

Peer Review File

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Reviewer A

Comment 1: Because of the retrospective character of the study, it remains unclear how was the decision to perform extended lymphnode dissection met by the surgeon - apparently extended lymphnode dissection was performed not only for borderline tumors but also for standard resectable tumors (n=49, Table 2). On the other hand, standard LN-Dissection was performed in 53 patients with large borderline tumors - why? Did the extent of resection depend upon the operating surgeon? how many surgeons performed the procedures and were they equally experienced. What about the 27 patients who received neoadjuvant therapy - these had suffered obviously advanced tumors before surgery - however half of them received only standard LN-dissection - please discuss it.

Reply 1: Thanks for your comment, this is indeed a difficult choice. At present, there is no clear indication for enlarged lymph node dissection in the world. Our center's enlarged lymph node dissection for pancreatic cancer is mainly based on preoperative imaging examination. When the tumor was more than 4cm, the imaging examination shown celiac lymph node enlargement. Imaging examination was considered as borderline resectable pancreatic cancer patient, which was recommended to extended lymphadenectomy. On the other hand, as our study is a retrospective study, it may be affected by the habits of the surgeons.

Comment 2: Would you explain the small number of patients who received adjuvant chemotherapy - 33% (line 152). This fact would explain the surprisingly poor survival compared to other contemporary series on multimodally treated PDAC.

Reply 2: For resectable PDAC, it is not clear whether neoadjuvant chemotherapy can improve survival, and our center does not recommend neoadjuvant chemotherapy for resectable patients, but we recommend that patients with smooth postoperative recovery and good PS score receive chemotherapy as soon as possible. However, due to the differences in individual conditions of patients, the postoperative chemotherapy rate of resectable PDAC was 40%. For borderline resectable PDAC, neoadjuvant chemotherapy can indeed improve the survival time reported in the literature, but this improvement is limited to patients who underwent sequential resection after neoadjuvant chemotherapy, so the effective rate of neoadjuvant chemotherapy determines whether it can ultimately improve the overall prognosis of junctional resectable PDAC. At present, it is reported in the international literature that the surgical conversion rate after neoadjuvant chemotherapy is about 60%, while the R0 resection rate after operation ranges from 40% to 80%. At present, the most commonly used neoadjuvant regimen is FOLFIRINOX, which has great side effects for Asian people, and the surgical conversion rate is only about 25% as asserted in the previously reported

literature (DOI: 10.5009 / gnl19182). Our center will fully inform patients of the advantages and disadvantages of direct surgery and neoadjuvant sequential surgery, and it is up to doctors and patients to make the choice of treatment plan. Therefore, the rate of adjuvant chemotherapy in this group is relatively low, about 33%.

Comment 3: line 125 - a total of... patients were identified - the number is missing.

Reply 3: We have added the number.

Comment 4: What is the reason for the extraordinary long duration of surgery in the standard LN-Dissection group - more than 9 hours (table 2)?

Reply 4: Sorry for this misunderstanding, but we calculated the duration of surgery here, which includes the total time of the patient from entering the operating room to leaving the operating room, so it may be misleading to readers.

Comment 5: Another major issue of concern is the small number of harvested Lymphnodes in both groups, especially in the extended LN-dissection group an average of only 21 lymphnodes was retrieved. If the authors did really perform extended LN-Dissection according to the scheme given in Table 1 there should be no single patient with less than 25 nodes harvested. Please discuss the role of pathological analysis of the specimen. Since the intraoperative images confirm a really extended LN dissection it should be the pathologist who found too little nodes?

Reply 5: Yes, indeed, there should be more than 30 nodes for every single patient who underwent extended LN-Dissection, however, all the data about the number of lymph nodes in postoperative pathology came from the pathology department of our center and were recorded and sorted out by professional pathologists, who may have a vague concept of the surgical method and scope. We will arrange specialized doctors to assist and accompany the pathologists to obtain the data in future prospective studies.

Comment 6: The authors should be congratulated for the low rate of clinically relevant POPF - 13/322 in the whole collective which equals to 4%! This POPF rate is significantly lower than all other reported current series and the technique of pancreatic anastomosis should be presented - was it a PJ or PG, were stents used, octreotide? DGE was also less than 10%, which is also a super result. In summary, all kind of procedure specific complications (POPF, biliary fistula, PPH and DGE) were very rare - what was then the reason for the relatively long postoperative stay of 17 days?

Reply 6: Sorry for this misunderstanding. As shown in Table 3, the rate of clinically relevant POPF should be 12.1% (39/322), because biochemical fistula, it used to be called grade A pancreatic fistula, which is also a type of pancreatic fistula. The overall incidence of postoperative complications in our study was 27.9%, which was consistent with the results reported in the literature. Diarrhea after celiac

lymph node dissection is mainly due to excessive dissection of mesenteric vessels, nerves and connective tissue or excessive amputation of mesenteric vessels, as for the extended LNectomy, we try to preserve the blood supply of the intestinal tract as much as possible and reduce excessive cleaning of nerve connective tissue during the surgery. In addition, we will also make different medication strategies according to the intraoperative pancreas texture and thickness of pancreatic duct after surgery.

In terms of postoperative hospital stay, it may be related to single center selection bias. On the one hand, all the patients in this study were operated by laparotomy, and they need to be hospitalized for at least 10 days after operation to remove sutures. On the other hand, this study included a higher proportion of patients with combined vascular resection and extended lymph node dissection, and the discharge criteria were more cautious. In addition, for China's national conditions, inpatients return to their families for recuperation after discharge, and there is no community hospital for rehabilitation, so the postoperative hospital stay is relatively long.

Comment 7: As the paper focused on LN-dissection it would be of interest to know the rate of chyle leak in both study groups - was it higher in patients with extended ln-dissection?

Reply 7: Sorry to delay so long time to reply your comments, it's very helpful, however as a result of our review the span is too long, many patients are not in postoperative early review of chyle leakage check, due to less data into groups, is likely to be biased overall data, so we couldn't added portion of the data, but in a prospective study of the future, We will definitely add this data

Comment 8: There should be a mistake in the total number of retrieved lymphnodes - in table 2 tha maximal number of harvested LN was 30 ragarding the whole study population, whereas table 6 says the maximal number was 32? how is this possible.

Reply 8: Here, due to our clerical error, the maximal number should be 32.

Comment 9: The conclusion that "Patients with borderline resectable pancreatic head cancer tended to have vast lymph node metastasis" is not supported by the reported results - even BRPC with extended dissection had only 4 positive LN out of 24 retrieved LN on average - a LH ratio of 0,16!

Reply 9: Since this is a retrospective study, at this point we consider that the proportion change may be caused by the large number of dissected lymph nodes. At the same time, we also change the meaning of the original sentence to say that "Patients with borderline resectable pancreatic head cancer have a higher possibility of lymph node metastasis".

Comment 10: Also, the authors` statement that extended LN dissection improves survival is not supported by the presented data. The conclusion of the paper should be revised to mirror the objective data. In my opinion, the real message of the manuscript is: with regards to long term survival extended lymphnode dissection cannot compensate for missing adjuvant chemotherapy.

Reply 10: Thanks for your valuable comments, which are the main gist of our manuscript. We believe that for borderline resectable pancreatic head cancer, expanded lymph node dissection is helpful for long-term survival compared with standard lymph node dissection. Of course, we also include your suggestions in the final conclusion and we have modified it (page27, line350-351).

Reviewer B

Comment 1: The study design should be reconsidered. For example, it seems better to select a historical cohort study in which only borderline resectable pancreatic head cancer is extracted. Then, a multivariate analysis is performed to adjust prognostic factors (number of lymph node metastases, etc.) to clarify the extended lymphadenectomy benefits patients with borderline resectable pancreatic head cancer.

Reply 1: Thanks for your comment, this is indeed a difficult choice. At present, there is no clear indication for enlarged lymph node dissection in the world. Our center's enlarged lymph node dissection for pancreatic cancer is mainly based on preoperative imaging examination. When the tumor was more than 4cm, the imaging examination shown celiac lymph node enlargement. Imaging examination was considered as borderline resectable pancreatic cancer patient, which was recommended to extended lymphadenectomy. On the other hand, as our study is a retrospective study, it may be affected by the habits of the surgeons. In addition, our retrospective study focuses more on the comparison between the two groups. In future prospective studies, we will conduct a more comprehensive multivariate analysis.

Comment 2: Previous randomized controlled trials comparing extended versus standard lymphadenectomy in pancreatoduodenectomy have not shown extended lymphadenectomy effectiveness. Are there any differences in the extended lymphadenectomy in this study in comparison with the dissection range of previous comparative studies? Are there anatomical landmarks in the area of peri-SMA lymph node dissection or per-aortic lymph node dissection?

Reply 2: See Table 1. We have added it in our manuscript, see page9,line114-126: Some studies have shown that enlarged dissection of retroperitoneal lymphoid tissue and nerve plexus was performed on the basis of radical pancreaticoduodenectomy for pancreatic head cancer. the postoperative histopathology showed frequent lymph node metastasis from celiac trunk to superior mesenteric artery. it is closely related to the prognosis of pancreatic cancer, suggesting that extended lymph node dissection can benefit the survival

of patients. Therefore, on the basis of standard dissection range, we dissected the lymph nodes behind the hepatic artery (8p), around the celiac artery (9), around the proper hepatic artery (12a), behind the portal vein (12p), around the superior mesenteric artery (14a-d), and around the abdominal aorta (16a2c16b1). The scope of dissection was up to the hepatic hilum, down to the beginning of the inferior mesenteric artery, left to the left edge of the abdominal aorta, and right to the right renal hilum to complete the dissection of lymph, nerve and connective tissue in this area.

Comment 3: Did borderline resectable pancreatic head cancer increase the number of lymph node metastases in the extended lymphadenectomy area? Where did the rate of lymph node metastasis increase?

Reply 3: Since this is a retrospective study, at this point we consider that the proportion change may be caused by the large number of dissected lymph nodes. At the same time, we also change the meaning of the original sentence to say that “Patients with borderline resectable pancreatic head cancer have a higher possibility of lymph node metastasis”.

Comment 4: Although the authors described prognostic factors associated with lymph node metastasis in the discussion part, this study aimed to examine the effectiveness of extended lymphadenectomy, not to investigate the prognosis of lymph node metastasis. I think it is better to delete the description that was not related to the research purpose and add the related information. It is not clear what “these” mean in “All these data support” and “all these suggest” in the discussion part.

Reply 4: Thanks for your valuable comments, which are the main gist of our manuscript. We believe that for borderline resectable pancreatic head cancer, expanded lymph node dissection is helpful for long-term survival compared with standard lymph node dissection. Of course, we also include your suggestions in the final conclusion and we have modified it (page27, line350-351).

Reviewer C

Comment 1: Extended LN dissection for PDAC is one of the most important topics remained. In this article, the authors have compared the extended lymphadenectomy and standard lymphadenectomy groups with a consideration of BLRPC. However, this article has not mention about multivariate analyses. Log-rank and HR should be presented, and then if extended lymphadenectomy is the significant, they can conclude as they mentioned.

Reply 1: Thanks for your valuable comments, which are the main gist of our manuscript. Our retrospective study focuses more on the comparison between the two groups. In future prospective studies, we will conduct a more comprehensive multivariate analysis. We believe that for borderline resectable pancreatic head cancer, expanded lymph node dissection is helpful for long-term survival

compared with standard lymph node dissection. Of course, we also include your suggestions in the final conclusion and we have modified it (page27, line350-351).