Review Article

Current update of treatment strategies for borderline resectable pancreatic cancer: a narrative review

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Background and Objective: Borderline resectable pancreatic cancer (BRPC) is a tumor that infiltrates into the large blood vessels, with a high probability that the tumor will remain after surgical resection. To date, there has been no confirmed treatment strategy for BRPC. However, high-level studies, such as those using the intention-to-treat analysis, have recently been published. This review aimed to update the current status of treatment strategies for BRPC.

Methods: We searched for studies, including those investigating patients with BRPC, either treated by upfront surgery or with neoadjuvant treatment and reported the R0 resection rate and overall survival using an intention-to-treat analysis.

Key Content and Findings: Consequently, 22 articles were identified. Twelve were prospective studies. Six studies compared neoadjuvant therapy with upfront surgery, and both the R0 resection rate and overall survival in patients who underwent upfront surgery were significantly worse than in those who underwent neoadjuvant treatment in all studies. Six studies evaluated neoadjuvant chemotherapy, while 15 studies neoadjuvant chemoradiation. No reports showed the superiority or inferiority of the two methods, and the optimal regimen was not determined in either treatment. The high-precision radiation therapy techniques have been studied, but the optimal method and dose fractionation were unclear.

Conclusions: The current standard of care for the BRPC is neoadjuvant therapy. Although the optimal regimen of neoadjuvant therapy was not determined, several prospective trials are underway to identify the optimal neoadjuvant treatment.

Keywords: Borderline resectable pancreatic cancer (BRPC); upfront surgery; neoadjuvant chemotherapy; neoadjuvant chemoradiotherapy; intention-to-treat analysis

Submitted Nov 29, 2021. Accepted for publication Feb 28, 2022.
doi: 10.21037/jgo-21-829
View this article at: https://dx.doi.org/10.21037/jgo-21-829

Introduction

Pancreatic cancer was estimated to be the 12th most common newly diagnosed cancer and the 7th leading cause of cancer-related deaths worldwide in 2020 (1,2). The prognosis of pancreatic cancer is still poor, and the 5-year survival rate is reported to be 2–9% (3). The only potentially curative treatment for pancreatic cancer is surgical resection. However, since many patients with pancreatic cancer exhibit

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Table 1 The search strategy summary

Items	Specification
Date of Search	12 Jan 2021
Databases and other sources searched	PubMed and Web of Science
Search terms used	"Borderline resectable pancreatic cancer", "neoadjuvant chemotherapy", "neoadjuvant chemoradiation therapy", and "upfront surgery"
Timeframe	01 Jan 2012 to 12 Jan 2021
Inclusion and exclusion criteria	Studies conducted in patients with BRPC, either treated with upfront surgery or neoadjuvant therapy, or those that reported the median overall survival were included. Studies conducted in patients with either resectable cancer or BRPC and in those with either BRPC or locally advanced cancer were included if the data on these patients with BRPC could be extracted. We selected studies that mentioned conducting or those that we judged to have conducted an intention-to-treat analysis. The articles were limited to full-text publications in English
Selection process	Eligible articles were screened by two authors (AO and YM)
Any additional considerations, if applicable	N/A

BRPC, borderline resectable pancreatic cancer.

tumor invasion in the surrounding organs or develop distant metastasis at the time of initial diagnosis, only less than 20% of them are eligible for surgery (4). Non-metastatic pancreatic cancer is divided into three levels based on its resectability status: resectable, borderline resectable, and locally advanced. Among them, borderline resectable pancreatic cancer (BRPC) consists of a group of diseases in which the tumor invades the major blood vessels, such as the portal vein and superior mesenteric artery, and it is difficult to determine whether the tumor is resectable. However, there is no uniform definition of BRPC, and the degree of venous and arterial involvement varies with each definition. BRPC is currently defined based on the international criteria of the following: the National Comprehensive Cancer Network (NCCN) (5), a research by MD Anderson (6), American Hepato Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) consensus (7), and the International Association of Pancreatology consensus (8). The existence of these multiple definitions and the fact that the diagnosis of this condition based on imaging results is not easy is related to the difficulty in assessing the therapeutic outcome of BRPC. The main treatment options for BRPC are upfront surgery, neoadjuvant chemotherapy (NACT) followed by surgery, and neoadjuvant chemoradiation therapy (NACRT) followed by surgery. To date, there has been no confirmed treatment strategy for BRPC. Previous studies on BRPC only included a small number of cases or performed analyses of patients in whom surgery were performed, resulting in a limited number of clinical studies with a high level of evidence. However, high-level studies, such as those using the intention-to-treat analysis, have recently been published. The intention-to-treat analysis studies included patients who did not undergo surgery, thus reducing potential bias in the treatment effects.

This review aimed to investigate the current status of treatment strategies for BRPC. To conduct a fair comparison, we investigated studies that performed an intention-to-treat analysis. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-829/rc).

Methods

Table 1 shows the search strategy summary. In this review, the PubMed and Web of Science databases were searched. Eligible articles were screened by two authors (AO and YM). The focused keywords were "borderline resectable pancreatic cancer", "neoadjuvant chemotherapy", "neoadjuvant chemoradiation therapy", and "upfront surgery". The reference lists of relevant articles were manually searched. Studies conducted in patients with BRPC, either treated with upfront surgery or neoadjuvant therapy, or those that reported the median overall survival (OS) were included. Studies conducted in patients with either resectable cancer or BRPC and in those with either BRPC or locally advanced cancer were also included if the data on these patients with BRPC could be extracted. We selected studies that mentioned conducting or those

Table 2 An overview of literatures extracted

Authors	Year	No. of pts. BR [All]	Design	Resectability	Assessor of resectability	Definition	Treatment
Dholakia (19)	2013	50	Retro	BR	Multidisciplinary team	Own criteria	NACRT
Chuong (20)	2013	57 [73]	Retro	BR+LA	Multidisciplinary team	NCCN	NACRT
Chakraborty (21)	2014	13	PII	BR	Multidisciplinary team	MD Anderson	NACRT
Mellon (22)	2015	110 [159]	Retro	BR+LA	Multidisciplinary team	NCCN	NACRT
Masui (15)	2016	18	PII	BR	Multidisciplinary team	Modified NCCN	NACT
Katz (23)	2016	22	PII	BR	Central review	Own criteria	NACRT
Rashid (24)	2016	101	Retro	BR	Multidisciplinary team	NCCN	NACRT
Murakami (9)	2017	77	Retro	BR	Not stated	NCCN	UPS *vs.* NACT
Fujii (10)	2017	231 [504]	Retro	BR+R	2 or more radiologists	NCCN	UPS *vs.* NACRT
Yoo (16)	2017	18	Retro	BR	Not stated	NCCN	NACT
Nagakawa (25)	2017	27	PII	BR	Not stated	Own criteria	NACRT
Masui (26)	2017	30	PII	BR	Not stated	NCCN	NACRT
Jang (11)	2018	50	PII/III	BR	Specialized radiologists	NCCN	UPS *vs.* NACRT
Murphy (27)	2018	48	PII	BR	Multidisciplinary team	NCCN	NACRT
Miyasaka (17)	2019	31	Retro	BR	Multidisciplinary team	NCCN	NACT
Motoi (18)	2019	38 [101]	PII	BR+R	Not stated	Own criteria	NACT
Hayashi (28)	2019	45	PII	BR	Central review	NCCN	NACRT
Inoue (12)	2020	151	Retro	BR	Multidisciplinary team	NCCN	UPS *vs.* NACT
Versteijne (13)	2020	113 [133]	PIII	BR+R	Not stated	Dutch Pancreatic Cancer Group	UPS *vs.* NACRT
Takahashi (29)	2020	41	PII	BR	Central review	Modified NCCN	NACRT
Tran (30)	2020	25	PII	BR	Not stated	NCCN	NACRT
Kimura (14)	2020	199	Retro	BR	2 or more radiologists	Japan Pancreas Society	UPS *vs.* NACT/NACRT

pts, patients; Retro, retrospective; P, phase; BR, borderline resectable; LA, locally advanced; R, resectable; NCCN, National Comprehensive Cancer Network; NACRT, neoadjuvant chemoradiotherapy; UPS, upfront surgery; NACT, neoadjuvant chemotherapy.

that we judged to have conducted an intention-to-treat analysis. The articles were limited to full-text publications in English. Data on the study design, treatment details, number of cases, resection rate, R0 resection rate, median OS, and number of cases with treatment-related mortality were extracted. The R0 resection rate in patients who underwent pancreatic cancer resection was calculated.

Discussion

Overview of the literature extracted

An overview of 22 studies (9-30) extracted for this review is shown in *Table 2*: 10 phase II studies, 1 phase II/III study, 1 phase III study, and 10 retrospective studies. Twelve articles were prospective studies, and a high number of prospective studies were found in articles with recent reporting years. Among the 10 retrospective studies, a propensity score-matched analysis was performed in one (10).

The diagnosis of BRPC was made by a multidisciplinary team in nine studies, a central review team in three studies, and multiple radiologists in three studies. No specific description was provided for the diagnosis in seven studies. For the definition of BRPC, 13 studies used the NCCN guidelines, two studies used the modified NCCN guidelines,

Table 3 Upfront surgery versus neoadjuvant therapy

Authors	Year	Design	Resectability	No. of pts.	Treatment	Resection rate (%)	R0 rate (%)	P	Median OS (months)	P
Murakami (9)	2017	Retro	BR-A	25	Upfront surgery	92	17	<0.001	11.6	0.003
				52	GEM+S-1	90	72		27.1	
Fujii (10)	2017	Retro (PSMA)	BR-PV	102 (21)*	Upfront surgery	82	61	<0.001	n.r. (20.1)*	(0.044)*
				27 (21)*	S-1/RT	93	96		n.r. (28.4)*	
			BR-A	81 (14)*	Upfront surgery	68	31	0.006	n.r. (10.0)*	(0.046)*
				21 (14)*	S-1/RT	67	71		n.r. (18.1)*	
Jang (11)	2018	PII/III	BR	23	Upfront surgery	78	33	0.01	12	0.028
				27	GEM/RT	63	82		21	
Inoue (12)	2020	Retro	BR	96	Upfront surgery	76	48	0.004	18.1	0.014
				55	GEM+NAB-PTX	78	73		31.9	
Versteijne (13)	2020	PIII	BR	59	Upfront surgery	64	13	<0.001	13.2	0.029
				54	GEM/RT	52	79		17.6	
Kimura (14)	2020	Retro	BR-PV	46	Upfront surgery	n.r.	n.r.	n.r.	16.1	0.004
				42	NACT/NACRT (various)				22.8	
			BR-A	48	Upfront surgery	n.r.	n.r.	n.r.	14.3	<0.001
				63	NACT/NACRT (various)				35.4	

*, Data of propensity score matched analysis. Retro, retrospective; P, phase; PSMA, propensity score-matched analysis; pts, patients; GEM, gemcitabine; NAB-PTX, nab-paclitaxel; NACT, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy; RT, radiotherapy; OS, overall survival; BR, borderline resectable; BR-PV, borderline resectable tumor infiltrating portal vein; BR-A, borderline resectable tumor infiltrating artery.

and seven studies used other criteria. Dholakia *et al.* (19) reclassified 50 BRPC patients classified by their institutional definition using the AHPBA/SSO/SSAT criteria. The results showed that 40 patients (80%) were classified as BRPC and ten patients (20%) as locally advanced pancreatic cancer using the AHPBA/SSO/SSAT criteria. Takahashi *et al.* (29) performed a multicenter, phase II study of patients with BRPC. In this study, 52 patients were eligible for BRPC. However, 41 were classified as BRPC by a central review, while the remaining 11 patients as locally advanced cancer. Thus, the imaging diagnosis of BRPC remains not an easy task. Although the NCCN definition tends to be used as the diagnostic criteria for BRPC, we still recognize many reports that use each institution's definition. In addition, the NCCN guidelines have been revised and updated over time. These may lead to bias in the assessment of treatment outcomes in patients with BRPC. Hence, it is important to establish the diagnostic criteria for BRPC. In addition, the diagnosis of BRPC should be made by a multidisciplinary team in single-center studies and by a central review in multicenter studies.

Upfront surgery versus neoadjuvant therapy (Table 3)

Six studies compared neoadjuvant therapy with upfront surgery (9-14). The neoadjuvant therapy group had a significantly higher R0 resection rate than the upfront surgery group as reported in five articles (9-13), while this information was not reported in one article (14). OS was significantly longer in the neoadjuvant therapy group than in the upfront surgery group as reported in all articles (9-14). The multicenter phase II/III trial by Jang *et al.* (11) compared the upfront surgery group and the NACRT group, which received 54 Gy of irradiation delivered in 30 fractions combined with gemcitabine as a treatment for BRPC. The median OS was significantly better in the NACRT group than in the upfront surgery group [P=0.028, hazard ratio (HR): 1.97, 95% confidence interval (CI):

1.07–3.36]. The R0 resection rate was also significantly higher in the NACRT group than in the upfront surgery group (P=0.004). The safety monitoring committee decided to discontinue the study early as the neoadjuvant treatment efficacy showed statistical significance. The multicenter phase III PREOPANC trial by Versteijne *et al.* (13) compared the upfront surgery group and the NACRT group, which received 36 Gy of irradiation delivered in 15 fractions combined with gemcitabine for resectable pancreatic cancer and BRPC. In this study, the analysis of all patients did not show any OS benefit in the NACRT group; in the subgroup analysis of BRPC patients, the NACRT group had significantly better OS than the upfront surgery group (P=0.029, HR: 0.62; 95% CI: 0.40–0.95), and the R0 resection rate was also high [P<0.001, odds ratio (OR): 24.20, 95% CI: 6.57–89.12]. Two retrospective studies compared the efficacy of upfront surgery and NACT. Inoue *et al.* (12) compared the efficacy of NACT with gemcitabine and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) with that of upfront surgery. The NACT group showed a significantly high R0 resection rate (P=0.004) and a long median OS (P=0.014, HR: 0.61). Murakami *et al.* (9) compared the outcomes of upfront surgery and NACT with gemcitabine and S-1 for BRPC with arterial involvement (BR-A) cases. Results showed that the NACT group had a significantly higher R0 resection rate (P<0.001) and longer median OS (P=0.003) than the upfront surgery group. Fujii *et al.* (10) used the propensity score-matched analysis to compare the results of upfront surgery and NACRT (50.4 Gy of irradiation delivered in 28 fractions combined with oral S-1) in three groups: resectable, BRPC with portal vein involvement (BR-PV), and BR-A. Results showed that NACRT significantly prolonged the median survival in BR-PV (P=0.044, HR: 0.451, 95% CI: 0.19–0.91) and BR-A patients (P=0.046, HR: 0.626, 95% CI: 0.27–0.95) but not in patients with resectable cancer (P=0.960, HR: 0.984, 95% CI: 0.48–2.02). In the NACRT group, the incidence of positive pathological margins was significantly reduced in both BR-PV and BR-A patients (P=0.01, OR: 0.06 and P=0.016, OR: 0.072, respectively). Kimura *et al.* (14) retrospectively compared the results of upfront surgery and neoadjuvant therapy in patients with BR-PV and BR-A. This study included various chemotherapeutic regimens and chemoradiation as neoadjuvant therapies. Results showed that neoadjuvant therapy significantly prolonged the median survival in both BR-PV (P=0.004, HR: 0.38, 95% CI: 0.19–0.75) and BR-A patients (P<0.001, HR: 0.36, 95% CI: 0.21–0.63). Five (9-13) of the six articles described the postoperative complications of upfront surgery and neoadjuvant treatment, and none of them reported statistical differences between the two.

As noted above, both the R0 resection rate and median OS in patients who underwent upfront surgery were significantly worse than those who underwent neoadjuvant treatment in all studies that investigated the overall BRPC cases, BR-PV and BR-A cases separately, and BR-A cases. In the 2020 annual meeting of an American Society of Clinical Oncology Group, the results of the ESPAC-5F trial (31), a four-arm, multicenter, randomized phase II trial that compared the efficacy of upfront surgery with that of neoadjuvant gemcitabine plus capecitabine or fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or chemoradiation therapy as a treatment for BRPC, was opened. In this study, neoadjuvant therapy significantly improved survival compared with upfront surgery (P<0.001, HR: 0.27, 95% CI: 0.13–0.55). At this moment, neoadjuvant therapy should be considered for patients with BRPC.

Neoadjuvant therapy

Neoadjuvant chemotherapy

Table 4 shows the six studies reporting the results of NACT followed by surgery for BRPC. Neoadjuvant gemcitabine plus S-1 was investigated in three studies conducted by Masui *et al.* (15), Murakami *et al.* (9), and Motoi *et al.* (18). The R0 resection rates were 80%, 72.3%, and 81%, respectively, and the median OS rates were 21.7, 27.1, and 21.1 months, respectively. Miyasaka *et al.* (17) and Inoue *et al.* (12) investigated the efficacy of neoadjuvant gemcitabine plus nab-paclitaxel. The R0 resection rates were 100% and 93%, respectively, while the median OS rates were 27.9 months and 31.9 months, respectively. Yoo *et al.* (16) investigated the use of neoadjuvant FOLFIRINOX. The R0 resection rate was 75%, while the median OS was 21.2 months. Treatment-related mortality was not observed in any of the studies.

The development of systemic chemotherapy for pancreatic cancer has traditionally focused on treating unresectable pancreatic cancer. Randomized controlled trials of gemcitabine in patients with unresectable pancreatic cancer, including those with locally advanced cases, have reported that gemcitabine is more effective than fluorouracil in prolonging survival and relieving the symptoms (32) and has been used as a first-line treatment for unresectable pancreatic cancer. Since then, many randomized controlled trials have been conducted using gemcitabine as a control.

Table 4 Neoadjuvant chemotherapy

Authors	Year	Design	Resectability	No. of pts	Chemotherapeutic regimen	Resection rate (%)	R0 rate (%)	Median OS (months)
Masui (15)	2016	PII	BR	18	GEM + S-1	83	80	21.7
Murakami (9)	2017	Retro	BR-A	52	GEM + S-1	90	72.3	27.1
Yoo (16)	2017	Retro	BR	18	FOLFIRINOX	67	75	21.2
Miyasaka (17)	2019	Retro	BR	31	GEM + NAB-PTX	87	100	27.9
Motoi (18)	2019	PII	BR	38	GEM + S-1	68	81	21.1
Inoue (12)	2020	Retro	BR	55	GEM + NAB-PTX	78	93	31.9

Retro, retrospective; P, phase; pts, patients; OS, overall survival; BR, borderline resectable; BR-A, borderline resectable tumor infiltrating artery; GEM, Gemcitabine; NAB-PTX, nanoparticle albumin-bound paclitaxel; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin.

The results of the Prodige4-ACCORD11 (33) and MPACT (34) trials showed that FOLFIRINOX and gemcitabine plus nab-paclitaxel were associated with a higher incidence of adverse events compared to gemcitabine; however, survival benefits were also observed in patients administered with these drugs. According to the NCCN guidelines (5), the preferred regimens for locally advanced disease consist of FOLFIRINOX and gemcitabine plus nab-paclitaxel for patients with good performance status (PS), and gemcitabine, capecitabine, and continuous infusion of 5-Fluorouracil for patients with poor PS. The efficacy of S-1 monotherapy and multi-drug combination therapy, including S-1, has been investigated mainly in Japan. The GEST study was a phase III trial on locally advanced pancreatic cancer aimed to evaluate the non-inferiority of S-1 over gemcitabine and the superiority of gemcitabine plus S-1. Results of this study showed that S-1 was non-inferior in terms of OS. On the contrary, the combination of gemcitabine and S-1 showed a significant improvement in progression-free survival but no superiority over gemcitabine in improving OS (35). It was difficult to determine which regimen is superior to the others at the time of this review. Recently, Kunzmann *et al.* (36) reported the results of the NEOLAP-AIO-PAK-0113 multicenter, randomized, phase II trial comparing nab-paclitaxel plus gemcitabine with nab-paclitaxel plus gemcitabine followed by FOLFIRINOX for locally advanced pancreatic cancer. No difference was found in OS and R0 resection rates. However, both showed significantly high surgical conversion rates: 35.9% in the nab-paclitaxel group and 43.9% in the sequential FORFIRINOX group. The sequential FORFIRINOX group showed a higher rate of histopathological downstaging in evaluable resection specimens than in the nab-paclitaxel group. In addition, the JCOG1407 randomized phase II trial of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel for locally advanced pancreatic cancer is still ongoing (37). A randomized phase II trial (PDAC-GS/GA-rP2, CSGO-HBP-015 trial) comparing neoadjuvant gemcitabine plus nab-paclitaxel with neoadjuvant gemcitabine plus S-1 in patients with resectable pancreatic cancer and BRPC is also underway (38).

Based on our review, the NACT regimens included FOLFILINOX in one study (16), gemcitabine plus nab-paclitaxel in two studies (12,17), and gemcitabine plus S-1 in three studies (9,15,18). These regimens have been shown to be useful in locally advanced pancreatic cancer; no studies have compared the efficacy of these NACT regimens in BRPC, and no definitive NACT regimen exists. However, the accumulation of evidence supporting the efficacy of chemotherapy regimens for locally advanced pancreatic cancer and their introduction into BRPC may lead to high resection and survival rates.

Neoadjuvant chemoradiation therapy

Table 5 shows the 15 studies reporting the results of NACRT followed by surgery for BRPC. Five prospective phase II studies investigating NACRT with induction chemotherapy followed by concurrent chemoradiation therapy were conducted (23,25-27,30). Among them, the induction chemotherapy regimen used was using FOLFIRINOX in three studies (23,27,30) and gemcitabine in two studies (25,26). Katz *et al.* (23) reported the results of the ALLIANCE trial, which was a prospective, multicenter, single-arm trial aimed to determine the feasibility of induction of modified FOLFIRINOX followed by external-

Table 5 Neoadjuvant chemoradiotherapy

Authors	Year	Design	Resectability	No. of pts	Chemotherapy-induction	Chemotherapy-concurrent	RT methods	Total/fractional RT dose (Gy)	Resection rate (%)	R0 rate (%)	Median OS (months)
Dholakia (19)	2013	Retro	BR	50	None/GEM-based/FOLFIRINOX/FOLFOX	None/Cape/GEM/others	3DCRT/IMRT/SBRT	50/2	58	93	17.2
Chuong (20)	2013	Retro	BR	57	GTX/GEM/GEM-based/FOLFIRINOX	–	SBRT	35–50/7–10	56.1	96.9	16.4
Chakraborty (21)	2014	PII	BR	13	–	Cape	IMRT/3DCRT	50/2.5	38.5	80	9.1
Mellon (22)	2015	Retro	BR	110	GTX/GEM/others	–	SBRT	40/8	51	96	19.2
Katz (23)	2016	PII	BR	22	FOLFIRINOX	Cape	3DCRT/IMRT	50.4/1.8	68	93	21.7
Rashid (24)	2016	Retro	BR	101	GTX	–	SBRT	30-40/6–8	54.5	96.4	18
Fujii (10)	2017	Retro	BR-PV	27 (21)*	–	S-1	3DCRT	50.4/1.8	93	96	n.r. (28.4)*
			BR-A	21 (14)*					67	71	n.r. (18.1)*
Nagakawa (25)	2017	PII	BR-A	27	GEM	GEM+S-1	IMRT	50.4/1.8	70.3	94.7	22.4
Masui (26)	2017	PII	BR-A	30	GEM	GEM	3DCRT	39/3	50	83	13.8 †
							IMRT	42/3	67	83	32
Jang (11)	2018	PII/III	BR	27	–	GEM	3DCRT	54/1.8	63	82.4	21
Murphy (27)	2018	PII	BR	48	FOLFIRINOX	Cape	Proton	25/5	67	97	37.7
							IMRT	58/1.8			
Hayashi (28)	2019	PII	BR	45	–	S-1/RT→GEM	3DCRT	50.4/1.8	62.2	96.4	17.3
Takahashi (29)	2020	PII	BR	41	–	S-1	3DCRT	50.4/1.8	85.4	74.3	30.8
Versteijne (13)	2020	PIII	BR	54	–	GEM	3DCRT	36/2.4	61	79	16
Tran (30)	2020	PII	BR	25	FOLFIRINOX	GEM	IMRT	50/2	52	100	24.4

*, Data of propensity score matched analysis. †, Median OS of IMRT cases showed significantly better than that of 3DCRT cases (P=0.0273). Retro, retrospective; P, phase; BR, borderline resectable; BR-PV, borderline resectable tumor infiltrating portal vein; BR-A, borderline resectable tumor infiltrating artery; pts, patients; RT, radiation therapy; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy; SBRT, stereotactic body radiotherapy; frs, factions; OS, overall survival; Cape, Capecitabine; GEM, Gemcitabine; NAB-PTX, nanoparticle albumin-bound paclitaxel; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; GTX, gemcitabine, docetaxel, and capecitabine; n.r., not reported; NACRT, neoadjuvant chemoradiotherapy.

beam irradiation (50.4 Gy in 28 fractions) concurrent with capecitabine prior to pancreatectomy for BRPC. This study showed a resection rate of 68%, an R0 resection rate of 93%, and a median OS of 21.7 months (95% CI: 15.7, not reached). The phase II trial by Murphy *et al.* (27) evaluated the efficacy of FOLFIRINOX followed by individualized chemoradiation therapy concurrent with capecitabine. Radiation therapy in this study included short-course proton therapy (25 GyE in 5 fractions) or intensity-modulated radiotherapy (IMRT) (30 Gy in 10 fractions) and long-course IMRT (58.8 Gy in 28 fractions). This study showed that the R0 resection rate was 97%, while the median OS was 37.7 months (95% CI: 19.4, not reached). Tran *et al.* (30) reported a phase II trial showing the results of induction FOLFIRINOX followed by IMRT (50 Gy in 25 fractions) with gemcitabine. This study showed that the R0 resection rate was 100%, while the median OS was 24.4 months (95% CI: 12.6–40.0). Nagakawa *et al.* (25)

reported the results of a phase II study of a previous administration of gemcitabine followed by concurrent IMRT (50.4 Gy in 28 fractions) with gemcitabine and S-1 for BR-A patients. This study showed that the R0 resection rate was 94.7%, while the median OS was 22.4 months (95% CI: not reported). Masui *et al.* (26) reported the results of a phase II study of a previous administration of gemcitabine followed by concurrent chemoradiation therapy with gemcitabine for BR-A patients. This study showed that the R0 resection rate was 94.7%, and the median OS was 22.4 months (95% CI: not reported). This study also compared the survival benefit of IMRT (42–45 Gy in 14–15 fractions) with that of 3DCRT (39 Gy in 13 fractions), and the IMRT group showed a significantly higher OS rate than the 3DCRT group (P=0.027). However, only the cumulative dose of S-1 was a significant factor in the multivariate analysis. So, caution may be exercised when interpreting these results.

Studies have been conducted to improve the resection rate using radiation therapy methods. Seven studies (19,21,23,25-27,30) used or allowed IMRT, and one study (27) used proton therapy. With regard to the irradiation dose, nine studies (10,11,19,23,25,27-30) used conventional fractionated doses of 1.8–2.0 Gy, while the other six studies (13,20-22,24,26) used an increased fractional dose. Three studies (20,22,24) investigated induction chemotherapy followed by planned stereotactic body radiation therapy (SBRT) as the radiotherapy method; all of them were retrospective studies. In all of the studies, chemotherapy was administered as induction chemotherapy and not concurrently with SBRT. Chuong *et al.* (20) adopted the volumetric modulated arc therapy technique using the simultaneous integrated boost method for SBRT, delivering 35 to 50 Gy to vessel abutment/encasement and 25 to 30 Gy to the remainder of the tumor in 5 fractions. The resection and R0 resection rates were 56.1% and 96.9%, respectively, while the median OS was 16.4 months. Mellon *et al.* (22) used a similar method, delivering 40 Gy to tumor-vessel interfaces and 30 Gy to the remainder of the tumor in 5 fractions. The resection and R0 resection rates were 51% and 96%, respectively, while the median OS was 19.2 months. Rashid *et al.* (24) reported the results of induction chemotherapy with gemcitabine, docetaxel, and capecitabine followed by SBRT. In this study, an irradiation dose of 30–40 Gy delivered in 5 fractions was used; however, the details of the SBRT method were not stated. The resection and R0 resection rates were 54.5% and 96.4%, respectively, while the median OS was 17 months (95% CI: 14.0–20.0 months).

Fujii *et al.* (10) retrospectively evaluated the outcomes of NACRT using an irradiation dose of 50.4 Gy delivered in 30 fractions concurrent with S-1 in patients with BR-PV and BR-A. The resection rates in the BR-PV and BR-A patients were 93% and 67%, respectively, while the R0 resection rates were 96% and 71%, respectively. The median OS by propensity score matching analysis were 28.4 months in the BR-PV patients and 18.1 months in the BR-A group. Although no statistical comparison was made, the outcomes of BR-A patients were worse than those of BR-PV patients.

In the 15 NACRT-related studies selected for this review, a wide range of methods was used, and it was difficult to determine the optimal NACRT in terms of the treatment outcome and safety. However, BRPC might lead to a prolonged prognosis if the resection rate and R0 resection rate are improved by treating the infiltrated areas of the major vessels with high-intensity radiation. Therefore, further research on multidisciplinary treatment using the latest high-precision radiation therapy is needed.

On the contrary, in NACRT, unlike NACT and upfront surgery, concerns have been raised regarding the risk of gastrointestinal toxicity due to irradiation. Chakraborty *et al.* (21) conducted a phase II study evaluating the efficacy of capecitabine combined with a fractionated dose of 2.5 Gy and a total dose of 50 Gy. However, this study was discontinued before a planned interim analysis as two cases of severe (grades 4 and 5) gastric ulcerations were reported. Mellon *et al.* (22) showed that gastrointestinal bleeding from the duodenum or stomach (grade 3 or higher) was the most common toxic effect. The avoidance of severe gastrointestinal toxicity must also be considered in the development of optimal NACRT for BRPC.

Neoadjuvant chemotherapy versus neoadjuvant chemoradiation therapy

In the studies extracted for this review, the R0 resection rate ranged from 72.3% to 100% in the NACT group and from 71% to 100% in the NACRT group. The median OS ranged from 21.1 to 31.9 months in the NACT group and from 13.8 to 37.7 months in the NACRT group. This suggests that there is no clear difference in treatment results between NACT and NACRT. At present, the results of comparative studies between NACT and NACRT for BRPC have not been reported, and the superiority of the two regimens remains unclear.

Table 6 Ongoing prospective trials of NACT versus NACRT for borderline resectable pancreatic cancer

Trial name	Start year	Resectability	Study design	Regimen
PREOPANC-2 (39)	2018	BR+R	P III	Arm 1: FOLFIRINOX → surgery
				Arm 2: GEM + RT → surgery → GEM
BRPCNCC-1 (40)	2018	BR	P II	Arm 1: GEM + NAB-PTX → surgery
				Arm 2: GEM + NAB-PTX → SBRT → surgery
				Arm 3: S-1 + NAB-PTX → SBRT → surgery
GABARNANCE (41)	2017	BR	P II/III	Arm 1: GEM + NAB-PTX → surgery
				Arm 2: S-1 + RT → surgery
ALLIANCE A021501 (42)	2016	BR	P II	Arm 1: mFOLFIRINOX → surgery → FOLFOX
				Arm 2: mFOLFIRINOX → SBRT → surgery → FOLFOX

BR, borderline resectable; R, resectable; GEM, Gemcitabine; Cape, capecitabine; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; NAB-PTX, nanoparticle albumin-bound paclitaxel; RT, radiotherapy; SBRT, stereotactic body radiotherapy; mFOLFIRINOX, modified FOLFIRINOX; FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

Future prospective

Ongoing studies of neoadjuvant therapy

There are several ongoing comparative studies investigating the superiority of NACT to NACRT (*Table 6*). The PREOPANC-2 trial (39) is a multicenter phase III randomized controlled trial conducted by the Dutch Pancreatic Cancer Group. This trial compared neoadjuvant FOLFIRINOX followed by surgery without adjuvant therapy with neoadjuvant gemcitabine combined with hypofractionated radiotherapy followed by surgery and adjuvant gemcitabine for resectable pancreatic cancer and BRPC. The BRPCNCC-1 trial (40) is a prospective, randomized phase II trial that compared and evaluated the efficacy of neoadjuvant gemcitabine plus nab-paclitaxel with that of gemcitabine plus nab-paclitaxel with SBRT versus S-1 plus nab-paclitaxel with SBRT for BRPC. The GABARNANCE trial (41) is a phase II/III randomized trial that compared the efficacy of gemcitabine and nab-paclitaxel with that of S-1 and concurrent irradiation as neoadjuvant therapy for BRPC. The ALLIANCE trial A021501 (42) is a randomized phase II trial that compared the efficacy of preoperative modified FOLFIRINOX with that of modified FOLFIRINOX followed by SBRT (33–40 Gy in 5 fractions) for BRPC of the head of the pancreas. The results of these ongoing clinical trials may provide a direction for a neoadjuvant treatment of patients with BRPC.

Molecular targeted therapy and immunotherapy

Studies on molecular-targeted therapy for pancreatic cancer has not shown promising results (43,44). Recently, Golan *et al.* reported that the common founder germline BRCA1 or BRCA2 mutation-positive (gBRCAm) patients with BRPC have an advantage in terms of pathologic complete response rate and long-term survival when treated with neoadjuvant FOLFIRINOX (45). In their study, the pathologic complete response rates were 44.4% for gBRCAm patients and 10% for BRCA non-carriers (P=0.009). The median disease-free survival was not reached for the gBRCAm patients and was 7 months for the BRCA non-carriers (P=0.03).

Pancreatic cancer is less likely to respond to immune checkpoint inhibitors because it mildly expresses programmed death-ligand 1 and tumor-specific neoantigens (46). Recently, the results of the KEYNOTE-158 study (47) have been reported. This multicenter phase II study evaluated the efficacy and safety of pembrolizumab in previously treated patients with advanced high levels of microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR) solid tumors in 27 cancer types other than colorectal cancer. A total of 233 patients were enrolled, 22 of whom had pancreatic cancer. The response rate for pancreatic cancer was 18.2% (95% CI: 5.2–40.3), while the median duration of response was 13.4 months (95% CI: 8.1–16.0), showing promising results. Although the frequency of MSI-H/dMMR in pancreatic cancer is not

high, a treatment incorporating immunotherapy should be developed.

Limitations

Our review had several limitations. The regimens for both NACT and NACRT were diverse. Furthermore, the number of cases in BRPC studies was limited, and the diagnostic criteria for BRPC used were not uniform. The quality of the evidence was limited in some studies, with few phase III trials. Some studies analyzed all cases of BRPC, while some analyzed BR-PV and BR-A cases separately, and some only included BR-A cases. Therefore, we considered it difficult to aggregate the data of NACT and NACRT and compare between them. For this reason, we adopted the style of narrative review in this paper. Despite these limitations, the present review provides the most reliable data reported for BRPC patients using an intention-to-treat analysis.

Conclusions

The current standard of care in the treatment of BRPC includes neoadjuvant therapy followed by the determination of resectability and, if possible, surgery. Although optimal neoadjuvant therapy for BRPC has not yet been determined, several clinical trials are being conducted to address this issue. A multidisciplinary treatment incorporating high-precision radiotherapy should be developed to increase the R0 resection rate.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.
Funding: An internship program at the International Atomic Energy Agency (IAEA; Vienna, Austria) was supported by the Hiroshima International Council for Health Care of Radiation-exposed and IAEA.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-829/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-829/coif). Abdel-Wahab M reports that she is the chair of the international committee of the American society for radiation oncology. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cancer Fact Sheets, Pancreas Source: Globocan 2020. Global cancer observatory: Cancer today. Lyon, France: International Agency for Research on Cancer, World Health Organization. Available online: https://gco.iarc.fr/today/fact-sheets-cancers. Accessed April 9. 2021.
2. American Cancer Society. Cancer Statistics Center. Cancer Facts & Figures 2020. Available online: http://cancerstatisticscenter.cancer.org. Accessed April 9, 2021.
3. Wild CP, Weiderpass E, Stewart BW, eds. World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. Available online: https://publications.iarc.fr/586. Accessed April 9, 2021.
4. White RR, Lowy AM. Clinical Management: Resectable Disease. Cancer J 2017;23:343-9.
5. Tempero MA, Malafa, MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Available online: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed April 9, 2021.
6. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. J Am Coll Surg 2008;206:833-46; discussion 846-8.
7. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable

pancreatic cancer: Expert consensus. Ann Surg Oncol 2009;16:1727-33.
8. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 2018;18:2-11.
9. Murakami Y, Uemura K, Sudo T, et al. Survival impact of neoadjuvant gemcitabine plus S-1 chemotherapy for patients with borderline resectable pancreatic carcinoma with arterial contact. Cancer Chemother Pharmacol 2017;79:37-47.
10. Fujii T, Satoi S, Yamada S, et al. Clinical benefits of neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreatic head: an observational study using inverse probability of treatment weighting. J Gastroenterol 2017;52:81-93.
11. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer. Ann Surg 2018;268:215-22.
12. Inoue Y, Saiura A, Oba A, et al. Neoadjuvant gemcitabine and nab-paclitaxel for borderline resectable pancreatic cancers: Intention-to-treat analysis compared with upfront surgery. J Hepatobiliary Pancreat Sci 2021;28:143-55.
13. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol 2020;38:1763-73.
14. Kimura N, Yamada S, Takami H, et al. Optimal Preoperative Multidisciplinary Treatment in Borderline Resectable Pancreatic Cancer. Cancers (Basel) 2020;13:36.
15. Masui T, Doi R, Kawaguchi Y, et al. Concurrent gemcitabine+S-1 neoadjuvant chemotherapy contributes to the improved survival of patients with small borderline-resectable pancreatic cancer tumors. Surg Today 2016;46:1282-9.
16. Yoo C, Kang J, Kim KP, et al. Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen. Oncotarget 2017;8:46337-47.
17. Miyasaka Y, Ohtsuka T, Kimura R, et al. Neoadjuvant Chemotherapy with Gemcitabine Plus Nab-Paclitaxel for Borderline Resectable Pancreatic Cancer Potentially Improves Survival and Facilitates Surgery. Ann Surg Oncol 2019;26:1528-34.
18. Motoi F, Satoi S, Honda G, et al. A single-arm, phase II trial of neoadjuvant gemcitabine and S1 in patients with resectable and borderline resectable pancreatic adenocarcinoma: PREP-01 study. J Gastroenterol 2019;54:194-203.
19. Dholakia AS, Hacker-Prietz A, Wild AT, et al. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor-vessel relationships. J Radiat Oncol 2013;2:413-25.
20. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys 2013;86:516-22.
21. Chakraborty S, Morris MM, Bauer TW, et al. Accelerated fraction radiotherapy with capecitabine as neoadjuvant therapy for borderline resectable pancreatic cancer. Gastrointest Cancer Res 2014;7:15-22.
22. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol 2015;54:979-85.
23. Katz MH, Shi Q, Ahmad SA, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg 2016;151:e161137.
24. Rashid OM, Pimiento JM, Gamenthaler AW, et al. Outcomes of a Clinical Pathway for Borderline Resectable Pancreatic Cancer. Ann Surg Oncol 2016;23:1371-9.
25. Nagakawa Y, Hosokawa Y, Nakayama H, et al. A phase II trial of neoadjuvant chemoradiotherapy with intensity-modulated radiotherapy combined with gemcitabine and S-1 for borderline-resectable pancreatic cancer with arterial involvement. Cancer Chemother Pharmacol 2017;79:951-7.
26. Masui T, Takaori K, Anazawa T, et al. A Prospective Study of Intensity-modified Radiation Therapy in Comparison with Conventional 3D-RT for BR Pancreatic Cancer Patients with Arterial Involvement. Anticancer Res 2017;37:7023-30.
27. Murphy JE, Wo JY, Ryan DP, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol 2018;4:963-9.

28. Hayashi T, Nakamura T, Kimura Y, et al. Phase II study of neoadjuvant treatment of sequential S-1-based concurrent chemoradiotherapy followed by systemic chemotherapy with gemcitabine for borderline resectable pancreatic adenocarcinoma (HOPS-BR 01). Int J Radiat Oncol Biol Phys 2019;105:606-17.
29. Takahashi S, Ohno I, Ikeda M, et al. Neoadjuvant S-1 with concurrent radiotherapy followed by surgery for borderline resectable pancreatic cancer: A phase II open-label multicenter prospective trial (JASPAC05). Ann Surg 2020. [Epub ahead of print]. doi: 10.1097/SLA.0000000000004535.
30. Tran NH, Sahai V, Griffith KA, et al. Phase II trial of neoadjuvant FOLFIRINOX and intensity modulated radiation therapy concurrent with fixed-dose rate-gemcitabine in patients with borderline resectable pancreatic cancer. Int J Radiat Oncol Biol Phys 2020;106:124-33.
31. Ghaneh P, Palmer DH, Cicconi S, et al. ESPAC-5F: Four-arm, prospective, multicenter, international randomized phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer. J Clin Oncol 2020;38:4505.
32. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-13.
33. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
34. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
35. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 2013;31:1640-8.
36. Kunzmann V, Siveke JT, Algül H, et al. Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase II trial. Lancet Gastroenterol Hepatol 2021;6:128-38.
37. Mizusawa J, Fukutomi A, Katayama H, et al. Protocol digest of randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer: Japan clinical oncology group study (JCOG1407). Pancreatology 2018;18:841-5.
38. Yamada D, Kobayashi S, Takahashi H, et al. Randomized phase II study of gemcitabine and S-1 combination therapy versus gemcitabine and nanoparticle albumin-bound paclitaxel combination therapy as neoadjuvant chemotherapy for resectable/borderline resectable pancreatic ductal adenocarcinoma (PDAC-GS/GA-rP2, CSGO-HBP-015). Trials 2021;22:568.
39. Janssen QP, van Dam JL, Bonsing BA, et al. Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial. BMC Cancer 2021;21:300.
40. Gao S, Zhu X, Shi X, et al. Comparisons of different neoadjuvant chemotherapy regimens with or without stereotactic body radiation therapy for borderline resectable pancreatic cancer: study protocol of a prospective, randomized phase II trial (BRPCNCC-1). Radiat Oncol 2019;14:52.
41. Randomized phase II/III study of gemcitabine and nab-paclitaxel therapy versus S-1 and concurrent radiotherapy as neoadjuvant treatment for Borderline resectable pancreatic cancer (GABARNANCE Trial). Available online: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030821. Accessed April 9, 2021.
42. Katz MHG, Ou FS, Herman JM, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. BMC Cancer 2017;17:505.
43. Ciliberto D, Staropoli N, Chiellino S, et al. Systematic review and meta-analysis on targeted therapy in advanced pancreatic cancer. Pancreatology 2016;16:249-58.
44. Eltawil KM, Renfrew PD, Molinari M. Meta-analysis of phase III randomized trials of molecular targeted therapies for advanced pancreatic cancer. HPB (Oxford) 2012;14:260-8.
45. Golan T, Barenboim A, Lahat G, et al. Increased Rate of Complete Pathologic Response After Neoadjuvant FOLFIRINOX for BRCA Mutation Carriers with

Borderline Resectable Pancreatic Cancer. Ann Surg Oncol 2020;27:3963-70.
46. Teng MW, Ngiow SF, Ribas A, et al. Classifying Cancers Based on T-cell Infiltration and PD-L1. Cancer Res 2015;75:2139-45.
47. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase II KEYNOTE-158 study. Lancet Oncol 2020;21:1353-65.

Cite this article as: Ono A, Murakami Y, Abdel-Wahab M, Nagata Y. Current update of treatment strategies for borderline resectable pancreatic cancer: a narrative review. J Gastrointest Oncol 2022;13(2):885-897. doi: 10.21037/jgo-21-829

