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Comparison of EUS-guided versus percutaneous and transjugular approaches for the performance of liver biopsies

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ABSTRACT

Background: Liver biopsy through endoscopic ultrasound (EUS) has become a novel approach for tissue acquisition. We aim to evaluate the adequacy of EUS-guided liver biopsies in comparison to those obtained through interventional radiology (IR) techniques.
Methods: A retrospective single-center analysis was performed of all IR (transjugular or image-guided percutaneous) and EUS-guided liver biopsies performed at an academic medical center from January 2016 to January 2018. Patient demographics, histologic characteristics, and clinical outcomes were collected.
Results: 152 procedures were included for analysis. 45% of liver biopsies were performed through EUS-guidance. The most common indication for liver biopsy was NASH fibrosis staging (n = 64). IR-guided biopsies contained a higher number of complete portal triads (13.6 vs. 10.8 $p \leq 0.01$) while EUS-guided biopsies produced an increased total specimen length (4.6 cm vs. 3.6 cm $p \leq 0.01$).47% of biopsy samples were fragmented with the majority of these (72%) occurring with EUS-guided procedures ($p \leq 0.01$). IR-guided biopsies led to more complications in comparison to EUS-guided procedures ($p = 0.03$)
Conclusion: Liver biopsies performed through EUS-guidance are comparable to IR-guided liver biopsies and may have an enhanced safety profile with acceptable tissue acquisition characteristics. Standardization of techniques and needles is needed for optimization of tissue sampling.

1. Introduction

Histological assessment of the liver, and thus, liver biopsy, is a cornerstone in the evaluation and management of patients with liver disease. Despite advances in serologic tests and the development of noninvasive measures to evaluate fibrosis, it is likely that liver biopsy (LB) will remain a valuable diagnostic tool for the foreseeable future. Currently, LB is the gold standard for determining the index of liver fibrosis in patients with chronic liver disease [1]. These biopsies are predominantly performed percutaneously (CT or US guided) or via a transjugular route (fluoroscopy guided). However, there are several complications related to liver biopsy, the most common of which are pain and bleeding [2,3]. A novel approach to obtaining a LB is by endoscopic ultrasound (EUS)-guidance. EUS-guided liver biopsy (EUS-LB) has shown to be technically simple, safe, and provides adequate diagnostic yield for evaluation of liver disease in both children and adults [4]. There are several advantages to EUS-LB. First, it would theoretically be less painful than the percutaneous approach, as it does not require skin puncture and also offers the comfort of sedation and analgesia. Furthermore, it is an image-guided approach which allows visualization and avoidance of blood vessels even 1 mm in size. Additionally, it provides an access area to a much wider segment of liver parenchyma as the entire left lobe, and the majority of the right lobe can be evaluated for possible needle puncture sites from the stomach and duodenal bulb, respectively. In addition to obtaining tissue, EUS-LB also offers the benefit of evaluating the biliary tree, gallbladder, pancreas, lymph nodes, and vascular anatomy for a more comprehensive evaluation in the same setting. Finally, in patients ultimately found to have biopsy-proven cirrhosis, it simultaneously provides the necessary variceal screening which would otherwise require an additional procedure. The aim of this study

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is to evaluate the adequacy and safety profile of EUS-guided liver biopsies in comparison to those obtained through interventional radiology (IR) techniques (e.g. transjugular and percutaneous).

2. Methods

2.1. Ethical considerations

Our study was reviewed and approved by the University of Florida Health Science Center Jacksonville (UFHSCJ) Institutional Review Board (IRB # 2017-03309, approval dated 01/19/2018).

2.2. Study design

We performed a retrospective observational cohort study from 01/01/2016 through 01/01/2018 of all patients who underwent liver biopsies at the University of Florida Health (Shands), Jacksonville.

2.3. Inclusion criteria

All patients aged 18 years or above, undergoing liver biopsy with a valid indication e.g. abnormal hepatic function tests, abnormal liver findings on imaging (e.g. fatty liver), assessing the degree of fibrosis etc. The techniques of liver biopsy included endoscopic ultrasound guided liver biopsy (EUS-LB), transjugular liver biopsy (TJ-LB) and percutaneous liver biopsy (PC-LB). The PC-LB technique was subdivided into ultrasound guided (US) and computed tomography (CT) guided liver biopsy.

2.4. Exclusion criteria

The exclusion criteria included patients below 18 years of age, thrombocytopenia (platelets <50,000/μL), coagulopathy (INR >1.5), pregnant patients, liver lesions (mass, tumors) and inability to provide informed consent. Patients who underwent surgical liver biopsy were also excluded.

2.5. Statistical analysis

Descriptive summaries were reported as frequencies and percentages for categorical variables and means, standard deviations, minima, medians, and maxima for numeric variables. Groups (EUS, PC, and TJ) were compared using the Pearson's Chi-square test (or Fisher's exact test if some cell frequencies were small) for categorical data, and using Wilcoxon rank sum tests for continuous data. The level of significance was set at 5%. That is, a p-value is significant if it was less than 0.05. All analyses were performed in SAS® for Windows Version 9.4.

2.6. Data sources

Data was obtained from two sources: the electronic medical record at University of Florida Health, Jacksonville (EPIC, Verona, WI), and the GI procedure documentation software (Provation MD Wolters Kluwer, Minneapolis, MN). Identifying information was removed from the subject data and was assigned unique identification numbers. The data was compiled electronically into a single encrypted database.

The indications for liver biopsy were studied and grouped as viral hepatitis (hepatitis A, B, C etc.), nonalcoholic fatty liver disease (nonalcoholic steatohepatitis (NASH)) and others (autoimmune hepatitis, drug induced liver injury, primary biliary cirrhosis etc.)

To compare EUS-LB cases with other LB methods, consecutive PC and TJ LBs, which had been done by our interventional radiology department from January 2016 to January 2018 at University of Florida Health, were retrospectively identified. For all biopsies (EUS-LB, PC-LB and TJ-LB), the total specimen length, length of longest core, complete portal triads were determined.

All patients were closely observed in the recovery area for 3–4 h after the procedure. Patients were followed-up by a phone call on day 3 and day 7 after the date of the procedure. Any procedure-related complications were recorded.

2.7. Liver biopsy techniques

Patients undergoing EUS-LB were deeply sedated with propofol administered by an anesthesiologist or a certified registered nurse anesthetist. A complete EUS examination was performed for the primary procedure indication by an advanced endoscopist (SDM), using a linear-array echoendoscope (GF-UCT180 and GF-UCT140P, Olympus America, Center Valley, PA, United States). All EUS-LB were performed using a 19-gauge FNA needle (Expect™ Flexible; Boston Scientific, Natick MA). Before needle puncture of the desired lobe, color Doppler imaging was used to ensure the lack of vascular structures or bile ducts in the expected trajectory of the needle. The right and left lobe of the liver were accessed by the transduodenal and transgastric approach respectively. The stylet was removed prior to needle insertion and the needle was primed with sterile saline. After the adequate side was identified, the liver was accessed, suction was applied, and one incursion was made into the liver for at least 3 cm in depth or longer if possible. The needle was pulled back to the edge of the liver, where suction was cut-off and then the needle was removed for tissue adequacy assessment. Usually 3 passes per procedure were made. Adequacy was determined by flushing the needle content into a clear contained and gently removing the liver tissue and placing it into a container with formalin before sending for histopathological evaluation (Fig. 1).

Both TJ-LB and PC-LB specimens were obtained by the interventional radiologists using conscious sedation (midazolam, fentanyl). Real-time ultrasound visualization was used for the vascular needle entry. The skin and subcutaneous tissues over the internal jugular vein were anesthetized with lidocaine. Using an 18-gauge or 21-gauge core biopsy needle (based on radiologist's preference) under ultrasound guidance, the right internal jugular vein was accessed, and a guidewire was introduced into the inferior vena cava. This was followed by sheath placement in the right internal jugular vein. With the assistance of angled tip catheter, right hepatic vein was selected. Slow contrast injection was performed which confirmed the positioning. Over the wire, the preassembled biopsy set was introduced and biopsies were performed.

Similarly, for PC-LB, CT or US imaging was used for needle positioning. The skin was anesthetized with lidocaine and an 18G

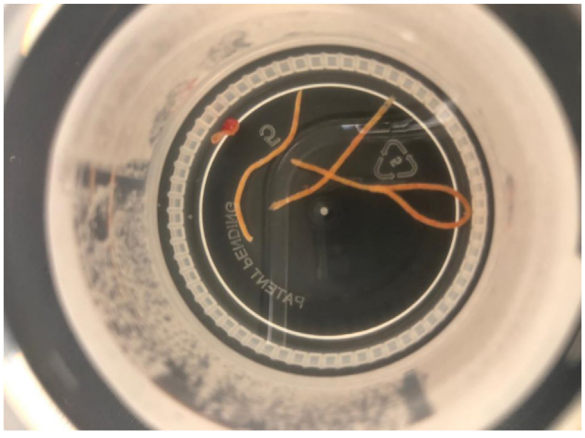

Fig. 1. Liver tissue specimen obtained via EUS guided 19 G FNA needle.

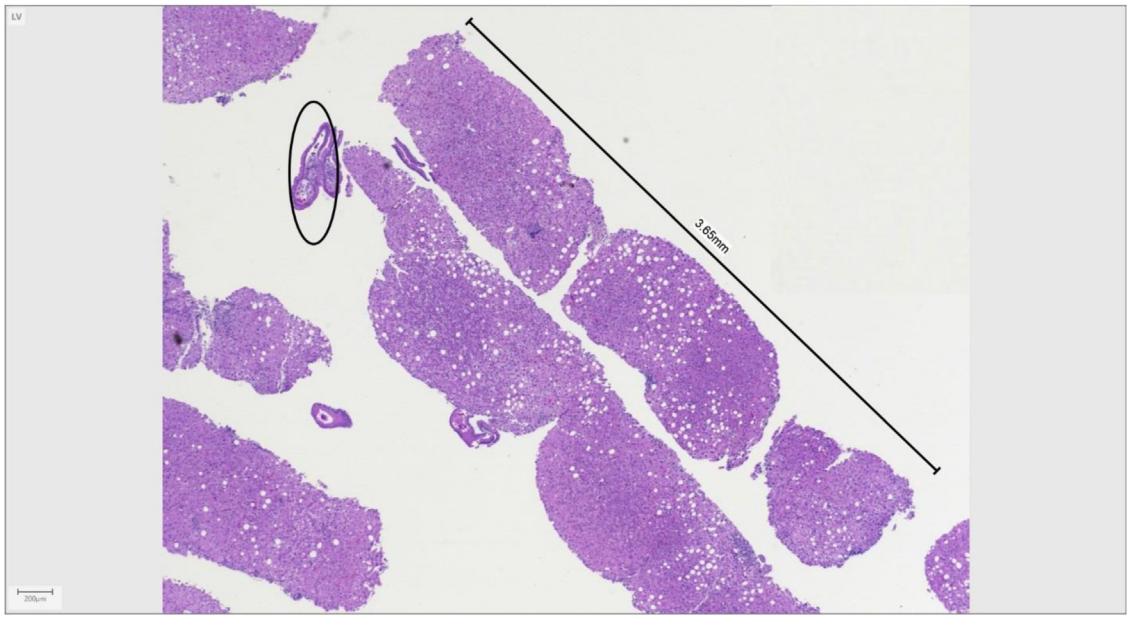

Fig. 2. EUS-guided liver biopsy. Histologic sections show core of liver with steatosis and adjacent bowel mucosa (circle) (25×, H&E stain).

needle was used to obtain the liver biopsy, primarily at the right hepatic lobe. The percutaneous entry site was then filled with a sealant for hemostasis. 2–3 passes were made for tissue acquisition on both percutaneous and transjugular routes. The samples were sent to pathology for further evaluation in formalin-filled container.

2.8. Sample processing and quantification of tissue yields

All collected specimens were received in formalin, and processed in similar way. Formalin-fixation and paraffin-embedding (FFPE) technique was used for preparing liver biopsy specimens. The slides were stained for histopathological characterization using hematoxylin and eosin [H&E], trichome, reticulin and Periodic acid–Schiff–diastase and iron stain as needed in selected patients (Fig. 2).

The collected specimens were examined by two gastrointestinal pathologists (A.S and A.A), blinded to the clinical information, technique of tissue acquisition and type of needle used. The tissue adequacy was assessed by measuring the following parameters: Total specimen length, length of the longest single core, complete portal triads and fragmentation (considered fragmented specimen if more than 3 small liver fragments each measuring less than 0.2 cm in length are present). A complete portal triad was defined as the presence of all 3 portal structures (portal vein, hepatic artery, and bile duct). The Aperio system has a ruler that can be used to measure the length of every piece of liver tissue in the digitized slide. A fibrosis score was also documented. Due to the heterogeneity of the patients in our cohort and the presence of different staging system for various disorders (for e.g. NASH versus chronic hepatitis fibrosis score), the degree of fibrosis was assessed as follows: F0 no fibrosis (cases with no significant fibrosis), F1–F2 fibrosis without bridging (cases with periportal &/or pericellular fibrosis without bridging fibrosis), F3 fibrosis with bridging, and F4 cirrhosis.

3. Results

Between January 2016 and January 2018, 152 patients fulfilled the inclusion criteria. Sixty-nine (45%, median age 56 years [range, 49–61]) patients underwent liver biopsies with EUS guidance, whereas forty-seven (31%, median age 55 years [range, 36–60]) patients underwent biopsies via TJ technique. PC liver biopsy was performed in thirty-six (24%, median age 57 years [range 47–67]) patients (Table 2). The most common indication for liver biopsy was NASH fibrosis staging (n = 64) and 19% of all biopsies contained evidence of advanced fibrosis (F3 or F4) (Table 4).

Average needles sizes were as following: transjugular 20G, EUS 19G, percutaneous 18G. Despite an equal number of biopsy pass attempts (median 3 passes), specimen taken via EUS guidance produced significantly more tissue in terms of total specimen length, compared to IR-guided procedures (4.6 cm vs. 3.6 cm $p \leq 0.01$). However, the overall tissue yield in terms of complete portal

Table 1
Association of different techniques (EUS vs IR) of liver biopsy with continuous variables.

Variable	Group	N	Mean	Std. dev.	P-value
Complete portal triads (CPT)	EUS	69	10.84	7.23	0.0057
	IR	83	13.61	6.8	
Length of longest core	EUS	69	1.16	0.55	0.0752
	IR	83	1.31	0.48	
Total specimen length (TSL)	EUS	69	4.58	2.07	0.0016
	IR	83	3.59	1.44	

IR = PC and TJ.
All tests done using Kruskal Wallis test.

Table 2
Association of different techniques (EUS, PC, TJ) of liver biopsy with continuous variables.

Variable	Group	N	Mean	Std. dev.	P-value
Complete portal triads (CPT)	EUS	69	10.84	7.23	<0.0001
	PC	47	15.91	6.74	
	TJ	36	10.61	5.66	
Length of longest core	EUS	69	1.16	0.55	<0.0001
	PC	47	1.51	0.44	
	TJ	36	1.04	0.39	
Total specimen length (TSL)	EUS	69	4.58	2.07	<0.0001
	PC	47	4.3	1.34	
	TJ	36	2.65	0.96	
Age	EUS	69	54.39	11.63	0.1715
	PC	48	55.33	14.49	
	TJ	37	49.7	14.85	

All tests done using Kruskal Wallis test.

Table 3
Association of different techniques of liver biopsy with categorical variables.

Variable	EUS n (%)	PC n (%)	TJ n (%)	Overall n (%)	P-value
Fragmentation	50 (72)	6 (13)	16 (43)	72 (47)	<0.001
Complications	0 (0)	3 (6)	3 (8)	6 (4)	0.033

% means percentage of total procedures performed via that specific technique.

Table 4
Association of fibrosis score with the indication for liver biopsy.

Variable	Category	Viral (n = 25, 16%)	NASH (n = 64, 42%)	Others (n = 63, 42%)	Overall (n = 152)	P-value
Fibrosis Score	F0	6 (24)	39 (61)	41 (66)	86 (57)	0.003
	F1–F2	8 (32)	19 (30)	10 (13)	37 (24)	
	F3	5 (20)	4 (6)	6 (9)	15 (10)	
	F4	6 (24)	2 (3)	6 (9)	14 (9)	

All tests done using Fisher's exact test.
F0 = no fibrosis, F1–F2 = fibrosis without bridging, F3 = fibrosis with bridging fibrosis, and F4 = cirrhosis.

triad was higher in IR-guided procedures (13.6 vs. 10.8 $p \leq 0.01$) (Table 1). Forty-seven percent of biopsy samples were fragmented with the majority of these (72%) occurring with EUS-guided procedures ($p \leq 0.01$) (Table 3).

3.1. Individual comparison of EUS versus TJ and percutaneous approach

While EUS guidance led to an increase in total specimen length, both EUS and transcutaneous approaches achieved superior tissue acquisition in comparison to the transjugular approach (4.6 cm vs. 4.3 cm vs. 2.7 cm, $p \leq 0.01$). The percutaneous approach also led to a higher number of complete portal triads in comparison to EUS and transjugular methods (15.9 vs. 10.8 vs. 10.6, $p \leq 0.01$) (Table 2).

The overall complication rate from IR-LB was 7% (6/83, $p \leq 0.05$), which led to an increased number of emergency department visits and hospitalizations in comparison to EUS-guided procedures, where no significant complication was noted ($p \leq 0.05$) (Table 3).

One of these patients developed iatrogenic pneumothorax requiring observation for 3 days in the hospital. One patient developed severe abdominal pain and acute blood loss anemia and was found to have hepatic artery pseudoaneurysm on arteriogram which was treated with coil embolization. Other four patients were observed in hospital for excruciating abdominal pain. For the six patients who were hospitalized, the average length of stay was 1.83 days.

4. Discussion

In the present study, we found that liver biopsies performed through EUS-guidance are comparable to IR-guided liver biopsies. In addition, EUS-guidance liver biopsy had an enhanced safety profile with significantly less post-procedural hospital admissions when compared to traditional IR-guided approach.

Liver biopsy is considered the gold standard method for assessment of fibrosis severity in chronic liver disease by using tissue sampling diagnosis to determine fibrosis degree [5]. However, it is widely known that traditional liver biopsy techniques are limited by several factors including potential life threatening complication, procedural and post-procedural costs, intra-observer variations and sampling error [1,5,6].

EUS-guidance liver biopsy is a novel approach for obtaining histology that produces adequate tissue in comparison to the percutaneous and transjugular biopsy routes [7]. Moreover, EUS-guidance liver biopsy has the advantage of being able to quickly and safely obtain multiple liver passes from both lobes that decreases the histologic variability through sampling different areas of the liver in addition to provide imaging assessment of other intra-abdominal organs.

There is no consensus on what an 'adequate' liver biopsy actually is. AASLD guidelines suggest that adequate liver biopsy specimens be at least 1.5 cm in length and contain greater than 11 portal tracts while the Royal College of Pathologists define adequacy as being greater than 1 cm in length and containing at least 6 portal tracts. In our study, we found that EUS-guidance liver biopsy provides adequate number of complete portal triads and total biopsy specimen length within adequacy defined by the Royal College of Pathologists and nearly met the recommended AASLD criteria [8]. Upon individual comparison between EUS-LB and TJ-LB, we found that EUS guided liver biopsy achieved more tissue specimen both in terms of total specimen length and complete portal triad. Similarly, when comparing EUS-LB with PC-LB, we noticed that EUS-LB had a higher tissue yield in terms of total specimen length. However, PC-LB achieved more tissue in terms of complete portal triad and length of longest core. It could be explained by the fact that a bigger sized needle (18 G) was used for PC route, so the difference in complete portal triads between the two routes can be expected. Furthermore, our study found that EUS-guidance liver biopsy carries less number of emergency department visits and hospitalizations with a better safety profile and potential trend to reduce overall costs over traditional IR-guidance techniques

While EUS and percutaneous guidance had advantages in regards to increase total specimen length and complete portal triads respectively, the transjugular approach did not offer any advantages in terms of tissue acquisition. An argument can be made that based on these findings EUS-guided liver biopsy may actually be superior and carry decreased risk in comparison to the TJ approach. However, TJ approach is still preferable in patients with ascites; those who cannot tolerate propofol sedation which is usually required for EUS procedures and when portal vein pressure measurements are needed at the time of biopsy.

There are limitations to our study. First, the number of patients evaluated in this study is small which may have compromised the power of the study. Second, there is a significant difference between the different types of needles used between the EUS-guidance approach (19 gauge FNA) and the IR-guidance approach (21 and 18-gauge core) with subsequent tissue sampling differences. Moreover, it is important to highlight that the gauge of the needle and the type of needle used (standard versus core) are important in tissue acquisition with any of the mentioned techniques. Regarding pathology evaluation of EUS-biopsy specimens, two challenges were encountered in some cases. First challenge is the presence of a limited number of portal tracts (mean of 10.9 portal tracts in EUS patients versus a mean of 15.9 in percutaneous cohort), which may not be optimal to evaluate for some liver disorders such as biliary diseases. For example, primary biliary cholangitis lesions might be patchy, and more tissue with portal tracts is necessary to establish the correct diagnosis. Also, 20 or more portal tracts are necessary for a confident diagnosis of chronic rejection in the setting of liver transplant, which would be a limiting factor in these cases. Second is the fragmentation of the liver cores (72% of EUS cases) which may have impact on assessment of fibrosis (i.e. assessing portal to portal or portal to central fibrosis in the same fragment), and this may give a false impression of the degree fibrosis. Careful histologic evaluation on multiple H&E levels and correlation with trichrome stain is necessary to avoid over- or under estimation of the degree of fibrosis.

Since a EUS guided core needle became commercially available, we have been using it and our fragmentation as well as number of complete portal tracts improved significantly as expected (personal experience, unpublished data). Lastly, this is a retrospective,

single center study which can potentially cause selection and referral biases, therefore, prospective, multicenter studies are needed to further clarify this topic.

In conclusion, liver biopsies performed through EUS-guidance are comparable to IR-guided liver biopsies regarding tissue acquisition characteristics with a potential advantage of fewer complications. Standardization of EUS-guided core biopsy needles may provide even better tissue acquisition. However, future prospective studies need to be performed to confirm this postulation. In summary, EUS-guided liver biopsy is a viable alternative for tissue acquisition and a "one stop shop" for a comprehensive endoscopic evaluation of a patient with chronic liver disease.

Conflict of interest

None declared.

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Author's contributions

Asim Shuja: study concept and design; acquisition of data; interpretation of data; drafting of the manuscript; administrative, technical or material support. The author has approved the final draft submitted.

Ahmad Alkhasawneh: acquisition of data; interpretation of data; drafting of the manuscript; administrative, technical or material support. The author has approved the final draft submitted.

Andre Fialho: study concept and design; acquisition of data; interpretation of data; drafting of the manuscript; administrative, technical or material support. The author has approved the final draft submitted.

Andea Fialho: study concept and design; acquisition of data; interpretation of data; drafting of the manuscript; administrative, technical or material support. The author has approved the final draft submitted.

Amal Shukri: acquisition of data; interpretation of data; drafting of the manuscript; administrative, technical or material support. The author has approved the final draft submitted.

Ciel Harris: acquisition of data; administrative, material support. The author has approved the final draft submitted.

Carmen Smotherman: statistical analysis. The author has approved the final draft submitted.

Miguel Malespin: critical revision of the manuscript for important intellectual content; administrative, technical or material support; study supervision. The author has approved the final draft submitted.

Silvio W. de Melo Jr: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; technical support; study supervision. The author has approved the final draft submitted.

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