**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**Manuscript NO:** 65147

**Manuscript Type:** OPINION REVIEW

**Borderline resectable pancreatic cancer: Certainties and controversies**

Nappo G *et al*. Borderline resectable pancreatic cancer

Gennaro Nappo, Greta Donisi, Alessandro Zerbi

**Gennaro Nappo, Greta Donisi, Alessandro Zerbi,** Pancreatic Surgery Unit, Humanitas Clinical and Research Center-IRCCS, Rozzano 20089, Italy

**Author contributions:** Nappo G and Zerbi A contributed to the conception and design of the study; Nappo G, Donisi G and Zerbi A drafted and critically revised the manuscript and approved the final version of the article; Nappo G and Zerbi A are directly responsibility for the manuscript.

**Corresponding author: Gennaro Nappo, MD, Surgeon,** Pancreatic Surgery Unit, Humanitas Clinical and Research Center-IRCCS, Via Manzoni 56, Rozzano 20089, Italy, gennaro.nappo@humanitas.it

**Received:** February 28, 2021

**Revised:** April 9, 2021

**Accepted:** May 25, 2021

**Published online:** June 27, 2021

**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 analyse critically 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 regimes 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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Nappo G, Donisi G, Zerbi A. Borderline resectable pancreatic cancer: Certainties and controversies. *World J Gastrointest Surg* 2021; 13(6): 516-528

URL: https://www.wjgnet.com/1948-9366/full/v13/i6/516.htm

DOI: https://dx.doi.org/10.4240/wjgs.v13.i6.516

**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 literature on this topic.

**INTRODUCTION**

Borderline resectable (BR) is currently a well-recognized subset of pancreatic ductal adenocarcinoma (PDAC), characterized by specific anatomical, biological and conditional features[[1]](#_edn1). However, even if during the last decades several studies on BR-PDAC have been published, some questions still remain open and they are 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 from the scientific pancreatic community[[2]](#_edn2). 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, difficulty to compare the results of published studies.

Currently, we should distinguish three different types of BR-PDAC[[7]](#_edn7): (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, that significantly increase the risk for morbidity or mortality after surgery.

The criteria defining BR-type A generated 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 cause difficult interpretation. Some of them used the term “reconstructable”, which is questionable because the potential for reconstruction differs between surgeons and institutions. In 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]](#_edn8). Two different BR-types A according to the invasion of venous or arterial vessels have been defined: (1) BR-PV (superior mesenteric vein/PV invasion alone): Tumour contact 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 understand better 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 from the heterogeneity of the adopted definition. Only in the next years, with the adoption of the criteria of the consensus of IAP, 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]](#_edn9) 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 mo; 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]](#_edn13). 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]](#_edn16), 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]](#_edn18); 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]](#_edn19). 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]](#_edn20) (Table 2).The first meta-analysis by Gillen *et al*[20] included 111 studies published from 1980 to 2009; chemotherapy 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 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]](#_edn21), 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]](#_edn22), 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]](#_edn23).

**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]](#_edn25). Gemcitabine + nab-paclitaxel is, currently, the most frequently adopted gemcitabine-base chemotherapy for BR-PDAC[[30-32]](#_edn30). The other one adopted as neoadjuvant strategy for BR-PDAC is FOLFIRINOX, because of its demonstrated efficacy for the metastatic disease[[33]](#_edn34). Paniccia *et al*[[34]](#_edn35) 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]](#_edn36).

***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]](#_edn38). Moreover, newer techniques such as stereotactic body radiation therapy and intensity-modulated radiation therapy are increasingly used[[38]](#_edn39). Stokes *et al*[[39]](#_edn40) 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]](#_edn41), 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]](#_edn42), 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]](#_edn43) 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]](#_edn44): 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 , a radiological and clinical restaging is performed; in case of good-response to the treatment, it is often difficult to decide the better 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]](#_edn45). Focusing on 40 BR/locally advanced (LA)-PDAC treated with FOLFIRINOX, Ferrone *et al*[[46]](#_edn47) 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]](#_edn48): Despite a significant tumour shrinkage after therapy, preoperative CT failed to predict accurately resectability. Katz *et al*[[48]](#_edn49) 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]](#_edn50); 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]](#_edn51). From a cohort of 83 patients with resectable or BR-PDAC receiving neoadjuvant chemoradiation, Akita *et al*[[51]](#_edn52) 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]](#_edn53). 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]](#_edn54). Some of them had shown similar morbidity rate between neoadjuvant approach and upfront surgery[[54-57]](#_edn55). 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]](#_edn59).

Neoadjuvant therapy has been generally associated with a reduction in POPF occurrence[[27,59-61]](#_edn60). 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]](#_edn64)), it determines pathologic changes in the pancreatic gland, resulting in increased fibrosis and atrophy[[63,64]](#_edn65). 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]](#_edn67). 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]](#_edn69) 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 and 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]](#_edn70).

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]](#_edn72); 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]](#_edn73), 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]](#_edn74) 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.

**REFERENCES**

1 **Varadhachary GR**, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006; **13**: 1035-1046 [PMID: 16865597 DOI: 10.1245/ASO.2006.08.011]

2 **Bockhorn M**, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhutt A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014; **155**: 977-988 [PMID: 24856119 DOI: 10.1016/j.surg.2014.02.001]

3 **Callery MP**, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009; **16**: 1727-1733 [PMID: 19396496 DOI: 10.1245/s10434-009-0408-6]

4 **Abrams RA**, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol* 2009; **16**: 1751-1756 [PMID: 19390900 DOI: 10.1245/s10434-009-0413-9]

5 **Tempero MA**, Malafa MP, Chiorean EG, Czito B, Scaife C, Narang AK, Fountzilas C, Wolpin BM, Al-Hawary M, Asbun H, Behrman SW, Benson AB, Binder E, Cardin DB, Cha C, Chung V, Dillhoff M, Dotan E, Ferrone CR, Fisher G, Hardacre J, Hawkins WG, Ko AH, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Thayer S, Wolff RA, Burns JL, Zuccarino-Catania G. Pancreatic Adenocarcinoma, Version 1.2019. *J Natl Compr Canc Netw* 2019; **17**: 202-210 [PMID: 30865919 DOI: 10.6004/jnccn.2019.0014]

6 **Japan Pancreas Society.** General rules for the study of pancreatic cancer. 7th ed. Tokyo: Kanehara & Co., Ltd.; 2016

7 **Katz MH**, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008; **206**: 833-46; discussion 846-8 [PMID: 18471707 DOI: 10.1016/j.jamcollsurg.2007.12.020]

8 **Isaji S**, Mizuno S, Windsor JA, Bassi C, Fernández-Del Castillo C, Hackert T, Hayasaki A, Katz MHG, Kim SW, Kishiwada M, Kitagawa H, Michalski CW, Wolfgang CL. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology* 2018; **18**: 2-11 [PMID: 29191513 DOI: 10.1016/j.pan.2017.11.011]

9 **Hartwig W**, Strobel O, Hinz U, Fritz S, Hackert T, Roth C, Büchler MW, Werner J. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. *Ann Surg Oncol* 2013; **20**: 2188-2196 [PMID: 23247983 DOI: 10.1245/s10434-012-2809-1]

10 **Anger F**, Döring A, van Dam J, Lock JF, Klein I, Bittrich M, Germer CT, Wiegering A, Kunzmann V, van Eijck C, Löb S. Impact of Borderline Resectability in Pancreatic Head Cancer on Patient Survival: Biology Matters According to the New International Consensus Criteria. *Ann Surg Oncol* 2021; **28**: 2325-2336 [PMID: 32920720 DOI: 10.1245/s10434-020-09100-6]

11 **Kato Y**, Yamada S, Tashiro M, Sonohara F, Takami H, Hayashi M, Kanda M, Kobayashi D, Tanaka C, Nakayama G, Koike M, Fujiwara M, Kodera Y. Biological and conditional factors should be included when defining criteria for resectability for patients with pancreatic cancer. *HPB (Oxford)* 2019; **21**: 1211-1218 [PMID: 30773450 DOI: 10.1016/j.hpb.2019.01.012]

12 **Medrano J**, Garnier J, Ewald J, Marchese U, Gilabert M, Launay S, Poizat F, Giovannini M, Delpero JR, Turrini O. Patient outcome according to the 2017 international consensus on the definition of borderline resectable pancreatic ductal adenocarcinoma. *Pancreatology* 2020; **20**: 223-228 [PMID: 31839458 DOI: 10.1016/j.pan.2019.12.001]

13 **Lind PA**, Isaksson B, Almström M, Johnsson A, Albiin N, Byström P, Permert J. Efficacy of preoperative radiochemotherapy in patients with locally advanced pancreatic carcinoma. *Acta Oncol* 2008; **47**: 413-420 [PMID: 17882555 DOI: 10.1080/02841860701592384]

14 **Abbott DE**, Baker MS, Talamonti MS. Neoadjuvant therapy for pancreatic cancer: a current review. *J Surg Oncol* 2010; **101**: 315-320 [PMID: 20187063 DOI: 10.1002/jso.21469]

15 **Tang K**, Lu W, Qin W, Wu Y. Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages. *Pancreatology* 2016; **16**: 28-37 [PMID: 26687001 DOI: 10.1016/j.pan.2015.11.007]

16 **Versteijne E**, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, van Eijck CHJ, Groot Koerkamp B, Rasch CRN, van Tienhoven G; Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 2018; **105**: 946-958 [PMID: 29708592 DOI: 10.1002/bjs.10870]

17 **Dhir M**, Malhotra GK, Sohal DPS, Hein NA, Smith LM, O'Reilly EM, Bahary N, Are C. Neoadjuvant treatment of pancreatic adenocarcinoma: a systematic review and meta-analysis of 5520 patients. *World J Surg Oncol* 2017; **15**: 183 [PMID: 29017581 DOI: 10.1186/s12957-017-1240-2]

18 **Jang JY**, Han Y, Lee H, Kim SW, Kwon W, Lee KH, Oh DY, Chie EK, Lee JM, Heo JS, Park JO, Lim DH, Kim SH, Park SJ, Lee WJ, Koh YH, Park JS, Yoon DS, Lee IJ, Choi SH. Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial. *Ann Surg* 2018; **268**: 215-222 [PMID: 29462005 DOI: 10.1097/SLA.0000000000002705]

19 **Versteijne E**, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, Buijsen J, Busch OR, Creemers GM, van Dam RM, Eskens FALM, Festen S, de Groot JWB, Groot Koerkamp B, de Hingh IH, Homs MYV, van Hooft JE, Kerver ED, Luelmo SAC, Neelis KJ, Nuyttens J, Paardekooper GMRM, Patijn GA, van der Sangen MJC, de Vos-Geelen J, Wilmink JW, Zwinderman AH, Punt CJ, van Eijck CH, van Tienhoven G; Dutch Pancreatic Cancer Group. 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**: 1763-1773 [PMID: 32105518 DOI: 10.1200/JCO.19.02274]

20 **Gillen S**, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; **7**: e1000267 [PMID: 20422030 DOI: 10.1371/journal.pmed.1000267]

21 **Pan L**, Fang J, Tong C, Chen M, Zhang B, Juengpanich S, Wang Y, Cai X. Survival benefits of neoadjuvant chemo(radio)therapy versus surgery first in patients with resectable or borderline resectable pancreatic cancer: a systematic review and meta-analysis. *World J Surg Oncol* 2019; **18**: 1 [PMID: 31892339 DOI: 10.1186/s12957-019-1767-5]

22 **Cloyd JM**, Heh V, Pawlik TM, Ejaz A, Dillhoff M, Tsung A, Williams T, Abushahin L, Bridges JFP, Santry H. Neoadjuvant Therapy for Resectable and Borderline Resectable Pancreatic Cancer: A Meta-Analysis of Randomized Controlled Trials. *J Clin Med* 2020; **9**: 1129 [PMID: 32326559 DOI: 10.3390/jcm9041129]

23 **Katz MHG**, Ou FS, Herman JM, Ahmad SA, Wolpin B, Marsh R, Behr S, Shi Q, Chuong M, Schwartz LH, Frankel W, Collisson E, Koay EJ, Hubbard JM, Leenstra JL, Meyerhardt J, O'Reilly E; Alliance for Clinical Trials on Oncology. 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 [PMID: 28750659 DOI: 10.1186/s12885-017-3441-z]

24 **Janssen Q,** Besselink MG, Wilmink JW, van Tienhoven G. The (cost)effectiveness of neoadjuvant FOLFIRINOX vs neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for (borderline) resectable pancreatic cancer: the PREOPANC-2 study. In: 13th IHPBA World Congress. Geneva. Available from: https://www.trialregister.nl/trial/7094

25 **Lee JL**, Kim SC, Kim JH, Lee SS, Kim TW, Park DH, Seo DW, Lee SK, Kim MH, Kim JH, Park JH, Shin SH, Han DJ. Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma. *Surgery* 2012; **152**: 851-862 [PMID: 22682078 DOI: 10.1016/j.surg.2012.03.010]

26 **Motoi F**, Ishida K, Fujishima F, Ottomo S, Oikawa M, Okada T, Shimamura H, Takemura S, Ono F, Akada M, Nakagawa K, Katayose Y, Egawa S, Unno M. Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multi-institutional phase 2 trial. *Ann Surg Oncol* 2013; **20**: 3794-3801 [PMID: 23838925 DOI: 10.1245/s10434-013-3129-9]

27 **Rose JB**, Rocha FG, Alseidi A, Biehl T, Moonka R, Ryan JA, Lin B, Picozzi V, Helton S. Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. *Ann Surg Oncol* 2014; **21**: 1530-1537 [PMID: 24473642 DOI: 10.1245/s10434-014-3486-z]

28 **Eguchi H**, Yamada D, Iwagami Y, Gotoh K, Kawamoto K, Wada H, Asaoka T, Noda T, Takeda Y, Tanemura M, Sakai D, Satoh T, Kudo T, Isohashi F, Mori M, Doki Y. Prolonged Neoadjuvant Therapy for Locally Advanced Pancreatic Cancer. *Dig Surg* 2018; **35**: 70-76 [PMID: 28482348 DOI: 10.1159/000475477]

29 **Saito K**, Isayama H, Sakamoto Y, Nakai Y, Ishigaki K, Tanaka M, Watadani T, Arita J, Takahara N, Mizuno S, Kogure H, Ijichi H, Tateishi K, Tada M, Hasegawa K, Fukayama M, Kokudo N, Koike K. A phase II trial of gemcitabine, S-1 and LV combination (GSL) neoadjuvant chemotherapy for patients with borderline resectable and locally advanced pancreatic cancer. *Med Oncol* 2018; **35**: 100 [PMID: 29846849 DOI: 10.1007/s12032-018-1158-8]

30 **Kunzmann V,** Hartlapp I, Scheurlen M, Einsele H, Mueller J, Steger WKU, Germer CT. Sequential neoadjuvant chemotherapy with nab-paclitaxel plus gemcitabine and FOLFIRINOX in locally advanced pancreatic cancer (LAPC): A PILOT study. *J Clin Oncol* 2013; **31**: e15193 [DOI: 10.1200/jco.2013.31.15\_suppl.e15193]

31 **Reni M**, Balzano G, Zanon S, Passoni P, Nicoletti R, Arcidiacono PG, Pepe G, Doglioni C, Fugazza C, Ceraulo D, Falconi M, Gianni L. Phase 1B trial of Nab-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with unresectable or borderline resectable pancreatic adenocarcinoma. *Br J Cancer* 2016; **115**: 290-296 [PMID: 27404453 DOI: 10.1038/bjc.2016.209]

32 **Hammel P,** Lacy J, Portales F, Sobrero AF. Phase II LAPACT trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC). *J Clin Oncol* 2018; **36**: 204 [DOI: 10.1200/JCO.2018.36.4\_suppl.204]

33 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

34 **Paniccia A**, Edil BH, Schulick RD, Byers JT, Meguid C, Gajdos C, McCarter MD. Neoadjuvant FOLFIRINOX application in borderline resectable pancreatic adenocarcinoma: a retrospective cohort study. *Medicine (Baltimore)* 2014; **93**: e198 [PMID: 25501072 DOI: 10.1097/MD.0000000000000198]

35 **Choi YJ**, Byun Y, Kang JS, Kim HS, Han Y, Kim H, Kwon W, Oh DY, Paik WH, Lee SH, Ryu JK, Kim YT, Lee K, Kim H, Chie EK, Jang JY. Comparison of Clinical Outcomes of Borderline Resectable Pancreatic Cancer According to the Neoadjuvant Chemo-Regimens: Gemcitabine versus FOLFIRINOX. *Gut Liver* 2020 [PMID: 32839360 DOI: 10.5009/gnl20070]

36 **Weniger M**, Moir J, Damm M, Maggino L, Kordes M, Rosendahl J, Ceyhan GO, Schorn S; RESPECT-study group. Respect - A multicenter retrospective study on preoperative chemotherapy in locally advanced and borderline resectable pancreatic cancer. *Pancreatology* 2020; **20**: 1131-1138 [PMID: 32739267 DOI: 10.1016/j.pan.2020.06.012]

37 **Neoptolemos JP**, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet* 2001; **358**: 1576-1585 [PMID: 11716884 DOI: 10.1016/s0140-6736(01)06651-x]

38 **Chapman BC**, Gleisner A, Rigg D, Meguid C, Goodman K, Brauer B, Gajdos C, Schulick RD, Edil BH, McCarter MD. Perioperative outcomes and survival following neoadjuvant stereotactic body radiation therapy (SBRT) versus intensity-modulated radiation therapy (IMRT) in pancreatic adenocarcinoma. *J Surg Oncol* 2018; **117**: 1073-1083 [PMID: 29448308 DOI: 10.1002/jso.25004]

39 **Stokes JB**, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW. Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer. *Ann Surg Oncol* 2011; **18**: 619-627 [PMID: 21213060 DOI: 10.1245/s10434-010-1456-7]

40 **Takai S**, Satoi S, Yanagimoto H, Toyokawa H, Takahashi K, Terakawa N, Araki H, Matsui Y, Sohgawa M, Kamiyama Y. Neoadjuvant chemoradiation in patients with potentially resectable pancreatic cancer. *Pancreas* 2008; **36**: e26-e32 [PMID: 18192876 DOI: 10.1097/mpa.0b013e31814b229a]

41 **Cho IR**, Chung MJ, Bang S, Park SW, Chung JB, Song SY, Seong J, Hwang HK, Kang CM, Lee WJ, Park JY. Gemcitabine based neoadjuvant chemoradiotherapy therapy in patients with borderline resectable pancreatic cancer. *Pancreatology* 2013; **13**: 539-543 [PMID: 24075521 DOI: 10.1016/j.pan.2013.07.064]

42 **Christians KK**, Tsai S, Mahmoud A, Ritch P, Thomas JP, Wiebe L, Kelly T, Erickson B, Wang H, Evans DB, George B. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 2014; **19**: 266-274 [PMID: 24569947 DOI: 10.1634/theoncologist.2013-0273]

43 **Katz MH**, Shi Q, Ahmad SA, Herman JM, Marsh Rde W, Collisson E, Schwartz L, Frankel W, Martin R, Conway W, Truty M, Kindler H, Lowy AM, Bekaii-Saab T, Philip P, Talamonti M, Cardin D, LoConte N, Shen P, Hoffman JP, Venook AP. 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 [PMID: 27275632 DOI: 10.1001/jamasurg.2016.1137]

44 **Dholakia AS**, Hacker-Prietz A, Wild AT, Raman SP, Wood LD, Huang P, Laheru DA, Zheng L, De Jesus-Acosta A, Le DT, Schulick R, Edil B, Ellsworth S, Pawlik TM, Iacobuzio-Donahue CA, Hruban RH, Cameron JL, Fishman EK, Wolfgang CL, Herman JM. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumour-vessel relationships. *J Radiat Oncol* 2013; **2**: 413-425 [PMID: 25755849 DOI: 10.1007/s13566-013-0115-6]

45 **Zins M**, Matos C, Cassinotto C. Pancreatic Adenocarcinoma Staging in the Era of Preoperative Chemotherapy and Radiation Therapy. *Radiology* 2018; **287**: 374-390 [PMID: 29668413 DOI: 10.1148/radiol.2018171670]

46 **Ferrone CR**, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, Sabbatino F, Santos DD, Allen JN, Blaszkowsky LS, Clark JW, Faris JE, Goyal L, Kwak EL, Murphy JE, Ting DT, Wo JY, Zhu AX, Warshaw AL, Lillemoe KD, Fernández-del Castillo C. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg* 2015; **261**: 12-17 [PMID: 25599322 DOI: 10.1097/SLA.0000000000000867]

47 **Wagner M**, Antunes C, Pietrasz D, Cassinotto C, Zappa M, Sa Cunha A, Lucidarme O, Bachet JB. CT evaluation after neoadjuvant FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma. *Eur Radiol* 2017; **27**: 3104-3116 [PMID: 27896469 DOI: 10.1007/s00330-016-4632-8]

48 **Katz MH**, Fleming JB, Bhosale P, Varadhachary G, Lee JE, Wolff R, Wang H, Abbruzzese J, Pisters PW, Vauthey JN, Charnsangavej C, Tamm E, Crane CH, Balachandran A. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012; **118**: 5749-5756 [PMID: 22605518 DOI: 10.1002/cncr.27636]

49 **Yasuta S**, Kobayashi T, Aizawa H, Takahashi S, Ikeda M, Konishi M, Kojima M, Kuno H, Uesaka K, Morinaga S, Miyamoto A, Toyama H, Takakura N, Sugimachi K, Takayama W. Relationship between surgical R0 resectability and findings of peripancreatic vascular invasion on CT imaging after neoadjuvant S-1 and concurrent radiotherapy in patients with borderline resectable pancreatic cancer. *BMC Cancer* 2020; **20**: 1184 [PMID: 33267820 DOI: 10.1186/s12885-020-07698-0]

50 **Schellenberg D**, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, Fisher GA, Goodman KA, Koong AC, Chang DT. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; **77**: 1420-1425 [PMID: 20056345 DOI: 10.1016/j.ijrobp.2009.06.049]

51 **Akita H**, Takahashi H, Ohigashi H, Tomokuni A, Kobayashi S, Sugimura K, Miyoshi N, Moon JH, Yasui M, Omori T, Miyata H, Ohue M, Fujiwara Y, Yano M, Ishikawa O, Sakon M. FDG-PET predicts treatment efficacy and surgical outcome of pre-operative chemoradiation therapy for resectable and borderline resectable pancreatic cancer. *Eur J Surg Oncol* 2017; **43**: 1061-1067 [PMID: 28389044 DOI: 10.1016/j.ejso.2017.03.015]

52 **Nappo G**, Capretti GL, Petitti T, Gavazzi F, Ridolfi C, Cereda M, Montorsi M, Zerbi A. The evolution of post-operative pancreatic fistula (POPF) classification: A single-center experience. *Pancreatology* 2019; **19**: 449-455 [PMID: 30890308 DOI: 10.1016/j.pan.2019.03.004]

53 **Verma V**, Li J, Lin C. Neoadjuvant Therapy for Pancreatic Cancer: Systematic Review of Postoperative Morbidity, Mortality, and Complications. *Am J Clin Oncol* 2016; **39**: 302-313 [PMID: 26950464 DOI: 10.1097/COC.0000000000000278]

54 **Hackert T**, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, Strobel O, Jäger D, Ulrich A, Büchler MW. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. *Ann Surg* 2016; **264**: 457-463 [PMID: 27355262 DOI: 10.1097/SLA.0000000000001850]

55 **Marchegiani G**, Andrianello S, Nessi C, Sandini M, Maggino L, Malleo G, Paiella S, Polati E, Bassi C, Salvia R. Neoadjuvant Therapy Versus Upfront Resection for Pancreatic Cancer: The Actual Spectrum and Clinical Burden of Postoperative Complications. *Ann Surg Oncol* 2018; **25**: 626-637 [PMID: 29214453 DOI: 10.1245/s10434-017-6281-9]

56 **Blair AB**, Rosati LM, Rezaee N, Gemenetzis G, Zheng L, Hruban RH, Cameron JL, Weiss MJ, Wolfgang CL, Herman JM, He J. Postoperative complications after resection of borderline resectable and locally advanced pancreatic cancer: The impact of neoadjuvant chemotherapy with conventional radiation or stereotactic body radiation therapy. *Surgery* 2018; **163**: 1090-1096 [PMID: 29395234 DOI: 10.1016/j.surg.2017.11.027]

57 **Hank T**, Sandini M, Ferrone CR, Rodrigues C, Weniger M, Qadan M, Warshaw AL, Lillemoe KD, Fernández-Del Castillo C. Association Between Pancreatic Fistula and Long-term Survival in the Era of Neoadjuvant Chemotherapy. *JAMA Surg* 2019; **154**: 943-951 [PMID: 31411659 DOI: 10.1001/jamasurg.2019.2272]

58 **Mellon EA**, Strom TJ, Hoffe SE, Frakes JM, Springett GM, Hodul PJ, Malafa MP, Chuong MD, Shridhar R. Favorable perioperative outcomes after resection of borderline resectable pancreatic cancer treated with neoadjuvant stereotactic radiation and chemotherapy compared with upfront pancreatectomy for resectable cancer. *J Gastrointest Oncol* 2016; **7**: 547-555 [PMID: 27563444 DOI: 10.21037/jgo.2016.03.15]

59 **Takahashi H**, Ogawa H, Ohigashi H, Gotoh K, Yamada T, Ohue M, Miyashiro I, Noura S, Kishi K, Motoori M, Shingai T, Nakamura S, Nishiyama K, Yano M, Ishikawa O. Preoperative chemoradiation reduces the risk of pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. *Surgery* 2011; **150**: 547-556 [PMID: 21621236 DOI: 10.1016/j.surg.2011.03.001]

60 **Czosnyka NM**, Borgert AJ, Smith TJ. Pancreatic adenocarcinoma: effects of neoadjuvant therapy on post-pancreatectomy outcomes - an American College of Surgeons National Surgical Quality Improvement Program targeted variable review. *HPB (Oxford)* 2017; **19**: 927-932 [PMID: 28747265 DOI: 10.1016/j.hpb.2017.07.001]

61 **Cooper AB**, Parmar AD, Riall TS, Hall BL, Katz MH, Aloia TA, Pitt HA. Does the use of neoadjuvant therapy for pancreatic adenocarcinoma increase postoperative morbidity and mortality rates? *J Gastrointest Surg* 2015; **19**: 80-6; discussion 86-7 [PMID: 25091851 DOI: 10.1007/s11605-014-2620-3]

62 **Ecker BL**, McMillan MT, Allegrini V, Bassi C, Beane JD, Beckman RM, Behrman SW, Dickson EJ, Callery MP, Christein JD, Drebin JA, Hollis RH, House MG, Jamieson NB, Javed AA, Kent TS, Kluger MD, Kowalsky SJ, Maggino L, Malleo G, Valero V 3rd, Velu LKP, Watkins AA, Wolfgang CL, Zureikat AH, Vollmer CM Jr. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg* 2019; **269**: 143-149 [PMID: 28857813 DOI: 10.1097/SLA.0000000000002491]

63 **Kalimuthu SN**, Serra S, Dhani N, Chetty R. The spectrum of histopathological changes encountered in pancreatectomy specimens after neoadjuvant chemoradiation, including subtle and less-well-recognised changes. *J Clin Pathol* 2016; **69**: 463-471 [PMID: 26915370 DOI: 10.1136/jclinpath-2016-203604]

64 **Chatterjee D**, Katz MH, Rashid A, Estrella JS, Wang H, Varadhachary GR, Wolff RA, Lee JE, Pisters PW, Abbruzzese JL, Fleming JB, Wang H. Pancreatic intraepithelial neoplasia and histological changes in non-neoplastic pancreas associated with neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma. *Histopathology* 2013; **63**: 841-851 [PMID: 24111684 DOI: 10.1111/his.12234]

65 **Cheng TY**, Sheth K, White RR, Ueno T, Hung CF, Clary BM, Pappas TN, Tyler DS. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. *Ann Surg Oncol* 2006; **13**: 66-74 [PMID: 16372154 DOI: 10.1245/ASO.2006.02.003]

66 **Knaebel HP**, Diener MK, Wente MN, Büchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. *Br J Surg* 2005; **92**: 539-546 [PMID: 15852419 DOI: 10.1002/bjs.5000]

67 **Kamarajah SK**, Bundred JR, Boyle C, Oo J, Pandanaboyana S, Loveday B. Impact of neoadjuvant therapy on post-operative pancreatic fistula: a systematic review and meta-analysis. *ANZ J Surg* 2020; **90**: 2201-2210 [PMID: 32418344 DOI: 10.1111/ans.15885]

68 **Christians KK**, Heimler JW, George B, Ritch PS, Erickson BA, Johnston F, Tolat PP, Foley WD, Evans DB, Tsai S. Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy. *Surgery* 2016; **159**: 893-900 [PMID: 26602840 DOI: 10.1016/j.surg.2015.09.018]

69 **Roland CL**, Katz MH, Tzeng CW, Lin H, Varadhachary GR, Shroff R, Javle M, Fogelman D, Wolff RA, Vauthey JN, Crane CH, Lee JE, Fleming JB. The Addition of Postoperative Chemotherapy is Associated with Improved Survival in Patients with Pancreatic Cancer Treated with Preoperative Therapy. *Ann Surg Oncol* 2015; **22 Suppl 3**: S1221-S1228 [PMID: 26350371 DOI: 10.1245/s10434-015-4854-z]

70 **Pietrasz D**, Marthey L, Wagner M, Blanc JF, Laurent C, Turrini O, Raoul JL, Terrebonne E, Hentic O, Trouilloud I, Coriat R, Regenet N, Innominato P, Taieb J, Cunha AS, Bachet JB. Pathologic Major Response After FOLFIRINOX is Prognostic for Patients Secondary Resected for Borderline or Locally Advanced Pancreatic Adenocarcinoma: An AGEO-FRENCH, Prospective, Multicentric Cohort. *Ann Surg Oncol* 2015; **22 Suppl 3**: S1196-S1205 [PMID: 26271395 DOI: 10.1245/s10434-015-4783-x]

71 **Barnes CA**, Krepline AN, Aldakkak M, Clarke CN, Christians KK, Khan AH, Hunt BC, Ritch PS, George B, Hall WA, Erickson BA, Evans DB, Tsai S. Is Adjuvant Therapy Necessary for All Patients with Localized Pancreatic Cancer Who Have Received Neoadjuvant Therapy? *J Gastrointest Surg* 2017; **21**: 1793-1803 [PMID: 28849366 DOI: 10.1007/s11605-017-3544-5]

72 **van Roessel S**, van Veldhuisen E, Klompmaker S, Janssen QP, Abu Hilal M, Alseidi A, Balduzzi A, Balzano G, Bassi C, Berrevoet F, Bonds M, Busch OR, Butturini G, Del Chiaro M, Conlon KC, Falconi M, Frigerio I, Fusai GK, Gagnière J, Griffin O, Hackert T, Halimi A, Klaiber U, Labori KJ, Malleo G, Marino MV, Mortensen MB, Nikov A, Lesurtel M, Keck T, Kleeff J, Pandé R, Pfeiffer P, Pietrasz D, Roberts KJ, Sa Cunha A, Salvia R, Strobel O, Tarvainen T, Bossuyt PM, van Laarhoven HWM, Wilmink JW, Groot Koerkamp B, Besselink MG; European-African Hepato-Pancreato-Biliary Association. Evaluation of Adjuvant Chemotherapy in Patients With Resected Pancreatic Cancer After Neoadjuvant FOLFIRINOX Treatment. *JAMA Oncol* 2020 [PMID: 32910170 DOI: 10.1001/jamaoncol.2020.3537]

**Footnotes**

**Conflict-of-interest statement:** None of the authors have conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** February 28, 2021

**First decision:** April 6, 2021

**Article in press:** May 25, 2021

**Specialty type:** Surgery

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Shayesteh AA **S-Editor:** Zhang H **L-Editor:** Filipodia **P-Editor:** Li JH

**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 \*. | 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. | - | - | - |

1Some 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.

**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 | 9591 | 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, 17381 | 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, 4111 | R-PDAC, BR-PDAC | Gem, Gem+S1 | +/- | RCT |

1Patients 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.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**