

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name "83959-Supplementary-Material-revision.docx"). It was uploaded with the file designation of "Supplementary Material" as the auto-generated manuscript file did not have appropriate formatting of the tables and images, thus it was downloaded and modified as this final file. Please do not consider the file "83959_Auto_Edited.docx" as the submitted manuscript file despite it having that designation in the online system.

Title: Role of Endoscopic Ultrasound for Pre-Intervention Evaluation in Early Esophageal Cancer

Authors: Sartajdeep Kahlon, MD, Ali Aamar MD, Zeeshan Butt MD, Shiro Urayama MD

Name of Journal: *World Journal of Gastrointestinal Endoscopy*

Manuscript NO: 83959

Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Thank you very much for your kind e-mail, which gave us the possibility to revise our manuscript. We emended the paper according to the reviewers' comments. We hope this revision will make our manuscript better to be accepted in your journal.

Each comment has been answered accordingly in the manuscript and each text that has been altered was highlighted yellow in the revised manuscript. Changes in statistical calculations were altered given the adjusted study period and sample size. We addressed each comment from reviewers on the pages below with answers in red text. We hope that the revised version will fulfill the requirements for publication in the World Journal of Gastrointestinal Endoscopy. Thank you very much.

Thank you for considering this review.

Best,
Sartajdeep Kahlon MD
UC Davis Internal Medicine

Answers to Reviewer Comments

Reviewer #1

I read with interest the paper by Kahlon and colleagues on the role of EUS to predict the role of EUS in cancer staging and therefore to assess how EUS might modify esophageal cancer management. Although the topic is of interest and some “grey-zone” are still present, the paper do not add new evidences nor provide additional information impacting on current management of Esophageal lesions. Due to the retrospective design of the study, indeed the relatively small sample size, and the wide study period, there are several limitations the severely affect the study and the results. Above all:

- the study population and the search method should be described more extensively

Answer: The search method and study population were more clearly described in the methods section including the use of specific ICD-10 codes and CPT codes in chart extraction.

- as the 8th edition of AJCC classification was published in 2017, how was the preoperative staging performed in patients before 2017?

Answer: The major changes from AJCC staging system 8th edition (2017) to 7th edition (2012) involve the redefinition of IA stage (pathologic staging taking into account), subdivision of T2-3 status in nodal-negative disease, and reclassification of IIIC stage (pathologic staging). Image summarizes the differences in IA staging, mainly separating 1a from 1b lesions on T-staging.

7th Stage	T	N	M	G	Location	8th Stage	T	N	M	G	Location
0	is (HGD)	0	0	1	Any	0	is (HGD)	0	0	1	Any
IA	1	0	0	1	Any	IA	1a	0	0	1	Any
IB	1	0	0	2-3	Any	IB	1a	0	0	2-3	Any
	2-3	0	0	1	Lower		1b	0	0	Any	Any

Citation: Zhang D, Zheng Y, Wang Z, et al Comparison of the 7th and proposed 8th editions of the AJCC/UICC TNM staging system for esophageal squamous cell carcinoma underwent radical surgery. Eur J Surg Oncol. 2017;43(10):1949-1955. [DOI:10.1016/j.ejso.2017.06.005]

We used descriptions of submucosal involvement in EUS (“irregular mucosa and submucosa border”) and/or pathology reports to differentiate 1b lesions from 1a lesions and therefore were able to stage pre-2017 studies using the 8th edition system. This thought process was added to the methodology

- how clinical staging revision was retrospectively performed (have any videos been reviewed and accessible? or it has been assessed only according to the written patients report?)

Answer: This was summarized in the methods section to include that only written reports were utilized and further mentioned as limitation of this study

- how was the retrospective analysis of EUS done? If based on written reports, the evaluation of submucosal invasion, especially for those examinations performed with older echoendoscope, may be highly affected.

Answer: As above, this was primarily based on written reports. The presence of submucosal invasion was described by the endoscopist as an “irregular mucosal, submucosal border” in written reports, including those prior to 2017. Additionally, given the study period was narrowed, all echoendoscopes were GF-UE160s and this is noted in the method section.

- was the concordance with histology changing and increasing over the study period?

Answer: No such pattern was noted in our cases, thus this was not further expounded upon.

- were other pre-operative imaging (eg: CT-scan) available?

Answer: Imaging was available to rule out metastatic lesions prior to EUS.

- the advent of HD imaging of endoscopes widely affected the reliability of endoscopic assessment of macroscopic features. How was this managed during the study period?

Answer: The study period was narrowed to 2012-2022 to mitigate this issue.

- proper and validated endoscopic classifications are available for the definition of endoscopic appearance and correlation with invasiveness: we suggest to report the Paris classification, and, if available, chromoendoscopy, NBI and pit pattern, and to report it on table I.

c written reports without these parameters identified. A majority of cases do not have retrievable images to retrospectively extract these parameters.

- an univariate analysis and multivariate may be needed to assess independent risk of invasion.

Answer: We did not consider this within the scope of our study at this time.

- the analysis method of is not clearly explained and should be further reported.

Answer: Further reporting of the analysis was done in the methods section.

- the paragraph of “Ethics” refers to study approval by the Institutional Review Board of the hospital: the number and date of protocol approval should need to be extensively reported.

Answer: This was done accordingly.

- Table 2 is misleading and difficult to be read

Answer: Improved the readability of this table

- authors should discuss if ancillary techniques (such as contrast enhancement) could improve the accuracy of EUS in the assessment of submucosal invasion

Answer: This was expounded upon and included as a potential future direction in the study discussion.

- English should be improved.

Answer: Improved English and prose throughout the study.

Reviewer #2

Thank you for the opportunity to read this interesting paper. Method Q During 16 years 102 patients were identified. Some people would say that the volume of patients is too low and that EUS may not be adequately depicted as the annual volume of patients in the study is too small. What are your thoughts on this?

Answer: This was included as a limitation of the study in the discussion. In the 16 year period, the pre-EMR era record may not be fully recovered. The study period was reduced from 2012-2022 by excluding 2 cases and including an additional case to give a total sample size of 49 patients.

Q Also, more than half patients were excluded for due to exclusion criteria which included “EUS unable to perform staging”, please elaborate on how this affects your results.

Answer: The inclusion and exclusion criteria were clarified and a flow chart was created to better visualize the number of patients excluded for a given criteria. A small sub-section of patients were excluded given EUS was unable perform staging.

Q Another exclusion criteria was “presence of metastatic lesions on imaging study”, why would EUS be done on a patient with metastatic lesion?

Answer: We agreed with the reviewer here and removed “presence of metastatic lesions on imaging study” as an exclusion criteria. EUS was not done on any patients with a metastatic lesion.

Q TNM 8th edition was published in 2017. Given that your study started in 2005 how were the data before 2017 handled and were there any issues in transferring data to the 8th edition?

Answer: The major changes from AJCC staging system 8th edition (2017) to 7th edition (2012) involve the redefinition of IA stage (pathologic staging taking into account), subdivision of T2-3 status in nodal-negative disease, and reclassification of IIIC stage (pathologic staging). Image summarizes the differences in IA staging, mainly separating 1a from 1b lesions on T-staging.

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We used descriptions of submucosal involvement in EUS (“irregular mucosa and submucosa border”) and/or pathology reports to differentiate 1b lesions from 1a lesions and therefore were able to stage pre-2017 studies using the 8th edition system. This thought process was added to the methodology

Results Q Other studies report T3 as the most common T stage, in your material T1a was the most common stage. Does this reflect a selection in which patients are referred to your center? If so, can the results be generalized for other populations? You mentioned this in the discussion but please elaborate on how this selection affects the results.

Answer: This was further expounded upon as a limitation of the study. In many cases, our department may have not gotten all esophageal cancers cases that were referred to oncology at our medical center. Additionally, we are specifically interested in early stage esophageal cancer cases and how we should utilize EUS in such cases, thus to emphasize this, we could have further selected for early stage cancers and may perhaps in future investigations.

Page 6 wessre – spelling error Table 2

Answer: This was fixed accordingly.

I would think that presenting the percentages in rows rather than columns would be interesting.

Answer: Table 2 was adjusted for formatting and readability.

Were any patients treated with neoadjuvant treatment before esophagectomy?

Answer: This was clarified as an exclusion criteria.

What does it mean that a lymphnode is non-diagnostic?

Answer: This was further explained and sources were included to clarify this designation at the beginning of our results section.

Singificantly- spelling error

Answer: This was fixed accordingly

Reviewer #3

Dear Editor, Dear Authors, I read with interest the manuscript entitled “Role of Endoscopic Ultrasound for Pre-Intervention Evaluation in Early Esophageal Cancer” by Sartajdeep Kahlon et al. This was a relatively small single-center retrospective study evaluating the role on pre-operative EUS in early esophageal cancer. Although interesting and well-written, I do not consider the manuscript of high enough relevance for publication in the WJG, for the following main reasons:

1) small sample size (especially taking into consideration the wide enrollment period)

Answer: The study period was reduced from 2012-2022 by excluding 2 cases and including an additional case to give a total sample size of 49 patients.

2) wide study period (2005-2021)

Answer: The study period was reduced from 2012-2022 by excluding 2 cases and including an additional case to give a total sample size of 49 patients.

3) absence of a flow chart study (how many patients were excluded and why?)

Answer: The inclusion and exclusion criteria were clarified and a flow chart was created to better visualize the number of patients excluded for a given criteria.

4) number and experience of the endosonographers (and pathologists as well) who have performed the procedures are not reported

Answer: Clarified that endoscopy was performed by a single endosonographer with over 10 yrs of experience at the beginning of the study period. Information regarding pathologist experience was unavailable and not commented upon.

5) adoption of the 8th edition of AJCC classification for the preoperative staging, which was published in 2017 only.

Answer: The major changes from AJCC staging system 8th edition (2017) to 7th edition (2012) involve the redefinition of IA stage (pathologic staging taking into account), subdivision of T2-3 status in nodal-negative disease, and reclassification of IIIC stage (pathologic staging). Image summarizes the differences in IA staging, mainly separating 1a from 1b lesions on T-staging.

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