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Research Article

EUS Guided Liver Workup Versus Percutaneous Guided in a Community Hospital

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Abstract

Background and Aims: Previous studies confirm endoscopic ultrasound (EUS) can complete liver biopsy, paracentesis and EGD during one procedure. This study evaluates translating these studies to a community hospital.

Methods: 17 patients requiring EUS liver biopsy were compared to 17 transcutaneous patients for quality, cost and safety. This included evaluation for varices and diagnostic paracentesis.

Results: Mean number of portal triads was 12.7 EUS vs. 12.4 percutaneous (p value 0.89). Mean length of the longest core 0.94 EUS vs. 1.06 cm percutaneous (p value 0.14). Etiology of hepatitis 4/7 EUS vs. 0/4 percutaneous (p value 0.03). Confirmation of cirrhosis 4/6 EUS vs. 1/3 percutaneous. Total cost $1705 EUS vs. $3984 percutaneous. No significant complications occurred.

Conclusion: No significant biopsy sample differences existed. EUS provided better diagnostic information and clearly has economic advantages. The benefits of EUS guided liver workup translate to a community hospital.

Keywords: EUS; Liver; Biopsy; Aspiration; Varices; Banding; Ascites; Fine Needle; Portal; Hepatic; Cirrhosis; Percutaneous; Bleeding; Banding; Adequacy; Portal Triads; Fibrosis

Introduction

In patients with liver disease, American Association for the Study of Liver disease (AASLD) guidelines state that a liver biopsy should be considered in patients whom diagnosis is in question, and when liver histology is an important adjunct in the management of patients with known liver disease [1]. AASLD guidelines also recommend abdominal paracentesis for patients with new onset ascites [2]. Esophagogastroduodenoscopy (EGD) is also recommended for cirrhotic patients with a liver stiffness of greater than or equal to than 20 kilopascals (kPa) and platelets count of less than or equal to 150,000 [3].

The standard at our community hospital is to complete an ultrasound guided paracentesis for new onset ascites. In patients with newly diagnosed cirrhosis, or those who are at risk for variceal bleeding, an EGD is arranged. When a liver biopsy is required, a percutaneous ultrasound guided biopsy is completed. Currently, there is no capacity for elastography at our hospital.

Our hospital does have EUS capability. EUS to obtain a biopsy of liver metastasis and completing fine needle aspirates (FNA) of ascites is well characterized.

Diehl., *et al*. demonstrated the efficacy of ultrasound guided liver biopsy. In their study, they looked at 110 patients from 8 differ-

ent centers. Through the use of EUS, they had pathologic samples adequate for diagnosis in 108 of the 110 patients in their study. The median length of each sample was 38 mm. The median number of complete portal triads was 14. They had one complication, where self-limited bleeding occurred. The complication was managed conservatively [4].

Sharma., *et al*. compiled a review of EUS guided FNA for ascites. In their study, they found EUS to be more sensitive for detecting ascites than traditional methods. The studies mostly addressed malignant ascites. Complications in this review were noted to be infrequent and included: fever, peritonitis, abdominal pain, and one report of hypertensive emergency [5].

The experience with our FNAs mirrored what was seen in the studies above. Of the most common liver biopsy complication, bleeding, there have been no documented cases thus far at our hospital. In regards to FNA of ascites, we have not had a documented case of peritonitis [5].

This study evaluates the efficacy, safety and economics of performing this type of liver work up at a community hospital.

Patients and Methods

Study design

Over the past few years, new fine needle biopsy needles have been developed that have improved on existing technology. These included the Shark Core System Exchange by Medtronic, in 2014, and the Acquire Needle by Boston Scientific, in 2016. Improvements in this technology have made EUS guided liver biopsies more practical [6,7]. Tissue has also been obtained using 19g fine needle aspirate needles with suction, and yields have been acceptable [8].

Potential EUS guided biopsy advantages include a safer procedure, due to the high-resolution images of EUS. Doppler is also available which allows vascular structures within and external to the liver to be viewed. Blood vessels, loops of bowel, and biliary structures can be avoided with the use of EUS. EUS is also able to identify both lobes of the liver, which allows both lobes to be biopsied during the same procedure, reducing sampling error [9]. The FNB needle used for this procedure is a 19 gauge needle versus the 16 gauge needle typically used for percutaneous biopsy. EUS guided biopsy does not require a needle passage through the skin. Conducted under sedation required for endoscopy, the patient tolerates the procedure better.

The first liver biopsy case done on a cirrhotic patient at our hospital occurred as part of a mass lesion work up. The lesion was thought to be malignant, and there was a concern for what functional capacity of liver would remain after resection. The mass lesion was biopsied, and an additional pass was made into the remaining liver. The biopsy from the liver clearly showed cirrhosis and contained 12 complete portal triads. After obtaining these results, EUS guided biopsy was offered as an option to patients with newly diagnosed cirrhosis who required EGD to evaluate for varices. The data on each case performed at our hospital was collected. Seventeen cases were performed. No complications were noted in the cases we performed.

The database of the hospital was then searched for the most recent seventeen cases of ultrasound guided liver biopsies. The slides from each case were available for review by pathologists. The University of South Alabama pathology department reviewed both sets of slides for number of portal triads, length of tissue sample, and adequacy of biopsy for cirrhosis, and diagnosis.

At the time of endoscopy, if ascites was identified and had not been sampled previously, AASLD guidelines were followed, and ascetic fluid was sampled [2]. Standard infectious precautions were observed for patients with ascites. Tests on the fluid were ordered, as indicated by each case, but all samples were sent for at least cell count, culture, and albumin. Serum-ascites albumin gradients (SAAGs) were determined for each case performed.

Initial cost estimates for each procedure were derived from national Medicare averages [10]. This included the physician fee and facility fee for all procedures completed. Pathology fees for both were considered to be the same, and not evaluated. Cost was dependent on which procedure each patient had undergone. Bundled codes for each endoscopy were included to capture the cost of FNA and FNB. Radiology costs were included for ultrasound guided liver biopsy and ultrasound guided paracentesis, but not blind paracentesis.

Main outcome

For accuracy of the pathologic sample, EUS guided biopsy was compared to the percutaneous biopsy. The total cost of each case

was computed and similar cases were compared. For example, the cost of an EGD and a EUS liver biopsy, was compared to EGD and ultrasound guided liver biopsy. EGD, EUS guided liver biopsy, and EUS guided paracentesis was compared to EGD, ultrasound guided liver biopsy and paracentesis costs.

Patients

Patients were not randomized. The initial set of EUS guided biopsies came from the first 17 patients that came to our hospital, after our technique had standardized. Standardizing the procedure took two procedures, one before and one after visiting a high volume EUS center. The ultrasound guided patients were the 17 most recent procedures done in our hospital system. One case where an ultrasound guided biopsy of a tumor, which yielded only neoplastic tumor was discarded and the next most recent biopsy from our hospital history included. The diagnosis mostly came from the chart review, but some were determined from the biopsy. The first table contains the pooled data describing the patients.

No. Patients	EUS	US guided
Male/Female	17	17
Mean age (range) (y)	63 (45 - 77)	61 (37 - 83)
Etiology		
Alcoholic Cirrhosis	4	2
Hepatitis C	5	3
Non-Alcoholic Steatohepatitis (NASH)	3	7
Increased liver function tests	6	12
Primary Biliary Cirrhosis (PBC)	1	
Superior Mesenteric Vein (SMV) thrombosis	1	
Cirrhosis/ rule out cirrhosis	9	2
Primary Sclerosing Cholangitis (PSC)		1
Autoimmune hepatitis	1	1
Hepatitis B		1
Congestive Heart Failure (CHF)		1
Hemochromatosis	1	

Table 1: Patient characteristics.

In reviewing the data above, there is one difference that should be noted. At the time most of the EUS biopsies were completed, the protocol for treatment of hepatitis C (HCV) depended on the presence of cirrhosis. This determination tended to increase the number of HCV patients in the study. The studies done earlier by ultrasound guidance, tended to be more for diagnosis.

	U/S Guided	EUS
Liver biopsy	12	2
Liver biopsy and EGD	1	11
Liver biopsy, EGD, Paracentesis	4	4

Table 2: Procedure allocation.

Endoscopic techniques

The EUS fine needle biopsy (FNB) technique is as follows: the linear scope is passed into the duodenum, and the right lobe of the liver is identified. A 19 gauge needle was prepared by placing a suction needle with ten cc of saline. Five cc of saline was injected through the needle leaving at least three cc in the syringe. The stopcock is then closed. The syringe plunger is then withdrawn to the ten cc mark creating a vacuum in the syringe. The needle was then advanced 4 - 5 cm into the liver. The stopcock was opened until a few cc of fluid was withdrawn into the syringe from the EUS needle and then the stopcock closed. This indicates negative pressure has been transmitted to the tissue within the needle. Then the needle was pulled back to the proximal edge of the liver. Two additional passes are made into the liver with only slight angle deviation and leaving the stopcock in the closed position. The needle is removed. The tissue is expressed using the needle stylet, which completes the biopsy acquisition. This is referred to as a wet suction technique [11].

Pathological assessment

The number of fragments, the minimal and maximal length of tissue fragments, and number of portal tracts (complete or incomplete), were recorded for each case. Specimen Adequacy was defined as presence of more than 5 complete portal tracts and/or > 15 mm in specimen length. Diagnostic/histologic adequacy was defined as ability to reach a definitive diagnosis independent of the count of portal tracts and number of fragments. The presence of fibrosis was assessed on trichome stain (in addition to hematoxylin

and eosin routine stained sections). Given the frequent fragmentation, distinction between mechanical fragmentation, and fragmentation related to advanced fibrosis is crucial. Mechanical fragmentation was assumed to be the reason for straight/geographic edges of tissue fragments whereas smooth edged round fragment was interpreted with the help of trichrome (reticulin stain was not available). For cases where a definitive diagnosis was not reached or where fibrosis assessment was challenging, a note was made whether the patchy nature of lesional changes was thought to be responsible, or whether the limited/fragmented nature of the specimen was the main reason (in this instance, additional tissue sampling could be helpful for final diagnosis).

Statistical analysis

The mean length of the longest segment using ultrasound was slightly longer than that measured by EUS, however the difference was not significant (2-sample T test, t = 1.513, df = 32, p = 0.1401). Outcome of the Shapiro-Wilk W test indicated no evidence to refute normality of the longest segment in the EUS group (W = 0.953, p = 0.4996), however the evidence indicates that the length of the longest segment of the ultrasound group is not normally distributed (W = 0.845, p 0.0089). It is likely due to an outlier with a length of 2 cm.

The mean number of complete portal triads using ultrasound was slightly lower than that measured with EUS, however again the difference was not significant (2-sample t test, t = -0.124, df = 32, p = 0.8879). Shapiro-Wilk W test for both groups indicated no evidence to refute normality of the number of complete portal triads (EUS: W = 0.893, p = 0.0511; ultrasound W = 0.937, p = 0.2819).

There is significant association between diagnosis and method used. Using EUS for diagnosis was better (Fisher's exact test, p = 0.0265).

Statistical analysis reported by Dr Mulekar was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001417. Statistical software Jump (JMP) v 14.2.0 was used for statistical analysis of data.

Results

Efficacy

The most significant determinant in the quality of a liver biopsy is the number of portal triads obtained. In this study, the mean number of portal triads in the EUS guided biopsy group was slightly more than the percutaneous biopsy group, 12.7 vs 12.4 with a p value of 0.8879. The length of every core fragment for every patient was measured. The longest core sample obtained for each patient was recorded. The average of the longest sample of the percutaneous group (1.06 cm) was found to be longer than the EUS (0.94 cm) with p value of 0.1401.

Length of Longest Segment	EUS	US guided
Range in cm	0.3 - 1.9	0.7 - 2.0
Average Length in cm	0.94	1.06
Median Length	0.9	1.1
Portal triads		
Range	4 - 30	3-32
Average number	12.7	12.3
Median number	12	11

Table 3: Specimen characteristics and adequacy.

In reviewing the data there was another important parameter evaluated. Did the biopsy provide the information that dictated the patient undergo the procedure? Biopsies were taken primarily to answer one of two questions. First, what is the etiology of the liver disease? Second, is cirrhosis present? In regards to the first question, the EUS biopsies diagnosed 4/7 unknown causes of hepatitis, while percutaneous biopsies diagnosed 0/4 with a p value of 0.0265. The diagnosis of cirrhosis suggested by lab values was confirmed on EUS guided biopsies in 4 of 6 patients. With percutaneous liver biopsies this occurred in 1 of 3 patients.

	EUS	US guided
Unknown Etiology	7	4
Etiology Determined	4	0
Known Etiology	10	12
Etiology Revised	0	1

Table 4: Liver biopsy information.

Complications

The charts of patient who underwent percutaneous biopsies were reviewed for complications. Specifically bleeding, infection and pain lasting more than 48 hours or severe enough to require another visit. No complications were identified. No documented complications from percutaneous paracentesis were found either.

With EUS guided biopsies, no complications occurred, nor did any complications occur with EUS guided paracentesis.

Cost

By using Medicare Final Rule, data for outpatient procedures performed in the hospital, the following cost breakdown was noted [10].

	U/S Guided	EUS
Liver biopsy	$1441	$1637
Liver biopsy and EGD	$3128	$1705
Liver biopsy, EGD, Paracentesis	$3984	$1705

Table 5: Cost comparison.

Discussion

This study is limited by its retrospective nature. A greater number of cases would also be an improvement. Because both cohorts were identified by time of presentation, they are not matched based on patient's demographics or main diagnosis. These represent the main limitations of the study.

Both the length and number of portal tracts of the biopsies obtained would indicate that percutaneous biopsies and EUS biopsies are similar. There were not significant differences in either measurement. In working with our pathology depart to improve the accuracy and yield of these samples, several changes in handling of tissue have been implemented.

First, tissue is expressed from the needle with the original stylet and not water pressure from the syringe. Liver biopsies are placed in a heparin bath to increase the ratio of tissue to blood [11]. The tissue itself is not directly manipulated. Instead, filter paper is placed over the collecting cups and the heparin bath is poured onto the paper. The fluid drains off into the cup and then filter paper is gently folded and placed in formalin. The pathology technician then places the package directly into the imbedding machine and does not manipulate the tissue. These measures are in place to reduce fracturing the sample and reducing crush artifact.

All pathology samples had to be sent to private pathologists associated with the community hospital immediately following the procedure. This is due to contractual obligations. After the patients were identified for the study, the slides were sent to the University of South Alabama Pathology Department for review. Of note, 36 total sets of biopsies were reviewed. If either the community reading, or the university reading, agreed with pre-procedure diagnosis, the etiology was considered confirmed. It is important to note that on 9 of the 36 biopsies, there were differences between the two pathology readings.

Fragmentation of the tissue was a major challenge for adequate morphologic assessment, particularly in the absence of a reticulin stain. In fact, a reticulin stain can be helpful in interpreting fragmented tissue. Thickened hepatocytic trabecula along with an abnormal reticulin pattern would be indicative of regenerative change and advanced fibrosis, whereas a normal reticulin pattern would be considered to be due to mechanical fragmentation [12].

Liver biopsy has become less popular as more physicians are making diagnoses based on history and laboratory values. On the positive side, this results in less risk to the patient. There is also a tendency when doing percutaneous biopsies to biopsy away from blood vessels and biopsy more into the periphery of the liver. This results in increased capsular biopsies and an over staging of cirrhosis. Sampling error can significantly affect percutaneous liver biopsies [1]. Patient discomfort and cost also tend to reduce the number of percutaneous liver biopsies ordered.

EUS guided biopsy is not without risk, but studies to date have not identified serious complications. In review of recent literature, there is one case of self-limited bleeding identified [4]. Both lobes of the liver are biopsied which reduces sampling error. If the liver biopsy is done at time of EGD, the increased risk to the patient is further reduced because additional sedation is not needed. The increased cost for the extra procedure is nominal.

The constraints that our community hospital pathologists were under during this study is likely similar to those elsewhere. The better the pretest information pathologists receive, history and laboratory workup, the better diagnosis they can provide. A trained gastroenterologist is likely to provide more pertinent information because they are trained in hepatology. In this study, the author believes that improved communication with the pathologist was the primary reason a greater number of etiologies were diagnosed in the EUS arm. These considerations raise the question, if EUS guided liver biopsy can be obtained with less risk, greater comfort, and nearly no extra cost, should they be obtained more often, versus relying on laboratory estimates to diagnose cirrhosis?

The indication for EGD and EUS guided paracentesis is straight from AASLD Guidelines. It was assumed in the study that there were no differences in an EGD performed as a stand-alone procedure verses an EGD performed in conjunction with EUS. In both cases, a forward viewing gastroscope is used. In regards to the paracentesis, 4 of the 17 procedures included paracentesis. In these four SAAG was consistent with cirrhosis 4 out of 4, and malignancy was found in 0 of 4 patients. These 4 cases represent perhaps the greatest gain in the EUS arm and bear a closer review.

Determining the portal pressure gradient is another potential capability of EUS guided liver workup. The portal pressure gradient is currently used to determine non-selective beta blocker dosing in patients with varices. Elevation in portal pressure is an indication of decompensation including variceal bleeding and ascites. Elevations are central to the development of hepato-renal syndrome. Reproducibly determining the portal pressure gradient during these procedures has the potential of objectively identifying those patients most at risk for decompensation. EUS could be used to identify patients more likely to need liver transplant. This information could aid in end of life decisions among those patients who are not transplant candidates, provide objective evidence for motivating alcohol abstinence, and motivate physicians to take a more aggressive approach to decompensating patients earlier.

In our hospital, there is no dedicated hepatologist. In these cases, the endosonographer was also treating these liver patients. This increases the number of EUS guided work ups done, due to the availability of those resources and a lack of resources a trained hepatologist would use. There certainly are cases where referral to a trained hepatologist is clearly indicated, but we cannot refer all chronic hepatitis and Non-Alcoholic Steatohepatitis (NASH) patients, due to the sheer number of patients with these conditions. The majority of these more common cases need to be seen at the facility the patients present to for care.

Conclusion

In conclusion, the ability to translate research on EUS guided liver biopsy is largely determined by the capabilities of the facilities that patients present to. The care patients receive will be determined to some extent by what resources the treating physician has available. In health care facilities where EUS is available, it is a reliable tool for managing the patients with liver disease and cirrhosis.

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