Internal Medicine
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Dear Mr. Kong:

Thank you for your consideration of the original manuscript no. 20976 titled "A Review of Current and Evolving Clinical Indications for Endoscopic Ultrasound". In addition to minor formatting revisions, I have addressed the following suggestions brought by Reviewer Xue-Mei Gong.

1. Please add the limitations of EUS in the text.

Endoscopic ultrasound (EUS) is often limited in its accuracy with diagnosing pancreatic cancer due to other underlying pancreatic pathologies:

> *Of course, EUS is not without limitations in the accuracy of diagnosing pancreatic cancer. The presence of pancreatitis, which can result in significant heterogeneous appearance of pancreatic tissue, may result in highly trained endosonographers missing an underlying pancreatic neoplasm.[4,10] As MRI techniques and equipment become more high-tech, magnetic resonance cholangiopancreatography (MRCP) has been used with increasing frequency in patients suspected of having a pancreatic malignancy. MRI has superior soft tissue contrast compared to CT imaging, resulting in the ability to differentiate pancreatic masses.[4,11] However, as EUS affords superb visualization of the pancreas and remains one of the most accurate means for identifying pancreatic lesions , it is considered a first-line modality for diagnosing and staging of pancreatic adenocarcinoma.*

EUS is unable to access upper mediastinal lymph nodes for confirmation of malignancy. Other nodes are located such that EUS-FNA is difficult due to positioning.

> *Specifically, EUS is unable to visualize anterior upper mediastinal nodes as a result of air within the trachea obstructing US imaging.[18,20]*
>
> *This accuracy drops to 66% for station 5 nodes based on one retrospective series by Cerfolio et al. due to logistical difficulties when inserting the biopsy needle in attempts to reach this sub-aortic locations.[18,21]*

EUS is as sensitive as and more specific than ERCP in detecting common bile ducts stones, but remains a diagnostic and nontherapeutic modality in this setting.

The use of EUS as the primary diagnostic tool, however, may be limited. While it is less invasive than ERCP resulting in lower rates of post-procedure pancreatitis, patients still require sedation. As with ERCP, EUS requires an experienced endoscopist to obtain acceptable images. Unfortunately if CBD stones are discovered on EUS imaging and require removal, these patients would require ERCP, an additional procedure.

EUS-guided celiac plexus neurolysis was developed in the 1990s for treatment of intractable pain related to intra-abdominal malignancies and chronic pancreatitis. However, other modalities exist to allow access to the celiac plexus.

The celiac plexus is also accessible percutaneously when combined with CT or fluoroscopy imaging. Prior to the 1990s, this was the primary manner of performing CPN in settings of chronic abdominal pain secondary to intra-abdominal malignancies and chronic pancreatitis.[24,31] Given EUS capability to visualize vascular structures in real-time and ability to perform FNA, EUS-guided CPN using ethanol was first developed in the late 1990s.[24] To further assess this new technique, Gress et al. performed a randomized-controlled trial involving 22 patients receiving either CT-guided or EUS-guided CPN for persistent, uncontrolled abdominal pain due to chronic pancreatitis.[31] Patients in the EUS arm had statistically significant ($p = 0.02$) reduced pain score. Neither group experience serious complications. Diarrhea was noted in three subjects (one from the EUS group, two from the CT arm) and attributed as a direct side effect of CPN. [31]Nine patients in the experimental group had a prior CT-guided CPN; the majority preferred the EUS technique citing less post-procedure back pain and "more completed sedation". [31] Furthermore, the use of EUS in guiding CPN resulted in lower cost per patient relative to CT-guided CPN.[24,31]

2. Please also compare EUS with other diagnostic and therapeutic tools.

Comparisons between endoscopic ultrasound and other diagnostic and therapeutic modalities have been included throughout the text of the article. One such example includes:

Imaging modalities may vary between CT, MRI, or US. A 2003 CHEST systematic database review evaluated the accuracy of mediastinal staging in CT compared to positron emission tomography (PET), MR, and EUS.[17] The analysis of EUS assessment consisted of five studies for a total of 163 patients and exhibited a pooled sensitivity of 78% (95% CI, 0.61-0.89) and specificity of 71% (95% CI, 0.56-0.82). However, PET scan demonstrated the highest accuracy in detecting malignant metastases to mediastinal nodes with sensitivity and specificity of 84% (95% CI, 0.78-0.89) and 89% (95% CI, 0.83-0.93), respectively.

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Sincerely,

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