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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Endoscopy*

Manuscript NO: 80522

Title: Gastric Cancer in 2022: is there still a role for EUS?

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03252941
Position: Editorial Board
Academic degree: MD
Professional title: Doctor, Professor
Reviewer's Country/Territory: Japan
Author's Country/Territory: Italy

Manuscript submission date: 2022-10-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-04 23:46

Reviewer performed review: 2022-10-07 14:16

Review time: 2 Days and 14 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors concisely summarized the utility of endoscopic ultrasound (EUS) in the diagnosis and treatment of gastric cancer (GC). They expounded the subject by citing several references, but the argument seems superficial. Their argument should be developed by specifically describing the contents of the cited papers.

In particular, my greatest concern is the utility of FNA and FNB in the diagnosis and staging of gastric cancer. The authors claim that they are useful for N staging, which would be necessary to determine treatment strategy, whether endoscopic resection (EMR/ESD), surgery, or chemotherapy (NAC). However, this reviewer, working in the tertiary hospital for more than 30 years as a pathologist, has scarcely diagnosed FNA samples of lymph nodes from GC patients scheduled to undergo EMR/ESD or surgery. Rather, I am afraid that FNA of metastasized lymph node will result in dissemination of cancer cells. If there are some references that reported the utility of FNA for N staging before EMR/ESD or surgery, please cite them and explain their contents specifically. Thank you for your precious comment. FNA-FNB is useful in selected cases better if discussed by a multidisciplinary team of experts. We added it in the test. "An advantage of EUS in GC is to biopsy mainly suspected malignant lymph nodes in order to improve N staging in high-selected cases. Usually the ultrasound evaluation is enough to establish the malignant nature of suspected enlarged lymph nodes, but EUS-FNA represents a valid tool in selected and discussed cases (by a multidisciplinary team) if biopsy can change the therapeutic management of the patient."

Furthermore, I want to stress that percutaneous needle biopsy would be more feasible than EUS/FNA for suspected liver metastasis, unless it is located at the hepatic hilus. By the way, the reviewer sometimes makes a diagnosis on FNA samples obtained from lymph nodes of patients with suspected GC recurrence. In short, the utility of FNA/FNB

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should be discussed in more detail according to the condition of the disease by citing the relevant literatures and referring to their contents. Thank you for the comment. We specify in the text that not the total liver is visible and can be sampled during EUS eamination but in case suspected secondary lesions of some liver segments can be sampled by linear EUS-scope. Also hepatic hilum lesions and lymph nodes can be sampled, as standard of care also in biliary and pancreatic diseases, respect to older and more invasive methods as percutaneous biopsies.

Other points that the reviewer has noticed:

1. (p.4, Histology) WHO classification (5th eds.) has been published in 2019. Why not refer to 5th edition instead of 4th? "G" is defined only for tubular adenocarcinoma in the 5th edition. Thank you for your precious comment and clarification. We modificed the issue as suggested and requested: The World Health Organization (WHO) fifth tumors classification issued in 2019 is probably the most detailed classification system, describing apart from stomach adenocarcinomas, also other types of gastric tumors with decreased attendance (13, 14).

"The present classification has distinguished every single histologic type of GC (such as micropapillary carcinoma, gastric adenocarcinoma of the fundic gland type and undifferentiated carcinoma have been added and explained). Concerning gastric adenocarcinoma the common histologic subtypes described (as well as in fourth edition) are: tubular, papillary, poorly cohesive, mucinous and mixed-type adenocarcinoma. Of these, tubular and papillary adenocarcinoma are graded using a two-tiered system: low grade (well or moderately differentiated) and high grade (poorly differentiated)

As new information, a molecular classification was introduced in GC: the Epstein–Barr virus-positive type, microsatellite instability type, genomically stable type and chromosomally unstable type) and many pages in this classification were dedicated to precancerous lesions (gastric dysplasia and gastric adenomas)."

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2. (p,7, Early phases of disease: pre …) mucosa/submucosa (M/SM1) and SM by EUS…: Is "SM" right? It seems to partially overlap with SM1. If this description is right, it may be better to describe SM (SM1/SM2) to avoid confusion. Thank you for your clarification. We changed in the text in M or SM1 and SM2 as indicated in the paper.

3. (p.8, Pre-operative role) Reference 38 may be incorrectly cited, because its content may be irrelevant to neoadjuvant therapy judging from the title. Thank you forn the comment. In order to avoid confusion we changed the sub-title in: ***"Advanced lesions: surgery/ neoadjuvant treatment".***

4. (p.8, Pre-operative role) Please explain what accuracy of EUS in the selection of patients with GC for neoadjuvant therapy means in reference 48. Thank you for your report, we changed the text In order to better specify the values.

5. (reference 35) Journal name is missing. The reference has been modified as suggested.

6. (Table 1 and Fig. 1) Are these necessary for this review? We inserted the table in order to better specify the TNM classification which is long and complex to keep in mind and we inserted the figure to permit a visualization of early lesions, as a direct image.

7. Finally, there are many grammatical errors. The whole manuscript must be revised well by one of the authors who is a native English speaker.
Thank you for the comment. The manuscript was checked by a native (New England) English speaker and also the final revised version.

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Position: Peer Reviewer
Academic degree:

Professional title:

Reviewer's Country/Territory: Reviewer_Country

Author's Country/Territory: Italy

Manuscript submission date: 2022-10-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-18 07:48

Reviewer performed review: 2022-10-30 09:03

Review time: 12 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
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SPECIFIC COMMENTS TO AUTHORS

The standardized treatment of gastric cancer must be based on the standardized staging diagnosis system. Endoscopic ultrasound (EUS) has a good accuracy in distinguishing T1~2 and T3~4 stage tumors, while distinguishing T1~2 and T3~4 stage tumors is of great value in the selection of late treatment plans. However, the detection rate of metastatic lymph nodes in gastric cancer by EUS is still affected by its location and size. Most of the retroperitoneal and mesenteric metastatic lymph nodes around the celiac artery and below the superior mesenteric vessels are far away from the ultrasound probe and are difficult to be detected by EUS. Therefore, EUS has some limitations on N and M staging of gastric cancer. Thank you for the comment. In the text we specified your remark. Particularly, regarding lymph nodes we added in the text the concept of "visible lymph nodes" in order to express the concept that EUS is not a systemic evaluation of all the disease but it represents a local staging.