients with pathological PV invasion, MST: 28 months in patients without pathological PV invasion,

(Continues)

TABLE 5 (Continued)

Author	Year	Country	Patient collection	Type of study	Treatment	Subjects and number	Prognostic factors	Survival (MST or 5YS)
Serenari M et al[89]	2019	Italy	2004-2016	Retrospective study	pancreatectomy with PVR	99 PDAC patients	Tangential venous resection (PPF)	MST: 15.6 months in all cases, MST: 29.5 months in patients who underwent PD with tangential venous resection
Sonohara F et al[90]	2020	Japan	1981-2018	Retrospective study	Pancreatectomy with AR	44 PDAC patients	Pre- and postoperative adjuvant therapies (PPF)	MST: 11.0 months in all 44 cases, MST: 60.0 months in 22 cases from 2010
Yang F et al[91]	2019	China	2010-2017	Retrospective study	Pancreatectomy with hepatic artery resection	14 PDAC patients (PD,11; TP, 3)	No description	MST: 30 months
Bachellier P et al[92]	2020	France	1990-2017	Retrospective study	Pancreatectomy with AR	118 PDAC patients	R0 resection (PPF), venous invasion (NPF)	MST after resection: 13.7 months
Klompmaker S et al[105]	2019	Netherlands, USA, Italy	2000-2017	Multi-institutional retrospective	Distal pancreatectomy with celiac artery resection	191 PDAC patients	Operation at high-volume center	MST: 19 months

5YS: 5-year survival; CA19-9, carbohydrate antigen 19-9; CA19-9, carbohydrate antigen 19-9; CRT, chemoradiotherapy; CS, conversion surgery; FOLFIRINOX, 5-fluorouracil+leucovorin+irinotecan+oxaliplatin; G-CRT, gemcitabine-based chemoradiation therapy; GEM, gemcitabine; GS-CRT, gemcitabine plus S1–based CRT; J2VR, resection of J2 vein; MST, median survival time; NAC, neoadjuvant chemotherapy; NCRT, neoadjuvant chemoradiotherapy; NPF, negative prognostic factor; OS, overall survival; PD, pancreatoduodenectomy; PPF, positive prognostic factor; PVR, portal venous resection; RFS, recurrence-free survival; RT, radiation therapy; USA, United States of America.

lymph node stations and recommend standard regional lymph node dissection for PDAC patients.[112] Imamura et al[113] retrospectively analyzed 495 PDAC patients who underwent pancreatectomy from 2002 to 2015 and evaluated the efficacy index (EI) of each lymph node station. The EI was calculated by multiplying the frequency of metastasis to the station and the 5YS of patients with metastasis to that station.[114] They showed the following: (a) mesocolon lymph nodes had a high EI in pancreatic head (Ph) tumors although not regional; for pancreatic body tumors, peri-Ph lymph nodes had a high EI although not regional; (b) for pancreatic tail (Pt) tumors, lymph nodes along the CA and CHA had an EI of 0, although regional; and (c) when the Ph was segmented into the pancreatic neck (Ph-neck), uncinate process (Ph-up), and periampullary regions, hepatoduodenal ligament lymph nodes had an EI of 0 for Ph-up, although regional; the mesojejunum lymph nodes also had an EI of 0, even for Ph-up, regardless of a high incidence of metastasis. Qian et al[115] analyzed 178 LAPC patients and suggested that PDAC located in the ventral Ph had a higher risk of LN14 involvement compared with those located dorsally; they recommended thorough dissection of LN14 located in the ventral Ph to optimize regional extended lymphadenectomy. Moreover, recent studies using national cancer databases from the United States and the JSPS reported that neoadjuvant therapies including NAC and NCRT significantly reduce the number of positive lymph node metastasis, ratio of positive lymph nodes, and lymphovascular invasion.[43,116] Therefore, the specific area of lymph node dissection associated with prognostic benefit might vary according to primary tumor location, adapted procedure, and presence or absence of neoadjuvant treatment.

5 | CONCLUSION

The recent development of multimodal treatment for localized PDAC has notably improved patient prognosis.

For RPDAC, neoadjuvant chemo- or chemoradiation therapy plays a key role, especially in patients with poor PS, elevated tumor marker levels, suspected peripancreatic lymph node metastasis, large tumor size, and tumor invasion of the splenic vessels. For BRPDAC, NAC and NCRT followed by surgery are preferred, and maintenance of nutritional status during treatment is important. Regimen standardization of pre- and postoperative chemotherapy for BRPDAC is indispensable as evidenced by a RCT. For LAPC, induction chemo- or chemoradiotherapy followed by surgical resection has a central role in improving survival; however, indications for surgical resection should be standardized. FOLFIRINOX or mFOLFIRINOX could be a desirable regimen of an induction therapy due to its anti-tumor effect. Together with these standard treatments, genetic profiling to guide corresponding appropriate anti-cancer treatment should be conducted immediately after diagnosis.

DISCLOSURE

ORCID
Hiroyuki Kato https://orcid.org/0000-0002-5798-2725
Akihiko Horiguchi https://orcid.org/0000-0002-2187-1396

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