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Reviewer's code: 01430761

COMMENTS TO AUTHORS

This is a well written, narrative review of early diagnosis of pancreatic cancer. 1. Although the authors described ERCP has little role in early diagnosis of pancreatic cancer in Page 22, there is an attempt to utilize ERP with pancreatic juice cytology called SPACE (J Gastroenterol. 2015;50:147-54, Clin J Gastroenterol. 2017;10:541-545). This should be discussed in detail. 2. Pancreatic cystic neoplasms and diabetes are two important keys to early diagnosis of pancreatic cancer. In particular, there are guidelines for IPMN surveillance. These topics should be included in "screening program" paragraph or as a new paragraph. 3. In Table 1, transabdominal ultrasound and ERP should be added. In Figure 1, ERP should be added in "no mass, no metastatic disease" category. 4. In Figure 2, mass, SpA, SpV should be shown using arrows. 5. Please clarify "reaction to chemotherapy" described in "Treatment protocols." In addition, did gastrointestinal reaction and myelosuppresion include all grades toxicities or severe ones? 6. In their conclusion, the study results aid prediction of survival in pancreatic cancer. However, for clinical use, nomogram analysis is more useful (Br J Cancer. 2014;110:1943-9). 7. In Page 11, CT also plays a role in detecting lung metastases and close attention should also be paid to lungs. 8. In Page 26, SPT should be changed to SPN. Neuroendocrine tumors should also be added as one of mimickers. 9. In Page 4, please describe who performed a manual review. All three authors? How did the authors decide which papers should be included when the review list was different from one reviewer to another? 10. In Page 11, please add short comments on neoadjuvant treatment on borderline resectable pancreatic cancer to clarify the importance of this category rather than just resectable vs. unresectable.)

Thank you for your review and suggestions. 1. We have added a section explaining the use of ERCP in pancreatic cancer, including a reference to the use of SPACE.

2. We have chosen not to further discuss cysts as this article only reviews solid pancreatic masses and pancreatic cyst would be an entire new topic. We already discussed about diabetes.

3. We have chosen not to add ERCP and US into the table as there would be very little to add regarding the benefits and limitations of these two modalities as neither are recommended.

4. We have added in arrows into the figures as suggested.

5. This section has been re-written to provide a better clarification regarding PET/CT's role in assessing response to chemo-radiation therapy:

PET/CT shows promising role in assessing tumour response to chemo-radiation therapy with the

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measurement of the change in standard uptake value (SUV) pre- and post- treatment, which could potentially serve as a trial for postoperative adjuvant therapies [55, 56]

6. This comment does not refer to our study: "In addition, did gastrointestinal reaction and myelosuppresion include all grades toxicities or severe ones?", We do not have a section called "treatment protocols"

7. We agree with this statement. We have added the diagnosis of lung metastasis with CT within the CT section.

8. We have changed SPT to SPN. We mentioned about neuroendocrine tumours in the contrast enhanced EUS section. They are usually well recognized by EUS as well defined hypervascular lesions and given the high accuracy of EUS FNA (over 95%) should not be a mimicker.

9. We updated the author contribution

10. This is a review of challenges in diagnosis of pancreatic cancer, and so we cannot also cover treatment as this will be a whole new topic.

Reviewer's code: 01518946

COMMENTS TO AUTHORS

This manuscript is an excellent review for pancreatic cancer in details. However, the authors should amend a few parts as described below before publication. There are 2 spaces between each word in some parts. In page 7, sens and specif should be described as sensitivity and specificity respectively. ERCP should be described as full spell, when it is described at first. The authors should show a benefit of ERCP for diagnosis of pancreatic cancer. Even though pancreatic mass is not detected by other image diagnosis, changes of pancreatic duct such as stenosis or disruption are detected by ERCP. There are many papers of possible biomarkers for pancreatic cancer. The authors should cite more papers about novel biomarkers with benefit and/or limitation.

Thank you for your review and suggestions. We have removed the 2 spaces between words (this was a document formatting issue). We changed the words sens and spec to the full words. ERCP has been spelled out now.

We have discussed more about the benefit of ERCP and added more references for biomarkers.

Additional Section about ERCP Given the excellent modern imaging, Endoscopic retrograde cholangiopancreatography (ERCP) plays a less prominent role in diagnosis of pancreatic cancer[61], and is mainly used as a therapeutic modality due to potential complications such as pancreatitis and perforation[62]. ERCP remains an important modality to provide biliary drainage in obstructing head

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of the pancreas cancer and can provide biliary and pancreatic duct brushing cytology in patients with invasive pancreatic cancer[63]. Pancreatogram obtained during the ERCP can show pancreatic duct stenosis, obstruction, narrowing and abnormal branching of the main pancreatic duct, obstruction and encasement of the common bile duct. There are few studies that looked at ways to attain cytological samples during ERCP through the use of an endoscopic naso-pancreatic drainage (ENPD) tube which is placed in the main pancreatic duct to collect pancreatic juice repeatedly – a technique known as serial pancreatic-juice aspiration cytologic examination or "SPACE"[64]. Only small-scale studies have examined the use of this technique with relatively promising results[64-66], but more research is required prior to recommendation of its use.

Additional Section about Biomarkers

More recently, a combined panel of protein and microRNAs serum exome for pancreatic cancer have emerged as potential diagnostic tools with improved sensitivities and specificities but have yet to have testing within larger cohorts[73]. There has also been early research reviewing the use of inorganic nanomaterials such as gold and carbon nanotubes which can be targeted towards specific pancreatic cancer cells, in early detection and diagnosis[74].

Reviewer's code: 02544727

COMMENTS TO AUTHORS

1) The statements "Its high mortality rate is attributed to its difficulty of diagnosis ..." in the Abstarct and "The high mortality rate undoubtedly relates to the difficulty in obtaining an early stage diagnosis, ..." in the Introduction, are not completely correct because the aggressive biological behaviour of pancreatic adenocarcinoma is the major determinant of poor prognosis. Therefore these statements should be modified. 2) The diagnostic algorithm for suspected pancreatic adenocarcinoma shown in Figure 1 is probably better and more sensible to be placed as a sum up after the presentation of the available diagnostic modalities. In this algorithm there are two options that might need an explanatory footnote. In the scenario of a patient with a diagnostic CT or MRI for pancreatic cancer (and resectable tumor) without distant metastases do the authors

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consider EUS+FNA as a pre-requirement for all patients before their referral to MDT? In the scenario of a patient with clinical suspicion for pancreatic adenocarcinoma but without pancreatic mass or distant metastatic lesions on imaging, the authors suggest EUS±FNA to confirm the absence of pancreatic cancer. The conditions imposing EUS±FNA in this scenario should be better clarified in a footnote. 3) The expression ".... and injection of neutral oral contrast." in the "Computed tomography scanning" paragraph is not accurate. You cannot inject an oral agent. 4) In the "Computed tomography scanning" paragraph the authors state "Discussions regarding general diagnosis of "borderline resectable" disease occurs later." No such section was found in the manuscript. 5) In the "Magnetic resonance imaging" paragraph, the authors state "... on post-contrast T1-weighted images, as seen in Figure 5." This is a skip in figure numbering. 6) Tumor size and nodal status might be more appropriate expressions instead of T1–2 staging, and N staging, respectively. 7) The diagnostic accuracy between MDCT and EUS for nodal staging an resectability has been similar. Showing percentages of diagnostic accuracy might be necessary. 8) "…. minimising the risk of tumour seeding." Tumor seeding during FNA or needle biopsy is a major concern and providing some data or extending a little a bit this issue might be useful. 9) "There was however no difference in diagnostic accuracy, technical failure or complication rates." in the "Fine needle aspiration technique" paragraph. It's good to present some figures or actual comparative data. The same applies to "... and a recent meta-analysis showing no significant difference in performance or diagnostic yield found between biopsy and aspiration needles" in the "EUS Fine needle aspiration vs. Fine needle biopsy" paragraph. 10) Panel (a) in Figure 5 is a coronal plane view not an axial view. 11) The pancreas is a retroperitoneal organ and hence the sensitivity of transabdominal ultrasound is poor in the "Ultrasound and ERCP"paragraph. Data supporting this statement? 12) "… depending if pre-cancerous lesions (cysts, branch duct IPMN) are included or not" in the "Screening programs" paragraph. Which are these cysts considered as premalignant lesions and what about main duct IPMNs? 13) The use of arrows or other indicators to delineate the lesions, points of interest or the findings presented in the figures might be useful for the readers. 14) Please pay attention to grammatical errors. Some examples include: Discussions regarding general diagnosis of "borderline resectable" disease occurs later. For this reason, while MRI is not widely used Longitudinal studies have also observed a significant increase in diagnostic accuracy over time, likely reflecting increasing operator proficiency The diagnostic accuracy between MDCT and EUS for nodal staging an resectability has been similar compared to the 4 passes needed for when real-time evaluation of specimens A study comparing 22-gauge FNA vs FNB .... and a recent meta-analysis showing no significant difference enhanced 18FDG-PET have been combined with CT to produce one fusion

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image, as seen in Figure 5. IgG4 staining of the ampulla biopsy are also suggestive It is also important to not incorrectly diagnoses adenocarcinoma in patients with SPT 15) Please be also consisted with the terminology: See …for indeterminate pancreato-biliary stricture and ….with pancreaticobiliary expertise.

Thank you for your review and suggestions.
1) We have altered the introduction to reflect this suggestion.
2) MDT was clarified and put earlier in the assessment of a mass to reflect the clinical practice in large pancreatic centres. Within the algorithm, regarding the scenario that CT shows a mass, after discussion in the MDT and with the patient consent, EUS+FNA should be considered as mimicker of the disease could the culprit (lymphoma, NET, AIP) and it would prevent unnecessary surgery. With the scenario where patient with clinical suspicion for pancreatic adenocarcinoma without pancreatic mass on CT, we suggest EUS due to its highest accuracy on excluding pancreatic cancer as quoted in the paper.
3) We have changed "injected" to administrated.
4) We have removed this sentence. We had initially written a section about borderline resectable disease but have decided to take this out of the review.
5) We have changed figure 5 to figure 3, and have changed all the previous references to this figure in the text.
6) We have chosen to keep these expressions as the referenced paper also uses these expressions.
7) We have included percentages to compare nodale staging for MDCT and EUS.
8) We have expanded on the tumour seeding in EUS-FNA.
Tumour seeding during EUS-FNA is a rare but important complication to be considered, with only a few case reports ever documented [34,35].
9) We have provided with comparative data between FNA and FNB:
So far, studies also demonstrated that there were no significant difference between the diagnostic accuracy of EUS-FNB and EUS-FNA, with a reported accuracy of 89% and 78% which was not significant as demonstrated in a small pilot study[46]. However, there were more technical issues experienced with EUS-FNB.
And:
Similarly, another recent meta-analysis showed no significant difference in diagnostic adequacy (75.2% vs 89.0%), or diagnostic accuracy (85.8% vs 86.2%) between biopsy and aspiration needles[47].
10) Yes we agree, figure 5 (now figure 3) is a coronal plane view.
11) We have expanded on the role of ERCP and provided reference for low accuracy of US in the text.

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Given the excellent modern imaging, Endoscopic retrograde cholangiopancreatography (ERCP) plays a less prominent role in diagnosis of pancreatic cancer[61], and is mainly used as a therapeutic modality due to potential complications such as pancreatitis and perforation[62]. ERCP remains an important modality to provide biliary drainage in obstructing head of the pancreas cancer and can provide biliary and pancreatic duct brushing cytology in patients with invasive pancreatic cancer[63]. Pancreatogram obtained during the ERCP can show pancreatic duct stenosis, obstruction, narrowing and abnormal branching of the main pancreatic duct, obstruction and encasement of the common bile duct. There are few studies that looked at ways to attain cytological samples during ERCP through the use of an endoscopic naso-pancreatic drainage (ENPD) tube which is placed in the main pancreatic duct to collect pancreatic juice repeatedly – a technique known as serial pancreatic-juice aspiration cytologic examination or "SPACE"[64]. Only small-scale studies have examined the use of this technique with relatively promising results[64-66], but more research is required prior to recommendation of its use.

12) We provided further details.
13) Yes, we have added arrows to figures
14) Grammatical errors have been highlighted and corrected now.
15) We changed to pancreato-biliary throughout the review.

Reviewer's code: 01468039

COMMENTS TO AUTHORS
Good review on a common topic.

Thank you for your assessment.