

Endoscopic ultrasound-guided tissue acquisition for the diagnosis of focal liver lesion

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Abstract

In patients with liver tumors, the histopathology examination can assist in diagnosis, staging, prognosis, and therapeutic management strategy. Endoscopic ultrasound (EUS)-guided tissue acquisition using fine needle aspiration (FNA) or more newly fine needle biopsy (FNB) is a well-developed technique in order to evaluate and differentiate the liver masses. The goal of the EUS-FNA or EUS-FNB is to provide an accurate sample for a histopathology examination. Therefore, malignant tumors such as hepatocarcinoma, cholangiocarcinoma and liver metastasis or benign tumors such as liver adenoma, focal hyperplastic nodular tumors and cystic lesions can be accurately diagnosed using EUS-guided tissue acquisition. EUS-FNB using 19 or 22 Ga needle provide longer samples and a higher diagnostic accuracy in patients with liver masses when compared with EUS-FNA. Few data are available on the diagnostic accuracy of EUS-FNB when compared with percutaneously, ultrasound, computer tomography or transjugular-guided liver biopsies. This review will discuss the EUS-guided tissue acquisition options in patients with liver tumors and its efficacy and safety in providing accurate samples. The results of the last studies comparing EUS-guided liver biopsy with other conventional techniques are presented. The EUS-guided tissue acquisition using FNB can be a suitable technique in suspected liver lesions in order to provide an accurate histopathology diagnosis, especially for those who

require endoscopy.

Key Words: Endoscopic ultrasound-guided liver biopsy; Liver tissue acquisition; Fine-needle aspiration; Fine-needle biopsy; Liver tumors; Focal liver lesions

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Core Tip: Endoscopic ultrasound (EUS) guided tissue acquisition with fine needle aspiration or biopsy needles are an effective and safe approach to obtain liver samples. In this review our goal is to discuss the EUS-guided tissue acquisition options in patients with liver tumors and its efficacy and safety in providing accurate samples. The results of the last studies comparing EUS-guided liver biopsy with other conventional techniques are presented.

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INTRODUCTION

In patients with liver tumors, the histopathology examination can help in diagnosis, staging, prognosis, and therapeutic management strategy. The gold standard for diagnosis of liver tumors is liver biopsy (LB). Transjugular (TJ) and percutaneous (PC) approaches are the most common techniques for LB[1-3].

Endoscopic ultrasound (EUS)-guided tissue acquisition (EUS-TA) using fine needle aspiration (FNA) or more recently fine needle biopsy (FNB), is a well-developed technique in order to evaluate and differentiate the liver masses. The goal of the EUS-TA is to provide an accurate sample for a histopathology examination[4]. The common indication for EUS-guided FNA (EUS-FNA) is to obtain cytology or histology from primary or metastatic malignancy[5].

Nguyen *et al*[6] reported the utility of EUS-FNA in histological examination of focal liver lesions. In the last two decades there were numerous studies that emphasized the role of EUS-LB in the diagnosis of hepatic malignancies such as hepatocarcinoma carcinoma (HCC), cholangiocarcinoma (CCA), and liver metastasis[7-17] (Table 1).

Furthermore, EUS-LB seems to be efficient in providing a high diagnostic accuracy even in benign liver lesions or diffuse liver conditions[18-24].

In the majority of EUS-FNA studies where 19 gauge (G) or 22 G needles were used, the diagnostic yield of focal liver lesions vary from 80% to 90%[6-10,14-16]. However, EUS-FNB using 19 G or 22 G needles provide longer samples and a higher diagnostic accuracy in patients with liver masses when compared with EUS-FNA[11-13,15,17].

Recent data are available on the diagnostic accuracy of EUS-FNB when compared with PC, ultrasonography (US), computer tomography (CT), or TJ-guided liver biopsies[25-30]. In the last studies the yield of EUS-LB and PC or TJ liver sampling was compared. Specimen accuracy and diagnostic yield are at least comparable between those three techniques, ranging from 90% to 100%[25-30].

In this review we intent to explore and discuss the studies from the last decade regarding EUS-TA options in patients with liver tumors. Furthermore, we assessed the efficacy and safety of EUS-FNA and EUS-FNB from liver masses in providing an accurate diagnostic.

ENDOSCOPIC ULTRASOUND LIVER ASSESSING

EUS has multiple advantages in the evaluation of the liver and its focal or diffuse conditions. Both the liver lobes and liver hilum can be accurately evaluated from the stomach and bulb using the EUS approach due to the close position of the transducer[5]. EUS is an adjuvant method to magnetic resonance imaging (MRI) and CT in detecting and characterizing liver tumors and is superior to CT in diagnosing liver lesions located in the left lobe or smaller than 10 mm in diameter[5,31,32].

Tissue acquisition under EUS guidance (FNA) or FNB is a helpful technique in the diagnosis of focal liver lesions, perihepatic adenopathy and in the evaluation of biliary tract disease. In contrast with other techniques, liver EUS has some advantages as targeting the caudal lobe, avoiding the biliary tree and vessels during puncture. It is a real-time technique and the perihepatic lymph nodes and portal vein thrombosis can be targeted in the same session[32].

The malignant tumors such as HCC, CCA, and liver metastasis or benign tumors such as liver adenoma, focal hyperplastic nodular tumors and cystic lesions can be accurately diagnosed using EUS-TA[4,5,31,32] (Figure 1).

There are various factors which can influence the diagnostic yield of EUS or EUS-LB: The features of the liver lesions (localization: Caudal or left lobe or right lobe, size and echogenicity), the examiner experience, the type of the needle, the number of passes, the aspiration /biopsy technique (stylet and suction), the presence of the cytopathologist in the

Table 1 Literature data: Diagnostic accuracy, success rate, adverse events, and complications of endoscopic ultrasound guided biopsies for liver lesions

Ref.	Study design	Lesions/patients, <i>n</i>	Results	Success rate, adverse events
DeWitt <i>et al</i> [9], 2003	Large study	77 SLT; FNA	77 liver specimens, 25 benign (33%); 45 malignant (58%), and 7 nondiagnostic (9%)	Sensitivity for the diagnosis of malignancy ranged from 82% to 94%
Lee <i>et al</i> [11], 2015	Prospective study	21 SLT with nonconclusive diagnosis after percutaneous biopsy	21 lesions were malignant	Diagnostic accuracy-85.7% (diagnosis of malignancy in 19 cases)
Oh <i>et al</i> [12], 2017	Study liver masses	47 patients with liver masses FNA; 24 left lobe (51.1%); 13 right lobe (27.7%); 10 both lobe (21.3%); size of lesion, median, 26 mm (15-37); number of needles passes 3	9 benign (19.15%); 38 malignant (80.95%); technical success 97.9%; EUS-FNA was diagnostic in 38 of 42 patients (90.5%); technical success similar in both lobes (100% left lobe vs 94.1% right lobe)	Adequate specimen higher in left lobe (93.3% vs 82.4%); diagnostic accuracy not different between lobes (89.3% vs 92.9%); no complications
Temnykh <i>et al</i> [13], 2020	Prospective study	180 solid lesions; FNB (Franseen) vs 183 solid lesions; FNA (acquire) 32 liver lesions (23 FNA, 9 FNB)	37.4 min (FNB) vs 44.9 (FNA) min; 2.9 passes FNB vs 3.8 passes FNA	Cytologic diagnostic yield 98.3% (FNB) vs 90.2% (FNA), <i>P</i> = 0.003; adverse events 1.1% (FNB) vs 0.5% (FNA)
Akay <i>et al</i> [14], 2021	Retrospective study	25 patients with SLT, FNA 22 G, 1 pass	16 malignancies: 7 HCC, 1 CCA, 1 adenoma, 6 metastasis, 1 GB cancer infiltration; 3 benign (3 steatosis), 3 inadequate materials	Diagnostic accuracy 86.30%, success rate 88.00% (22 patients), 94.45% aspirate sufficiency, 86.30% biopsy sufficiency rate
Chen <i>et al</i> [15], 2020	Retrospective study	34 patients with cirrhosis and suspected left lobe HCC, FNB	30 adequate biopsies specimens; 25 patients confirmed HCC, 5 benign	Se/Sp/PPV/NPV, 88.0%/100.0%/100.0%/62.5%
Chen <i>et al</i> [16], 2014	Retrospective study	4312 patients with suspected HCC with AFP under 200ng/dL FNA; 1756 underwent FNA	1590 malignant (1145 primary liver neoplasm: HCC 1067, CCA 63, HCC-CCA 8, hepatoblastoma 1, lymphoma 6, metastasis neoplasms 75), 166 benign	112 false negative, Se 92.00%, Sp 96.00%, PPV 100.00%, NPV 59.71%; overall accuracy 93.62%; complications: 4 implantation metastasis, 6 hemorrhage
Zhang <i>et al</i> [17], 2020	Retrospective study	624 malignant liver cases FNB	448 metastases (71.8%), 97 HCC (28.2%), 73 CCA, 3 HCC-CCA, 58 NET (11.7%), 24 SSC (3.8%); embryonal sarcoma, hepatoblastoma, leiomyosarcoma	30 different types of malignant tumors
Ichim <i>et al</i> [40], 2019	Prospective study	48 patients with malignant SLT FNA 22 G	47 malignancies, 1 insufficient, metastasis pancreatic ADK 26% CCA 17%	Diagnostic yield 98%, 83% from left lob, 17% from right lob, no adverse events/complications
Gheorghiu <i>et al</i> [41], 2022	Head-to-head study, prospective trial	38 SLT; 22 G FNB vs 22 G FNA	25 malignant lesions (14 metastases and 11 primary liver tumors); 6 benign lesions (abscesses); 7 inconclusive	Diagnostic rate for FNB-93.9%; insufficient core 4.0% (FNB) vs 20.0% (FNA)
Choi <i>et al</i> [65], 2017	Liver study	28 patients with SLT located in the left liver lobe FNB	KRAS mutation was analyzed	Diagnostic accuracy for malignancy 89.3%; adding KRAS diagnostic accuracy 96.4%

FNA: Fine needle aspiration; FNB: Fine needle biopsy; SLT: Solid liver tumor; HCC: Hepatocarcinoma carcinoma; CCA: Cholangiocarcinoma; GB: Gallbladder; Se: Sensibility; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predicting value; AFP: Alfa feto protein; NET: Neuroendocrine tumor; ADK: Adenocarcinoma; SSC: Squamous cell carcinoma.

endoscopy room (ROSE), the preparation of the specimen for cytohistologic examination and the cytopathologist experience[33-38].

EUS-GUIDED LIVER ACQUISITION

Tru-cut needles: Mathew *et al* [21] published the first case of EUS-LB using a novel Tru-Cut (Quick-Core, Cook Medical) core biopsy needle. Later in a study by DeWitt *et al* [19], 21 patients underwent EUS-guided Tru-Cut biopsy from benign liver disease. A histology diagnosis was obtained in the majority of the cases (90%) but the standard criteria for histology assessment was not met due to the small size of samples[19]. More recently, in a large retrospective study the Tru-Cut needle was compared with a non Tru-Cut needle (ProCore needle, Cook Medical) and the results showed that the ProCore needle was easier to use and provided good tissue with fewer passes than the Tru-Cut needle[39]. Nowadays, the widespread adoption of the Tru-Cut needle is limited due to the inflexibility and the difficulty of use resulting in the manufacturers considering removing this needle from clinical practice.

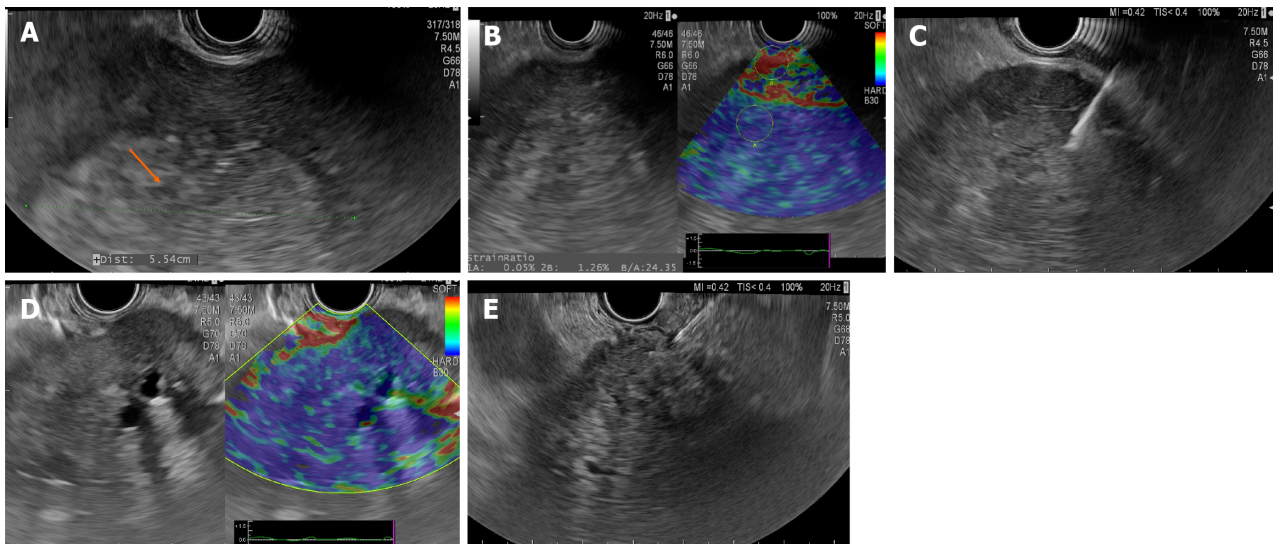


Figure 1 Endoscopic ultrasound. A and B: Endoscopic ultrasound view of a right lobe hepatocarcinoma. Large hyperechoic tumor mass with halo segments V-VIII (A); Ultrasound elastography showing high strain ratio predicting malignant character of the lesion (B); C: Endoscopic ultrasound guided fine needle biopsy from a left lobe hepatocarcinoma in a patient with liver cirrhosis; D and E: Endoscopic ultrasound view of a left lobe cholangiocarcinoma. Large inhomogeneous tumor mass with intratumoral left bile duct dilatations (D); Endoscopic ultrasound guided fine needle aspiration from the tumor mass (E).

EUS-FNA FOR LIVER TUMORS

Stavropoulos *et al*[22], published in 2012, an important study which demonstrated the efficacy of a 19 G FNA in EUS-LB. Moreover, the efficacy of 19G FNA in EUS-LB was shown in a multicenter prospective study conducted by Diehl *et al*[23] in patients with elevated liver enzymes or hepatic disease. EUS-LB was performed in 110 patients and in the majority (108 patients) the specimens obtained were sufficient for a pathological diagnosis. The study demonstrated high tissue specimen lengths and portal tract counts. No differentiation in yield was detected between the right lobe, left lobes or both lobes[23].

In the last two decade, EUS-FNA has demonstrated its role in patients with liver tumors. Earlier previous studies demonstrated a sensitivity of 19G EUS-FNA for liver malignancy and ranged 75%-100% with very low morbidity and mortality[8-10]. In a large study, Dewitt *et al*[19] assessed the role of EUS-FNA in differentiation benign lesions from malignant liver lesions. From 77 liver specimens, 25 were benign, 45 were malignant, and 7 were nondiagnostic. Of the patients with malignancy identified *via* cytology, EUS-FNA changed the management in 86% of the subjects[19].

Studies from the last decade using 22 G FNA evidenced high efficacy and diagnostic accuracy for liver malignancy diagnosis[14,40,41]. In a retrospective small study conducted by Akay *et al*[14] on 25 patients with liver masses, the success rate and the diagnostic accuracy using FNA 22G and only 1 pass were evaluated. The success rate was 88.00% (22 patients). In 94.45% of cases the rate of aspirate was sufficient. The diagnostic accuracy was 86.30%. Sixty cases were malignant, 3 lesions were benign and in 3 cases the material was inadequate. The results were better, in a prospective study conducted by Ichim *et al*[40], on 48 consecutive patients; for those diagnosed with liver lesions, EUS-guided 22G FNA yielded positive results for malignancy in 47 out of 48 patients. Only one case had an inadequate sample, resulting in a diagnostic yield of 0.98. The majority of the biopsies, 83%, were from the left liver lobe and 17% from the right, with no significant difference in diagnostic accuracy between the lobes. Similar results were obtained by Gheorghiu *et al*[41].

EUS-FNB FOR LIVER TUMORS

FNB is another approach developed to enhance the histology diagnosis. In the past years, to improve the diagnostic accuracy of EUS-FNB, several core needles were developed. This approach was able to obtain histology core specimens [42,43]. The 3rd generation of EUS biopsy needles had demonstrated a better diagnostic yield compared to the first generation of FNB needles and FNA needles[44,45]. There are several types of FNB needles available for clinical practice (Acquire, ProCore, SharkCore, EchoTip, EZ shot 3, etc.). The available diameter of needles is 19, 20, 22 and 25 G.

EUS-FNB demonstrated a high diagnostic rate of 93.9%-100.0% with a low complication rate and a lower incidence of inadequate sample size[26,46,47]. In 2015, a prospective randomized study conducted by DeWitt *et al*[46] compared EUS-TA using two different 19 G core biopsy needles. Eighty-five patients were randomized to FNB (44 patients) and true-cut biopsy (41 patients). FNB specimens had a higher prevalence of diagnostic histology (85 % *vs* 57 %), accuracy (88 % *vs* 62%), mean total specimen length (TSL) (19.4 mm *vs* 4.3 mm), mean complete portal triads (CPTs) from liver biopsies (10.4 *vs* 1.3). Shah *et al*[26] showed a similar results in a retrospective study ($n = 24$) of patients with pancreatobiliary conditions and abnormal liver functional tests (LFTs) who had underwent EUS-TA with a 19 G FNB (SharkCore). A histology diagnosis was obtained in the majority of cases (96%), with a median CPT of 32.5, median TSL of 65.6 mm, and a median of two passes. Nieto *et al*[47] conducted a retrospective study on 165 patients with elevated LFTs using the wet

suction technique FNB in patients with elevated LFTs who had undergone EUS-LB. The median number of CPTs was 18, the median TSL was 60 mm.

FNA biopsy with 19 G needle is the most commonly used method for the diagnosis of liver tumors. Previous studies have revealed a better specimen, a higher diagnostic accuracy and less needle passes when EUS-FNB is used for liver masses diagnostic[11-13,15,17,48,49]. Lee *et al*[11] conducted a prospective, single center in order to assess the role of EUS-FNB of solid liver lesions following an inconclusive LB guided under abdominal US. A 25 or 22G FNB needle was used according to whether the biopsy was performed using the duodenum approach or stomach approach, respectively. EUS-FNB was able to diagnose malignant lesions in 19 of 21 cases (85.7%). Adler *et al*[49] performed a multicenter retrospective study of 200 patients undergoing EUS-FNB for solid lesions. Liver lesions were presented in only 14 patients (8 CCA and 6 liver lesions). The median passes were 3 and the rate of a core of tissue was 90%. No adverse events were detected. Chen *et al*[15] evaluated 34 patients with cirrhosis and left lobe suspected hepatocarcinoma performing EUS-FNB with 30 adequate biopsy specimens. HCC was confirmed in 25 patients and in 5 patients the lesions were benign. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EUS-FNB for histology diagnosis were 88.0%, 100.0%, 100.0%, respectively 62.5%[15].

The majority of studies have found that FNB with 19 G needle is better than FNB with 22 G needle in terms of length of the specimens, numbers of portal tracts and eventual histological diagnosis accuracy[26,39,48,50]. In a prospective case series of patients ($n = 20$) undergoing EUS-LB, Shah *et al*[50] sought differences in liver tissue acquisition obtained by wet suction technique using a 22 G FNB needle and a 19 G FNB needle from the left lobe of the liver. The mean TSL was significantly longer for the 19 G core sample *vs* the 22 G core sample: 25.2 mm and 12.7 mm respectively ($P < 0.0001$). The 19 G needle also resulted in a significantly higher number of CPTs (5.8 *vs* 1.7, $P < 0.0001$) when compared to the 22 G needle. The 19 G needle was also superior in providing an adequate and diagnostic specimens (85% *vs* 10%) and pathology samples (60% *vs* 5%) than 22 G needle. There were no adverse events in either group[50].

Interestingly, some recent studies concluded that the diameter of 19 G and 22/25 G of FNB needles seem to be similar in terms of the length of specimen and the diagnostic accuracy from focal and diffuse liver diseases[11,51]. For example, Hasan *et al*[51] conducted a single-center, prospective, open label, nonrandomized trial on 48 patients with elevated liver function test findings (8 were excluded due to biliary obstruction). The authors compared 22 G FNB with 19 G FNB in terms of the length of specimen and the diagnostic accuracy from diffuse liver diseases. Three passes were made in each of the 40 patients (total 120 passes). An adequate tissue specimen, as judged by on-site visual estimation, was obtained in 119 passes (99.2%). All 40 patients (100.0%) had adequate core tissue samples by visual estimation within the first two passes. Per patient analysis, the median TSL was 55 mm, the median CPTs was 42[51].

FNB VS FNA FOR LIVER TUMORS

In the case of focal liver lesions, there have been several articles published concerning the needle size or type. The rate of EUS-FNA diagnosis varied between 75% to 100% with two to three needle passes[8-10]. The latter studies have demonstrated that FNB needles are better than FNA needles in terms of tissue specimen acquisition, yield of histology accuracy and regarding time spent[26,46,47]. In a prospective study published by Temnykh *et al*[13], compared EUS-FNB in 180 patients with EUS-FNA in 183 patients with solid lesions; the number of passes was higher in the FNA group *vs* the FNB group (3.8 *vs* 2.9). The procedural time was longer in the FNA group. The yield of histology accuracy was significantly higher in the FNB group. The same results reached Iqbal *et al*[52] when two FNB needles (SharkCore, Medtronic and Acquire, Boston Scientific) and FNA needle (Echotip Cook) were compared. The diagnostic yield was much higher in the EUS-FNB group (96.0%/94.9%) than the EUS-FNA group (86.2%). No difference was reported when FNB needles were compared.

A head-to-head comparison of 22G FNA *vs* 22G FNB in the diagnosis of focal liver lesions was conducted by Gheorghiu *et al*[41]. This trial prospectively included 32 patients diagnosed with solid hepatic masses by CT scan and unsuitable for PC LB or requiring a EUS-guided sampling from both pancreas and focal liver lesions. The final diagnosis was based on EUS-FNB or EUS-FNA results in 25 patients with malignant lesions (14 metastases and 11 primary liver tumors). The remainder of the six benign lesions were abscesses. The diagnostic rate for EUS-FNB was reported to be 93.9%, with an adverse rate of 2.3%, and an insufficient core was considered to be 4% compared to 20% in the case of FNA needles. Franseen FNB needles obtained better results than Fork-tip needles. They obtained 100% diagnostic accuracy with Franseen FNB needles[41].

A small study conducted by Rodrigues-Pinto *et al*[53], on 33 patients compared the FNA with ROSE performed with a standard FNA needle with FNB with ROSE performed with a new dedicated core needle in patients with malignancies. The authors did not find any differences in terms of the diagnosis of malignancy, sensitivities, specificity, and accuracy for cancer between these two EUS sampling methods. However, FNB provided qualitative information as a degree of differentiation in malignancy, metastatic origins, and rate of proliferation. The authors concluded that when using FNB the role of the onsite cytopathologist was no longer mandatory[53].

LOCALISATION OF LIVER TUMORS: LEFT VS RIGHT LIVER LOBE

EUS can properly evaluate the left lobe of the liver but the latest case reports and studies have shown that even lesions located in the right lobe can be targeted[12,14,41,54].

Oh *et al*[12], reported the utility of EUS-FNA on liver masses on 47 patients (24 patients with lesions in the left lobe, 13 patients with lesions in the right lobe and 10 patients with lesions in the both lobes). The median size of the lesion was 26 mm (15-37) and three median number of needle passes were needed. Technical success was reported in 97.9% of cases. EUS-FNA was diagnostic in 38 of 42 patients (90.5%). The technical success was similar in both lobes (100.0% in the left lobe *vs* 94.1% in the right lobe) but the adequate specimen rate was statistically higher if the FNA was performed from the left lobe rather than from the right lobe (93.3% *vs* 82.4%). However, the diagnostic accuracy was similar (89.3% *vs* 92.9%, $P = 0.86$). There were no complications reported[12].

Recently, Ichim *et al*[40] included 48 patients with hepatic tumors. The authors targeted lesions from the left and right lobe (83% lesions from left lobe, 17% lesions from right lobe). In almost all patients (47 patients) the malignancy was detected and in only 1 case the material was insufficient for a proper diagnosis.

COMPARISON OF EUS-GUIDED TISSUE ACQUISITION WITH OTHER CONVENTIONAL TECHNIQUES

EUS-TA were compared with other techniques such as CT, US, and TJ in terms of diagnostic accuracy of hepatic tumors. The majority of the studies found similar results between those techniques with a high diagnostic accuracy[25-30].

A recent meta-analysis conducted by Shah *et al*[24] on 12 studies which comprised 885 adults patients who underwent EUS-LB due to elevated liver function tests without biliary obstruction demonstrated the efficacy and safety of EUS-guided LB. Pineda *et al*[25] compared the liver specimens and diagnostic accuracy of LB guided-EUS with PC-LB and TJ-LB. The authors found no differences between the techniques, the EUS-LB having similar diagnostic accuracy varying between 90% to 100% with the other techniques. Similar results were obtained in a recent study conducted by Bhogal *et al* [27]. The authors compared EUS-LB, with PC-LB and TJ-LB in terms of adverse events rate, technical success, and diagnostic adequacy of the sample for histology analysis. A total of 513 patients were retrospectively included (135 EUS-LB, 287 PC-LB, and 91 TJ-LB). The indication for EUS-FNB was liver test abnormality. No difference was detected regarding adverse events between the groups. The technical success rate was 100% in each group. No statistical difference was noted in terms of diagnostic adequacy (100% in the YJ-LB group and 99% in both EUS-LB and PC-LB groups).

In a more recent study, Takano *et al*[28] compared PC-LB (16 G needle) and EUS-LB (19/22 G needle) on a total of 106 patients with liver tumors (47 in the PC group and 59 in the EUS group), the authors discovered similar results in terms of sensitivity, specificity, and accuracy of the procedure (95%, 100%, and 96% in the PC group and 100%, 100%, and 100% in the EUS group) respectively. Adverse events were reported in 17% of the PC group, with a significantly lower rate reported in the EUS group (2%; $P < 0.01$)[28].

Liver biopsies for focal liver lesions conducted using EUS guidance are comparable with those guided by interventional radiology (IR). Moreover, liver biopsies performed under EUS guidance demonstrated a superior safety profile, evidenced by a notable reduction in hospital admission post-procedure compared to the conventional IR-guided method as it was demonstrated in a retrospective observational cohort study on 152 patients[29]. Shuja *et al*[29] sought to compare EUS-LB, TJ-LB and PC-LB. The PC-LB technique was subdivided into US and CT guided LB. Average needles sizes were the following: TJ 20G, EUS 19G, PC 18G. Despite an equal number of biopsy pass attempts (median 3 passes), specimen taken *via* EUS guidance produced significantly more tissue in terms of TSL, compared to IR-guided procedures (46 mm *vs* 36 mm, $P \leq 0.01$). However, the overall tissue yield in terms of CPTs was higher in IR-guided procedures (13.6 *vs* 10.8, $P \leq 0.01$). The overall complication rate from IR-LB was higher compared to EUS-LB (7% *vs* 0%, $P \leq 0.05$)[29].

A recent study conducted by Patel *et al*[30], indicates that performing EUS-LB by new 19 G FNB needles outperforms PC-LB and TJ-LB in numerous respects. The authors, included a total of 92 patients in this study (52 patients underwent 53 EUS-LB). These were compared to 20 patients that underwent PC-LB and 20 patients that underwent TJ-LB. EUS-LB was performed from both lobes (31; 58.5%) and one lobe (22; 41.5%) while PC-LB and TJ-LB were performed from one lobe. Significantly fewer needle passes, were performed in EUS-LB group compared to TJ-LB group. EUS-LB produced a greater number of CPTs compared to PC-LB. The mean TSL was higher in EUS-LB than both PC-LB and TJ-LB. The recovery after EUS-LB was significantly shorter compared to the other procedures. Post procedure pain refractory to narcotics and requiring admission was similar among all 3 groups (EUS, 5.7%; PC, 5.0%; TJ, 5.0%)[30].

The latter findings underscore the high efficiency and safety profile of EUS-guided liver biopsies, advocating its widespread adoption in patients who require a LB in conjunction with an endoscopic procedure.

LIVER TUMORS

Malignant liver tumors

Metastasis are the most frequent malignant liver tumors detected by diverse imagistic techniques. The liver is a common site for metastases, especially from malignant epithelial tumors in sites drained by the portal venous system (gastrointestinal tract, pancreas). For primary neoplasms, HCC is usually suspected in cirrhotic liver, while CCA is more common in non-cirrhotic liver[55].

HCC

In cirrhotic patients with hepatic nodules larger than 10 mm, the experts recommend 2 or more imaging techniques for HCC diagnosis[56,57]. In suspected lesions smaller than 20 mm, a histology conformation is mandatory. The European guidelines recommend histology confirmations only in patients with nodules smaller than 20 mm with a value of alpha

feto-protein under 200 ng/mL and without a pathognomonic vascularization pattern at imaging assessment[56,57].

Although liver imaging is typically accurate, in some cases distinguishing between hepatocellular neoplasms and regenerative or dysplastic nodules can be challenging and necessitates histology assessment. Tissue samples can be obtained *via* ultrasound or CT-guided PC biopsies, or through EUS-guided biopsies[5,7,8].

Aside of tissue acquisition, the EUS has a lot of advantages when it is performed in patients with cirrhosis. In the same session, it can assess the portal or biliary tree and it can detect focal lesions, even smaller than 10 mm diameter. Moreover, it can be associated with some additional methods such as contrast enhancement and elastography for better characterization of the tumoral lesions. Contrast enhancement EUS can provide information regarding vascular behavior of focal tumors. HCC has an hyperenhancement behavior with a fast wash-out pattern. Elastography with shear wave assess the rigidity of the liver and can provide a histogram and by adding strain ratio calculation it can be helpful in assessing the rigidity and malignancy of the tumor[5,8,58-61].

In recent literature there are some studies which have assessed the efficacy of either EUS-FNA or EUS-FNB on cirrhotic patients with suspected HCC[15,16]. Chen *et al*[15] evaluated 34 patients with cirrhosis and left lobe suspected hepatocarcinoma using EUS-FNA. HCC was confirmed in 25 patients, the remaining lesions were benign. The sensitivity was 88%. Chen *et al*[16] conducted a large retrospective study on 4312 patients with suspected HCC and serum AFP under 200 ng/dL. From 1756 who underwent EUS-FNA, in 1590 cases the malignancy was confirmed (1145 primary liver neoplasms: HCC in 1067 cases, CCA in 63 patients, HCC with CCA in 8 cases and 75 metastasis neoplasms) and in 166 cases the specimens were benign. One hundred and twelve punctures were false negative. The overall accuracy of EUS-FNA was 93.62% without any differences between tumors size under 20 mm or larger than 20mm in terms of sensitivity, specificity, PPV, and NPV, which showed the advantage of FNA in the diagnostic efficacy in small hepatic lesions. The hemorrhage was present in 6 patients but in 3 patients it was fatal. Implantation metastasis was present in four cases (0.23%)[16] (Table 1).

LIVER METASTASIS

Transabdominal US, CT scan, and MRI are the diagnostic tests of choice to detect hepatic lesions suspicious of metastasis [62,63]. Unfortunately, the detection rate of small liver tumors less than 10 mm is low. Liver EUS evaluation is an additional technique to CT and RMN in order to diagnose focal liver masses, having a better detection rate for small lesions[60].

The liver is a common site for metastases from the digestive tract or pancreas. Other common primary sites include the lung, breast, kidney, and melanoma. Sarcomas, sarcomatoid carcinomas and lymphomas may also involve the liver[62, 63].

In cases with liver metastasis of unknown origin, EUS is the best method. An endoscopy with an evaluation of the esophagus, stomach and duodenum is performed in conjunction with an EUS assessing the pancreas, CBP, gallbladder, adrenal cortex, retroperitoneal space, mediastinum, and liver[60].

Recently, Fujii-Lau *et al*[64] in order to differentiate benign and malignant metastatic liver tumors reported 7 EUS-derived features. The authors obtained a modest inter-observer agreement among experts with a positive predictive value of 88% and an area under the curve of 0.92. The EUS features proposed by Fujii-Lau *et al*[64] are not suitable for HCC.

Zhang *et al*[17] retrospectively evaluated 624 malignant cases. The authors performed EUS-FNB and detected 448 cases of metastasis (71.8%). The majority were adenocarcinoma from the gastrointestinal tract and pancreas. The lower frequency of metastasis was from the thyroid, prostate, and adrenal cortex. In 24 cases metastasis from squamous cell carcinoma (3.8%) was detected. The were rare cases of embryonal sarcoma, hepatoblastoma, and leiomyosarcoma[17]. EUS-FNA has also good results on liver malignant lesions in terms of histology diagnosis. For example, in a study conducted on 30 patients, in 97% of patients, the results of EUS-FNA were adequate for diagnosis, with 27/30 (90%) being malignant and 2/30 (7%) being benign[40]. However, in suspected malignant focal liver lesions, EUS-FNB is the preferred method for tissue acquisition providing accurate specimens for immunohistochemistry or genetic tests[59]. For example, a study conducted by Choi *et al*[65] performed an EUS-FNB from solid liver masses from the left lobe and analyzed the KRAS mutation by the PNA-PCR clamping method and the NGS method. Adding the results of KRAS mutation analysis to the histopathology evaluation, the overall diagnostic accuracy of EUS-guided tissue sampling was high (96.4%).

CONCLUSION

In the light of previous and recent results regarding the efficacy of EUS-guided liver FNA and with the further support of new FNB needles, we consider that the EUS-TA is an optimal tool for an accurate histology diagnosis. EUS-LB has comparable efficacy with conventional techniques but with fewer adverse events and a shorter duration of hospitalization. The EUS-TA can be a suitable technique in patients with suspected liver lesions in order to provide an accurate histopathology diagnosis, especially for those who need endoscopy.

FOOTNOTES

Author contributions: Tantău A wrote the paper and provided the endoscopic ultrasound imagines from her personal collection; Sutac C and Pop A collected the data and draft the paper; Tantău M revised the paper; and all authors contributed with expert opinion on the

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