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Clinical Efficacy of Liver Tumor Biopsy With Radiofrequency Ablation of the Puncture Route Using a Co-access Needle

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Abstract. *Background/Aim: Tumor biopsy are needed frequency for accurate diagnosis. However, percutaneous liver tumor biopsy presents a risk of complications such as bleeding and tumor seeding. We investigated the feasibility of liver tumor biopsy, followed by cauterization with expandable radiofrequency ablation. Patients and Methods: Tumor biopsies using a co-access needle were performed in 102 patients. Expandable radiofrequency ablation was used to ensure cauterization and hemostasis of the puncture route. We evaluated the clinical background and complications. Results: The average (±standard deviation) tumor diameter was 56.87±39.45 mm. Pathological diagnosis was possible in all cases. In 20 patients, the postoperative pathological diagnosis differed from the preoperative diagnosis. No significant anemia progression was observed in any patients after biopsy, and no peritoneal seeding was observed during a mean follow-up observation period of 18.5 months. Conclusion: Liver tumor biopsy, followed by cauterization with expandable radiofrequency ablation via a co-access needle, is safe and useful for obtaining reliable diagnoses.*

Early detection and treatment are essential for improving the diagnosis of hepatic malignancies. Nevertheless, there are still instances wherein hepatic malignancies are detected at an advanced stage (1, 2). In most cases, a definitive diagnosis can be obtained with radiological imaging owing to the remarkable advances in various diagnostic imaging equipment in recent years. However, an accurate differential diagnosis may be elusive despite blood tests and different imaging modalities adopted. In such cases, an ultrasound-guided percutaneous liver tumor biopsy is often required.

Despite the low frequency of use of percutaneous biopsy for liver tumors, various complications, including bleeding and tumor seeding, have been reported (3). At our Institution, to avoid these complications, we use a co-access needle when performing biopsies and conduct cauterization and hemostasis of the puncture route using expandable radiofrequency ablation (RFA) *via* a deployment needle. This study aimed to describe our experience with 102 patients with liver tumors, wherein a definitive diagnosis was obtained using the aforementioned method. This approach for performing tumor biopsy has not been previously described. Additionally, we evaluated the pre- and postoperative diagnostic concordance rate, rate of true-positives, and occurrence of complications, such as bleeding and tumor seeding.

Patients and Methods

Study patients. This retrospective study included 102 patients who underwent liver tumor biopsy for definitive diagnosis between November 2006 and December 2020. Cauterization and hemostasis of the puncture route were achieved using RFA *via* a co-access needle. Biopsy was performed in patients with liver tumor lesions in whom it was not possible to confirm the diagnosis clinically or by imaging and wherein a biopsy-based diagnosis was deemed essential to guide subsequent treatment planning decisions.

The indications for tumor biopsy were as follows: (i) Presence of nodular lesions of the liver that could not be definitively diagnosed by clinical or imaging examinations; (ii) cases wherein the mass was regarded as a determinant of the patient's prognosis or quality of life; (iii) cases of rare or special liver tumors wherein it was difficult to distinguish whether the lesion was a primary liver tumor or an inflammatory pseudotumor; and (iv) cases wherein a biopsy-based diagnosis was considered essential for subsequent treatment. The clinical background and presence of complications were evaluated in these patients. Patients in whom treatment was not possible (based on the patient's general condition or hepatic

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reserve) or in whom no prognostic factors indicative of improvement could be identified, even if the mass was a malignant tumor, were excluded.

Biopsy technique. A schema illustrating the use of a co-access needle is shown in Figure 1. As pre-medication, 25 mg of intramuscular hydroxyzine and 15 mg of pentazocine were administered to hospitalized patients under conscious sedation.
A co-access needle was inserted after induction of local anesthesia with 10 ml of 1% lidocaine, and a 20 cm 18-G Majima biopsy needle was inserted after the inner cylinder was removed. The expandable RFA needle electrode (LeVeen™ CoAccess™ Needle; Boston Scientific, Boston, MA, USA), which was used for deployment of RFA, was inserted into the outer mantle needle after the biopsy, and small bursts of RFA were repeatedly delivered to ablate the needle route (Figure 1).

Midazolam and atropine sulfate were intravenously administered as additional analgesics for patients who experienced severe pain and developed bradycardia due to the vasovagal reflex during the procedure.

After collection, all tissue specimens were fixed in 10% formalin, dehydrated, embedded in paraffin, cut into 5-μm-thick sections, and subsequently stained with hematoxylin and eosin.

Statistical analysis. Continuous variables are reported as the mean±standard deviation, whereas categorical data are expressed as frequencies. Data were analyzed using EZR ver. 1.42 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (4).

Ethical considerations. The Ethics Committee of Saiseikai Niigata Hospital approved the study protocol (approval number: E20-25), and the study was conducted per the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient before enrollment into the study.

Results

The average patient age was 69.83±11.13 years, and the study included 63 men and 39 women. The average tumor size was 56.87±39.45 mm. The S1, S2, S3, S4, S5, S6, S7, and S8 hepatic segments included a total of 2, 5, 16, 12, 30, 10, 10, and 17 lesions, respectively. There was a significantly greater involvement of the right lobes than the left (Table I).

The concordance between the pre- and post-procedure diagnoses is shown in Table II. The concordance rate between the pre- and post-procedural diagnosis was 80.2% (82/102). Tumors with a pre- and post-procedure diagnosis concordance rate of 100% were differential cases of intrahepatic cholangiocarcinoma (ICC) or colon cancer, breast cancer or colon cancer, lung cancer or colon cancer, and hepatocellular carcinoma (HCC) or colon cancer. The concordance rate decreased significantly to 42.8% ($p<0.05$) in the cases without confirmed colon cancer.

In some patients, the pre-procedural diagnosis of colon cancer deviated from the final diagnosis; the tumors in such patients were small nodules, with diameters of 15-30 mm, and normal carcinoembryonic antigen values. Additionally, two cases of mucosa-associated lymphoid tissue lymphoma had slightly elevated interleukin 2 receptor levels (899 U/ml and 452 U/ml). However, there were cases with markedly high levels of interleukin 2 receptor (6,140 U/ml for pancreatic cancer and 3,190 U/ml for liver cancer). Moreover, the concordance rate was low for the differentiation of hepatic tumors from pancreatic cancer. Two cases diagnosed as neuroendocrine carcinomas (NECs) were small nodules with a tumor diameter of 30 mm. Histological diagnosis was possible in all cases of cancer of unknown origin, and treatment was administered according to the recommended guidelines. In addition, there were significantly more cases of neuroendocrine tumor (NET) and NECs among the identified discordant cases (nine out of the 20 cases).

No progression of bleeding-related anemia was observed after biopsy in any of the patients, and no patient developed disseminated tumors during an average of 18.5 months of follow-up observations. Mild biopsy-related pain was observed in 18 patients; however, there were no cases of severe pain (5, 6).

Discussion

Drug therapy for unresectable liver tumors depends on the final diagnosis (HCC, ICC, etc.). Therefore, histological confirmation by tumor biopsy is essential for planning a suitable drug regimen (7-9). However, complications, including bleeding and tumor seeding from liver biopsy, have been reported (10).

To address these complications, we developed a biopsy method involving the use of a co-access needle through which cauterization and hemostasis of the needle track is performed by RFA. In our experience with 102 patients, we found that the proposed method was safe, with no cases of bleeding-related anemia after biopsy and no disseminated cases reported after a mean follow-up period of 18.5 months.

In a retrospective study, complications related to liver biopsy performed to diagnose liver mass lesions were reported in 0.5% (11/2,091) of patients, and they were mostly related to bleeding (six cases of intra-abdominal bleeding, one case of intrahepatic hematoma, one case of biliary bleeding) (10). Biopsies of hepatic adenoma have reportedly exhibited a high rate (2%) of cases requiring blood transfusion (11). However, with our method, there were no bleeding complications.

Moreover, peritoneal dissemination is a notable late-stage complication. A meta-analysis of HCC cases reported that the overall dissemination rate after a biopsy was 2.7%, with an annual rate of 0.9% (12). The risk of tumor seeding depends on the origin of cancer. For example, as far as we are aware there have been no reports of seeding in cases of liver metastasis from breast cancer; however, seeding has been reported in cases of liver metastasis originating from

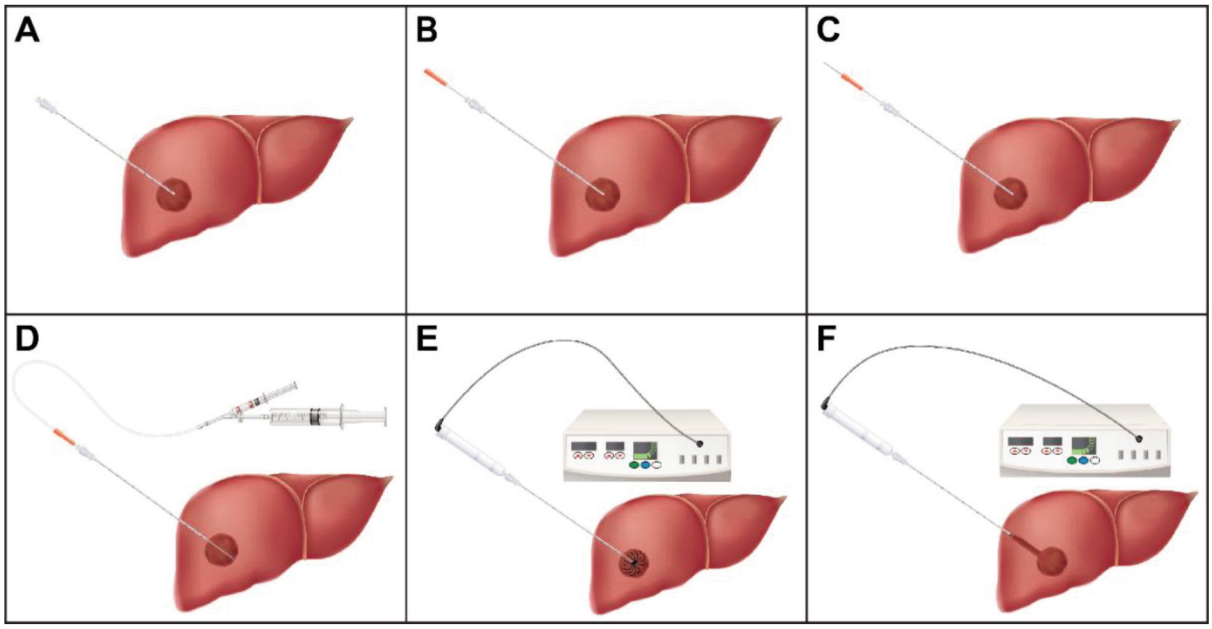

Figure 1. *Schema illustrating biopsy with a co-access needle. A: A co-access needle is inserted into the target tumor. B: A 20-cm 18-G Majima biopsy needle is then inserted after removing the inner cylinder. C: The inner needle of the biopsy needle is removed and the stylet inserted. D: The biopsy needle and suction kit are connected, and the aspiration biopsy is performed. E: The LeVeen™ CoAccess™ Needle (expandable radiofrequency ablation needle) is inserted, which is the needle to deploy radiofrequency ablation into the outer needle after the biopsy. F: Repeat small bursts of radiofrequency ablation are applied via the deployment needle to ablate the needle route.*

colon cancer (13). Moreover, the risk of dissemination due to HCC has been higher with diagnostic biopsy alone than with percutaneous treatment (14-19).

There may have been cases of needle tract implantation in which patients have died before it was clinically discovered (20). It is thought that the mechanism of needle tract implantation may involve the transfer of cancer cells from the needle tip during the biopsy or backward flow of some of the cancer cells during needle removal and their adherence to subcutaneous tissue. Possible dissemination mechanisms along the puncture route include attachment of tumor cells to the puncture needle, transport by bleeding through the puncture route, and a rapid increase in intratumoral pressure (21, 22). Subcutaneous dissemination has been reported following RFA in which a cool tip unipolar needle was used (23). However, our approach involved the use of an expandable ablation needle after small bursts of RFA, with a route wider than the unipolar needle puncture diameter. This method prevented bleeding and tumor dissemination by performing aspiration biopsy while keeping the mantle needle fixed. Although there were some adverse effects such as pain, there were no cases of dissemination, and definitive diagnoses were obtained for all patients. Thus, despite being a seemingly complicated procedure, our method allows safe liver tumor biopsy.

Table I. *Patient demographic and clinical characteristics (n=102).*

Parameter		Value
Age, years	Mean±SD	69.83±11.13
Gender, n (%)	Male	63 (61.76)
	Female	39 (38.24)
Tumor location, n (%)	S1	2 (1.96)
	S2	5 (4.90)
	S3	16 (15.69)
	S4	12 (11.76)
	S5	30 (29.41)
	S6	10 (9.80)
	S7	10 (9.80)
	S8	17 (16.67)
Tumor size, mm	Mean±SD	56.87±39.45

S: Segment.

In obtaining a diagnosis of liver lesions by biopsy, the sensitivity for HCC and metastatic liver cancer was 89.6-97.5% and 92.7-95.8%, respectively (10). Although false-negative cases have been reported (6.4%), the false-positive rate was low (0.08%). Therefore, it is crucial to bear in mind the possibility of false-negatives in the pathological results of liver biopsy.

Table II. *Concordance rate between pre- and post-procedure diagnoses.*

Diagnosis			
Pre-procedure	Post-procedure	n	Concordance (%)
Adenoma (n=4)	Adenoma	3	75.0%
	NRH	1	
ICC (n=14)	ICC	13	92.8%
	EHE	1	
ICC vs. colon cancer (n=4)	ICC	2	100.0%
	Colon cancer	2	
ICC vs. HCC (n=13)	ICC	6	92.3%
	HCC	5	
	Combined	1	
	Lymphoma	1	
Colon cancer (n=7)	Colon cancer	3	42.8%
	Lymphoma	2	
	NEC	1	
	IPT	1	
Colon cancer vs. breast cancer (n=1)	Colon cancer	1	100.0%
Colon cancer vs. lung cancer (n=1)	Colon cancer	1	100.0%
EHE (n=1)	NET (grade 2)	1	0.0%
Gastric cancer (n=2)	HCC	1	0.0%
	IPT	1	
GIST (n=2)	GIST	1	50.0%
	NET (grade 2)	1	
HCC (n=19)	HCC	16	84.2%
	Hemangioma	2	
	NRH	1	
HCC vs. colon cancer (n=3)	HCC	3	100.0%
Lung cancer (n=4)	Lung cancer	4	100.0%
Lung cancer vs. ICC (n=2)	ICC	2	100.0%
Lung cancer vs. breast cancer (n=2)	Lung cancer	1	100.0%
	Breast cancer	1	
Breast cancer (n=7)	Breast cancer	5	71.4%
	ICC	1	
	NRH	1	
Ovarian cancer (n=1)	Ovarian cancer	1	100.0%
Pancreatic cancer (n=5)	Pancreatic cancer	2	40.0%
	NEC	3	
Pancreatic cancer vs. HCC (n=3)	Pancreatic cancer	2	66.6%
	NEC	1	
Unknown origin (n=7)	ICC	2	n.a
	NEC	2	
	SCC	1	
	Adenocarcinoma	1	
	IPT	1	

EHE: Epithelioid hemangioendothelioma; GIST: gastrointestinal stromal tumor; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; IPT: inflammatory pseudo-tumor; n.a.: not applicable; NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor; NRH: nodular regenerative hyperplasia; SCC: squamous cellular carcinoma.

Considering these complications, unnecessary liver tumor biopsies should not be performed for cases that can be diagnosed using other imaging modalities. However, there are cases in which a definitive histological diagnosis is required. With recent advances in drug therapy and genetic diagnosis, tumor biopsies are increasingly being performed as a reference for treatment policy decisions in patients receiving drug therapy.

Regarding indications for tumor biopsy in clinical practice, the histological type is determined from resected specimens, without tumor biopsies, when malignant tumors are suspected based on images, and where treatment and surgical resection are indicated. However, it is thought that the histological type of nodules that require treatment, but not surgical resection, should be confirmed by tumor needle biopsy as a general rule.

Furthermore, differentiation would likely be challenging when the primary carcinoma is double cancer.

In addition to basic histological diagnosis, patients should undergo the following procedures to decide on the optimal treatment: Fission images in NET cases, with Ki-67 index determination; estimation of the primary lesion in cases of adenocarcinoma (ICC or liver metastasis from other organs); microsatellite instability and neurotrophic tyrosine receptor kinase (*NTRK*) gene test; and tumor biopsies with an oncogene panel test as an index. In our cases, immunohistochemical diagnoses were possible in all lung cancer cases, and appropriate systemic chemotherapy was administered.

Based on the final diagnosis, a definitive diagnosis that differed from the pre-procedure diagnosis was obtained in 20 out of the 102. Thus, the diagnosis concordance rate was 80.2%. Of these 20 cases, seven were NET or NEC. Furthermore, imaging-based diagnosis and differentiation using tumor markers in NEC/NET cases were difficult. Additionally, differentiation of pancreatic cancer had a low concordance rate. The two cases diagnosed as NEC had small nodules with a diameter of 30 mm. Therefore, we consider that biopsies should be actively performed using our proposed method for cases with small nodules, wherein a definitive diagnosis is difficult by imaging alone.

This study had several limitations. Firstly, it included various liver tumors. Secondly, the influence of selection bias cannot be excluded. Thirdly, the follow-up period was not long enough. Lastly, this was a retrospective study with a small sample size derived from a single center. Therefore, the findings from this study need to be validated in a multicenter study. Despite these limitations, the results of this study can provide the basis for future, larger studies.

In conclusion, tumor biopsy tract ablation is technically feasible in patients with liver tumors and may effectively control needle tract bleeding and seeding. Appropriate use of this method for liver biopsy tract ablation may help reduce the risk of complications associated with liver biopsy.

Conflicts of Interest

None declared.

Authors' Contributions

Conceptualization: T. Ishikawa. Data curation: T. Ishikawa, E. Kodama, T. Kobayashi, M. Azumi, Y. Nozawa, A. Iwanaga, T. Sano and T. Honma. Formal analysis: T. Ishikawa. Investigation: T. Ishikawa, E. Kodama, T. Kobayashi, M Azumi, Y. Nozawa, A. Iwanaga, T. Sano and T. Honma. Methodology: T. Ishikawa. Project administration: T. Ishikawa. Resources: T. Ishikawa. Software: T. Ishikawa. Visualization: T. Ishikawa, Writing – original draft: T. Ishikawa, Writing – review and editing: E. Kodama, T. Kobayashi, M. Azumi, Y. Nozawa, A. Iwanaga, T. Sano and T. Honma.

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