

## Peer Review File

Article information: <http://dx.doi.org/10.21037/tcr-22-1258>

### Reviewer A

Huang et al. published a single center retrospective study to evaluate the usefulness of the biological and the conditional resectability criteria of BR-PDAC as proposed by the IAP. It is an interesting and relevant topic. This is a well-conducted study and the data are presented logically and clearly.

I have two major comments.

#### Comment 1:

The study included patients with resectable PDAC according to the NCCN guidelines. These anatomical criteria are different from the anatomical definition of BR-PDAC at the IAP in 2016. In the analysis, the authors compared resectable PDAC versus borderline resectable PDAC according to the IAP definitions. It is confusing because in fact they only include BR PDAC considering the biological criteria, the conditional criteria but not the anatomical criteria. The authors should clarify this point in the introduction and the method.

#### Reply 1:

Thanks for your advice!

As the title of this article suggests, the study focuses on the significance of IAP biological and conditional resectability criteria for the evaluation of resectability of pancreatic cancer, and to avoid analysis bias due to unbalanced anatomical baseline characteristics, the study requires that included subjects should be evaluated as anatomically resectable before surgery.

The hypothesis of our study was that even if the patient was diagnosed as anatomically resectable PDAC according to NCCN criteria and underwent radical resection, the prognosis was still poor due to unfavorable biological and conditional factors.

Indeed, it should be noted that the anatomical resectability criteria of NCCN differ from the IAP criteria, but all the included patients met the IAP anatomical resectable criteria as well as the NCCN by retrospective assessment: although preoperative CT imaging in 14 (14.4%) subjects suggested tumor contact with PV/SMV, but no PV/SMV contact 180° or greater and no venous vein contour irregularity.

We have added relevant texts as advised (see Page 04, line 97).

#### Changes in the text:

Page 04, line 97: The hypothesis of this retrospective study was that even if the patient was diagnosed as anatomically resectable PDAC according to NCCN criteria and underwent radical resection, the prognosis was still poor due to unfavorable biological and conditional factors.

Page 08, line 211 : It should be noted that the anatomical resectability criteria of NCCN differ from the IAP criteria, but all the included patients met the IAP anatomical resectable criteria as well as the NCCN by retrospective assessment: although preoperative CT imaging in 14 (14.4%)

subjects suggested tumor contact with PV/SMV, but no PV/SMV contact 180° or greater and no venous vein contour irregularity.

**Comment 2:** Only three patients were considered borderline resectable due to conditional criteria. The power of the study is then too low to conclude that IAP criteria should be considered to evaluate the resectability of pancreatic cancer. According to the results of this study, it would be more appropriate to conclude on the importance of the biological criteria according to IAP guidelines to assess the resectability of PDAC.

**Reply 2:**

Thanks for your advice!

We acknowledge that the present study was limited to a single-center retrospective design and a small sample size. Whether conditional factors should be included in the resectability criteria needs to be validated by prospective and large cohorts.

We have modified our text as advised (see Page 02, line 43 and Page15, line 424).

**Changes in the text:**

Page 02, line 43: The prognosis of patients with PDAC that undergo resection can be predicted more accurately by assessing the resectability of pancreatic cancer combined with anatomical and biological factors according to IAP criteria. Whether conditional factors should be included in the resectability criteria needs to be validated by prospective and large cohorts.

Page15, line 424: In summary, the IAP-criteria marked the way forward for future studies, and it is justified to evaluate the resectability of pancreatic cancer, combined with anatomical and biological factors according to IAP criteria. Whether conditional factors should be included in the resectability criteria needs to be validated by prospective and large cohorts.

**Reviewer B**

The authors reviewed their experience of patients with anatomically resectable pancreatic cancer who underwent upfront resection and test the validity for the classification for biological borderline resectable by IAP. They demonstrated that the patients with IAP-BR disease had shorter RFS and OS compared with those with IAP-R disease, and they concluded IAP criteria was valid.

**Comment 3:** While the number of patients was large enough and their statistical method appeared sound, this issue was tested and reported by many other series. Given they did not provide any novel findings, at least they should review the literature more extensively and cited appropriate references in the discussion.

**Reply 3:**

Thanks for your advice!

Although the IAP criteria have been proposed for many years, clinical practice in pancreatic surgery still pays less attention to the significance of biological and conditional factors for resectability assessment of PDAC in China. We conducted the present study in the hope that

the IAP criteria would attract more attention and discussion among experts and scholars. We acknowledge that this is only a retrospective study from a single-center, and more prospective studies are needed to verify our research conclusions or generate new ideas.

We have made relevant additions to the discussion section by referring to the latest research papers as advised. A review of several currently prevailing definitions of borderline resectable pancreatic cancer is presented as Table 3 (see Page 15, line 409 and Table 3).

**Changes in the text:**

Page 15, line 409: In fact, there is still a great heterogeneity of borderline resectable definition of PDAC can be observed in different guidelines and criteria at present (Table 3). From the anatomical dimension, for example, many different terms (“abutment”, “encasement” and “occlusion”) can lead to biased interpretations (20) and cross-sectional comparison of different research findings becomes difficult. Although the IAP criteria have been proposed for many years, biological and conditional criteria of BRPC are still not widely adopted by the clinical practice (21-22). An increasing number of studies have begun to focus on the importance of biological and conditional factors on the resectability of pancreatic cancer, however, most studies, including present study, are limited by a retrospective design or a relatively small sample size. More prospective studies are required to clarify the controversial issues on IAP-criteria and promote its transformation from an expert consensus to a widely accepted clinical practice guideline.

**Comment 4:** The more detailed data for adjuvant chemotherapy should be presented in the method.

**Reply 4:**

Thanks for your advice!

The impact of adjuvant chemotherapy on the prognosis of patients with anatomically resectable pancreatic cancer was not specifically analyzed in this study, limited by inconsistent adjuvant chemotherapy regimens.

We added more detailed data about adjuvant therapy in the results section as advised (see Page 10, line 261).

**Changes in the text:**

Page 10, line 261: A total of 70 (72.2%) pancreatic cancer patients received at least one cycle of postoperative adjuvant chemotherapy after undergoing radical resection. Among them, 40 (57.1%) patients received adjuvant chemotherapy for more than 3 months; 18 (25.7%) patients received adjuvant chemotherapy for more than 6 months. 38 (54.3%) patients changed their regimen during adjuvant chemotherapy because of disease progression or toxicity intolerance or other reasons. Adjuvant chemotherapy regimens including Gemcitabine (Gem) (n=41), FOLFIRINOX (n=10), Gem+Nab-Paclitaxel (n=7), S-1 (n=5), Gem+S-1 (n=4) and Gem+Capecitabine (n=3). There was no significant difference in the rate of adjuvant chemotherapy between the IAP-R and IAP-BR groups (68.4% vs. 78.6%;  $p>0.05$ ).