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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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OPINION REVIEW

Borderline resectable pancreatic cancer: Certainties and controversies

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Abstract

Borderline resectable (BR) pancreatic ductal adenocarcinoma (PDAC) is currently a well-recognized entity, characterized by some specific anatomic, biological and conditional features: It includes patients with a stage of disease intermediate between the resectable and the locally advanced ones. The term BR identifies a tumour with an aggressive biological behaviour, on which a neoadjuvant approach instead of an upfront surgery one should be preferred, in order to obtain a radical resection (R0) and to avoid an early recurrence after surgery. Even if during the last decades several studies on this topic have been published, some aspects of BR-PDAC still represent a matter of debate. The aim of this review is to critically analyse the available literature on this topic, particularly focusing on: The problem of the heterogeneity of definition of BR-PDAC adopted, leading to a misinterpretation of published data; its current management (neoadjuvant *vs* upfront surgery); which neoadjuvant regimen should be preferably adopted; the problem of radiological restaging and the determination of resectability after neoadjuvant therapy; the post-operative outcomes after surgery; and the role and efficacy of adjuvant treatment for resected patients that already underwent neoadjuvant therapy.

Key Words: Borderline resectable pancreatic cancer; Pancreatic cancer; Neoadjuvant treatment; Chemotherapy; Radiotherapy; Pancreatic tumour

Core Tip: The term borderline resectable identifies a tumour with an aggressive biological behaviour, on which a neoadjuvant approach instead of upfront surgery one should be preferred, in order to obtain a radical resection (R0) and to avoid an early recurrence after surgery. The aim of this review is to critically analyse the available

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literature on this topic.

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INTRODUCTION

Borderline resectable (BR) is currently a well-recognized subset of pancreatic ductal adenocarcinoma (PDAC), characterized by specific anatomical, biological and conditional features[1]. However, even if, during the last decades, several studies on BR-PDAC have been published, some questions still remain open and they are a matter of debate. The aim of this article is to review critically the available literature on BR-PDAC, focusing on some of the most important aspects on this topic: (1) The heterogeneity of the definition of BR-PDAC and the need to find a universally accepted one in order to allow the comparison among published studies; (2) The choice of the best management of BR-PDAC: Upfront surgery or neoadjuvant strategy? Moreover, which neoadjuvant regimen should be adopted; (3) The restaging of primary tumour after neoadjuvant treatment: The limitations of radiological imaging and the decision whether to consider the patient for surgical exploration; (4) The post-operative outcomes after surgery for BR-PDAC that underwent neoadjuvant treatment; and (5) The role of adjuvant therapy after neoadjuvant strategy for BR-PDAC.

DEFINITION OF BORDERLINE-RESECTABLE (BR-PDAC)

The term "borderline resectable" was firstly introduced by Varadhachary *et al*[1] in 2006, identifying a subgroup of tumours technically resectable but at high risk of non-radical resection (R1) and/or early recurrence after surgery. From its introduction, the concept of BR-PDAC was adopted in almost all pancreatic surgery centres; and, currently, it is universally accepted by the scientific pancreatic community[2]. However, during the last decade, many definitions of BR-PDAC have been proposed and included in several different international guidelines[1,3-6]. This heterogeneity determines great confusion and, consequently, a difficulty to compare the results of published studies.

Currently, we should distinguish three different types of BR-PDAC[7]: (1) BR-type A: It takes into account only anatomic features, particularly the relationship between the tumour and peripancreatic vessels; (2) BR-type B: It considers some biological factors that raise the possibility (but not certainty) of extra-pancreatic metastatic disease; and (3) BR-type C: It evaluates some conditional criteria, such as the performance status and patient comorbidities, which significantly increase the risk for morbidity or mortality after surgery.

The criteria defining BR-type A generated a great discussion in the scientific community; in fact, a great heterogeneity of BR-type A can be observed in several different guidelines (Table 1)[1,4-6]. They evaluated differently the interface between tumour and vessels; they adopted terms as "abutment", "encasement", "occlusion" and "impingement", which can lead to cause difficult interpretation. Some of them used the term "reconstructable", which is questionable because the potential for reconstruction differs among surgeons and institutions. In the National Comprehensive Cancer Network (NCCN) classification, the definition of resectability was divided according to the tumour location (head/uncinate process or body/tail), and the extent of vascular invasion was detailed for each vein and artery. In the Japan Pancreas Society classification, BR is sub-classified into venous invasion alone [BR-portal vein (PV)] or arterial invasion (BR-A) (in the case where there is both venous and arterial involvement this is classified as BR-A). In order to solve this heterogeneity and to obtain an international consensus on the definition of BR-PDAC, a symposium was arranged during the 20th meeting of the International Association of Pancreatology (IAP) held in Sendai, Japan in 2016[8]. Two different BR-types A have been defined

Table 1 Criteria of Borderline Resectability according to MD Anderson Cancer Center, AHPBA/SSAT/SSO, National Comprehensive Cancer Network, Japan Pancreas Society classification (7th edition)

MD Anderson Cancer Center	AHPBA/SSAT/SSO	National Comprehensive Cancer Network 2021	Japan Pancreas Society classification (7th edition)
Anatomical	Anatomical	Anatomical	Anatomical
Arterial: SMA/CA: Tumour abutment ≤ 180° of the circumference of the artery; periarterial stranding and tumour points of contact forming a convexity against the vessel improve chances of resection; CHA: Short-segment incasement/abutment (typically at the GDA origin); the surgeon should be prepared for vascular resection/interposition grafting.	Arterial: GDA: Encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; SMA: tumour abutment < 180° of the circumference of the vessel wall.	Arterial: Pancreatic head/uncinate process: SMA: Solid tumour contact ≤ 180°; CHA: Solid tumour contact without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction; Solid tumour contact with variant arterial anatomy (*e.g.*, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery). Pancreatic body/tail: CA: Solid tumour contact < 180°; CA: Solid tumour contact ≥ 180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure[1].	Arterial: SMA/CA: Tumour contact or invasion ≤ 180° without showing stenosis or deformity; CHA: Tumour contact or invasion without showing tumour contact or invasion of the PHA and/or CA.
Venous: SMV/PV: Short-segment occlusion with suitable vessel for reconstruction above and below.	Venous: SMV/PV: Venous involvement demonstrating tumour abutment with or without impingement and narrowing of the lumen; SMV/PV: Encasement but without encasement of the nearby arteries; SMV/PV: Short segment venous occlusion resulting from either tumour thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.	Venous: SMV/PV: Solid tumour contact ≥ 180°, contact of < 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. IVC: solid tumour contact.	Arterial: SMA/CA: Tumour contact or invasion ≤ 180° without showing stenosis or deformity; CHA: Tumour contact or invasion without showing tumour contact or invasion of the PHA and/or CA.
Biological: CT findings suspicious, but not diagnostic of metastatic disease; Histologically confirmed N1 disease.	-	-	-
Conditional: ECOG performance status ≥ 3.	-	-	-

[1]Some panel members prefer these criteria to be in the locally advanced category.

SMA: Superior mesenteric artery; CHA: Common hepatic artery; SMV: Superior mesenteric vein; PV: Portal vein; GDA: Gastroduodenal artery; CA: Celiac artery; CT: Computed tomography; ECOG: Electrocorticography; IVC: Inferior vena cava; PHA: Polyhydroxyalkanoates.

according to the invasion of venous or arterial: (1) BR-PV (superior mesenteric vein/PV invasion alone): Tumour contact of 180° or greater; invasion of the superior mesenteric vein/PV with bilateral narrowing or occlusion and not exceeding the inferior border of the duodenum; and (2) BR-A (arterial invasion): Tumour contact with the superior mesenteric artery and/or celiac axis less than 180° without showing stenosis or deformity and tumour abutment of the common hepatic artery without showing tumour contact with the proper hepatic artery and/or celiac axis.

This consensus should be universally adopted from all pancreatic surgery centres, and it represents a fundamental step in order to speak the same language and to better understand the management of BR-PDAC. In fact, the majority of available literature on this topic has been published before this consensus, and so, currently, all the results about BR-PDAC are biased by the heterogeneity of the adopted definition. Only in the next years, with the adoption of the criteria of the IAP consensus, it may be possible to draw definitive conclusions on this topic.

The definition of BR-type B takes into account three different biological features[7]: (1) The radiological suspicion (not histologically proven) of distant metastases; (2) A high value of carbohydrate antigen 19-9 (CA19-9) at diagnosis. Hartwig *et al*[9] investigated the correlation between CA19-9 levels and tumour resectability and prognosis: In patients with preoperative CA19-9 levels > 500 IU/mL, resection rate was < 70% and the median survival was < 20 months; and (3) the radiological diagnosis of extra-regional nodal metastases.

All these factors are expression of a more aggressive biological disease, with consequently a higher risk of recurrence after surgery and a poor prognosis, even if the tumour is technically resectable. During the consensus meeting of IAP, a standardized definition of BR-type B was also established[8]: "Tumour potentially resectable anatomically with clinical findings suspicious but nor proven distant metastasis, including CA19-9 Level more than 500 units/mL, or regional lymph nodes metastasis diagnosed by biopsy or positron emission tomography-computed tomography".

The definition of BR-type C takes into accounts conditional host-related factors (*i.e.* patient comorbidities) that can be associated with resistance to the neoadjuvant therapy, postoperative morbidity/mortality and poor overall prognosis. Also, for BR-type C, the consensus of IAP established a clear definition[8]: "Patients with anatomically resectable PDAC and with performance status of 2 or more". Even if BR-type B and C are currently well defined and recognized, after evaluating the available literature, only few studies focused on these two subtypes of BR-PDAC[10-12], while the majority of them focused only on BR-type A; it is possible, thus, that many studies included BR-type B and C in resectable series. This aspect represents another important bias, and it does not allow a correct interpretation of the results of the published studies on this topic.

In conclusion, the available literature on BR-PDAC has several biases due to the heterogeneity of definition of the disease. The only way to solve this problem is that the future studies should adopt the recent consensus of IAP, evaluating separately the three types of BR-PDAC.

CURRENT MANAGEMENT OF BR-PDAC: NEOADJUVANT TREATMENT *VS* UPFRONT SURGERY

The definition of BR-PDAC was born with the aim of identifying a subset of tumours with more aggressive biological features, on which a neoadjuvant approach, instead of classic upfront surgery, could be preferable. Some advantages of the neoadjuvant therapy have been advocated: Early systemic treatment for undetected micro metastases; an increase of R0 resection rate; a reduction in terms of post-operative pancreatic fistula (POPF)[7,13]. On the other hand, this approach could have some possible disadvantages: A reduction of the chance of surgery, due to disease progression during the treatment; a limited significant down staging[14,15]. Currently, the NCCN guidelines recommend neoadjuvant treatment rather than upfront surgery for BR-PDAC[5].

However, the debate about the choice of the best management for BR-PDAC still remains open due to the fact that the available literature does not provide high-level evidence. Most of the studies that advocate neoadjuvant treatment are non-randomized trials[16,17], with selection bias by reporting survival after resection rather than by intention to treat (ITT); moreover, due to the extreme heterogeneity of the definition of BR-PDAC adopted by publishes studies, the interpretation and comparison of the results are very difficult. The first prospective randomized study to show the superiority of neoadjuvant therapy in BR-PDAC was published only in 2018 by Jang *et al*[18]; in the ITT analysis, 1-year and 2-year survival in the neoadjuvant group (74% and 41%) were significantly better when compared to the upfront surgery group (48% and 26%). It is important to note that this trial was stopped early due to the statistical significance of neoadjuvant treatment efficacy. The PREOPANC trial was the first completed multicentre, randomized trial comparing neoadjuvant treatment *vs* upfront surgery in patients with resectable or BR-PDAC[19]. It did not demonstrate a median overall survival (OS) benefit in the ITT analysis in either one of the two groups (16.0 mo *vs* 14.3 mo for neoadjuvant and upfront surgery, respectively; $P = 0.096$); however, the analysis of BR-PDAC only showed better OS after neoadjuvant treatment, suggesting a benefit of this approach. Both the above mentioned randomized controlled trials had important bias: They are limited by small sample sizes; they had, like the other retrospective published studies, a heterogeneity in terms of definition of BR-PDAC, and they took into account BR-type A only.

Different meta-analyses comparing outcomes after neoadjuvant treatment *vs* upfront surgery for BR-PDAC have been published[16,17,20] (Table 2). The first meta-analysis by Gillen *et al*[20] included 111 studies published from 1980 to 2009; chemothe-rapy regimens were mainly gemcitabine or 5-fluorouracil (5-FU) based, and almost all studies adopted chemo-radiotherapy. This meta-analysis showed that, in BR and locally advanced patients, the prognosis following neoadjuvant treatment and resection was comparable to patients with resectable disease (median OS: 23 mo *vs* 21

Table 2 Systematic reviews and meta-analysis on neoadjuvant treatment for borderline resectable pancreatic ductal adenocarcinoma

Ref.	N° of studies	N° of included patients	Tumour	NAT regimen	RT	Included studies
Gillen *et al*[20], 2010	111	4394	R-PDAC, BR-PDAC, LA-PDAC	Gem, 5-FU, 5-FU + Mytomin C, 5-FU + Ox, Gem + Ox, taxanes	+/-	Prospective, retrospective
Tang *et al*[15], 2015	18	959[1]	BR-PDAC	FOLFIRINOX, Cap, Gem, Gem + Docetaxel, Gem + S1, 5-FU + Pac + Gem + Cap, Gem + Ox	+/-	Prospective
Dhir *et al*[17], 2017	96	5520	R-PDAC, BR-PDAC, LA-PDAC	FOLFIRINOX, Cap, Gem, 5-FU, Gem + Docetaxel, Gem + S1, Pac + Gem + Cap, Gem + Ox, Gem + Pac	+/-	Prospective, retrospective, RCT
Versteijne *et al* [19], 2018	38	3484, 1738[1]	R-PDAC, BR-PDAC	NR	+/-	Prospective, retrospective, RCT
Pan *et al*[21], 2019	17	2286	R-PDAC, BR-PDAC	5-FU + Cis, Cap, 5-FU, Gem, Gem + Cap, Gem + Cis, Gem + S1, Gem + Pac	+/-	Prospective, retrospective, RCT
Cloyd *et al*[22], 2020	6	850, 411[1]	R-PDAC, BR-PDAC	Gem, Gem+S1	+/-	RCT

[1]Patients who underwent NAT.

BR: Borderline resectable; LA: Locally advanced; PDAC: Pancreatic ductal adenocarcinoma; NR: Not reported; Cap: Capecitabine; Gem: Gemcitabine; 5-FU: 5-fluorouracil; Pac: Paclitaxel; Ox: Oxaliplatin; Cis: Cisplatin; RCT: Randomized controlled trial.

mo, respectively). A second meta-analysis by Dhir *et al*[17] provided an update of the literature published since 2009, which marks the endorsement of the AHPBA/SSAT/SSO consensus criteria[3,4]; it confirmed the excellent results of neoadjuvant approach for BR-PDAC. However, these two meta-analyses had important limitations; they excluded patients who did not undergo resection after neoadjuvant treatment and who did not undergo adjuvant chemotherapy after resection. This bias was solved by a third meta-analysis by Versteijne *et al*[16] that included only studies that performed an ITT analysis; it found a better survival for neoadjuvant treatment if compared to upfront resection (median OS: 19 mo *vs* 15 mo, respectively). It is important to note that all these meta-analyses presented some weaknesses: Most of the included studies were observational; some studies were phase III trials; some studies were not completed (early interruption, ongoing). A more recent meta-analysis was published by Pan *et al*[21], including only comparative trials from 2011 to 2018 and mainly comparing survival outcomes between neoadjuvant treatment and upfront surgery for BR-PDAC; a higher OS was shown in neoadjuvant group, both considering all patients (HR = 0.49, $P < 0.001$) or only resected ones (HR = 0.66, $P = 0.001$). Moreover, patients who underwent neoadjuvant treatment had better disease free survival, lower recurrence rate, higher R0 rate, and similar overall resection rate. The most recent meta-analysis was published by Cloyd *et al*[22], including only prospective randomized controlled trials comparing neoadjuvant *vs* upfront surgery for resectable or BR-PDAC. Based on ITT analysis, neoadjuvant treatment resulted in improved OS compared to upfront surgery [hazard ratio (HR) = 0.73, $P < 0.05$].

In conclusion, even if without a high level of evidence, the available literature supports the adoption of a neoadjuvant approach for BR-PDAC, to such an extent that it is currently considered the gold standard for this subset of disease[5]. Several randomized controlled trials are ongoing, and they will give useful results, in support or not of this strategy[23,24].

CHOICE OF NEOADJUVANT REGIMEN FOR BR-PDAC

Even if the neoadjuvant approach is frequently adopted for the management of BR-PDAC[5], the treatment regimen is still a matter of debate, and no international guidelines have been published. Three possible strategies have been described.

Chemotherapy alone

Historically, gemcitabine-based chemotherapy has been the most frequently adopted regimen[25-29]. Gemcitabine + nab-paclitaxel is, currently, the most frequently adopted gemcitabine-base chemotherapy for BR-PDAC[30-32]. The other one adopted as neoadjuvant strategy for BR-PDAC is FOLFIRINOX, because of its demonstrated efficacy for the metastatic disease[33]. Paniccia *et al*[34] reported the outcomes of BR

patients treated with neoadjuvant FOLFIRINOX: 94% underwent R0 resection and, with a median follow-up of 14.5 mo, median OS was not yet reached. Several other studies demonstrating the efficacy of FOLFIRINOX as neoadjuvant treatment for BR-PDAC have been published[35,36].

Chemo-radiotherapy

The efficacy of this approach for BR-PDAC is still under debate, even if it is commonly adopted, especially in the United States[37]. Moreover, newer techniques such as stereotactic body radiation therapy and intensity-modulated radiation therapy are increasingly used[38]. Stokes *et al*[39] reported the outcomes of 40 BR-PDAC on which neoadjuvant chemoradiation with capecitabine was administrated, obtaining a median OS of 12 mo. In another study by Takai *et al*[40], BR-PDAC patients were treated with radiotherapy and concurrent 5-FU and cisplatin/gemcitabine. Gemcitabine-based chemoradiation demonstrated less disease progression compared with the 5-FU based one (5.6% *vs* 42.9%); median OS for the entire cohort was 20.5 mo, without significant difference between the different chemotherapies. These results have been confirmed by Cho *et al*[41], adopting radiotherapy with gemcitabine, gemcitabine + cisplatin or gemcitabine + capecitabine.

Induction chemotherapy followed by chemo-radiotherapy

The rationale for this approach is to combine the efficacy of chemotherapy to treat the undetected micro-metastatic disease and of radiotherapy to sterilize the tumour boundaries in contact with the vessel. Katz *et al*[7] reported a large series from the MD Anderson Cancer Center (Houston, TX) of 160 BR-PDAC; the majority of patients were treated with induction gemcitabine-based chemotherapy followed by chemoradiation; median OS was 40 mo for resected patients and 15 mo for unresected ones. Christians *et al*[42] reported the results of 18 BR-PDAC treated with induction FOLFIRINOX followed by chemoradiation (radiotherapy with gemcitabine or capecitabine): 83% underwent surgery and 80% successfully underwent R0 resection; median OS was 12.5 mo. The ALLIANCE trial evaluated FOLFIRINOX followed by chemoradiation (radiotherapy with capecitabine) in 22 BR-PDAC[43]: R0 resection rate was 93%; median OS was 21.7 mo.

Several meta-analyses evaluating the different neoadjuvant strategies for BR-PDAC have been published. Dhir *et al*[17] demonstrated that chemotherapy alone was used in 20.8% of cases, chemoradiotherapy in 34.4%, induction chemotherapy followed by chemoradiation in 42.7%, while radiation alone in 2.1%. FOLFIRINOX provided the best prognosis (median OS: 22.1 mo) followed by gemcitabine + taxane + capecitabine (19.4 mo); moreover, median OS with single-agent chemotherapy was 14.7 mo, conversely it was 16.1 mo with the adoption of multi-agents chemotherapy. Similar results were obtained by another meta-analysis by Gillen *et al*[20]; chemotherapy was used as neoadjuvant treatment in the majority of the studies: Gemcitabine, 5-FU, mitomycin C, and platinum compounds were the most adopted agents; moreover, a significant increase in the resection rate was observed with the use of combination chemotherapy.

Another unsolved problem is the duration of neoadjuvant treatment. In daily clinical practice, after some cycles of neoadjuvant therapy, a radiological and clinical restaging is performed; in case of good-response to the treatment, it is often difficult to decide the best timing for surgical intervention (particularly, in determining the completion or not of the neoadjuvant treatment). Due to the heterogeneity of the studies in terms of neoadjuvant adopted regimens, no studies have focused on this aspect, and the best timing for surgery during neoadjuvant treatment still remains debated and not universally standardized.

In conclusion, there is currently no consensus on which neoadjuvant therapy for BR-PDAC should be adopted, due to the lack of high-level evidence in published studies. According to the most recent NCCN guidelines, acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel; moreover, subsequent chemoradiation may be included[5].

"CHALLENGE" OF RADIOLOGICAL RE-EVALUATION OF BR-PDAC

Due to the growing adoption of neoadjuvant strategy for the management of BR-PDAC, an important challenge is the re-staging of the tumour at the end of treatment. Generally, it includes a standard contrast-enhanced computed tomography (CT) scan, even if there is growing consensus that it has some relevant limitations: It is not able to

distinguish the tumour from inflammation/fibrosis and it fails to reflect tumour response to neoadjuvant therapy[44,45]. Focusing on 40 BR/locally advanced (LA)-PDAC treated with FOLFIRINOX, Ferrone *et al*[46] demonstrated that, after preoperative therapy, 70% of cases were re-classified BR/LA-PDAC, although an R0 resection was achieved in 92% of them. Similar results were achieved in a multicentre retrospective study with 36 BR patients treated with FOLFIRINOX[47]: Despite a significant tumour shrinkage after therapy, preoperative CT failed to predict accurately resectability. Katz *et al*[48] reported a retrospective analysis of 122 BR-PDAC that underwent restaging after neoadjuvant therapy. Using the RECIST criteria, 69% had stable disease, 12% had a partial response and 19% had progressive disease, with only 0.8% downstaged to resectable status; however, 66% underwent resection, with a R0 resection rate of 95%. Similar results were obtained by Yasuta *et al*[49]; even if, at radiological imaging, partial responses were observed in 10% of cases, stable disease in 86% and progressive disease in 3%; R0 resection rate was 93%.

Metabolic tumour activity has been also investigated for predicting the response after neoadjuvant therapy[50]. From a cohort of 83 patients with resectable or BR-PDAC receiving neoadjuvant chemoradiation, Akita *et al*[51] demonstrated that the maximal standardized uptake value was significantly lower in good responders compared with poor responders.

Thanks to a large body of evidence, we can conclude that imaging alone does not seem to be adequate enough to determine disease response to neoadjuvant therapy. If there is a stable disease after induction therapy, it should not be considered an exclusion criterion for surgery; moreover, all BR-PDAC that do not show any disease progression after neoadjuvant treatment should undergo surgical exploration to evaluate resectability[7,46,48].

SURGICAL OUTCOMES AFTER NEOADJUVANT THERAPY FOR BR-PDAC

Pancreatic surgery is generally affected by a high morbidity rate, even if performed in high-volume centres[52]. Moreover, surgical resection of BR-PDAC after neoadjuvant therapy can be technically challenging, requiring often-difficult tissue dissection and vascular resections. The impact of neoadjuvant treatment on perioperative outcomes after pancreatic surgery is an aspect to take into account. Evaluating the available literature, definite conclusions cannot be drawn; in fact, the majority of published studies had a small series of patients, including heterogeneous neoadjuvant regimens and without comparison with upfront resection groups[53]. Some of them had shown similar morbidity rate between neoadjuvant approach and upfront surgery[54-57]. For example, Hank *et al*[57] observed an overall morbidity rate of 52% for the neoadjuvant group *vs* 56% in the upfront resection group, with a rate of severe complications of 14% and 17%, respectively; moreover, the length of hospital stay was generally shorter in neoadjuvant patients. On the other hand, a recent large series of BR/LA-PDAC reported no significant difference in postoperative morbidity compared with those who underwent upfront resection[58].

Neoadjuvant therapy has been generally associated with a reduction in POPF occurrence[27,59-61]. In the cohort of Hank *et al*[57], the rate of POPF was significantly lower in the neoadjuvant group when compared with upfront surgery (3.8% *vs* 13.8%, respectively). Even if neoadjuvant therapy is responsible for longer operations, increased blood loss and a higher rate of vascular resections (all factors associated theoretically with an increased risk of CR-POPF[62]), it determines pathologic changes in the pancreatic gland, resulting in increased fibrosis and atrophy[63,64]. This hard texture of pancreatic parenchyma is quite certainly responsible for the lower rate of POPF observed after neoadjuvant therapy for BR-PDAC[59,65,66]. A systematic review by Verma *et al*[53] demonstrated comparable rates of overall POPF in patients with and without neoadjuvant therapy; however, this review had the great bias to not differentiate between patients undergoing pancreatoduodenectomy and distal pancreatectomy. Another recent meta-analysis[67] showed that any neoadjuvant treatment was associated with lower rates of POPF after pancreatoduodenectomy but not after distal pancreatectomy.

In conclusion, the available literature demonstrates that surgical resection after neoadjuvant treatment for BR-PDAC, even if technically demanding, offers comparable or even better post-operative results if compared with the upfront surgery approach.

ROLE OF ADJUVANT TREATMENT AFTER NEOADJUVANT THERAPY AND RESECTION FOR BR-PDAC

One of the miliary stones for the management of PDAC is that the gold standard treatment is represented by surgery followed by adjuvant therapy[5]. In BR-PDAC, considering that a chemo/radiotherapy is already performed as neoadjuvant setting, it is a matter of debate whether an adjuvant treatment is necessary. Theoretically, if micro-metastatic disease is still present in patients after completion of neoadjuvant therapy and surgery, it is reasonable to assume that adjuvant therapy should be useful and improve survival. However, the usefulness of adjuvant treatment in patients who have undergone neoadjuvant therapy is still debated and, in fact, some studies report only 14%-60% of patients receiving adjuvant therapy after neoadjuvant therapy[68,69].

Evaluating the available literature, the benefit of additional adjuvant after neoadjuvant therapy is assumed, but not proven. In a large multicentre AGEOFRENCH cohort, including 80 patients who underwent surgery for BR/LA-PDAC after neoadjuvant FOLFIRINOX, 54% of them received adjuvant chemotherapy[70]; the authors failed to find association with improved survival (HR, 0.85; P = 0.62). Conversely, Roland *et al*[69] has shown that administration of adjuvant therapy in BR-PDAC that underwent neoadjuvant treatment was associated with improved median OS (72 *vs* 33 mo; P = 0.008), but only in absence of extensive nodal metastatic disease (lymph node ratio < 0.15). It is important to note that only 14% of analysed patients in this study received adjuvant therapy. Similar results were obtained by Barnes *et al*[71], which examined 234 patients with resectable and BR/LA-PDAC who had undergone neoadjuvant therapy and surgery, 59% of which received adjuvant therapy; it was associated with a significant decreased risk of death among patients with nodal metastatic disease (HR 0.39; P = 0.002). Similarly, an international, multicentre, retrospective cohort study[72] demonstrated that adjuvant therapy was associated with improved survival in subgroup analyses of patients with nodal metastases, independently from the adopted regimen (FOLFIRINOX or gemcitabine-based). Moreover, the authors demonstrated that this effect was mostly expressed in BR/LA-PDAC (if compared with resectable disease) and diminished after an increasing number of preoperative cycles of FOLFIRINOX[72]. The lack of evidence is demonstrated by the unclear indications of NCCN guidelines[5], which state: "Consider additional chemotherapy and/or chemoradiation"; moreover, they do not give any recommendation about the kind of adjuvant treatment to administer, which should be chosen considering mainly the response to the previous neoadjuvant chemotherapy regimen.

In conclusion, data about the efficacy of adjuvant treatment seem to be promising, but no definite conclusion can be drawn due to the low level of evidence; randomized controlled trials are urgently needed.

CONCLUSION

BR-PDAC is a well-recognized entity in pancreatic surgical community. The recent international consensus of IAP represented a crucial step for the standardization of its definition, which should be universally adopted. Neoadjuvant treatment followed by surgery has become the gold standard for BR-PDAC, even if it is unclear which is the best chemotherapeutic regimen to adopt. Surgery after neoadjuvant treatment can be challenging, but the available literature demonstrated comparable or even better post-operative results when compared with the upfront surgery approach. Randomized studies on the role of adjuvant therapy after neoadjuvant treatment for BR-PDAC are urgently needed.

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