World Journal of Gastroenterology

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World J Gastroenterol 2024 October 28; 30(40): 4333-4338

DOI: 10.3748/wjg.v30.i40.4333

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Endo-hepatology: Why should we do endoscopic ultrasound-guided interventions to the liver that we could do through the skin?

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade B, Grade C

P-Reviewer: Bian JM; Cai QY

Received: April 2, 2024

Revised: September 13, 2024

Accepted: September 25, 2024

Published online: October 28, 2024

Processing time: 196 Days and 16.8 Hours

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Abstract

Endoscopic ultrasound (EUS)-guided interventions on the liver such as diffuse biopsy and portal pressure gradient measurement are emerging as potential alternatives to percutaneous procedures. The purpose of this editorial was to address all the indications that could potentially make an EUS-guided approach a possible alternative to the percutaneous procedures with respect to the procedures that could join the EUS examination such as upper endoscopy for gastroesophageal varices, pancreaticobiliary investigation with EUS, and other potential advantages in terms of patient safety. The issue of a holistic gastroenterologist approach was also discussed along with the potential for developing clinical research.

Key Words: Endo-hepatology; Endoscopic ultrasound; Endosonography; Liver disease; Liver biopsy; Portal hypertension

Core Tip: Endo-hepatology is a new branch of gastroenterology that integrates skills of advanced endoscopy with hepatology. New endoscopic and endoscopic ultrasound (EUS) techniques have emerged that are tailored for the management of hepatological patients, such as EUS-guided liver biopsy, EUS-guided measurement of the porto-systemic gradient. The potential advantage of performing such procedures from the inside of the stomach and duodenum instead of the outside of the patient, *i.e.* percutaneously, were discussed.

Citation: Calvanese C, Fusaroli P. Endo-hepatology: Why should we do endoscopic ultrasound-guided interventions to the liver that we could do through the skin? *World J Gastroenterol* 2024; 30(40): 4333-4338
URL: https://www.wjgnet.com/1007-9327/full/v30/i40/4333.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i40.4333

INTRODUCTION

Endo-hepatology is a relatively new branch of gastroenterology that integrates the skills of advanced endoscopy with those of hepatology. In the past, the integration was limited to only a few procedures, such as the management of esophagogastric varices. However, new endoscopic and endoscopic ultrasound (EUS) techniques have emerged that are tailored for the management of hepatological patients. These include EUS-guided liver biopsy (EUS-LB), EUS measurement of the portosystemic gradient (EUS-PPG), and EUS treatment of gastric varices. the creation of EUS portosystemic shunts is still limited to animal models. For this editorial, we focused on EUS-LB and EUS-PPG.

EUS–LB

Despite the extensive development over the last 20 years of non-invasive techniques for the study of liver stiffness, biopsy remains a cornerstone in the diagnosis and staging of liver parenchymal diseases[1]. This is crucial for some hepatic parenchymal diseases such as autoimmune hepatitis, overlap syndromes, drug-induced liver injury, and metabolic-associated fatty liver disease (MAFLD). To date, liver biopsy has been performed through two modalities: The percutaneous approach and the trans-jugular approach. Percutaneous liver biopsy (PC-LB) is usually performed under ultrasound or computed tomography guidance, while transjugular liver biopsy (TJ-LB) is performed under fluoroscopic guidance. EUS-LB has emerged as a valid alternative to the other methods.

Pros and cons

Performing a liver biopsy *via* EUS has numerous advantages. First, EUS provides a high-definition examination of the liver parenchyma. This allows the identification of thin vascular and biliary structures, reaching greater safety during the sampling phase as well as greater precision for sampling small focal lesions even < 10 mm. Second, EUS-LB allows relatively easy sampling of both liver lobes, while PC-LB and TJ-LB almost exclusively allow right liver lobe sampling. In contexts such as MAFLD, the parenchymal damage has been shown to be inhomogeneous, and obtaining a biopsy of both lobes guarantees a better diagnostic definition[2]. Third, EUS-LB can overcome somatic characteristics such as abdominal obesity and meteorism that are limitations to PC-LB. Fourth, EUS-LB is considered more comfortable for patients than PC-LB because it involves procedural analgesia sedation. Lastly, the most important advantage of EUS-LB is represented by the possible combination with other endoscopic procedures such as upper endoscopy for varices detection, EUS-PPG in patients with advanced chronic liver disease, and biliopancreatic EUS. The combination of different endoscopic procedures in the same session appears to be cost-effective[3].

On the other hand, alteration of coagulation parameters is considered one of the principal contraindications in performing EUS-LB with cutoff values defined at international normalized ratio 1.5 and 50.000/mm^3 platelets, or concomitant anti-coagulant/anti-platelet therapy that cannot be withheld. Moreover, a massive ascites is considered a contraindication to EUS-LB as well as PC-LB. In both coagulopathy and ascites, TJ-LB is the preferred technique. Concerning bleeding risk, TJ-LB seems to be safer as it avoids puncturing the liver capsule, although intrahepatic hematomas and hemobilia can occur with this technique too. Additionally, access to EUS-LB constitutes a relevant limitation considering the relatively low number of expert endosonographers to practice it compared to PC-LB. Lastly, procedural costs represent another limitation for EUS-LB, especially when compared to PC-LB; nevertheless, costs can be significantly reduced when EUS-LB is combined with other endoscopic procedures.

Efficacy and safety

Liver biopsy can be considered effective if it provides an adequate sample. According to the American Society for the Study of the Liver guidelines, a tissue sample can be defined adequate when the total specimen length (TSL) is at least 2-3 cm and contains at least 11 complete portal triads (CPT)[1]. The British clinical practice guidelines require similar standards[4].

Diehl *et al*[5] published one of the first studies investigating the efficacy and safety of EUS-LB in 2015. They showed a high diagnostic yield of the procedure (98%) and a low rate of adverse events down to 0.9% (one self-limiting bleeding). One year later, the same authors published a comparative study[6] on the efficacy of EUS-LB *vs* PC-LB *vs* TJ-LB. The three procedures showed the same efficacy when only a left liver lobe biopsy was carried out by EUS-LB. However, the efficacy of EUS-LB was superior in terms of TSL and CPT when both the right and the left liver lobes were sampled.

Mohan *et al*[7] published a meta-analysis concerning EUS-LB efficacy and safety in 2020 (9 studies, 437 patients) and showed a 94% diagnostic yield and a 2.3% rate of adverse events. A more recent and larger meta-analysis by Baran *et al*[8] (23 studies, 1326 patients) demonstrated a diagnostic yield of 93% with an overall adverse event rate of less than 10%, mainly of moderate entity (abdominal pain). Severe adverse events were in the range of only 1% requiring hospital admission (hemorrhagic complications or bile leaks; one death of uncertain cause was recorded in the 24 h after the

procedure).

Lastly, Ali *et al*[9] demonstrated a better performance of EUS-LB compared with PC-LB, both in terms of post-procedure pain and hospital length of stay. Albeit no studies directly compared the adverse events rate of EUS-LB, PC-LB, and TJ-LB. According to the literature data, the adverse event rates seem comparable (EUS-LB < -2.3%, PC-LB < 3.1%, TJ-LB < 6.5%)[3].

Technique

The left lobe can be easily sampled through a transgastric route, while the right lobe can be reached *via* the duodenal bulb. The technique aims to find an adequate window of hepatic parenchyma free from biliary or vascular structures and then inserting the needle inside the parenchyma at least 3-4 cm deep.

Concerning needles, the right type for fine needle aspiration (FNA) *vs* fine needle biopsy (FNB) should be used. Ching-Companioni *et al*[10] published a prospective randomized study in which 40 patients underwent EUS-LB [20 with a 19 G FNA needle and 20 with a 19 G FNB needle (Franseen-tip)]. The FNB needle was superior for both TSL and CPT, making the FNB needle the device of choice for EUS-LB.

Regarding needle size, Shah *et al*[11] compared a 19 G FNB needle (Fork-tip) with a 22 G FNB needle (Fork-tip) in a prospective small experience with 20 patients who underwent EUS-LB with both needles. The 19 G needle showed better diagnostic adequacy and diagnostic yield. Similar results were obtained by Diehl *et al*[12] in a prospective randomized study comparing 19 G *vs* 22 G FNB needle (Franseen-tip). Concerning the FNB needle tip, Nieto *et al*[13] published a retrospective study on 420 patients who were sampled either with the Fork-tip needle or with the Franseen-tip needle. The Franseen-tip needle proved to be superior in terms of adequacy of the sample obtained regarding both TSL and CPT. Similar results were replicated by Aggarwal *et al*[14] who published a prospective head-to-head comparative study in 108 patients who were sampled with both needle shapes.

Regarding sample acquisition, there are currently no definitive data. Mok *et al*[15] compared dry suction to wet suction (pre-filled with heparin), highlighting superior results in terms of diagnostic yield and sample adequacy with wet suction. However, Baran *et al*[8] concluded that the slow-pull technique was better than the suction technique in their meta-analysis.

Finally, regarding the number of needle passes and actuations, Ching-Companioni *et al*[16] published a prospective randomized study on a total of 40 patients comparing one pass with one actuation *vs* one pass with three actuations (where actuation means the number of movements of the needle in the target parenchyma). All patients underwent bilobar biopsy (two passes per patient). Carrying out three actuations and two passes (bilobar) guaranteed the best sample adequacy.

EUS-PPG

Portal hypertension (PH) is one of the most important consequences of chronic liver disease. PH is defined as portal pressure > 5 mmHg, while clinically significant PH (CSPH) is defined as ≥ 10 mmHg. CSPH leads to hepatic decompensation and is characterized by the development of gastroesophageal varices, ascites, kidney dysfunction, and/or cardiopulmonary issues. These conditions are mainly related to liver cirrhosis and its progression even though there are non-cirrhotic conditions that may be aggravated by the development of PH.

PH quantification helps define different disease stages in patients with cirrhosis and implementing individualized interventions, such as prevention of CSPH, decompensation, and overall disease worsening. Moreover, it allows stratification of surgical risk when major hepatic or extrahepatic surgery are required. Tailoring therapy to individual characteristics and risk of PH-related complications has been demonstrated to improve prognosis[17-19].

EUS-PPG vs hepatic venous pressure gradient

Measurement of the hepatic venous pressure gradient (HVPG) *via* transjugular/transfemoral hepatic vein catheterization represents the current gold standard for assessing PH. HVPG is the difference between the free hepatic venous pressure and the hepatic wedge pressure that reflects the hepatic sinusoidal pressure and constitutes an indirect measurement of portal pressure[17]. Although considered safe, HVPG measurement may be complicated by adverse events such as contrast agent allergy and cardiac arrhythmia during catheter insertion or bleeding, especially in patients with coagulation impairment. Moreover, the HVPG measurement technique has limitations in clinical practice. Most importantly, HVPG does not provide the measurement of PH in presinusoidal liver conditions. In fact, HVPG provides an indirect measurement of portal pressure calculating the difference between the free hepatic venous pressure and the hepatic wedge pressure that reflects only the hepatic sinusoidal pressure.

In cases of presinusoidal PH (*e.g.*, primary sclerosing cholangitis, primary biliary cholangitis, polycystic liver disease, and malignancy), HVPG is considered inappropriate[20]. HVPG has also been demonstrated to provide inaccurate PH determination in MAFLD, which is now considered the leading cause of cirrhosis and liver transplantation probably due to a different etiopathogenetic mechanism that causes development of PH in this setting[21,22]. Finally, HVPG measurement is still limited to few referral centers as it requires special skills and a dedicated radiological setting despite being considered the gold standard.

Unlike HVPG, EUS-PPG assesses hepatic venous and portal pressure directly producing a direct measurement of PH. It consists of transgastric EUS-guided puncture of these vessels with a 25 G FNA needle coupled to a digital pressure transducer at the proximal needle port. EUS-PPG is determined by subtracting the hepatic venous pressure from the portal pressure. In 2016, Huang *et al*[23] published the first preclinical experience on EUS-PPG in a porcine model to

assess clinical feasibility. They demonstrated successful EUS identification, access, and manometry in all target vessels and excellent correlation comparing EUS-PPG and HVPG methods in all pressure ranges. No adverse events were encountered.

Based on promising results, the same authors subsequently published the first human experience of EUS-PPG[24] in 28 patients. EUS-PPG measurements were performed with a linear echoendoscope and a 25 G FNA needle connected to a pressure gauge. The portal and hepatic veins (or inferior vena cava) were targeted either through the stomach or the duodenum. The technical success rate of EUS-PPG measurement was 100%, and no adverse events were recorded. This study showed that this technique was feasible, safe, and effective, showing excellent correlation with the standard of care.

A dedicated device (EchoTip Insight® Portosystemic Pressure Gradient Measurement System; Cook Medical, Bloomington, IN, United States), approved by the Food and Drug Administration, is now commercially available to perform EUS-PPG. Subsequent studies, such as the one by Choi *et al*[25], combined EUS-PPG with EUS-LB and reported excellent correlation with the histological stage of liver fibrosis and various clinical, laboratory, endoscopic, and imaging predictors of advanced liver disease, with no major adverse events.

The only human study directly comparing EUS-PPG and HVPG evaluated the role of EUS-PPG in patients with acute or subacute PH[26]. Technical success was achieved in 92% of the cases with EUS-PPG demonstrating a higher success rate than HVPG measurement. A good correlation was seen on the manometry between EUS-PPG and HVPG values. Again, no adverse events were observed.

Technique

The EUS-PPG device consists of a simple 25 G FNA needle in direct connection with non-compressible tubing and a compact digital manometer. The pressure gauge and the 25 G needle are primed with either saline or dilute heparinized saline.

The patient is kept in the supine position during EUS-PPG measurement, and the manometer is placed at the patient's mid axillary line, approximately at the right atrium level. The middle hepatic vein is usually targeted first. Pulse-wave Doppler flow is used to confirm the typical multiphasic flow. The needle is pushed through the liver parenchyma into the hepatic vein within 2 cm from its confluence to the inferior vena cava. Approximately 1 cc of heparinized saline is then used to flush the needle and confirm a good position of the tip within the vessel. The pressure gauge should be observed to rapidly rise with the flush and then equilibrate to a steady state. Once the latter has been reached, the lowest value on the pressure gauge display must be recorded. The measurement is repeated thrice in the same manner, and the average of the values is annotated. The needle is then slowly withdrawn from the vessel through the liver parenchyma under color Doppler view to rule out ongoing bleeding, which could be controlled just by leaving the needle inside the parenchyma for a few more seconds.

The intrahepatic portal vein or one of its main branches is then punctured in the same manner, and pressure is recorded likewise. The portosystemic pressure gradient is then obtained by subtracting the mean portal vein pressure from the mean hepatic vein pressure[20,27].

Although EUS-LB and EUS-PPG are safe, precautions must be observed. During the procedure, the liver parenchyma must be carefully explored under B-mode and power Doppler to avoid undesired puncture of vascular and biliary structures. The needle retraction must be accurate as well, accurately checking for possible bleeding points with the possibility of using the needle itself to tamponade. Clinical observation after the procedure should always be done up to 4 h, while an overnight hospital stay is preferable for patients undergoing EUS-PPG. Abdominal pain is the most common side effect, most often self-limiting or responsive to analgesics. The need for subsequent investigations or access to the emergency room remains anecdotal. In such circumstances, a computed tomography scan may be necessary to check for adverse events and establish the subsequent management.

CONCLUSION

Tissue sampling by liver biopsy remains pivotal for the diagnosis, staging, and management of several hepatic disorders. EUS-LB has emerged as an interesting alternative to standard methods and has been shown to be accurate and safe. Integrating EUS-LB with other endoscopic or EUS procedures in the same session is deemed cost-effective. PH quantification is crucial in liver diseases, providing fundamental information on treatment and patient prognosis. EUS-PPG has been shown to be as adequate and safe as the current gold standard HVPG. HVPG is not routinely performed in clinical practice due to its invasiveness and limited availability, mostly limited to academic settings and scientific trials. Thanks to its simple technique, similar to EUS-FNA, EUS-PPG may bring the advantage of easier adoption in daily practice. Moreover, EUS-PPG can be performed in the same endoscopic session as other endoscopic or EUS procedures, with the possibility of obtaining more clinical information and even treatment options at the same time.

FOOTNOTES

Author contributions: Calvanese C and Fusaroli P contributed to this paper; Calvanese C designed the overall concept and outline of the manuscript; Fusaroli P contributed to the discussion and design of the manuscript; Calvanese C and Fusaroli P contributed to the writing and editing of the manuscript; Fusaroli P revised the manuscript for relevant intellectual content.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

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S-Editor: Li L
L-Editor: Filipodia
P-Editor: Chen YX

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