ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript No. 7216).

Title: Borderline Resectable Pancreatic Cancer: Definitions and Management

Authors: Lopez, N.E., Prendergast, C. , Lowy, A.M.

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 7216

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
2 Revisions have been made according to the suggestions of the reviewers
Reviewer #1
This is a fine and thorough review of borderline resectable pancreatic cancer, and I have no significant criticisms to offer. I look forward to the results of the Alliance protocol.

Thank you.

Reviewer #2
The manuscript by Lopez and Lowy well presents the historical evolution of the concept of "borderline resectable PDAC and the justification for the current Alliance clinical trial. The following comments are offered to increase the impact of the manuscript:

1. The authors may wish to more clearly define the Ishikawa classification in the text of the manuscript, as well as reference the figure when this is first introduced (page 4).

Thank you for this comment. We have amended out manuscript to read as follows:

The Ishikawa classification, established by Ishikawa et al. in 1992, is based on radiographic findings that demonstrate the relationship of the tumor to the SMV-PV (I) normal, (II) smooth shift without narrowing, (III) unilateral narrowing (IV) bilateral narrowing and (V) bilateral narrowing and the presence of collateral veins (Figure 1). This classification has also been used to report the relationship between SMV-PV appearance by cross-sectional imaging and prognosis.

2. The major paragraph on page 5 is a bit confusing as a presentation for neoadjuvant chemotherapy blurring the focus on the impact on R0 resection, as well as the conversion from unresectable to resectable. Although both of these points are often covered in the same report, the authors may wish to break up these two impacts of neoadjuvant therapy.

Thank you for this suggestion, we have attempted to improve our manuscript by

separating these aspects in order to clarify the effects of neoadjuvant therapy.

Studies of patients with more advanced disease have also proposed that neoadjuvant therapy may result in downstaging, thereby improving the likelihood of R0 resection. In 1999 White et al. performed a study of 25 patients with locally advanced pancreatic cancer treated with neoadjuvant chemoradiation at Duke University finding that only a small percent were downstaged. 22 of 25 patients underwent restaging after chemoradiation, six of 22 (27.3%) had a decrease in size of the primary tumor and three of the 22 (13.6%) had overall disease regression by radiographic imaging.[1] White et al. later reported on 111 patients with PDAC, 53 with potentially resectable and 58 with locally advanced disease who underwent neoadjuvant treatment with chemoradiation followed by restaging and surgery as deemed appropriate. 11 of 58 (19%) patients with locally advanced disease underwent resection. 6 of 58 (11%) tumors were radiographically downstaged from locally advanced to potentially resectable by neoadjuvant.[2] Similarly, a slightly larger study at Memorial Sloan-Kettering published in 2001 reported only 3 of 87 (3.4%) patients with locally advanced disease who received neoadjuvant therapy had significant enough responses to warrant surgical exploration.[3] Together, these studies indicate that a small, but real population exists, in which neoadjuvant therapy appears to downstage pancreatic cancer. However, the lack of sensitivity of radiographic staging of pancreatic adenocarcinoma after chemoradiation indicates that radiographic tumor downstaging may not accurately reflect the benefit of neoadjuvant therapy.

Instead, margin status and histologic response may offer more reliable evidence of the efficacy of neoadjuvant therapy. In the above-mentioned studies published by White et al. in 1999, five of eight patients with either stable disease or disease regression at the time of restaging who underwent exploration were resected. One (4.5%) was resected with negative margins and negative nodes (R0).[1] A later study by the same group reported on 103 patients with potentially resectable or locally advanced disease that underwent neoadjuvant therapy followed by re-staging CT. Of 49 with locally advanced tumors on restaging CT, 11 (22%), were resected, and 6 (55%) of these were resected with negative margins, suggesting that reliance on the standard CT criteria for unresectability will deprive some patients of the opportunity for curative (R0) resection after neoadjuvant therapy.[4]

3. In the last section on page 5, the authors imply that reliance on CT will deprive 20% of patient the "opportunity for curative resection". This number applies to both R0 and R1, and the authors have already argued that R0 is the best chance for curative resection. So they may wish to re-word, or more accurately state that 6/49 (12%) of patients can achieve R0 resection.

Thank you for pointing this out, we have corrected the segment:

Of 49 with locally advanced tumors on restaging CT, 11 (22%), were resected, and 6 (55%) of these were resected with negative margins, suggesting that reliance on the standard CT criteria for unresectability will deprive approximately 6 of 49 or 12 % of patient of the opportunity for curative (R0) resection after neoadjuvant therapy.[4]

4. On page 8 for the Preoperative Imaging, the authors may wish to change this to Preoperative Evaluation and consider inclusion on the use of CA 19-9 to predict unresectable disease despite localized disease by preoperative imaging. This is briefly touched on for selection of laparoscopy, but there is significant data on preoperative CA 19-9.

Thank you, we have changed our text as follows:

Preoperative Evaluation

Role of CA 19-9

Among many tumor antigens that have been associated with pancreatic cancer, CA 19-9 is the best validated. It is a sialylated Lewis antigen and therefore is not detectable in Lewis antigen negative individuals.[5] Unfortunately, while relatively sensitive, its specificity is suboptimal as CA19-9 levels are often elevated in association with other pancreatic and hepatobiliary pathology, obstructive jaundice in particular.[6] Still, preoperative CA 19-9 has been shown to correlate with pancreatic cancer staging and therefore, resectability[7, 8]. Furthermore, post-resection CA 19-9 levels prior to initiation of adjuvant chemotherapy have been shown to have independent prognostic value and can be followed to indicate response to therapy.[9-11] As such, CA 19-9 levels should typically be drawn prior to surgery, following surgery prior to adjuvant therapy and during active surveillance.

Preoperative Imaging

5. On page 9, the authors discuss the placement of biliary stents for decompression during neoadjuvant therapy. They should be clear that covered stents (rather than uncovered) are preferred in the setting of potential resection.

Thank you for this suggestion, we have added the following to our discussion:

In the setting of neoadjuvant therapy, expandable short metal stents are preferred as they have longer patency, and therefore are associated with a lower risk of stent occlusion and resultant complication during induction therapy.[12, 13] Additionally, covered stents are associated with decreased tumor ingrowth and improved patency and are therefore preferred to uncovered stents.[14, 15]

6. On page 15 for the discussion of the radiologic criteria, do the authors mean that interfaces exist in criteria 1, 2, and 4, or a loss of the interface with the noted extent? Perhaps more consistent terminology with the Table should be used.

We agree. Accordingly, we have changed the content of the text and the table to be

consistent as follows:

With an aim to establish a clear, reproducible means by which to define borderline resectable PDAC by radiologic criteria, the trial has recognized any one or more of the following identifiers of borderline resectable PDAC: 1) Interface exists between tumor and the SMV/portal vein measuring 180 degrees or greater of the vessel wall circumference, and/or reconstructable venous occlusion 2) Interface exists between tumor and the SMA measuring less than 180 degrees of the vessel wall circumference 3) A reconstructable, short-segment interface of any degree exists between tumor and the common hepatic artery and/or 4) Interface exists between tumor and the celiac trunk measuring less than 180 degrees of the vessel wall circumference.

	AHPBA/SSAT/SSO/NCCN[16]	M.D. Anderson[17]	Alliance[18]
SMV/PV	Abutment, impingement, encasement of the SMV/PV or short segment venous occlusion	Occlusion	Tumor-vessel interface ≥180° of vessel wall circumference, and/or reconstructable occlusion
SMA	Abutment	Abutment	Tumor-vessel interface <180° of vessel wall circumference
HA	Abutment or short segment encasement	Abutment or short segment encasement	Reconstructable short segment interface of any degree between tumor and vessel wall
CA	Uninvolved	Abutment	Tumor-vessel interface <180° of vessel wall circumference

7. In Table 2, the data on % resected and % negative margins should be rounded to the whole figure (the data does not allow that precision).

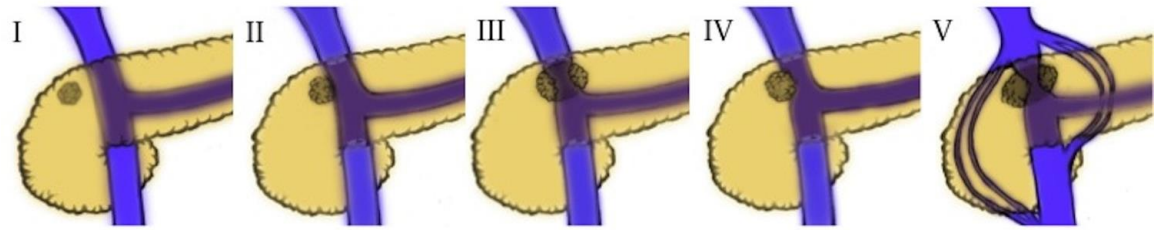
We have amended the table as suggested.

Author	Year	Study type	Study size	Number with borderline	Neoadjuvant	% Resected	% Negative	Median OS (mont

				resectable (Definition)			Margins	hs)
Chuong[86]	2013	Single institution retrospective	73	57 (NCCN)	Majority gemcitabine based induction chemotherapy, SBRT	56	96	16.4
Katz[87]	2012	Single institution retrospective	129	115 (AHPBA/SSAT/ SSO/NCCN) or 72 (MDA)	Gemcitabine based chemotherapy and chemoradiation or chemoradiation alone	84 or 78	95*	33*
Barugola[91]	2012	Single institution retrospective	362	27 (Other)	Gemcitabine based chemotherapy and chemoradiation or chemotherapy alone	NR	NR	NR
Kang[93]	2012	Single institution retrospective	202	35 (NCCN)	Gemcitabine based chemoradiation	91	87	26.3
Stokes[81]	2011	Single institution retrospective	170	40 (MDA)	Capecitabine-based Chemoradiation	46	75	23
Chun[78]	2010	Single institution retrospective	109	109 (Other) 74 received neoadjuvant (#)	5-FU or gemcitabine based chemoradiation	100	59#	23#
McClaine[103]	2010	Single institution retrospective	29	29 (MDA+NCCN hybrid)	Gemcitabine based chemotherapy, chemoradiation or both	46	67	23.3
Landry[84]	2010	Randomized Phase II Trial	21	21 (Other)	Gemcitabine based	24	60	26.3
Turrini[89]	2009	Single institution	64	49 (MDA)	5-FU/Cisplatin based chemoradiation	18	100	24

		retrospective						
Katz[31]	2008	Single institution retrospective	160	160 (MDA)	Gemcitabine based chemotherapy, chemoradiation	41	94	40

8. In Figure 1, the exact details of the SMV/PV involvement is difficult to see. The authors may wish to enlarge that part of the figure (ie the entire pancreas does not need to be illustrated).
We agree, we have adjusted the figure to reflect this:



Reviewer #3
Minor comments:
1.Please write "Gastroduodenal artery encasementup to the hepatic artery....." and not "GDA encasement up to the HA". The abbreviations have not been explained earlier in the text.

Thank you, we have corrected the text to read:

2) Gastroduodenal artery encasement up to the hepatic artery and short segment encasement/direct tumor abutment of the hepatic artery with no extension to the celiac axis, or

2. The feasibility and associated morbidity and mortality of combined vascular resection with pancreaticoduodenectomy for pancreatic cancer remain important concerns for the surgical oncologist. The authors describe the complication rate of EUS guided FNA in pancreatic cancer. However, there are no comments on the morbidity of pancreatic resections and concomitant vascular resection in patients with borderline resectable pancreatic cancer in the current paper. This topic has been highlighted in some recent reports from the United States (Castleberry et al: Ann Surg Oncol 2012: The Impact of Vascular Resection on Early Postoperative Outcomes after Pancreaticoduodenectomy: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program Database + J Tseng:Ann Surg Oncol 2012: Proceed with Caution: Vascular Resection at Pancreaticoduodenectomy+Worni M: JAMA Surg 2013: Concomitant vascular

reconstruction during pancreatectomy for malignant disease: a propensity score-adjusted, population-based trend analysis involving 10,206 patients). The authors state that patients with borderline resectable pancreatic cancer "often require more complex resections". This issue should be addressed in more detail and with some references.

Role of Vascular Resection

The increasing safety and feasibility of aggressive surgical resections have been central to the evolution of the concept of borderline resectable pancreatic cancer. Still, vascular resection in PD remains an area of controversy. Several studies confirming similar outcomes after PD with SMV-PV resection in comparison to PD alone were crucial in the advent of borderline resectable disease.[29-32] Even so, two recent, large database studies have called these data into question. In 2012 Castleberry et al. published a study using the National Surgical Quality Improvement Program (NSQIP) database to analyze all patients undergoing PD. They found that PD with VR was associated with significantly increased morbidity and mortality.[33] Similarly, Worni et al. used the National Inpatient Sample (NIS) database to show comparable increases in morbidity and mortality associated with the addition of VR to PD.[34] These studies are subject to the criticisms of any large database study. In particular, they cannot distinguish the operations performed in which vascular resection was anticipated and planned as opposed to the vascular resection performed in the setting of vascular injury when an adherent tumor is attempted to be removed. These no doubt result in much different rates of blood loss, and morbidity. Nevertheless, these studies call attention to the continued risks associated with vascular resection and are a reminder to emphasize multidisciplinary treatment and planning prior to proceeding with surgical resection in order to reduce perioperative risk in these patients.[35]

Data with regard to arterial resection (AR) are even fewer. Some groups suggest similar morbidity and mortality in PD with AR in comparison to PD alone.[36][37] However, most studies indicate that AR significantly increases morbidity and mortality and therefore recommend this approach only for the purposes of obtaining an R0 resection.[38] Additionally, some suggest that AR may provide improved survival in comparison to palliation alone.[39-41]

Though not unanimously employed, SMV-PV resection is more widely accepted than AR. In either case, patient selection is paramount to achieving favorable outcomes.

3. In the literature, it seems to be a relatively good agreement on the anatomical definitions of borderline resectable pancreatic cancer. However, the authors describe a non-anatomical definition of borderline resectable pancreatic cancer based on clinical criteria, recommended by MD Anderson Cancer Centre. Has other centres or associations/societies supported this as part of the definition of borderline resectable pancreatic cancer? If not, why?

Katz groups B and C were established to recognize clinical subgroups, in addition to the well-recognized anatomic subgroup (Katz Group A), in which staging and treatment for pancreatic cancer were unclear. Many authors acknowledge these clinical definitions, however, few have utilized Katz groups in defining study populations.[42-44] Staging and treatment in clinically defined borderline resectable disease (Groups B and C) deserves attention, however, current efforts focusing on the more widely accepted anatomic

definitions have tended to take precedence.

4. Regarding the anatomic guidelines I recommend to update the reference list with a recent paper (Tran Cao et al: J Gastrointest Surg 2013: Radiographic Tumor-Vein Intreface as a Predictor of Intraoperative, Pathological, and Oncological Outcomes in Resectable and Borderline Resectable Pancreatic Cancer).

Thank you, to our section on anatomic guidelines we have added:

More recently, Tran Cao et al. have employed a simplified radiographic classification system—Tumor-vein circumferential interface (TVI)—grouping findings as: no interface, ≤180° of vessel circumference, >180° of vessel circumference, or occlusion. The TVI system was found to be predictive of the need for venous resection, histologic venous invasion, and survival.[45]

5. The authors recognize a growing national interest (i.e. in the United States) in serving patients with borderline pancreatic cancer. In this comprehensive review, submitted to the World Journal of Gastroenterology, it would be interesting to have some comments by the authors on the international interest on this topic. Are there any differences between the United States, Asia or Europe in the management of borderline pancreatic cancer?

Like the United States, Asia and Europe have tended toward increasingly aggressive treatment of borderline resectable pancreatic cancer. Europeans have focused on chemotherapy rather than radiation therapy, seeking improved neoadjuvant and adjuvant regimens to control systemic disease—as this is the most common cause of treatment failure.[21, 27, 46-49] Asian countries have also employed neoadjuvant strategies, but with increased emphasis on determining how it effects surgical resection.[22, 50-52] Additionally, they have focused on defining radiographic criteria to predict surgical outcomes as well as surgical aspect that influence outcomes, such as likelihood of R0 resection, and need for vascular resection.[53-56]

Major comment: "Borderline Resectable Pancreatic Cancer: Definition and Management" is a well written scientific paper. It addresses an important topic and gives an extensive review on the history, progress, current treatment recommendations and future directions for research in borderline resectable pancreatic cancer. I am more than happy to support the acceptation of this manuscript in its original format, but the authors are recommended to incorporate my minor comments into the manuscript.

Your feedback is much appreciated. We believe the suggested revisions have improved the quality of the paper and hope that you agree.

Reviewer #4
The review is well written and suitable for surgeons. However, the interest for other professionals such as gastroenterologist, oncologist or researchers is limited. Difficult to understand for these other professionals, it would be helpful to make some modifications:

-Define acronyms (such as SMV/PV etc)

-In Table I should be clarified describing whats is the first column/line
Thank you, we have added a column heading as indicated below:

Effected vessel	AHPBA/SSAT/SSO/NCCN[16]	M.D. Anderson[17]	Alliance[18]
SMV/PV	Abutment, impingement, encasement of the SMV/PV or short segment venous occlusion	Occlusion	Tumor-vessel interface ≥180° of vessel wall circumference, and/or reconstructable occlusion
SMA	Abutment	Abutment	Tumor-vessel interface <180° of vessel wall circumference
HA	Abutment or short segment encasement	Abutment or short segment encasement	Reconstructable short segment interface of any degree between tumor and vessel wall
CA	Uninvolved	Abutment	Tumor-vessel interface <180° of vessel wall circumference

-Discussion section should be included. Here, a summary and discussion of studies presented should be presented.

We accept this criticism, however upon review of the text we believe we have provided this in the original draft.

-Last part of the review, when authors talk about chemotherapy is very confusing and should be re-structured. For example, the sentence "adjuvant chomotherapy with gemcitabine.....As of November 1, 2013, 10 of the targeted 20 patients had been accrued" Is this paragraph complete?

-Last paragraph before the conclusion is incomprehensible

Thank you for your comments. We have attempted to clarify the two points stated above by revising the paragraphs as follows:

The use of modified FOLFIRINOX (mFOLFIRINOX) as induction therapy in the Alliance Trial is based on the superior survival and response rates observed for FOLFIRINOX in metastatic pancreatic cancer in a randomized controlled trial of 342 patients with metastatic pancreas cancer. The dosing was modified in an attempt to partially circumvent the greater toxicity associated with FOLFIRINOX in comparison to gemcitabine. While FOLFIRINOX displayed improved median overall survival (11.1 months versus 6.8 months; P<0.001), median progression-free survival (6.4 months versus 3.3 months; P<0.001) and objective response (31.6% versus 9.4%; P<0.001), toxicities including neutropenia, febrile neutropenia, fatigue, vomiting and diarrhea were all worse with FOLFIRINOX.[57] The Alliance Trial is therefore utilizing a modified regimen, or mFOLFIRINOX, in which the 5-FU bolus has been dropped, but all other dosing remains the same, in an effort to reduce these toxicities.

After resection, borderline resectable pancreatic caner is treated similar to any other resected PDAC. Consequently, adjuvant chemotherapy in this trial is administered according to the standard gemcitabine regimen used following resection of PDAC.[58]

This benchmark trial will assess the feasibility of multi-institutional efforts to study the subset of patients regarded as having borderline resectable disease and establish a foundation for future studies in this group of patients. While the primary endpoint of the study is, in fact, accrual, it will be of great interest to assess the activity of the neoadjuvant regimen by secondary endpoints such as the number of patients who undergo negative margin resection and overall survival. As of December 14, 2013, 14 of a targeted 20 patients had been accrued, suggesting a promising outcome for this trial.

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3 References and typesetting were corrected

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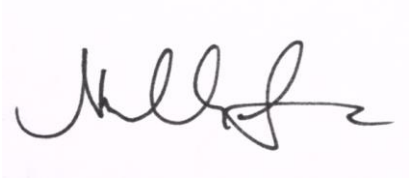

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