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Column: Review

Title: Is Endoscopic Ultrasound examination necessary in the management of Esophageal Cancer?

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Reviewer code: 01437020 and 02468626

Scientific editor: Yuan Qi

Reviewer 1:

The authors are to be commended for their thorough literature review and extensive coverage of the topic of the role of EUS in esophageal cancer.

1) Overall, the manuscript is well written.

2) Some figures, although nice, are not necessary for this topic. I would omit figures 1 and 6

3) Table 3 is not necessary as the same concepts are reported elsewhere in the text and figures

Dear Reviewer 1,

Thank you for your kind remarks and constructive comments. We have removed Figures 1 and 6; as well as, Table 3.

Reviewer 2:

Dear Editors: Please refer to the following comments on the paper entitled "(Invitation ID: 01430821) Is Endoscopic Ultrasound examination necessary in the management of Esophageal Cancer?", which was submitted as a review article. This paper was well structured. However, I would like to recommend "minor revision" to make it more educative in considering its publication in WJG. The followings are the recommendations:

Dear Reviewer 2,

We greatly appreciate your thoughtful evaluation and guidance. We have updated the manuscript to incorporate your suggestions.

1. The authors can try provide more discussions about the difference of advantages and disadvantages between high frequency miniprobe and traditional radial-array EUS.

Please refer to the section titled 'DISCUSSION' on page 9, paragraph 2. The following discussion has been added.

If malignant lesions extend to the fundus or gastric cardia, or if intra-esophageal cancers are small; conventional radial or linear EUS may not accurately evaluate the depth of the lesion due to the technical difficulty in reaching or locating the lesion by the echoendoscopes. In those cases, a high frequency EUS mini-probe may be employed under endoscopic guidance to most accurately stage the tumor. For example, in distinguishing T1a versus T1b intramucosal lesions, high frequency mini-probes have been shown to more accurately assess depth of invasion in

comparison to radial or linear EUS. The disadvantage of using an EUS mini-probe is the limited sonographic width and depth, which precludes a comprehensive survey of regional lymph nodes. Furthermore, if the lesion is large (i.e. 5 cm), EUS mini-probes cannot expediently assess penetration depth of the entire lesion.

2. The authors can try to discuss the roles of PET-CT and EUS-guided FNA in proving malignant lymph nodes. Can PET-CT spare the need of EUS-guided FNA in differentiating the nature of lymph nodes?

Please refer to the section 'DISTANT METASTATIC ESOPHAGEAL CANCER STAGING' on page 10, paragraph 2. The section has been expanded to include the following comments.

Use of PET and/or CT may spare the need of performing EUS when distant metastases are detected, as evaluation of the regional lymph nodes is not necessary prior to initiation of palliative chemotherapy or chemoradiotherapy. When indicated, EUS may be used to confirm the presence distant metastases and exclude benign findings. Confirmation or exclusion of nodal involvement by EUS will help calculate the exact radiation field, especially when the lymph node is away from the primary tumor, thus minimizing radiation induced complications.

3. The authors should provide discussion about the potential roles of elastography and contrast-enhanced EUS in approaching esophageal cancers. The authors should provide the potential contribution of 3-D EUS to the management of esophageal cancers. Many thanks for your invitation to review this paper. Best regards,

The following section has been added to address these topics starting on page 16.

EMERGING ADJUNCTS TO SONOMORPHOLOGIC EVALUATION

Generally, healthy tissue is softer and more elastic than cancerous tissues. Elastography, or elasticity imaging, may be combined with ultrasound or magnetic resonance modalities and is a non-invasive method to measure the flexibility of tissues. There are many elastography techniques under investigation, such as quasistatic/strain imaging and shear wave elasticity imaging; however, all techniques rely on measuring the degree of distortion within the tissue. Much like Doppler ultrasound, which uses color to highlight flow in vessels, EUS elastography provides the operator with a colorized image displaying the variation of elasticity of tissues. Typically, when using EUS elastography, firm tissues appear blue to violet, while softer tissues appear red, yellow or green. Elastography-enhanced EUS has been shown in small studies to improve the diagnostic accuracy of regional lymph node staging in esophageal cancer patients when compared to standard EUS sonomorphologic evaluation.^[90-92] Currently, the role and clinical efficacy are undefined for EUS elastography in esophageal cancer, although we speculate the technique could replace FNA cytology, as it is noninvasive and possibly lower risk for the patient.

When unique contrast agents are parenterally administered, contrast-enhanced harmonic EUS (CEH-EUS) may be used to further characterize the microvascular pattern of lesions identified by standard imaging modalities.^[93] In 2016, the United States Food and Drug

Administration (FDA) approved the use of sulfur hexafluoride lipid-type A microspheres (Lumason®) for ultrasonographic characterization of focal liver lesions. CEH-EUS has not been rigorously studied in esophageal carcinomas, but preliminary data suggest contrast-enhanced images are of limited value due to the relative avascularity of common esophageal malignancies.^[93, 94]

Tridimensional (3D) endoscopic ultrasound may be used alone, or with ultrasonographic contrast, to evaluate the invasion depth of tumors. The 3D images are thought to more accurately convey the relationship of cancers to nearby organs and vessels, and may reduce the operator-dependent error that is inherent to standard EUS.^[95]

Thank you again for your kind remarks and guidance. We look forward to contributing our manuscript to WJG.

APPLICABLE REFERENCES:

- 90 Sazuka T, Akai T, Uesato M, Horibe D, Kuboshima M, Kitabayashi H, Matsunaga A, Kagaya A, Muto Y, Takeshita N, Maruyama T, Miyazawa Y, Shuto K, Shiratori T, Kono T, Akutsu Y, Hoshino I, Matsubara H. Assessment for diagnosis of lymph node metastasis in esophageal cancer using endoscopic ultrasound elastography. *Esophagus* 2016; **13**: 254-263 [PMID: 27429608 PMCID: PMC4923115 DOI: 10.1007/s10388-016-0521-0]
- 91 Paterson S, Duthie F, Stanley AJ. Endoscopic ultrasound-guided elastography in the nodal staging of oesophageal cancer. *World journal of gastroenterology : WJG* 2012; **18**(9): 889-895 [PMID: 22408347 PMCID: PMC3297047 DOI: 10.3748/wjg.v18.i9.889]
- 92 Knabe M, Gunter E, Ell C, Pech O. Can EUS elastography improve lymph node staging in esophageal cancer? *Surgical endoscopy* 2013; **27**(4): 1196-1202 [PMID: 23093233 DOI: 10.1007/s00464-012-2575-y]
- 93 Reddy NK, Ioncica AM, Saftoiu A, Vilmann P, Bhutani MS. Contrast-enhanced endoscopic ultrasonography. *World journal of gastroenterology : WJG* 2011; **17**(1): 42-48 [PMID: 21218082 PMCID: PMC3016678 DOI: 10.3748/wjg.v17.i1.42]
- 94 Nomura N, Goto H, Niwa Y, Arisawa T, Hirooka Y, Hayakawa T. Usefulness of contrast-enhanced EUS in the diagnosis of upper GI tract diseases. *Gastrointestinal endoscopy* 1999; **50**(4): 555-560 [PMID: 10502181]
- 95 Saftoiu A, Gheonea DI. Tridimensional (3D) endoscopic ultrasound - a pictorial review. *J Gastrointestin Liver Dis* 2009; **18**(4): 501-505 [PMID: 20076829]