Reviewed by 01199795

This is a well written manuscript on a new and interesting topic. I would accept the paper for publication in its current form

Reviewed by 03354735

Nice review. Very honest and complete.

Reviewed by 01150514

There are some comments that could usefully be addressed:

An introductory line or two on the CLE platforms to be discussed and the ‘spyglass’ technology (e.g at the end of the Confocal Laser endomicroscopy sub-headed paragraph) and on other existing (competing?) needle or probe (and why they may be suboptimal etc.-or maybe non-existent) would set the scene for the less technical readership.

Answer: An introductory paragraph preceding the nCLE paragraph, and another competing (Spyglass) technology paragraph following the nCLE statement has been added under the heading of Confocal Laser endomicroscopy.

A statement of any conflict of interest of the authors vis a vis the AQ-Flex 19; Mauna Kea Technologies or the Spyglass Boston Scientific platforms should be stated either in the text or as a disclaimer.

Answer: This is now stated in the title page of the manuscript

In the introduction the authors should give the current specificities and sensitivities, NPV and PPV of the existing methodologies (CEA/cytology mucin-amylase) in discriminating the malignant potential of a cyst. This is absolutely necessary as the specificity and sensitivity, NPV and PPV of the nCLE technology is not established in its entirety against the pathological gold standard (i.e. histological verification of the lesion) but in many of the cases were ‘certainty cases’ on ‘expert consensus’ which has taken into consideration EUS appearances –existing size and anatomical criteria- and the results of the fluid analysis and inter-observer variability.

Answer: The introductory paragraph now includes pooled data for predicting mucinous vs. non mucinous lesion and presence of malignancy.

The fact that most of the data presented later has been gleaned in this fashion needs to be explained in a paragraph here.

Answer: The introductory paragraph now ends with this comment.

Without years of follow up to absolutely exclude the possibility of cystic lesions left behind in patients exhibiting malignant potential there remains an element of doubt on the presented figures of NPV,PPV and Sensitivity and specificity when established on only around 20% of the lesions having been studied pathologically (e.g. the INSPECT study discussed later in the text).

Authors should also include ‘symptomatic’ in the guidelines they review in the introduction (size anatomy features etc.) as symptoms are included in cyst assessment algorithms.

Answer: This is now included as well. The introduction includes this statement in addition: A majority of the data involving the novel technology of confocal laser endomicroscopy in evaluating CPLs is hence gleaned from consensus rather than diagnostic histopathology.

A better summary of some of the studies would also be welcome for example reference 17 relates to cystic and solid masses of the pancreas and the wording is slightly confusing (e.g. in both the pancreatic mass and malignant lymph node… these were actually different patients) or the criteria for concordance in the certainty cases of the DETECT study (i.e. what was the concordance of ‘mucin diagnosis’ by laser vs actual pathological verification of the existence of mucin).

Answer:

Corrected the description of reference 17 (now reference 20 in the revised version).

For DETECT study: Added objectives and diagnostic criteria. The paper does not mention the concordance between nCLE finding papillae and presence of mucin on pathology. Rather the paper establishes diagnosis of cysts after 2 blinded endosonographers reviewed cyst data (ie clinical and imaging features, follow-up, fluid analysis and cytology).

Aim of some of the abstracted work needs to be included. For example reference 22 (despite having the largest numbers) does not report any efficacy results so the aims were ? Adverse events? Technical success? This needs to be clarified as access to abstracts is limited.

Refrence 22 (now 24) is this context is actually to qualify low risk of acute pancreatitis following EUS-FNA of pancreatic cysts.

The reviewer perhaps implied reference 21 (now 23):

The objectives are now included. A column in table 2 has been changed with a new title of ‘study objectives’.

What would also be useful is the opinion of the reviewers of the optimal way to establish validity of some of the patterns suggested to be diagnostic of BD-IMPN or SCA or MCN. An inventory an Atlas?

Answer: This is mentioned in the paragraph: Further areas of research. The sentence has been modified thus to reflect the reviewer's thoughts. In fact, we have just started enrolling patients into this study.

https://clinicaltrials.gov/ct2/show/NCT02516488?term=somashekar&rank=1

We think it is too premature to include this in this review paper.

Table 3 purports to correlate some of the imagery with hard and fast histopatholgocal elements of the cyst. How accurate are these correlations? E.g. how sure are the investigators that 'inflammatory cells' are 'clusters of bright floating heterogeneous particles'. Radiological experience of hemorrhagic cysts for example often have debris that is unlikely to be just 'small black particles' only etc… I think

Answer: As summarized in the manuscript:

We need larger studies to validate nCLE findings for IPMNs, SCAs, MCNs and pseudocysts. The image patterns identified are from smaller studies and available literature. As the reviewer suggested before (and now included in the manuscript), the crux of the problem is that most of these image patterns are not verified by confirmed histopathology. We need large multicenter studies to validate these image patterns. Unfortunately the technology is novel and is gradually being adapted by other centers.