Peer Review File

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Reviewer A

Thank you, dear professor, for your opinion in our study and for your valuable comments that added a lot to our manuscript. All the following responses were added to the manuscript.

Comment 1: 93 - I know it was prospective, but I can't figure out if pts were required to sign consent, or if this was a dry data review? Possibly address that here or in line 157.

Reply 1: I t was dry data review, but patients were required to sign an informed consent as recommended by the ethical committee at our institute before taking the patient's data for research purpose.

Comment 2: 163- i think you should consider reporting in this section other risk factors such as deleterious cancer germline mutations, eg BRCA NHPCC CDKN2A; or deleterious non cancer germline mutations, eg for hereditary pancreatitis, or Peutz Jehgers; or if there was a family history of pancreatic cancer in the family? I understand that combines these represent perhaps only ~10% of risk factors for PC, but the more this is discussed and considered, then the more families can be screened in the future.

Reply 2: I agree that germline mutations are of great value when screening for cancer pancreas, unfortunately, regarding the cancer germline mutations, the tests are not available in our country and couldn't be done while regarding the non-cancer germline mutations, I added the family history of pancreatic cancer in the results section at the paragraph with the starting line 163 and added it as well in table 1, but cases of hereditary pancreatitis and Peutz-Jehger syndrome are not common in our country but it could be considered in future studies.

Changes in the text: The prevalence of DM, hypertension, hyperlipidaemia, smoking, obesity, **family history of PC** and alcohol were 60%, 52%, 40%, 52%, 80%, **12%** and 8% respectively.

Comment 3: 170 - Table 1 - i don't think any presenting symptoms eg jaundice or pain, should be included with 'baseline characteristics'. I think presenting symptoms merit a separate mention, either alone in the text as you have on line 169, and / or a smaller new table.

Reply 3: I removed them from Table 1.

Comment 4: 183 - out of curiosity, of the patients who were considered to borderline resectable by either CT or EUS, were any offered neoadjuvant chemo, and did any accept and not be included in this analysis? I understand that this was not the purpose of the study, but I am curious about the big picture and flow of patients? That is, what sort of selection bias might be occurring?

Reply 4: As you kindly mentioned, this was not the purpose of the study but it is an important topic for future studies, they were offered neoadjuvant chemo and they refused to receive it and wanted to proceed to surgery. Patients who choose to receive neoadjuvant chemo were omitted from the study as mentioned in the exclusion criteria as they can impact our results by changing the size of the tumor thus affecting its relation to the nearby blood vessels.

Comment 5: 289 when you are completing the discussion of prior LN findings, please consider reviewing your LN findings in 304-309. (Move 304-309 to the end of 289?)

Reply 5: I moved 304-309 to the end of 289. Thank you for your comment.

Change in the text: Regarding peri-pancreatic LN and overall vascular involvement, there have been only a limited number of studies that have investigated this matter. Significantly, the systematic review and meta-analysis conducted by Dewitt et al. included 11 meticulously conducted studies involving a total of 678 individuals. The findings revealed that both CECT and EUS demonstrated similar diagnostic accuracy in terms of local nodal staging and overall vascular invasion[(29)]. Other studies, unlike our study, have reported that CECT is superior to EUS in the diagnosis of vascular involvement, these studies were conducted by Soriano et al. and Ramsay et al[(30, 31)]. Regarding peri-pancreatic LN involvement, the current study demonstrated that the diagnostic performance of EUS for diagnosis of peri-pancreatic LN showed a sensitivity of 78.6%, PPV of 84.6% and an accuracy of 80% compared to 28.6%, 57.1% and 48% for CECT respectively. This was supported by a study conducted by Gress et al. which showed that EUS has a diagnostic accuracy of 72% in identifying peri-pancreatic LN as compared to only 55% by CECT[(32)].

Comment 6: 289 - 292 - this seems to an unnecessary place to laud your study. possibly remove and put 304-309 there instead, as above.
Reply 6: I removed lines 289-292 and put 304-309 instead.
Change in the text 6: as mentioned above in change in the text 5.

Comment 7: 292 - you mention gold standard, and again gold standard at 319. Please consider mentioning it only once. As above, 289-292 might be unnecessary at this point in the manuscript.
Reply 7: As you kindly mentioned in the previous comment, and I mentioned in the previous reply, I removed lines 289-292 including the phrase gold standard.

Comment 8: 302 - thank you for this explanation / supposition!
Reply 8: Thank you for your kind comment.

Comment 9: 303 - similarly to 302, can you hypothesize why we are still missing significant % of vascular involvement by both EUS and - even more so by - CT??
Reply 9: I added some interesting theories regarding this matter in the discussion in line 303.
Change in the text: Unfortunately, some cases are still missed by EUS, this could be attributed to the operator dependence of EUS, anatomical variations in the celiac and superior mesenteric arteries, and limited number of experienced EUSonographers.[(38)].

Comment 10: 310 - Finally, can you hypothesize the reasons for your current findings, eg Are there more and more skilled EUSonographers? are we ordering the wrong technical CTs? would CE -MRI be another option?
Reply 10: I added some interesting theories regarding this matter in the paragraph starting with line 310 in the discussion. Regarding CE-MRI, it is more useful in detection of small liver metastatic lesions, it has some limitations, to mention few, lower spatial resolution, vulnerability to motion artifacts, and limited multiplanar reformation capability.
Change in the text: this could be attributed to the growth of learning curve for the endoscopist, availability of doppler examination which clearly verifies vascular relation, proximity of the US probe to the tumor and degree of magnification[(38)]. The data emphasize that EUS is a dependable substitute for CT, especially due to its capability to obtain tissue samples and avoid the need of contrast agents. CECT has few limitations in detection of vascular involvement in these types of cancer, to mention few, CECT is subjected to artificial artifacts, it is more subjected to interobserver agreement and for a proper evaluation of pancreatic lesions and adjacent vascular structures, both the pancreatic phase (40–50 seconds from intravenous contrast injection) and venous phase (65–70 seconds) should be included, which may subject to human fallacies[(38)].

Reviewer B
Thank you, dear professor, for your valuable comments that added greatly to our manuscript. All the following responses were added to the manuscript.

Comment 1: The study involved a small number of patients, which can impact the generalizability and robustness of the statistical findings. The limited sample size is due to its prospective nature and the exclusion of individuals with non-resectable or metastatic cancers.
Reply 1: As mentioned in the discussion, one of the limitations in our study is the limited sample size, this is mainly attributed to omitting individuals with non-resectable and metastatic cancers as you kindly mentioned, which couldn't be included in our study as it was necessary for surgery to be done to compare EUS and CECT findings to surgery.

Comment 2: The exclusion of patients who were discovered to have non-resectable or metastatic cancers during the evaluation process introduces a potential bias. This exclusion is necessary since these patients cannot undergo surgical resection, which is crucial for the study, but it may skew the results.
Reply 2: As you kindly mentioned, exclusion of these patients was vital to our study because we needed to compare the findings to that presented during surgery which as we mentioned is the gold standard to add more value to our study.

Comment 3: Statistical tests used in this study may not have enough power due to limited sample size and non-parametric statistical tests should be considered.
Reply 3: In table 3, instead of using a parametric test which is the t-test, I used a non-parametric test which is the Wilcoxon Signed Rank test and updated the P value.

Comment 4: Interpretation of CT is highly subjective - more information is needed regarding the readers, and the imaging technical specifications. Furthermore, the same details are also needed for EUS.
Reply 4: All CECT images were reviewed by a single, expert radiologist and it was done in a highly qualified radiology center in our country, unfortunately the imaging technical specifications data is not currently available for us. Regarding EUS, it was done by an expert, single endoscopist who is highly experienced in this field, and it was done using a highly advanced endoscopy unit as mentioned and updated in the methods.
Change in the text: A CT scan of the abdomen and pelvis to assess the local stage of the disease and evaluate blood vessels, using a pancreatic CT protocol with high-resolution images taken by a 16-channel multi-detector CT scanner; all scans were seen by a single expert radiologist (4) an EUS examination performed under general anesthesia by a single, expert endoscopist using a linear echoendoscope (PENTAX EG38-J10UT) and Hitachi Arietta V60 ultrasound system.

Reviewer C
Thank you, dear professor, for your valuable comments that added greatly to our manuscript. All the following responses were added to the manuscript.

Comment 1: As none of patients in the study cohort received neoadjuvant therapy, the potential impact of neoadjuvant therapy on the outcome of this study should be discussed.
Reply 1: The impact of neoadjuvant therapy is added in the discussion at the end.
Change in the text: The same goes for patients who received neoadjuvant chemotherapy, as the size of the cancer and its relationship to nearby blood vessels could be affected thus affecting the results of our study.

Comment 2: The sample size is small in this study. The authors shall acknowledge this limitation.
Reply 2: We know that the sample size is small, and we mentioned it thoroughly in the discussion and all authors acknowledged this limitation. It will be considered to conduct further studies on a larger sample size in the future.

Comment 3: Variations on EUS assessment among different EUS operators would be anticipated to be higher than CT radiologists' reading. This should be discussed.
Reply 3: Yes, this is an interesting reading, but we feel that this is not a topic of interest in our study as all our EUS examination was done by a single endoscopist and all the CECT images were read by a single radiologist. This was updated in the methods section.
Change in the text: A CT scan of the abdomen and pelvis to assess the local stage of the disease and evaluate blood vessels, using a pancreatic CT protocol with high-resolution images taken by a 16-channel multi-detector CT scanner; all scans were seen by a single expert radiologist (4) an EUS examination performed under general anesthesia by a single, expert endoscopist using a linear echoendoscope (PENTAX EG38-J10UT) and Hitachi Arietta V60 ultrasound system.

Comment 4: Page 9: "All of this data is well presented in table 1.". Manuscript language shall be neutral. Please avoid using the word "well".
Reply 4: the word well is removed from the text on page 9.
Change in the text: Most of the patients presented with jaundice (76%), abdominal pain (68%) and weight loss (64%). All this data is presented in table 1.