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Endoscopic ultrasound-guided tissue acquisition for focal liver lesions can be safely performed in patients with ascites

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ABSTRACT

Background and study aims In patients with ascites, percutaneous liver biopsy is generally contraindicated. Because endoscopic ultrasound-guided tissue acquisition (EUS-TA) allows tissue sample obtention from the digestive tract lumen, a biopsy without the intervention of ascites may prevent adverse events (AEs). This study aimed to evaluate the safety of EUS-TA for focal liver lesions in the presence of ascites.

Patients and methods A retrospective study was conducted using medical records of cases in which EUS-TA was performed on focal liver lesions between 2016 and 2022. Study participants were classified into two groups: those with ascites and those without it, and the outcomes were compared. The primary outcome was AEs.

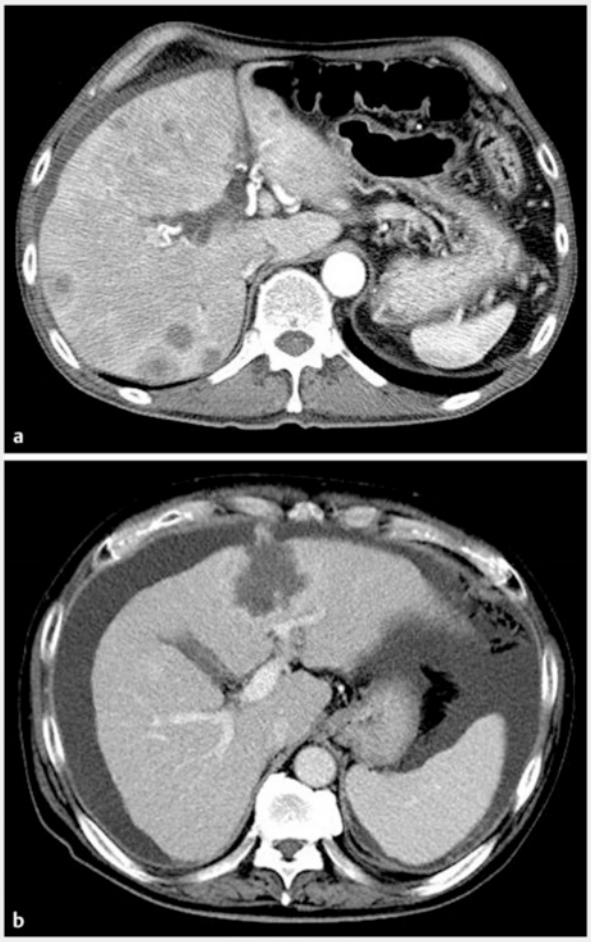
Results We included 109 cases of EUS-TA for focal liver lesions. Ascites was present in 20.1% of cases (22/109) and absent in 79.8% of cases (87/109). There were no significant differences between the two groups in clinical backgrounds and EUS-TA procedure, although fine-needle biopsy needles were significantly more frequently used in patients without ascites. In the ascites group, puncture without intervening ascites was successful in 90.9% of cases (20/22). The incidence of AEs was 4.5% (1/22) in the ascites group and 1.1% (1/87) in the non-ascites group, showing no significant difference. The two AEs were mild self-limiting abdominal pain.

Conclusions In focal liver lesions with ascites, EUS-TA allows biopsy without the intervention of ascites in most cases. The incidence of AEs did not differ significantly between patients with and without ascites.

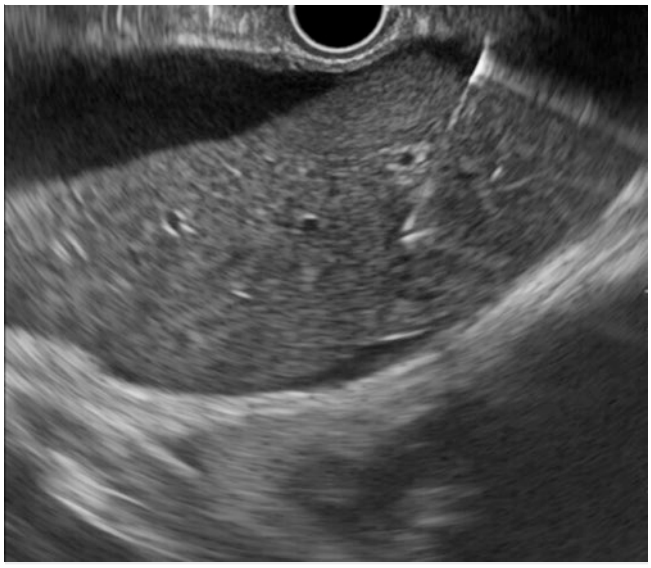
Introduction

Percutaneous liver biopsy, an essential modality for liver disease diagnosis, is widely performed in daily clinical practice [1, 2]. However, in patients with ascites, the procedure is generally contraindicated due to the risk of uncontrollable bleeding into the ascites [2, 3, 4]. In patients with ascites, transjugular liver biopsy is recommended and its safety has been established [5]. Transjugular liver biopsy is useful for diagnosing diffuse liver disease; however, it is not indicated for focal liver lesions because targeted biopsy is impossible. Therefore, there is no consensus on the appropriate biopsy method for focal liver lesions with ascites.

In recent years, the usefulness of endoscopic ultrasound-guided tissue acquisition (EUS-TA) for focal liver lesions has been widely reported [6]. Because EUS-TA enables puncture



▶ **Fig. 1** **a** Computed tomography scan revealed multiple focal liver lesions with ring-enhancement. Ascites is only found on the surface of the liver. **b** Computed tomography scan revealed hypovascular focal liver lesion in the left lobe. Ascites is found on the surface of the liver, around the spleen, and around the stomach.



▶ **Fig. 2** Endoscopic ultrasound-guided tissue acquisition was performed for a focal liver lesion with an unclear border in the left lobe. The endoscopic ultrasound image shows that the puncture needle has penetrated the ascites. In this case, the puncture without the intervening ascites was unsuccessful.

from the digestive tract lumen, a biopsy without the intervention of ascites may prevent adverse events (AEs). To our knowledge, there are no studies evaluating the safety of EUS-TA for focal liver lesions with ascites.

Patients and methods

This was a single-center, retrospective, observational study approved by the ethics committee of Showa University. The objective was to assess the safety of EUS-TA for focal liver lesions with ascites. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

The study included patients who underwent EUS-TA for local liver lesions between 2016 and 2022. Cases in which needle puncture was not possible owing to intervening blood vessels or other organs (such as the gallbladder) were excluded. The clinical backgrounds of the patients and details of EUS-TA were retrospectively reviewed using the medical records. The primary outcomes were AEs associated with EUS-TA. Outcomes were compared between patients with ascites and without ascites.

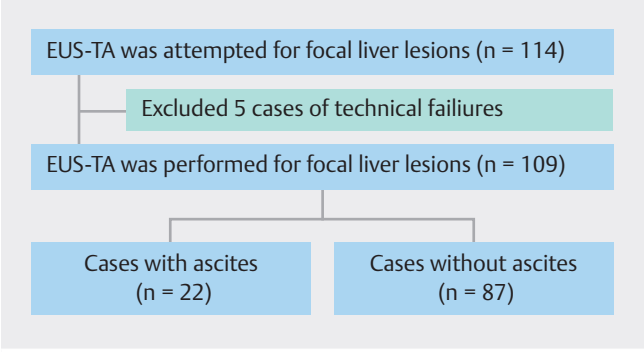
Definition

Two EUS experts reviewed computed tomography scans performed within 1 month prior to EUS-TA to determine presence of ascites (▶ **Fig. 1**). Two EUS-experts reviewed the EUS images and determined whether ascites had entered the puncture line during EUS-TA (▶ **Fig. 2**).

Cytologically or histologically confirmed malignant results indicated malignancy. Cases that were histologically diagnosed as benign but subsequently diagnosed as malignant (e. g., tumor growth on imaging with elevated tumor marker levels) were also defined as malignant. Histologically confirmed benign results with no tumor growth after 1-year follow-up indicated a benign state. The definition of AEs established by the workshop of the American Society of Gastrointestinal Endoscopy was used [7].

EUS-TA procedure

During EUS-TA, analgesics and sedatives (pethidine hydrochloride [35 mg] or pentazocine [7.5–15 mg] + midazolam [1.0–5.0 mg]) were administered. Furthermore, a GF-UCT260 endoscope (Olympus Medical Systems, Tokyo, Japan) and a UE-ME1 or UE-ME2 observation device (Olympus Medical Systems) were used. The gauge of the puncture needle was 19G to 25G at operator discretion. The number of strokes was 10 to 20 and the suction pressure was 10 to 20 mL (negative pressure). If the obtained specimen contained a lot of blood, the slow pull technique was used. Rapid on-site cytology was not performed. In cases with antithrombotic drugs, EUS-TA was performed in



▶ **Fig. 3** Flowchart of the study patients.

accordance with the Japanese Gastrointestinal Endoscopy Society guidelines [8].

The needles used were Expect SlimLine (Boston Scientific Japan, Tokyo, Japan), Acquire (Boston Scientific Japan), and SonoTip TopGain (Medico's Hirata, Tokyo, Japan). Expect SlimLine was a fine-needle aspiration (FNA) needle, while Acquire and SonoTip TopGain were fine-needle biopsy (FNB) needles. Contrast-enhanced EUS was not performed in this study. The operators were endosonographers with experience in performing EUS-TA more than 30 cases.

Pathological examination

Tissues obtained from EUS-TA were fixed in formalin, followed by histological diagnosis using hematoxylin and eosin staining. Immunohistochemistry was performed as necessary. After the tissue was fixed in formalin, the remaining liquid component was cytologically examined with Papanicolaou staining. Cytological examination was used as an auxiliary diagnostic approach.

Statistical analysis

Continuous variables are expressed as medians. Incidence and concordance were compared between the two groups using Fisher's exact test and the Mann-Whitney U test as appropriate. $P < 0.05$ was considered to indicate statistical significance.

Results

Case selection

EUS-TA for focal liver lesions was attempted in 114 cases. There were five cases of technical failure (puncture was impossible in three cases because of an intervening blood vessel, and in two cases because the gallbladder was in the puncture line), and EUS-TA was performed in 109 cases. Ascites was present in 20.1% of cases (22/109) and absent in 79.8% of cases (87/109) (▶ **Fig. 3**). Outcomes of the two groups were compared.

Clinical background

The clinical backgrounds of the participants are shown in ▶ **Table 1**. There were no significant differences in age, female ratio, tumor size, or tumor location between the two groups.

▶ **Table 1** Clinical backgrounds of the two groups.

	Cases with ascites (N = 22)	Cases without ascites (N = 87)	*P* value
Age, median (range), years	69 (55–79)	71 (25–90)	0.31
Female, no. (%)	12 (54.5)	29 (33.3)	0.06
Size, median (range), mm	24.5 (10–170)	31 (6–111)	0.94
Left lobe lesions, no. (%)	15 (68.1)	60 (68.9)	0.94
Right lobe lesions, no. (%)	5 (22.7)	23 (26.4)	0.72
Caudate lobe lesions, no. (%)	2 (9.0)	4 (4.5)	0.41

Details of EUS-TA

The details of EUS-TA are shown in ▶ **Table 2**. There were no significant differences in the rate of transduodenal puncture, needle gauge, or the number of punctures between the two groups. FNB needles were significantly more frequently used in the non-ascites group. In the ascites group, puncture without the intervention of ascites was successful in 90.9% of cases (20/22). There was no significant difference in the final diagnosis between the two groups.

Outcomes of EUS-TA

Sensitivity and accuracy rates in the ascites group were both 100%, whereas they were 96.2% and 96.5%, respectively, in the non-ascites group, showing no significant difference. Incidence of AEs was 4.5% (1/22) in the ascites group and 1.1% (1/87) in the non-ascites group, showing no significant difference (▶ **Table 3**). The two AEs were mild, self-limiting abdominal pain. There were no cases of bleeding, perforation, or infection. None of the patients experienced any serious AEs requiring blood transfusion or surgery.

Discussion

Percutaneous liver biopsy in patients with ascites is considered a relative contraindication due to the risk of uncontrollable bleeding into the ascites [2, 3, 4]. However, there is very little evidence of occurrence of AEs associated with percutaneous liver biopsy in the presence of ascites.

Murphy et al. examined percutaneous liver biopsies in 48 patients (15 of them had focal liver lesions), dividing them into 28 with ascites and 28 without ascites [9]. They found that AEs occurred in 32.1% (9/22) in the ascites group and 42.8% (12/28) in the non-ascites group (only one of these patients required a blood transfusion), with no significant difference between the two groups. Little et al. classified 476 percutaneous liver biopsy cases (277 of which were focal liver lesions) into 173

▶ **Table 2** Details of endoscopic ultrasound-guided tissue acquisition in the two groups.

	Cases with ascites (N = 22)	Cases without ascites (N = 87)	*P* value
Transduodenal puncture, no. (%)	5 (22.7)	24 (27.5)	0.64
25-gauge needle, no. (%)	12 (54.5)	39 (44.8)	0.41
22-gauge needle, no. (%)	10 (45.4)	46 (52.8)	0.53
19-gauge needle, no. (%)	0 (0)	2 (2.2)	0.47
FNB needle, no. (%)	2 (9.0)	29 (33.3)	0.02
Number of punctures, median (range)	2 (1–2)	2 (1–3)	0.49
Puncture without intervening ascites, no. (%)	20 (90.1)	–	–
Immunohistochemistry, no. (%)	12 (54.5)	53 (60.9)	0.35
Final diagnosis			
Metastatic liver tumor, no. (%)	10 (45.4)	38 (43.6)	0.88
Intrahepatic cholangiocellular carcinoma, no. (%)	7 (31.8)	14 (16.0)	0.09
Hepatocellular carcinoma, no. (%)	3 (13.6)	10 (11.4)	0.78
Gallbladder cancer, no. (%)	2 (9.0)	7 (8.0)	0.87
Malignant lymphoma, no. (%)	0 (0)	5 (5.7)	0.25
Other malignant neoplasms, no. (%)	0 (0)	4 (4.5)	0.3
Benign lesions, no. (%)	0 (0)	6 (6.8)	0.37

▶ **Table 3** Outcomes of endoscopic ultrasound-guided tissue acquisition in the two groups.

	Cases with ascites (N = 22)	Cases without ascites (N = 87)	*P* value
Sensitivity	100% (22/22)	96.2% (78/81)	0.36
Specificity	–	100% (6/6)	–
Accuracy	100% (22/22)	96.5% (84/87)	0.37
Adverse events, no. (%)	1 (4.5)	1 (1.1)	0.29

with ascites and 303 without, and compared the outcomes [10]. Overall incidence of AEs was 9.2% (16/173) in the ascites group and 8.2% (25/303) in the non-ascites group. Incidence of severe bleeding requiring blood transfusion or surgery was 3.4% (6/173) in the ascites group and 3.3% (10/303) in the non-ascites group, with no significant difference between the two groups. No deaths were reported in either group, and they concluded that presence of ascites was not associated with an increase in the rate of AEs.

The results of these reports leave doubts as to whether presence of ascites truly leads to an increase in the rate of AEs. However, these papers have some problems such as: 1) being relatively old literature because they were published before the year 2000; 2) the frequency of AEs is high; and 3) focal liver lesions and diffuse liver disease are mixed together.

The British Society of Gastroenterology's liver biopsy guidelines published in 2020 state that "Percutaneous biopsy of the liver in the presence of large volume ascites is considered a contraindication in many texts. The reasons for this vary and include technical challenges and the risk of uncontrollable bleeding into the ascites; however, the evidence for these concerns is weak. If a liver biopsy is clinically indicated in a patient with large volume ascites, an image-guided percutaneous biopsy following total paracentesis or a transjugular biopsy can be considered [4]." The usefulness of transjugular liver biopsy has been established in diffuse liver disease with ascites [5]. However, transjugular liver biopsy cannot be indicated for focal liver lesions. Therefore, there is no consensus on the appropriate biopsy method for focal liver lesions with ascites.

Since EUS-TA for focal liver lesions was first reported in 1999 [11], favorable results have been reported from around the world, with high diagnostic accuracy (88%-100%) and low rates of AEs (0%-6%) [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24]. EUS-TA has been attracting attention as an alternative to percutaneous liver biopsy. Because EUS-TA enables puncture from the digestive tract lumen, it is possible to perform biopsies in cases where percutaneous biopsy is technically challenging (such as caudate lobe lesions and patients with Chilaiditi's syndrome) [23, 24]. In addition, it has been reported that EUS-TA causes less pain to patients and has fewer AEs compared with percutaneous liver biopsy [23, 24, 25]. However, disadvantages of EUS-TA include the need for sedation, making it difficult to perform in patients with severe cardiorespiratory failure, the

limited observation range in patients with surgically altered anatomy, and experience required to acquire skills [23].

In this study, we compared outcomes of EUS-TA or focal liver lesions between patients with ascites and those without it. There was no significant difference in the rate of AEs between the two groups, and none of the patients experienced any serious AEs requiring blood transfusion or surgery. These results suggest that EUS-TA may be performed safely even in focal liver lesions with ascites.

Several factors may explain these favorable outcomes. The first is that EUS-TA allows for puncture via the digestive tract lumen; therefore, in many patients with ascites (90.1%, 20/22), a biopsy can be performed without the intervention of ascites. Puncture without the intervention of ascites may have prevented AEs, including bleeding.

The second reason is that a thin puncture needle is used in EUS-TA. In percutaneous biopsies, thicker needles (usually 16G for diffuse liver disease and 20G for focal liver lesions) are used compared with EUS-TA. A 22G needle is most often used in EUS-TA, with 19G and 25G being selected depending on the cases. In this study, 22G and 25G needles were used in the majority of cases (98.1%, 107/109), which may have contributed to the reduction in the rate of AEs.

The third reason is the high spatial resolution of EUS. Using EUS, the liver can be observed at close range without being affected by subcutaneous fat. Even small blood vessels can be visualized, and by using the Doppler mode, blood vessels can be avoided.

The last reason is that, as stated in previous studies [9, 10], presence of ascites may not be associated with incidence of AEs in the first place. Currently, there is little evidence that presence of ascites is significantly associated with an increase in the rate of AEs. Despite this, ascites is considered a relative contraindication to percutaneous liver biopsy in clinical guidelines and reviews, and there may be a discrepancy between evidence and guidelines [2, 3, 4]. It is too early to draw a conclusion as to whether presence of ascites is truly associated with occurrence of AEs, and further evidence needs to be accumulated.

The limitations of this study are that it was single-center and retrospective study and the number of cases was relatively small. From this study, it is premature to conclude that the safety of EUS-TA in cases of ascites has been established. In the future, it would be desirable to conduct clinical studies at multiple institutions with a large number of cases.

Conclusions

Even in focal liver lesions with ascites, EUS-TA enables biopsies to be performed without the intervention of ascites in most cases. Incidence of AEs was similar to that in patients without ascites, and EUS-TA can be performed safely even in patients with ascites.

Conflict of Interest

The authors declare that they have no conflict of interest.

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