

[ORIGINAL ARTICLE]

Comparative Study of an Ultrasound-guided Percutaneous Biopsy and Endoscopic Ultrasound-guided Fine-needle Aspiration for Liver Tumors

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Abstract:

Objective Both a percutaneous biopsy and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) have been widely performed for liver tumors. However, no studies have compared these two biopsy methods. **Method** A retrospective study was conducted using medical records for patients who underwent a liver tumor biopsy from 2012 to 2019. The cases were classified into two groups for a comparison: an ultrasound-guided percutaneous biopsy group (percutaneous group) and an EUS-FNA group (EUS group).

Results A total of 106 patients (47 in the percutaneous group and 59 in the EUS group) were included. The final diagnosis was malignant in 100 cases and benign in the remaining 6 cases. While the median lesion diameter was 62 mm in the percutaneous group, it was significantly smaller (34 mm) in the EUS group (p < 0.01). The EUS group had more left lobe tumors than right lobe tumors. All cases of caudate lobe tumor (four cases) underwent EUS-FNA. The sensitivity, specificity, and accuracy of the procedure were 95%, 100%, and 96% in the percutaneous group and 100%, 100%, and 100% in the EUS group, respectively showing no significant difference. Adverse events were reported in 17% of the percutaneous group, which was significantly lower than in the EUS group (2%; p < 0.01).

Conclusion A percutaneous biopsy and EUS-FNA have equivalent diagnostic qualities for liver tumors, although EUS-FNA tends to be associated with fewer adverse events. A complete understanding of the characteristics of each procedure is essential when choosing the best biopsy method for each particular case.

Key words: EUS-FNA, liver tumor, percutaneous biopsy

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Introduction

In recent years, there have been remarkable advances in diagnostic imaging, and as a result, the majority of liver tumors can be diagnosed without a pathological examination (1, 2). Since a liver biopsy involves the risk of bleeding and needle tract seeding, a histological examination is not essential in cases that can be diagnosed by imaging or where malignancy is suspected and surgery is scheduled. However, some cases still require a histological evaluation, including those with atypical imaging findings, tumors in which it is difficult to distinguish benign and malignant lesions, and metastatic liver tumors in cases with multiple malignant neoplasms.

Ultrasound-guided percutaneous biopsies have been performed frequently with high diagnostic accuracy (3). However, the notion of a liver tumor biopsy by endoscopic

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ultrasound-guided fine-needle aspiration (EUS-FNA) was first introduced in 1999 (4). EUS-FNA is indicated for small liver tumors or when a biopsy by other methods is difficult (5). However, no studies have compared these two biopsy methods, and in some cases, the choice of biopsy method may be challenging in clinical practice.

Study Aim

To compare the results of an ultrasound-guided percutaneous biopsy and EUS-FNA for liver tumors and examine the appropriate indications for each biopsy method.

Materials and Methods

A retrospective study was conducted using medical records for patients who underwent a liver tumor biopsy at our hospital from 2012 to 2019. The cases were classified into two groups for a comparison: an ultrasound-guided percutaneous biopsy group (percutaneous group) and an EUS-FNA group (EUS group). The decision of whether to perform a percutaneous biopsy or EUS-FNA was made by the operator.

Abdominal ultrasonography and computed tomography (CT) were performed before the biopsy. A percutaneous biopsy was performed on patients in whom the lesions could easily be visualized with abdominal ultrasonography. In contrast, EUS-FNA was selected for cases in which it was difficult to visualize the lesions using abdominal ultrasound and for tumors located close to the gastrointestinal tract (stomach or duodenum).

The clinical background, biopsy procedure, diagnostic ability, and adverse events were examined. The definition of malignant was "a case with histologically malignant findings", and benign cases were those with "histologically benign findings and no tumor growth even after one-year follow-up".

The study was performed with the permission of the Showa University Ethics Committe.

Biopsy method

A percutaneous biopsy was performed using an analgesic (pentazocine 15 mg), and the liver tumor was visualized by abdominal ultrasound. A small incision was made on the skin with a scalpel, and the tumor was punctured 1-2 times with a 16-G tru-cut type puncture needle.

EUS-FNA was performed by administering analgesics and sedatives (petidine hydrochloride 35 mg or pentazocine 7.5-15 mg + midazolam 2-5 mg). A GF-UCT260 endoscope (Olympus Medical Systems, Tokyo, Japan) and a UE-ME1 or UE-ME2 observation device (Olympus Medical Systems) were used. The puncture needle was between 19-25 G and was selected at the operator's discretion. The number of strokes was 10-20, and the suction pressure was 10-20 cc negative pressure. A rapid on-site evaluation of the cytology was performed in neither group. The percutaneous liver biopsy was performed by 4 operators, all of whom had experi-

ence with more than 30 cases. EUS-FNA was performed by 3 endoscopists with experience with more than 50 cases.

Definition of adverse events (including severity grade)

The definition of adverse events established by the workshop of American Society of Gastrointestinal Endoscopy (ASGE) was used (6). In this study, pain was defined as "pain requiring analgesics within 24 hours after the procedure."

Statistical analyses

Statistical analyses were performed using Student's *t*-test and the chi-square test to compare the two groups, and p values <0.05 were considered to indicate a statistically significant difference.

Results

Clinical background characteristics

A total of 106 patients (47 in the percutaneous group and 59 in the EUS group) were included (Table 1). The patients had a median age of 68 (range, 32-87) years old, and 60 were men while 46 were women. A total of 100 patients had a final diagnosis of malignancy, including metastatic liver tumor in 45 cases and primary tumors as follows: pancreatic cancer, 10 cases; colorectal cancer, 9 cases; lung cancer, 7 cases; breast cancer, 5 cases; gallbladder cancer, 3 cases; esophageal cancer, 2 cases; gastric cancer, 2 cases; pancreatic neuroendocrine tumor, 2 cases; pancreatic neuroendocrine carcinoma, 1 case; renal cell carcinoma, 1 case; colorectal neuroendocrine tumor, 1 case; ovarian cancer, 1 case; and small intestine gastrointestinal stromal tumor, 1 case. Furthermore, there were 32 cases of cholangiocellular carcinoma, 18 cases of hepatocellular carcinoma, 4 cases of malignant lymphoma, and 1 case of leiomyosarcoma. A total of six patients had a final diagnosis of benign tumor, including two cases of liver abscess, one case of focal nodular hyperplasia, one case of inflammatory pseudotumor, one case of hepatic sarcoidosis, and one case of necrotic tissue.

A total of 21 patients (20%) received oral administration of antithrombotic drugs, of whom 17 completely discontinued receipt before the biopsy, while 4 underwent the biopsy with oral aspirin alone (all 4 were in the EUS group). Table 2 shows the clinical background characteristics of the two groups, with no significant difference in clinical background findings noted.

Biopsy procedure (Table 3) (Fig. 1-3)

The puncture needles used in the percutaneous group were tru-cut type 16-G in all cases, and those used in the EUS group were 19-G in 5% (3 cases), 22-G in 61% (36 cases), and 25-G in 34% (20 cases). The median lesion diameter was 62 (range, 12-167) mm in the percutaneous group but was significantly smaller (34 mm; range, 6-170

Number of patients	106 cases
Age, median (range)	68 (32-87)
Sex	male: female=60 cases : 46 cases
Final diagnosis	malignant tumor, 100 case
	metastatic liver tumor, 45 cases
	cholangiocellular carcinoma,32 cases
	hepatocellular carcinoma, 18 cases
	malignant lymphoma, 4 cases
	leiomyosarcoma, 1 case
	benign tumor, 6 cases
	liver abscess, 2 cases
	focal nodular hyperplasia, 1 case
	inflammatory pseudotumor, 1 case
	hepatic sarcoidosis, 1 case
	necrotic tissue, 1 case
Oral administration of antithrombotic drugs	21 cases (20%)
Lesion diameter, median (range)	45mm (6-170)
Lesions in right lobe	47% (50/106)
Lesions in left lobe	49% (52/106)
Lesions in caudate lobe	4% (4/106)

Table 1. Clinical Background of All Cases.

Table 2. Comparison of Clinical Backgrounds between Two Groups.

	Percutaneous group (n=47)	EUS group (n=59)	p value
Age, median (range)	68 (32-81)	66 (39-87)	n.s. *
Sex (male : female)	23, 25	37, 22	n.s. **
Final diagnosis malignant	96% (45/47)	93% (55/59)	n.s. **
Final diagnosis benign	4% (2/47)	7% (4/59)	n.s. **
Oral administration of antithrombotic drugs	17% (8/47)	22% (13/59)	n.s. **
n.s.: not significant			

*Student's t-test

**Chi-square test

Table 3. Comparison of Biopsy Procedure between Two Groups.

	Percutaneous group (n=47)	EUS group (n=59)	p value
Puncture needle	16G in all cases	19G: 5%, 22G : 61%, 25G : 34%	-
Lesion diameter, median (range)	62mm (12-167)	34mm (6-170)	<0.01 *
Lesions in right lobe	70% (33/47)	28% (17/59)	<0.01 **
Lesions in left lobe	30% (14/47)	64% (38/59)	<0.01 **
Lesions in caudate lobe	0%	7% (4/59)	n.s. **
Immunostaining	74% (35/47)	68% (40/59)	n.s. **
Length of the specimen, median (range)	9.7mm (3.1-14.4)	3.3 mm (1.1-6.8)	< 0.05*

n.s.: not significant

*Student's t-test

**Chi-square test

mm) in the EUS group (p <0.01). In the percutaneous group, the localization of lesions was 30% (14 cases) in the left lobe and 70% (33 cases) in the right lobe. In the EUS group, the localization of lesions was 64% (38 cases) in the left lobe, 28% in the right lobe (17 cases), and 7% (4 cases) in the caudate lobe. The percutaneous group had a higher number of right lobe tumors, while the EUS group had more left lobe tumors (p <0.01). EUS-FNA was performed

as a transgastric puncture in 72% cases, and as a transduodenal puncture in 28% of cases. Immunostaining was performed in 74% (35/47) of the percutaneous group and 68% (40/59) of the EUS group, showing no significant difference. Immunostaining was performed when the pathologist deemed it necessary. Thus, immunostaining was not performed in cases that could be diagnosed only by Hematoxylin-Eosin staining.



Figure 1. a: Abdominal contrast-enhanced CT showed a large tumor with cystic degeneration in the pancreas tail and small liver metastasis in the caudate lobe (arrow). Since dissemination and infection from a pancreatic tumor biopsy were a concern, we decided to perform a biopsy of the liver metastases. b: Abdominal ultrasonography revealed an obscure tumor in the caudate lobe (arrow). A percutaneous biopsy was difficult for this case. c: The liver tumor in the caudate lobe was easily visualized by EUS (arrowhead), and EUS-FNA was performed with a 22-G needle. d: The pathological diagnosis was adenocarcinoma consistent with pancreatic cancer metastasis, and chemotherapy was initiated. Ad: adenocarcinoma, H: Hepatocyte (Hematoxylin and Eosin staining, ×400)

The median length of the specimen was 9.7 (range, 3.1-14.4) mm in the percutaneous biopsy group and 3.3 (range, 1.1-6.8) mm in the EUS group; specimens were thus significantly longer in the percutaneous biopsy group (p < 0.05). The portal vein area could not be evaluated due to the many cases of malignant tumors, as sometimes the portal vein area was replaced with tumor tissue.

Diagnostic ability and adverse events (Table 4) (Fig. 4)

The percutaneous biopsy revealed that 43 cases were malignant, and 4 cases were benign. In two of the four benign cases, the tumor disappeared spontaneously, and the diagnosis was unchanged; however, in the remaining two cases, the tumor increased in size, and a percutaneous biopsy was performed again. Adenocarcinoma was detected in both cases, and the diagnosis changed from benign to malignant.

EUS-FNA diagnosed 55 cases as malignant and 4 cases as benign. The four benign cases showed no tumor growth, even after one-year follow-up, and the diagnosis was unchanged.

The sensitivity, specificity, and accuracy of the procedure were 95%, 100%, and 96% in the percutaneous group and

100%, 100%, and 100% in the EUS group, respectively showing no significant difference.

Adverse events were reported in 17% of the percutaneous group [mild pain in 6 cases, moderate bleeding in 1 case (blood transfusion and interventional radiology performed), mild infection in 1 case], with a significantly lower rate reported in the EUS group (2%; mild pain in 1 case; p < 0.01). The median observation period was 3.4 (range, 0.3-7) years in the percutaneous group and 2.5 (range, 0.6-5) years in the EUS group; no cases of needle-tract dissemination were observed.

Discussion

In this study, we retrospectively compared the results of an ultrasound-guided percutaneous biopsy and EUS-FNA for liver tumors. Although there was no significant difference in the diagnostic ability between the two groups, the number of adverse events was significantly lower in the EUS group than in the percutaneous group.

An ultrasound-guided percutaneous liver tumor biopsy is a classic procedure, with a reported sensitivity of $\geq 90\%$ and a complication rate of 1%-3% (3, 7). EUS-FNA for liver tu-



Figure 2. a: A case with a history of ovarian cancer, thyroid cancer, and colorectal cancer. Abdominal enhanced computed tomography revealed a 30-mm tumor in segment 6 of the liver. A histological evaluation was required to identify the primary tumor that gave rise to the metastasis. b: The hyperechoic tumor was clearly visualized by abdominal ultrasound. A percutaneous biopsy was performed. c: Adenocarcinoma with spindle-shaped nuclei was detected. The patient was diagnosed with liver metastasis of colorectal cancer. Ad: adenocarcinoma, H: Hepatocyte (Hematoxylin and Eosin staining, ×400)

mors is also reported to have a sensitivity of 88-100%, specificity of 99-100%, and a complication rate of 0-4% (4, 8-12). Previous studies have shown that both procedures have equivalent results. However, a percutaneous biopsy and EUS-FNA are fundamentally different procedures, and as such, it is inappropriate to simply compare the results.

In a percutaneous biopsy, the puncture needle has a large diameter (16 G), and the obtained specimen tends to be relatively large, although the tissue damage may also be more severe than with EUS-FNA. Thus, complications such as bleeding and pain are a concern. In contrast, EUS-FNA is performed with a relatively small needle (\geq 19 G). As a result, there is minimal tissue damage, but the obtained sample may be small. Although this procedure is expected to be associated with fewer complications, it may be difficult to collect a sufficient specimen for the diagnosis.

For pancreatic tumors, in which EUS-FNA is most frequently performed, high diagnostic accuracy has been reported with 22- and 25-G puncture needles. According to a recent meta-analysis, the sensitivity and specificity of EUS-FNA for pancreatic cancer have been reported to be 89% and 96%, respectively, and in many studies, fine-puncture needles of ≥ 22 G have been used (13, 14). A needle with a diameter of ≥ 22 G is sufficient to obtain a specimen for making a diagnosis of adenocarcinoma.

In the current study, the EUS group had high diagnostic accuracy, although the majority of cases involved needles that were ≥ 22 G at 56/59 (95%). The 3 cases managed using a 19-G needle were strongly suspected of being malignant lymphomas, and many samples were required for the gene analysis and immunostaining. In all three cases, sufficient samples for the diagnosis were collected, and a definite diagnosis of malignant lymphoma was made, with no reported complications.

In this study, only one case that received a percutaneous biopsy was evaluated for gene mutations (a mutation in exon 11 was found in a patient with gastrointestinal stromal tumor). The use of precision medicine is expected to increase in the future; however, in the present study, whether or not ample sample material for genetic testing could be obtained with these two biopsy methods could not be determined, so further research is needed in this regard.

The median lesion size in the percutaneous group was 62 mm, and that in the EUS group was 34 mm; the EUS group thus had significantly smaller tumors. Nevertheless, it should



Figure 3. a: Abdominal enhanced CT showed an irregular tumor of 30 mm in segment 8 of the liver. An ascending and transverse colon was located in front of the liver (Chilaiditi syndrome). A histological examination was required for chemotherapy because the patient refused surgery. b: It was difficult to visualize the tumor due to gastrointestinal gas (arrowhead) on abdominal ultrasound. c: EUS was able to visualize the tumor (arrow) without being affected by gastrointestinal gas. EUS-FNA was performed from the duodenal bulb. d: The patient was diagnosed with intrahepatic cholan-giocellular carcinoma. Ad: adenocarcinoma, H: Hepatocyte (Hematoxylin and Eosin staining, ×400)

 Table 4.
 Diagnostic Ability and Adverse Events.

	Percutaneous group (n=47)	EUS group (n=59)	p value
Sensitivity	95% (43/45)	100% (55/55)	n.s. *
Specificity	100% (2/2)	100% (4/4)	n.s. *
Accuracy	96% (45/47)	100% (59/59)	n.s. *
Adverse events	17% (8/47)	2% (1/59)	< 0.01*
n.s.: not significant			

*Chi-square test

be noted that the EUS group showed as high a diagnostic ability as the percutaneous group. Nguyen et al., who first reported EUS-FNA for liver tumors, reported that a histological diagnosis was possible in all included cases (n = 14cases), although the average tumor diameter was as small as 1.8 cm (4). Thus, EUS-FNA is useful for small liver tumors. Another advantage of EUS is that it is not affected by respiratory fluctuations because the evaluation is synchronized with breathing.

Regarding localization, most patients in the percutaneous group had lesions in the right lobe, while in the EUS group, the majority of patients had lesions in the left lobe. With EUS, the left lobe can be easily visualized transgastrically, and a tumor in the left lobe is likely to be punctured. In addition, lesions of the caudate lobe are difficult to puncture with a percutaneous biopsy, but EUS is close to the lesion and can be safely punctured. In contrast, it has traditionally been considered difficult to visualize tumors in the right lobe with EUS. However, EUS-FNA has been recently shown to be useful even for lesions in the right lobe (15, 16). Tumors in the right lobe can be visualized from the gastric antrum or the duodenal bulb.

In a percutaneous biopsy, the left lobe can be visualized from the epigastric region and the right lobe from the right



Figure 4. a: Abdominal ultrasonography showing numerous hypoechoic masses in the liver. A fullbody evaluation failed to reveal any clear primary lesion, and a percutaneous liver biopsy was performed prior to chemotherapy. The patient was diagnosed with intrahepatic cholangiocellular carcinoma. No antithrombotic drug was taken in this case, and the platelet count and coagulation ability were normal. b: The day after the biopsy, the patient complained of abdominal pain and exhibited a decreased blood pressure and tachycardia. A decrease in blood hemoglobin was observed (from 9.5 to 6.8 g/dL), and blood transfusion was performed. Contrast-enhanced computed tomography showed extravasation on the surface of the liver (arrowhead). c: Angiography showed extravasation from the periphery of the right hepatic artery (arrow), and transcatheter arterial embolization was performed.

intercostal space, and both lobes are suitable for puncture. Since EUS-FNA is often performed for left-lobe lesions, there may have been a greater number of right-lobe lesions in the percutaneous group than left-lobe tumors.

Adverse events were more common in the percutaneous group (17%) than in the EUS group. Pain was the most frequent (6 cases), with fever/bleeding occurring in 1 case each. A percutaneous biopsy carries a particular risk of adverse events due to the requirement for a skin incision (which cause abdominal pain), the use of a puncture needle with a large diameter, and difficulty avoiding small vessels. Since our case of hemorrhaging required blood transfusion and transcatheter arterial embolization, it should be noted as a rare but potentially fatal complication.

The rate of adverse events in the percutaneous group was markedly higher than in previous reports. This difference may be due to differences in the definition of complications. For example, in an older study (3), pain was not included as a complication, which may have resulted in a lower complication rate. The rate of adverse events in the EUS group were extremely low (2%). The incidence of complications in the EUS group is considered to have been reduced for a number of reasons, including the lack of a skin incision, the use of a puncture needle with a small diameter, and the high spatial resolution, making it possible to avoid small vessels.

Hollerbach et al. (10) examined 44 cases of EUS-FNA for liver tumors, including 15 patients with bleeding tendency (liver cirrhosis, ascites, or oral administration of aspirin). Although local bleeding was observed in two cases, the bleeding spontaneously improved, indicating that EUS-FNA may be safely performed even in cases with bleeding tendency. The present study included four cases of oral administration of aspirin in the EUS group, but no bleeding was observed.

The advantages and disadvantages of the two methods are shown in Table 5, and we investigated the indications for each biopsy procedure. A percutaneous biopsy is a classic method and well-indicated for both the left and right lobes. However, there is a tendency for adverse events to occur. In addition, it is difficult to puncture deep lesions far from the

	EUS-FNA	Percutaneous biopsy
Advantages	Able to visualize deep lesion of the liver (including caudate lobe)	Able to visualize the liver surface lesion
	Not affected by subcutaneous fat or intestinal tract on the surface of the liver (Chilaiditi syndrome)	Both left and right lobe lesions can be visualized easily
	Low complication rate	No need to be sedated
	Able to visualize small lesions	
Disadvantages	Poor visualization of the liver surface lesion	Difficult to visualize deep lesion of the liver (including caudate lobe)
	Sedation is required	Affected by subcutaneous fat or intestinal tract on the surface of the liver (Chilaiditi syndrome)
		Relatively high complication rate
		difficult to visualize small lesions

Table 5	5.	The Advantages and Disadvantages of Each of the Two Biopsy Methods.

body surface (such as the caudate lobe) as well as small lesions. A percutaneous biopsy should also be avoided in cases of Chilaiditi syndrome, where the colon enters the front of the liver. Given the above, a relatively large tumor that can be clearly seen on abdominal ultrasound with no bleeding tendency is considered a good indication for a percutaneous biopsy. Conversely, good indications for EUS-FNA are cases where a percutaneous biopsy is difficult due to a deep location (including the caudate lobe), left lobe location, or relatively small size as well as cases with Chilaiditi syndrome.

Although a percutaneous biopsy and EUS-FNA for liver tumors are both excellent techniques, it is important to have a solid understanding of their characteristics in order to select the best biopsy method for each individual case.

Conclusion

A percutaneous biopsy and EUS-FNA for liver tumors have equivalent diagnostic abilities, although EUS-FNA tends to be associated with fewer adverse events. A complete understanding of the characteristics of each procedure is essential when choosing the best biopsy method for each individual case.

The authors state that they have no Conflict of Interest (COI).

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