

Date: 6th Dec 2020

Dear Editor in Chief

World Journal of Gastrointestinal Surgery

Re: Manuscript NO.: 60077, Review

Many thanks for peer review of manuscript and we submit revisions as per comments of reviewer 1 and science editor. Please find below the point by point reply to the comments.

Reviewer 1:

Comment 1:

The role of Ca19.9 in IPMN and pancreatic cystic diseases after sampling in echo endoscopy should be investigated.

Response 1: This is important issue. We agree that role of CA19.9 in potentially malignant conditions is worthy of inclusion and needs adequate discussion in this manuscript. Thus, we have made substantial edits to the section “Clinical utility in benign pancreatic diseases’. The section is now elaborated to include CA19.9 utility in IPMN and mucinous cystic neoplasms.

We have rephrased the section on pancreatic cystic neoplasms to ‘pancreatic cystic lesions’ and merged the section of pancreatic pseudocysts into this section. We have edited the paragraph as

“Pancreatic cystic lesions are classified into pseudocysts, simple retention cysts and pancreatic cystic neoplasms (PCNs). PCNs comprise a spectrum of conditions which either have low malignant potential (such as serous cystic adenomas) or are premalignant (commonly mucinous lesions such as mucinous cystic neoplasms and IPMNs).

Both serum CA 19-9 and cyst fluid CA 19-9 obtained from endoscopic ultrasonography-guided fine-needle aspiration have been evaluated for its ability to differentiate between various pancreatic cystic lesions.

Regarding serum CA 19-9, a meta-analysis by Cao *et al.* involving 1437 patients in 13 studies found that serum CA 19-9 alone is ineffective in distinguishing malignant PCNs (47% sensitivity and 88 % specificity), but useful when complementary to other diagnostic techniques, such as imaging or cyst size >3cm^[33]. Serum CA 19-9 levels >37 U/ml are validated as a relative indication for IPMN resection per the 2018 European evidence-based guidelines on pancreatic cystic neoplasms (EEBGPCN)^[34].”

With regards to cystic fluid analysis, the following text is inserted –

“Cyst fluid CA 19-9 is less accurate than other cyst fluid tumour markers such as CEA and CA 125 in differentiating between different pancreatic cystic lesions. Nevertheless, cyst fluid CA 19-9 may have supplementary roles in IPMNs and pseudocysts.

A multicenter prospective study by Brugge *et al.* involving 341 patients demonstrated that cyst fluid CA 19-9 (cut-off of 2900 ng/mL) alone has limited ability in distinguishing between mucinous and non-mucinous cystic lesions (Area Under Curve (AUC) = 0.665), as it is less accurate than cyst fluid CEA (cut-off of 192 ng/mL) alone (AUC = 0.793)^[35]. Similarly, van der Waaij *et al.* demonstrated amongst 450 patients across 12 studies that while cyst fluid CA 19-9 is less accurate than CEA, CA 19-9 <37 U/mL distinguishes pseudocysts and serous cystic adenomas from other pancreatic cystic lesions with specificity (98.0%) and sensitivity (19.0%)^[36]. Furthermore, Nagashio *et al.* demonstrated amongst 68 patients that cyst fluid CA 19-9 can differentiate mucinous cystic neoplasms from IPMNs (AUC = 0.792), though less accurately than CA 125 (AUC = 0.960)^[37].

In IPMNs, cyst fluid CA 19-9 can be used after initial analysis with CEA to further differentiate mucinous cyst subtypes. In a study by Snozek *et al.* involving 387 patients, for cysts presumed to be mucinous as cyst fluid CEA > 30 ng/mL, cyst fluid CA 19-9 <8000 U/mL distinguished 71% of IPMNs from other mucinous cyst subtypes^[38]. However, cyst fluid CA 19-9 is less effective in differentiating between benign and malignant IPMNs. A study by Maire *et al.* involving 41 patients revealed that cyst fluid CA 19-9 > 1000 U/mL (PPV = 0.360, NPV = 0.920) is less effective compared to CEA > 200 ng/mL (PPV = 0.500, NPV = 0.960) and CA 72-4 > 40 U/mL (PPV = 0.470, NPV = 0.960)^[39]. Thus, the role of cyst fluid CA 19-9 remains supplementary to other tumour markers in IPMNs.”

Comment 2:

In cholestatic liver diseases, I would cite and comment on the 1994 Gut paper; 35: 707-708. Also, Eur J Gastroenterol Hepatol. 2018 Feb; 30 (2): 226-232 paper will allow the authors to comment on how drug-induced cholestatic liver disease can also cause increased Ca19.9.

Response 2:

Many thanks for pointing the study team to an important publication and we agree that this paper on cholestatic liver disease/drug induced liver injury is a value add to our citation and we have added in discussion and cited 1994 Gut paper. We have retrieved the full text of this manuscript (Licata A, Puccia F, Lombardo V, Serruto A, Minissale MG, Morreale I, Giannitrapani L, Soresi M, Montalto G, Almasio PL. Rivaroxaban-induced hepatotoxicity: review of the literature and report of new cases. Eur J Gastroenterol Hepatol. 2018 Feb;30(2):226-232. doi: 10.1097/MEG.0000000000001030. PMID: 29120909.) and unable to find any comment in discussion or result section in relevance to CA19.9. We have checked this twice. In addition, we performed literature search and found some evidence on drug induced liver injury and CA19.9 relevance. Thus, we have added the following in paragraph on ‘Hepatic diseases’ –

Pearce *et al.* reported a case of possible drug-induced CA 19-9 elevation in a 50-year-old man with alcohol-related chronic pancreatitis and recent dothiepin use. PDAC was initially suspected as he presented with anorexia, pale stools, transaminitis and elevated serum CA 19-9 at 2690 U/ml. However, CA 19-9 decreased on pancreatic enzyme replacement and dothiepin cessation^[59]. While the cause for the elevated CA 19-9 is likely multifactorial (including alcohol-induced pancreatitis and hepatitis) and since dothiepin can cause cholestasis^[60], the possibility of dothiepin-induced cholestasis causing CA 19-9 elevations cannot be excluded.

Science Editor

Comment 1: Format: There are no tables and figures. Authors should add some figures and tables.

Response 1: We have added Figure 1 (titled “Clinical uses of CA 19-9 based on organ involvement”) at the end of the manuscript to illustrate the various diseases we have found CA 19-9 to be implicated in.

Comment 2: The authors should provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

Response 2: We have included both forms in our resubmission.

Comment 3: Please provide the author contributions.

Response 3: We have added the author contributions in our resubmission. Additionally, we have reformatted the paper to better align with the journal’s requirements.

We hope that above edits are considered acceptable to reviewer and editorial team.

Thanking you

Sincerely

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Thomas Teng Zheng Jie

Vishal G Shelat