Dear Editor and reviewers, thanks for considering our cohort prospective study for publication in the World Journal of Methodology, and thanks for your efforts in reviewing the manuscript.

Here is our point to point response to the reviewers' comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors:

JUL4th, 2023

Dear authors submitting to WJG

Manuscript ID: 86275

MS. Title: Role of endoscopic ultrasound (EUS) and EUS-guided tissue acquisition in diagnosing hepatic focal lesions

The aim of this study is to aimed to evaluate the role of EUS features, strain elastography (SE), and EUS-tissue acquisition in diagnosing hepatic focal lesions

TYPE OF STUDY AND POPULATION: **This cross-sectional study included 215 patients with pancreatic, biliary, or gastrointestinal malignant lesions referred for EUS examination- included 43 patients with hepatic focal lesions**

Intervention: EUS-FNA/FNB were performed by a single Endoscopist; EUS-FNA was conducted with 22G Echotip needles from Cook Company; however, the FNB was conducted with 22G Acquire needles from Boston

Outcomes - Key findings:

- Most of the hepatic focal lesions were present in the left lobe liver (67.44%)., with a mean size of 29.23 x 29.14 mm. Lymph node enlargement was present in 93%

- The cytopathological confirmed malignant lesions were found in 35 (81.4%) of patients, while benign lesions were found in 8 (18.6%) of patients

There are some major comments to address as follows.

1. Regarding to patient management, there are several information needed to be clarified in methods as follows.

a. How to choose FNA or FNB with 22 g needle – in terms of risk of complications and adequacy of sampling tissue.

Answer: Thanks a lot for your comment.

Initially we were using FNA needles as FNB needles were not available at the beginning of this prospective study. Then we were using FNB acquire needles from Boston scientific as it has better tissue acquisition. No significant adverse events had been encountered as liver biopsy is very safe worldwide, as liver is very near to the Echoendoscope. Also if intrahepatic hematoma occurred, the blood will trickle to one of the portal or hepatic vessels, so the patient will bleed in its own circulation! This was added to the end of the result section and the discussion section, pages 9 and 10.

b.   In case of both lobe liver lesions; how to choose locations for biopsy

Answer: Thanks a lot for your comment.

We targeted the nearest mass to the Echoendoscope, with no intervening vessels along the needle tract and with the presence of a rim of normal liver tissue between the liver capsule and targeted mass to minimize bleeding. This was added to the material and method section (page 5).

c.   Most of the cases have concomitant lesions at other sites? Or not such as pancreatic or lymph node

Answer: Thanks a lot for your comment.

Yes. The 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 metastatic liver lesions (Figure 1A and B) from malignant pancreatic masses, This was added to the result section in page 6.

2.   For results,

-       BASELINE DATA esp. number of complete portal triads (CPTs) should be reported.

Answer: Thanks a lot for your comment.

The FNB/FNA samples were taken from pathological lesions, mostly malignant lesions, so no CPTs were not reported as it were mostly destroyed by the pathological mostly malignant tissue.

- page – 6; regarding to high accurate in diagnosing hepatic focal lesions with 100% sensitivity, specificity, and diagnostic accuracy- what is the gold standard for diagnosis? Please clarify in the methods.

Answer: Thanks a lot for your comment.

The gold standard of malignant lesions is the FNB as it has extremely high specificity, about 95-100% in most articles in the literature. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over six months, as mentioned in pages 7 and 8 in the discussion section.

- page 8- The role of mean elastographic strain ratio of the hepatic focal lesions needed to be addressed more and how to interpret the results

Answer: Thanks a lot for your comment.

Real-Time strain Elastography and scoring were done to all hepatic focal lesions. We considered grades 1 and 2 as benign and grades 3 and 4 as malignant lesions.

Five patients were suggested to have benign lesions while 38 lesions were suggested to have malignant lesions. This was added to the patients and methods (page 5) and results (page 6) sections.

- There was no complications reported in this study- please add

Answer: Thanks a lot for your comment. We added it.

For discussion and conclusion, The authors should suggest the number of needle pass or the location of hepatic lesion in right or left lobe and the size of needle used (22G vs 19G) are appropriate or not or which technique should be applied eg. FNB needles with a slow-pull technique may provide better results. In addition, the role of rapid on-site evaluation (ROSE) on the diagnostic accuracy of EUS-guided fine-needle biopsy is necessary or not.

Answer: Thanks a lot for your comment.

All biopsies were done by high pressure technique and fanning, at least two passes, no Rapid On-Site evaluation (ROSE) was available in any of the cases. This was added to the patients and methods section (page 5).

References

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- Phan, V. A., et al. (2023). "Methods of tissue preparation after EUS-guided tissue acquisition without rapid on-site assessment: Results of a randomized study." J Gastroenterol Hepatol 38(5): 733-739.
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Answer: Thanks a lot for your comments and your great help. We added new sentences from some of those papers.

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Rejection

Specific Comments to Authors: Authors have done great job by performing EUS examination, elastography and FNAC/FNAB in identification of hepatic SOL.

Here are my concerns:

1. Authors have not explained in methods as which EUS findings were considered for diagnosis and differentiation of benign versus malignant hepatic SOL. It should be thoroughly explained and can be added as supplement also.

Answer: Thanks a lot for your valuable comment.

Based on EUS features, we considered the mass as malignant if any one of the following criteria is present:

1- **The presence of peripheral hypoechoic halo.**
2- **The presence of mass effect as compression or interruption of the course of a blood vessel or a biliary radicle, or the presence of contour bulge. This was added to the method section.**

2. There is no section of statistical analysis which can explain what methods were used to compare different diagnostic methods.

Answer: Thanks a lot for your comment.

Sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy of elastography, EUS &FNAC were calculated using 2x2 table against the gold standard method (pathology). We compared EUS results against pathology results.

3. Authors have compared EUS against which investigation. Have they compared EUS diagnosis of benign/ malignant lesions against CT findings.

Answer: Thanks a lot for your comment.

We compared EUS against the gold standard method (pathology)

This study was aimed to highlight the role of endoscopic ultrasound (EUS) and EUS-guided tissue acquisition in diagnosing hepatic focal lesions. No comparison with CT or any other modalities was done. The gold standard of malignant lesions is the FNB as it has extremely high specificity, about 95-100% in most articles in the literature. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over six months, as mentioned in pages 5 and 6 in the methods section.

4. If they are comparing different diagnostic methods, they should also perform correlation analysis. Whether EUS examination findings for benign lesions were correlating with CT or FNAC findings.

Answer: Thanks a lot for your comment.

CT not done for all patients, so due to missing CT data for many patients we cannot compare EUS results against CT results.

We did not compare different modalities as CT was dome to some patients, MRI or abdominal US was done to others, so not all patients have undergone the same modality. Missing CT or MRI data for many patients so we cannot compare EUS results against CT or MRI results.

So, we deleted the table 1.

5. They combined EUS examination findings and elastography together and as a whole these two were compared against EUS FNAC/FNAB results.

Answer: Thanks a lot for your comment.

The gold standard of malignant lesions is the FNB as it has extremely high specificity, about 95-100% in most articles in the literature. All benign-looking lesions were followed up with the disappearance of all cholangitis abscesses under antibiotic therapy, while the two benign liver nodules were constant in size over six months. Then, we compared The EUS findings, Elastography to the gold standard.

6. they have not given etiological break up of benign and malignant hepatic lesions.

Answer: Thanks a lot for your comment.

The 35 malignant lesions were five primary hepatocellular carcinomas, one neuroendocrine tumor, and 29 metastatic liver lesions (Figure 1A and B) from malignant pancreatic masses, This was added to the result section in page 6.

The 8 benign lesions were 6 cholangitic abscesses and two benign looking lesions that were followed for 6 months without change in its size, mostly cirrhotic nodules.

7. Table 1 gives size of lesion in CT as 29.23x 29.14 mm. There is no range or standard deviation. They should have written size in 3 dimensions separately with Mean±SD/range.

Answer: Thanks a lot for your comment.

CT not done for all patients, so due to missing CT data for many patients we cannot compare EUS results against CT results.

We did not compare different modalities as CT was dome to some patients, MRI or abdominal US was done to others, so not all patients have undergone the same modality. Missing CT or MRI data for many patients so we cannot compare EUS results against CT or MRI results.

So, we deleted the table 1.

8. Table 3 gives size of hepatic lesion in EUS as 23.47 x 39.19 (17.81 x 24.31) mm. Please explain. There is no Mean±SD/range.

Answer: Thanks a lot for your comment.

	Mean ±SD (range)
Shortest diameter Size (mm)	**19±12.8 (3-67)**
Longest diameter Size (mm)	**26±19.1 (4-109)**

9. If sensitivity and specificity both are low, how accuracy can be higher. Many deficiencies in the manuscript considering its analysis.

Answer: Thanks a lot for your comment.

The percent of overall accuracy of Elasticity score and EUS findings lies beween the percent value ot its sensitivity and specificity as demonstrated in the last table. The sensitivity, specificity and diagnostic accuracy of FNB/FNA are 100%.

We are extremely grateful to the reviewer for their time, kind comments and recommendations. We would request reviewer and editorial board to offer kind consideration to our reply.