

Lian-Sheng Ma, Science Editor, Company Editor-in-Chief, Editorial Office

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Dear Mr. Ma:

We thank the Reviewers and editors for their valuable comments for our invited review. We have addressed each comment in the point-by-point response below, and believe these changes have improved the manuscript as well as value to the readership of World Journal of Hepatology.

## **RESPONSES**

### **Reviewer #1**

1. According to the figure 2, ascites is a contraindication for EUS-FNB. Is there any report about the application of EUS-FNA in patients with portal hypertension but minimal ascites? For example, a patient with one tumor in the caudate lobe but only localized ascites in the right sub-diaphragm area, EUS-FNB may be a feasibility.

**Response:** This is an important issue raised by the reviewer. The characterization of ascites as a "contraindication" stems from reference 6. Within that AASLD Position Paper, the authors recognize the limited data available to guide the practice of liver biopsy in patients with ascites prompting their recommendation "...transvenous approach is generally recommended, although percutaneous biopsy (after removal of ascites) or laparoscopic biopsy are acceptable alternatives". This recommendation was given Class I, Level C. They additionally offer the alternative of image-guided biopsy with the same Class/Level of evidence.

Thus, we characterize ascites as a "relative" contraindication to EUS-LB. In practice, we believe clinical judgment allows this determination to be made on a case-by-case basis, similar to the example Reviewer #1 suggests in their comments.

2. Do authors review the comparison of procedure time or cost between PC LB, TJ-LB, and EUS-LB?

**Response:** We agree with the reviewer that cost and procedure time are important variables. In Table 1, cost is mentioned in the comparison between modalities. Given significant variation in methods/practice/cost of liver biopsy from center-to-center (in United States) and worldwide, we believe the data that directly compares procedure/recovery times or the cost is too variable so we kept this as qualitative comparison rather than quantitative.

We believe the more generalized acknowledgements in Table 1 of "high cost" as a disadvantage for EUS-LB and TJ-LB and "lower cost" as an advantage of PC-LB still address the Reviewer's concerns as they pertain to cost. We also acknowledge "decreased recovery time" as an advantage of EUS-LB in Table 1.

3. In clinical practice, larger needle size, such as 18 or 19 gauge needle, are used in percutaneous liver biopsy. Small needle, such as 22 or 25 gauge needle are used in EUS-guided FNB. The captured volume of specimens may also be different between the different designs of core needles. Studies by EUS-FNA or EUS-FNB should be analyzed separately. Moreover, EUS-FNB is a trend in capturing more liver tissue and equal adverse effects than FNA.

**Response:** We agree with Reviewer #1 that larger needle diameters are utilized in percutaneous liver biopsy (generally 16-18 gauge). We also agree that smaller needles (22 or 25-gauge) needles are typically used in EUS FNB. However, we wish to clarify that all studies included in the meta-analysis (reference 14) discussed were performed with 19-gauge needles (6 studies with core needle, 3 studies with FNA needle).

We agree that the captured volume of specimens may be different between different needle designs, and that the ideal technique and needle types remain a topic of debate. Within the text, we note that the results reported from reference 14 are pooled, and include core and FNA needles. Although we do not specifically analyze the core vs. FNA needle studies separately, we do note differences seen in the subgroup analysis which we believe addresses that concern.

4. Is there any report concerned the application of EUS for portosystemic shunt to resolve the portal hypertension question?

**Response:** To our knowledge, the only data regarding EUS-guided creation of intrahepatic portosystemic shunts are in animal models. Though the studies would suggest technical feasibility, concerns regarding increased risk of in-stent thrombosis and infection due to the nonsterile approach suggest limitations to its implementation in clinical practice.

#### Science Editor

1. Authors should compare procedure time or cost between PC LB, TJ-LB, and EUS-LB  
Response: Addressed in 2<sup>nd</sup> question from Reviewer #1

Again, we thank the Reviewers and Editors for their time and thoughtful suggestions to improve this manuscript.

Sincerely,

Sean R. Rudnick, MD