Real-world outcomes of endoscopic ultrasound–guided tissue acquisition for actionable diagnosis in suspected primary or recurrent lymphoma

Ho Seung Lee, MD,[1,*] Gunn Huh, MD,[2,*] Hyungwoo Cho, MD, PhD,[3] Sunguk Jang, MD,[4] John Vargo, MD,[4] Steven Edmundowicz, MD,[5] Dok Hyun Yoon, MD, PhD,[3] Do Hyun Park, MD, PhD[2]

Seoul, Republic of Korea; Cleveland, Ohio; Aurora, Colorado, USA

Background and Aims: Although excisional biopsy is the reference standard for diagnosing lymphoma, EUS-guided biopsy offers a less-invasive alternative. However, its utility in both newly suspected and recurrent lymphomas remains limited.

Methods: We retrospectively reviewed 87 consecutive patients who underwent EUS-guided tissue acquisition for suspected lymphoma (46 primary and 41 recurrent cases). An actionable diagnosis was defined as confirmed lymphoma with definitive subtyping or exclusion of lymphoma by alternative pathology or ≥12 months of disease-free follow-up. Technical success, safety, diagnostic outcomes, and longitudinal trends were analyzed.

Results: Technical success was achieved in 98.9% of patients, with minor adverse events in 3.4%. An actionable diagnosis was made in 74 patients (85.1%), including 38 of 46 with primary suspicion (82.6%) and 36 of 41 with suspected recurrence (87.8%). Among the recurrent cases—most of which were previously diagnosed by excisional or percutaneous biopsy—EUS fine-needle biopsy confirmed the subtype in 25 patients (61.0%) and excluded lymphoma in 11 (26.8%), yielding a negative predictive value of 90.9%. No clinical or procedural predictors of actionable diagnosis were identified. Eventually, indications increasingly shifted toward recurrence (annual increase 1.82-fold; 95% CI, 1.46-2.38; $P < .001$), paralleled by greater use of the 22-gauge Acquire (Boston Scientific, Marlborough, Mass, USA) needle.

Conclusions: EUS-guided biopsy is safe and yields accurate results in most patients with suspected lymphoma. In clinical practice, the use of EUS-guided biopsy for suspected recurrent lymphoma with a confirmed biopsy is increasing. These findings support its expanding role as a minimally invasive alternative diagnosis method. (Gastrointest Endosc 2026;104:33-42.)

INTRODUCTION

Lymphadenopathy has diverse causes, including reactive changes, infections, and malignancies.[1] Among these, lymphomas are a major concern. Accurate tissue diagnosis with subtype classification is essential for treatment selection and prognosis.[2] In patients with suspected recurrence, repeat biopsy is often required to confirm relapse, exclude benign diseases, or detect histologic transformation.[3-6]

Excisional biopsy is the reference standard for diagnosing lymphoma.[2] However, in patients with deep-seated lymphadenopathy and a challenging surgical approach, minimally invasive modalities such as EUS-guided biopsy may provide a safer and more accessible alternative.[7-9]

Current affiliations: Department of Internal Medicine, Korea University Anam Hospital, Seoul, Korea (1), Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea (2), Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea (3), Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, Cleveland, Ohio, USA (4), Division of Gastroenterology and Hepatology, University of Colorado School of Medicine, Aurora, Colorado, USA (5).

Corresponding author: Do Hyun Park, MD, PhD, Digestive Diseases Research Center, Division of Gastroenterology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea. E-mail: dhpark@amc.seoul.kr.

*Drs Lee and Huh contributed to this article as the first authors.

Recent EUS-guided fine-needle biopsy (FNB) needles provide larger and better preserved tissue specimens, enabling immunohistochemistry (IHC) and subtype classification.[10,11] Previous studies demonstrated that EUS-guided biopsy achieves high technical success and diagnostic yield, particularly for pancreatic masses and other solid lesions[12,13]; however, evidence focusing specifically on lymphoma is limited, particularly regarding its role in newly suspected and recurrent cases and its impact on clinical decision-making.

In this study, we evaluated the diagnostic performance and clinical impact of EUS-guided biopsy in patients with suspected lymphoma by assessing its technical success, safety, and rate of actionable diagnoses. We further calculated the negative predictive value (NPV) for lymphoma exclusion, analyzed the potential predictors of actionable diagnosis, and explored the temporal trends in clinical indications and needle types.

METHODS

Patients and procedures

We retrospectively reviewed the institutional lymphoma database at Asan Medical Center to identify patients who underwent EUS-guided tissue acquisition (TA) for suspected or recurrent lymphoma between March 2016 and December 2024. Eligible patients were ≥19 years and had clinical or radiological suspicion of lymphoma at initial presentation or recurrence. In routine practice, patients suspected of having lymphoma were first evaluated by hematology/oncology specialists. When TA from deep-seated lesions was considered appropriate, a gastroenterologist was consulted for the EUS-guided biopsy. This decision followed multidisciplinary discussion with surgeons and interventional radiologists, when an excisional or percutaneous biopsy was technically challenging or associated with high procedural or surgical risk, or when the patient refused surgery. Patients with a concurrent malignancy at the time of lymphoma suspicion or with a history of another cancer within the preceding 5 years were excluded from the analysis (Supplementary Fig. 1).

All procedures were performed with the patient under conscious sedation using intravenous midazolam and meperidine and a linear array echoendoscope (GF-UCT260; Olympus Medical Systems, Tokyo, Japan). Before the procedure, CT images were reviewed. During EUS, real-time Doppler imaging was performed to avoid the intervening vasculatures. The available needles included a 19-gauge EchoTip Ultra; 19-, 20-, and 22-gauge ProCore (Cook Medical, Bloomington, Ind, USA) and a 22-gauge Acquire (Boston Scientific, Marlborough, Mass, USA). Needle selection and the number of passes were determined at the discretion of the endosonographer based on the lesion characteristics, clinical context, procedural conditions, and availability of each needle. After each needle pass, macroscopic on-site evaluation was performed to assess specimen adequacy.[14] Visible tissue cores distinguishable from blood or mucus were considered adequate, and additional passes were made if necessary. After confirming the absence of immediate adverse events (AEs), the procedure was terminated. In situations where excisional biopsy was not feasible or was associated with disproportionate surgical risk, EUS-guided TA was performed after careful risk–benefit evaluation, consistent with institutional standards and multidisciplinary consensus.

Data collection and definitions

Data from the electronic medical records of a prospectively collected lymphoma cohort were retrospectively reviewed. Among patients with biopsy-proven lymphoma, primary diagnostic methods, including excisional, percutaneous, and endoscopic biopsies, were evaluated. The demographic variables included age and sex. Clinical information included indications for biopsy (primary diagnosis vs suspected recurrence), target organ, lesion size, and radiological findings. The target lesion location was classified into 4 quadrants based on the Q-line-derived anatomical division on cross-sectional imaging.[15] Procedural details included the procedure date, route of approach, needle type, number of passes, and endosonographic features, such as echogenicity and border characteristics.

The clinical outcomes included technical success, AEs, and subsequent treatment decisions.[16] Technical success was defined as the successful puncture of the target lesion and acquisition of tissue specimens. Diagnostic yield reflected the number of specimens that provided a pathologic diagnosis of lymphoma or an alternative condition, regardless of the adequacy for subtype classification. For benign cases, follow-up data of at least 12 months were reviewed to confirm the absence of lymphoma recurrence. Survival status was ascertained from medical records and outpatient follow-ups.

All histopathologic evaluations were performed by expert hematopathologists at a high-volume tertiary referral center, using IHC to support definitive lymphoma subtyping and enhance diagnostic accuracy. From a clinical decision-making perspective, histologic outcomes were categorized into 4 groups: (A) lymphoma confirmation with definitive subtype classification; (B) exclusion of lymphoma by alternative pathologic diagnosis and/or at least 12 months of clinical–radiological follow-up without evidence of recurrence; (C) nondiagnostic samples; and (D) lymphoma without sufficient material for subtype classification (incomplete subtype). For the purposes of this study, the clinical impact was defined as the proportion of patients achieving an actionable diagnosis (categories A or B).

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center, Seoul, Republic of Korea (IRB number: 2025-1105), and the requirement for informed consent was waived because of its retrospective design. All diagnostic and therapeutic decisions followed

institutional and international guidelines in consultation with experienced oncology and hematology specialists.

Statistical analysis

Baseline characteristics are summarized as counts and percentages for categorical variables and as medians with IQRs for continuous variables. Comparisons between the primary presentation and recurrence cohorts were performed using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The rates of actionable diagnoses were reported with 95% CIs, calculated using the Wilson method. Diagnostic accuracy (sensitivity, specificity, positive predictive value, and NPV) was assessed only in the recurrence-suspicious cohort, excluding nondiagnostic cases. The primary cohort consisted only of confirmed lymphoma cases for which accuracy measures could not be calculated. Logistic regression models were constructed to identify predictors of an actionable diagnosis. Univariate analyses were performed for baseline clinical and procedural variables. Variables with $P < .20$ in the univariable analyses, as well as clinically relevant covariates, were subsequently included in the multivariable model. Given the relatively small sample size and sparse data for some categorical variables, Firth bias-reduced logistic regression was applied to mitigate the issues of complete or quasi-complete separation and provide more stable estimates. Temporal trends in indication (primary vs recurrence) and needle type (22-gauge ProCore vs 22-gauge Acquire) were further assessed using logistic regression with year as a continuous variable, and the results were expressed as odds ratios (ORs) with 95% CIs and P values for trend. A sensitivity analysis was performed, including patients with at least 24 months of follow-up, because the 12-month window for defining benign outcomes may not fully capture late or indolent relapses. A 2-sided P value <.05 was considered statistically significant. All analyses were performed using R version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 87 patients (46 with suspected primary lymphoma and 41 with suspected recurrent disease) were included in the analysis (Table 1). Among patients with suspected recurrent lymphoma, prior confirmation was achieved mainly through excisional biopsy ($n = 25$, 61.0%) and percutaneous core needle biopsy ($n = 8$, 19.5%; Supplementary Table 1, available online at www.giejournal.org). The median age was marginally greater in the recurrence group (65 years [IQR, 59-68 years]) than in the primary group (62 years [IQR, 54-66 years]), although this difference was not statistically significant ($P = .171$). The proportion of male patients was similar in the 2 groups (59% vs 61%, $P > .999$) (Table 1).

The most common target organs for biopsy were the lymph nodes (76% overall), followed by the adrenal gland (9.2%), pancreas (8.0%), and other sites such as the liver, gallbladder, and spleen. Adrenal gland involvement was more frequently observed in the recurrence group (17% vs 2.2%; $P = .028$). The median follow-up duration was 44 months (IQR, 19-74 months), with no significant difference between the groups ($P = .478$). During follow-up, 21 patients (24%) died, with no significant difference in mortality rates between the primary (20%) and recurrence (29%) groups ($P = .325$) (Table 1).

Lymph node lesions were most frequently located in the para-aortic region, accounting for 71.4% of the primary cohort and 65.2% of the recurrence cohort. Other target sites included the celiac, mesenteric, peripancreatic, splenic hilum, and retroperitoneal areas, with a broadly similar distribution between the cohorts (Supplementary Fig. 2).

Procedural characteristics

In the overall cohort, technical success was achieved in 86 of the 87 procedures (98.9%), with a diagnostic yield of 87.4%. The median number of needle passes was 3 in both groups ($P = .187$). The target lesion location was more frequently in the left upper quadrant in the recurrence group (46% vs 26%) and in the right upper quadrant in the primary group (54% vs 29%); however, the overall difference was not statistically significant ($P = .062$), and the approach routes were similar. Most lesions demonstrated heterogeneous echogenicity, and irregular borders were observed in approximately half of the cases without significant group differences. The median target lesion size was significantly larger in the primary tumor group (35 vs 24 mm; $P < .001$). Representative imaging findings are shown in Figure 1. AEs occurred in 3 patients (6.5%) in the primary group, with no events in the recurrence group ($P = .245$). All AEs consisted of transient fever that resolved with conservative management. The detailed procedural characteristics are summarized in Table 2.

Final histology and diagnostic modalities

In the primary diagnosis cohort, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma were the most common subtypes, with the majority diagnosed by EUS-guided biopsy. In the suspected recurrence cohort, DLBCL predominated, followed by follicular lymphoma and several rarer subtypes; in addition, benign lesions were identified. Benign findings included lymph node lesions with histologic indications, such as reactive lymphoid hyperplasia and foam cell infiltration without evidence of malignancy, Kikuchi disease, or abscess, and were confirmed by the absence of lymphoma recurrence during at least 12 months of clinical–radiological follow-up. The detailed distributions of the final histology and diagnostic modalities are provided in Supplementary Table 2.

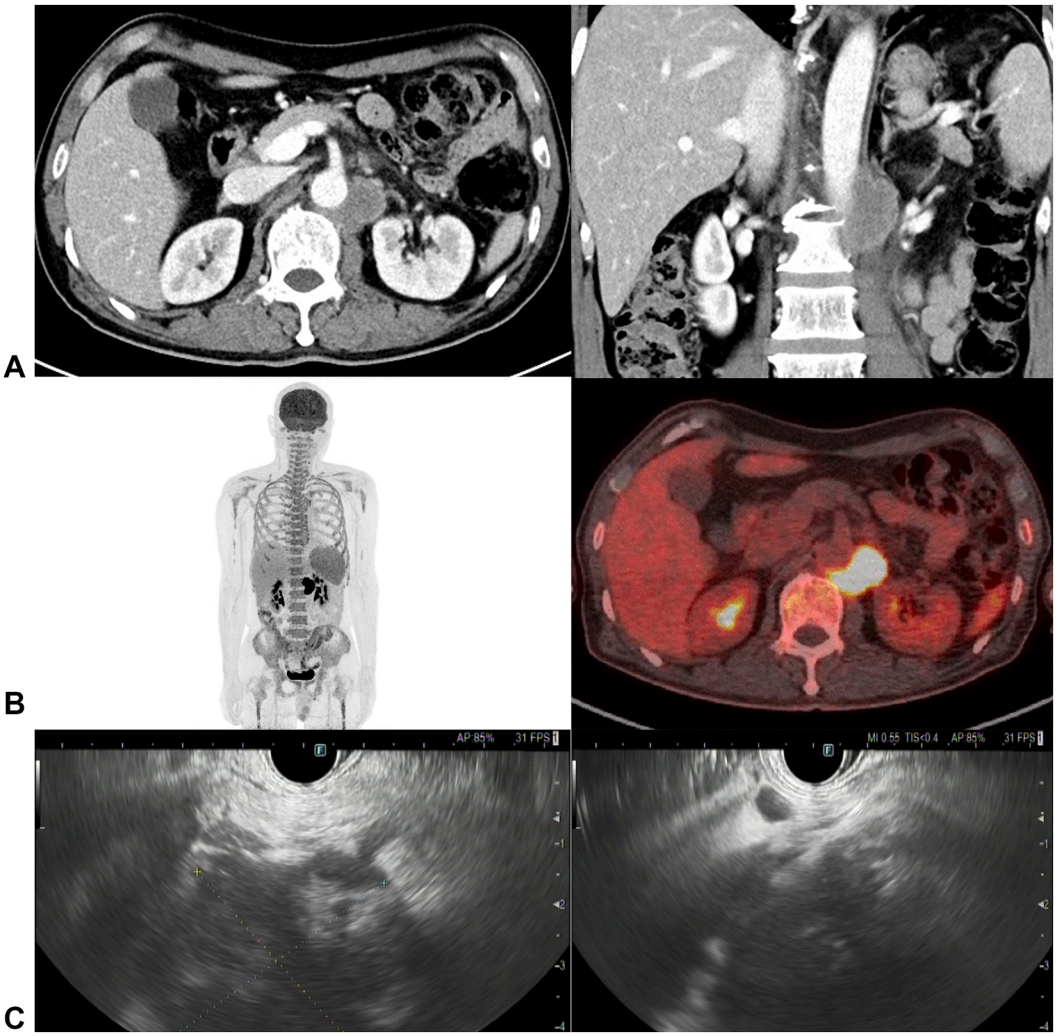

Figure 1. Representative images of target lymph nodes in suspected lymphoma. **A,** Contrast-enhanced CT showing bulky para-aortic lymphadenopathy. **B,** Positron emission tomography-CT showing fluorodeoxyglucose-avid mesenteric lymph nodes. **C,** EUS image of a hypoechoic lymph node during EUS-guided core biopsy using a 22-gauge needle.

Figure 2 shows the 10-year longitudinal trends of EUS-guided lymphoma biopsies. During the early study period (2016-2017), most procedures were performed for primary diagnosis using a 22-gauge ProCore needle. Since 2018, the use of the 22-gauge Acquire has increased steadily and almost completely replaced the ProCore in recent years. During the same period, recurrence progressively surpassed primary presentation as the predominant indication, with nearly all procedures by 2024 performed for suspected recurrence using the Acquire needle. Logistic regression confirmed these temporal shifts, showing a 1.82-fold annual increase in recurrence indication (95% CI, 1.46-2.38; $P < .001$) and a 2.97-fold annual increase in the use of the Acquire needle over the ProCore (95% CI, 1.81-6.32; $P < .001$).

Clinical impact of EUS-guided biopsy

Of the 87 patients who underwent EUS-guided TA, 74 (85.1%; 95% CI, 76.1%-91.1%) achieved actionable results, including subclassification, whereas 11 (12.6%) were nondiagnostic, and 2 (2.3%) had incomplete subtyping (Table 3). In the primary cohort ($n = 46$), 38 (82.6%; 95% CI, 69.3%-90.9%) patients were actionable, 6 (13.0%) were nondiagnostic, and 2 (4.3%) had incomplete subtyping. In the recurrence cohort ($n = 41$), 36 (87.8%; 95% CI, 74.5%-94.7%) were actionable, including subclassification, and 5 (12.2%) were nondiagnostic. Notably, in the recurrence cohort, EUS-guided biopsy enabled the reclassification of one case from an initial diagnosis of DLBCL to mantle cell lymphoma. The details of subsequent diagnostic management in nondiagnostic cases are summarized in Supplementary Table 3.

The NPV in the suspected recurrence cohort was 90.9%. The full set of diagnostic accuracy metrics is presented in Supplementary Table 4. Among 11 patients with category B results, the median follow-up duration was 39 months (IQR: 28-44 months). In a sensitivity analysis including patients with at least 24 months of

TABLE 1. Baseline characteristics of patients undergoing EUS-guided biopsy for suspected or recurrent lymphoma

Characteristic	N	Primary N = 46	Recurrence N = 41	Overall N = 87	P value
Sex	87	–	–	–	>.999
Male	–	27 (59%)	25 (61%)	52 (60%)	–
Female	–	19 (41%)	16 (39%)	35 (40%)	–
Age	87	–	–	–	.171
Median [Q1, Q3]	–	62 [54, 66]	65 [59, 68]	63 [55, 67]	–
Organ	87	–	–	–	.028
Gallbladder	–	1 (2.2%)	0 (0%)	1 (1.1%)	–
Liver	–	2 (4.3%)	1 (2.4%)	3 (3.4%)	–
Lymph node	–	35 (76%)	31 (76%)	66 (76%)	–
Left adrenal gland	–	1 (2.2%)	7 (17%)	8 (9.2%)	–
Pancreas	–	6 (13%)	1 (2.4%)	7 (8.0%)	–
Right adrenal gland	–	0 (0%)	1 (2.4%)	1 (1.1%)	–
Spleen	–	1 (2.2%)	0 (0%)	1 (1.1%)	–
Follow-up duration, mo	87	–	–	–	.478
Median [Q1, Q3]	–	51 [15, 88]	43 [21, 60]	44 [19, 74]	–
Death during follow-up	87	9 (20%)	12 (29%)	21 (24%)	.325

–, Not applicable.

follow-up, the NPV was 90% (9/10). One false-negative case—lost to follow-up just 2 years prior—was retained to minimize bias, and 1 patient with a shorter follow-up was excluded. The remaining 9 patients maintained stable findings during extended follow-up.

Predictors of actionable diagnosis in EUS-guided biopsy for suspected or recurrent lymphoma

In the univariate analysis, none of the clinical or procedural factors were significantly associated with obtaining an actionable diagnosis (Table 4). Lesion location and number of needle passes showed no meaningful differences in the likelihood of achieving an actionable diagnosis. Moreover, other variables, including the target organ, EUS approach, lesion size, needle type, echogenicity, and border characteristics, were not predictive of actionable outcomes. No independent predictors were identified in the multivariate logistic regression model.

DISCUSSION

Lymphoma is potentially curable when appropriate treatment is administered in a timely manner.[17,18] Recently, less-invasive diagnostic approaches, such as core needle biopsy and liquid biopsy based on circulating tumor DNA, have provided substantial benefits in clinical practice.[19] In the setting of suspected recurrence, particularly for deep-seated lymph nodes, EUS-guided biopsy can provide a more suitable alternative to aggressive excisional biopsy, considering the patients' prior chemotherapy exposure and general condition.[8-11] However, data directly addressing its clinical impact remain scarce.

In this retrospective study of 87 patients with suspected lymphoma, EUS-guided TA provided a high rate of actionable diagnoses. Technical success was nearly universal (98.9%), and most biopsies yielded sufficient tissue for pathologic diagnosis, corresponding to a diagnostic yield of 87%. Only 1 technical failure occurred, wherein the lymph node visualized on positron emission tomography could not be accessed via the transduodenal approach. The diagnostic accuracy of EUS fine-needle aspiration or FNB for lymphoma ranges from approximately 66% to 87%,[20,21] which is consistent with our findings. Our study adds to this evidence by quantifying the diagnostic yield and the proportion of cases in which EUS-guided biopsy provided an actionable diagnosis with a direct clinical impact. In addition, we observed 1 patient in the recurrence cohort whose histology result was reclassified from DLBCL to mantle cell lymphoma, underscoring the potential of EUS-guided biopsy to detect histologic transformation during disease evolution.

Specifically, among 41 patients evaluated for suspected recurrence with a previously confirmed biopsy using excisional, percutaneous core needle, or endoscopic forceps biopsy, EUS-guided biopsy confirmed the lymphoma subtype in 25 (61.0%) and reliably excluded lymphoma in 11 (26.8%). These results highlight the dual clinical utility of EUS-guided biopsy in recurrent cases, enabling timely

TABLE 2. Procedural details of EUS-guided biopsy for suspected or recurrent lymphoma

Characteristic	*N*	Primary, *N* = 46	Recurrence, *N* = 41	Overall, *N* = 87	*P* value
Diagnostic yield	87	40 (87%)	36 (88%)	76 (87%)	–
Technical success, *n* (%)	87	46 (100%)	40 (97.6%)	86 (98.9%)	.954
Needle passes, *n*	86	–	–	–	.187
Median [Q1, Q3]	–	3.00 [3.00, 3.00]	3.00 [3.00, 3.00]	3.00 [3.00, 3.00]	–
Target lesion location (Q-line)	87	–	–	–	.062
LLQ	–	3 (6.5%)	6 (15%)	9 (10%)	–
LUQ	–	12 (26%)	19 (46%)	31 (36%)	–
RLQ	–	6 (13%)	4 (9.8%)	10 (11%)	–
RUQ	–	25 (54%)	12 (29%)	37 (43%)	–
EUS-TA approach	86	–	–	–	.900
Transduodenal	–	31 (67%)	29 (73%)	60 (70%)	–
Transgastric	–	14 (30%)	11 (28%)	25 (29%)	–
Transrectal	–	1 (2.2%)	0 (0%)	1 (1.2%)	–
Needle type	86	–	–	–	<.001
19-gauge Cook	–	0 (0%)	2 (5.0%)	2 (2.3%)	–
19-gauge ProCore	–	1 (2.2%)	0 (0%)	1 (1.2%)	–
20-gauge ProCore	–	4 (8.7%)	0 (0%)	4 (4.7%)	–
22-gauge Acquire	–	26 (57%)	37 (93%)	63 (73%)	–
22-gauge ProCore	–	15 (33%)	1 (2.5%)	16 (19%)	–
Target lesion echogenicity	86	–	–	–	.334
Heterogeneous	–	45 (98%)	37 (93%)	82 (95%)	–
Homogenous	–	1 (2.2%)	3 (7.5%)	4 (4.7%)	–
Target lesion border	86	–	–	–	.666
Irregular	–	25 (54%)	19 (48%)	44 (51%)	–
Ovoid	–	21 (46%)	21 (53%)	42 (49%)	–
Target lesion size, mm	86	–	–	–	<.001
Median [Q1, Q3]	–	35.0 [26.0, 48.0]	24.0 [16.0, 34.0]	30.0 [20.0, 42.0]	–
AEs	86	3 (6.5%)	0 (0%)	3 (3.5%)	.245

–, Not applicable; *EUS-TA*, EUS-guided tissue acquisition; *LLQ*, left lower quadrant; *LUQ*, left upper quadrant; *RLQ*, right lower quadrant; *RUQ*, right upper quadrant.

confirmation of relapse and initiation of appropriate systemic therapy in most patients, and allowing clinicians to confidently withhold treatment in patients without evidence of recurrent lymphoma. It should be noted, however, that although lymphoma exclusion (category B) was defined as a benign pathology with at least 12 months of disease-free follow-up, 1 patient subsequently developed clinical progression beyond this window but declined a confirmatory biopsy. This case was conservatively classified as a false negative, resulting in an NPV of 90.9%, which is comparable to the reported range of 85% to 92%.[22-24] Although short-term follow-up may support the reliable exclusion of lymphomas, indolent or late-relapsing lymphomas can still emerge, highlighting the inherent limitations of EUS-guided biopsy and the need for continued vigilance and, in selected cases, repeat biopsies. Nevertheless, sensitivity analysis including patients with ≥24 months of follow-up showed a comparable NPV of 90%, indicating the robustness of this finding.

Notably, even in the 5 nondiagnostic cases within the recurrence cohort, patient management was not compromised. Two patients who were deemed unfit for surgery received radiotherapy based on clinical and imaging findings, whereas the other 3 underwent additional procedures (laparoscopic excision or ultrasound-guided core needle biopsy) that confirmed recurrent lymphoma. Thus, although initially categorized as nondiagnostic, these cases ultimately reached a definitive diagnosis without delaying appropriate therapy. This finding supports the "EUS first" approach over the more invasive surgical approach in whom a definitive diagnosis is needed, because it does not result in clinically significant delay in patient care.

In addition to these performance metrics, our longitudinal analysis revealed important shifts in the clinical application of EUS-guided biopsy over the past decade (Fig. 2). In earlier years, procedures were mainly performed for primary diagnosis. However, oncologists often emphasize that excisional biopsy is preferable at the time of the initial

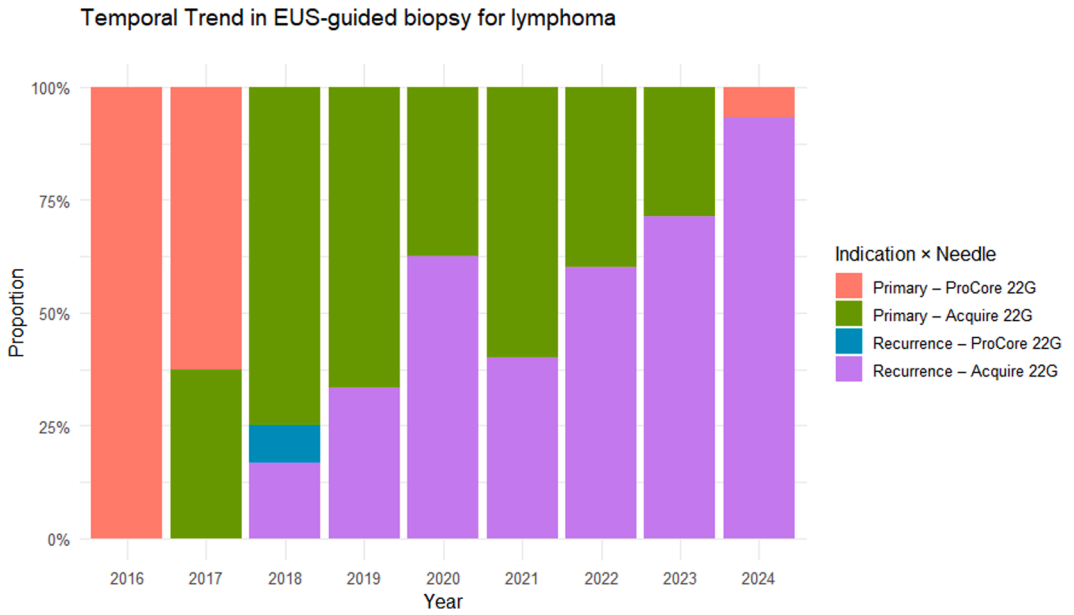

Figure 2. Longitudinal trends in indication and needle type of EUS-guided biopsy for lymphoma. Over 10 years, EUS-guided biopsies gradually shifted from primary diagnosis using the 22-gauge ProCore needle to recurrence evaluation using the 22-gauge Acquire. Logistic regression confirmed significant annual increases in recurrence indication (OR, 1.82; 95% CI, 1.46-2.38) and Acquire needle use (OR, 2.97; 95% CI, 1.81-6.32; $P < .001$).

TABLE 3. Clinical impact of EUS-TA in patients with suspected or recurrent lymphoma

	Total (*n*)	Nondiagnostic *n* (%)	Incomplete subtype *n* (%)	Actionable, *n* (%) [95% CI]	A_Confirm *n* (%)	B_Exclude *n* (%)
Overall	87	11 (12.6)	2 (2.3)	74 (85.1), [76.1-91.1]	63 (72.4)	11 (12.6)
Primary	46	6 (13.0)	2 (4.3)	38 (82.6), [69.3-90.9]	38 (82.6)	0 (0.0)
Recurrence	41	5 (12.2)	0 (0.0)	36 (87.8), [74.5-94.7]	25 (61.0)	11 (26.8)

Proportion of actionable diagnoses, nondiagnostic cases, and incomplete subtypes according to clinical indications (primary vs recurrence).
EUS-TA, EUS-guided tissue acquisition.

diagnosis because it provides sufficient tissue architecture for accurate subtyping, an element that is sometimes limited with EUS-guided FNB.[2] In contrast, in the setting of suspected recurrence, the clinical priority is to confirm or exclude relapse rather than to redefine the lymphoma subtype because the baseline histology is already known. In this scenario, EUS-guided biopsy offers clear advantages as a minimally invasive procedure that can provide adequate histology and IHC without the morbidity associated with surgical excision. Consistent with this rationale, recurrence has recently become a leading indication for EUS-guided biopsy, reflecting the improved tissue adequacy and technical performance.

Taken together, these findings suggest that although EUS-guided biopsy may have inherent limitations compared with surgical excision, it plays an increasingly valuable role in real-world lymphoma management. A multidisciplinary and multimodal strategy combining an optimized sampling technique, IHC, and flow cytometry is essential to maximize the diagnostic and therapeutic impact.[24,25]

In this study, EUS-guided biopsy established the diagnosis for most lymphoma subtypes observed, including DLBCL, follicular lymphoma, and mucosa-associated lymphoid tissue lymphoma, whereas excisional biopsy was required in only a minority of cases. Para-aortic lymph nodes were the most common targets, followed by the celiac, mesenteric, peripancreatic, splenic hilum, and retroperitoneal nodes. This distribution aligns with previous imaging and biopsy studies that showed a predilection for intra-abdominal lymphoma.[26,27] The broadly similar distribution between the primary and recurrence cohorts suggests that relapse frequently involves the same nodal regions as initial presentation.[5,28,29] Overall, these findings indicate that EUS-guided biopsy enables the diagnosis of major lymphoma subtypes and provides access to deep abdominal nodal stations that are difficult to reach using other approaches, reinforcing its clinical utility in this setting.

In the present analysis, none of the evaluated clinical or procedural variables, including target lesion size, number of needle passes, EUS approach, or lesion location by

TABLE 4. Univariable and multivariable logistic regression analyses of predictors of actionable diagnosis in EUS-guided biopsy for suspected or recurrent lymphoma

		Univariable			Multivariable		
Characteristic	***N***	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Group	87	–	–	–	–	–	.5
Primary	–	–	–	–	–	–	–
Recurrence	–	1.52	0.46-5.42	.5	1.67	0.40-8.26	–
Age	87	1.00	0.95-1.04	>.9	0.99	0.92-1.04	.7
Sex	87	–	–	–	–	–	.6
Female	–	–	–	–	–	–	–
Male	–	0.92	0.26-3.02	.9	0.69	0.15-2.83	–
Target organ	87	–	–	–	–	–	.6
Lymph node	–	–	–	–	–	–	–
Others	–	1.90	0.46-13.0	.4	1.59	0.26-13.7	–
Location of target lesion	87	–	–	–	–	–	.4
LLQ	–	–	–	–	–	–	–
LUQ	–	4.14	0.44-39.9	.2	1.53	0.13-49.4	–
RLQ	–	1.14	0.11-11.7	>.9	5.56	0.71-63.3	–
RUQ	–	1.22	0.16-6.54	.8	0.77	0.11-6.95	–
EUS approach	87	–	–	–	–	–	.4
Transduodenal	–	–	–	–	–	–	–
Transgastric	–	1.29	0.35-6.25	.7	0.38	0.04-3.34	–
Transrectal	–	0.18	0.01-4.73	.2	–	–	–
Target lesion size, per 10 mm	86	0.67	0.02-33.5	.8	3.45	0.04-621	.6
Needle passage	86	2.23	0.58-8.37	.2	2.57	0.56-11.9	.2
Echogenicity	86	–	–	–	–	–	–
Heterogenous	–	–	–	–	–	–	–
Homogenous	–	1.60	0.15-216	.7	–	–	–
Border	86	–	–	–	–	–	–
Irregular	–	–	–	–	–	–	–
Ovoid	–	2.11	0.61-8.47	.3	–	–	–
Needle type	86	–	–	–	–	–	–
22-gauge ProCore	–	–	–	–	–	–	–
22-gauge Acquire	–	2.35	0.60-8.43	.2	1.76	0.35-8.67	.5
Others	–	1.80	0.26-20.5	.6	6.85	0.50-1143	.2

–, Not applicable; *LLQ*, left lower quadrant; *LUQ*, left upper quadrant; *OR*, odds ratio; *RLQ*, right lower quadrant; *RUQ*, right upper quadrant.

quadrant, were significantly associated with the likelihood of achieving an actionable diagnosis (Table 4). This suggests that, if adequately accessible on EUS, a target lesion biopsy can be performed across a wide range of nodal stations. Importantly, the procedure also demonstrated an excellent safety profile, with only 3 transient febrile events (3.4%) and no major AEs, a rate comparable to that reported previously.[21,24] Taken together, these findings indicate that EUS-guided biopsy combines broad feasibility with a favorable risk–benefit profile, reinforcing its role as a practical, minimally invasive diagnostic option for both primary and recurrent lymphomas.

This study had some limitations. First, its retrospective single-center design may have introduced bias in patient selection, despite the use of a prospectively maintained lymphoma database. Referral for EUS-guided biopsy was based on multidisciplinary judgment, and factors such as lesion accessibility and patient preference may still have influenced case selection. Second, the modest overall sample size—including limited numbers of rare lymphoma subtypes and cases with histologic transformation—may have reduced the statistical power to identify predictors of diagnostic success. Therefore, nonsignificant findings in several secondary variables should be interpreted with caution because they

may reflect limited power rather than the true absence of association. Third, the heterogeneity of the needle types and devices chosen at the discretion of the endoscopist may have introduced variability in tissue adequacy and diagnostic outcomes. Fourth, although cases were confirmed as benign through at least 12 months of follow-up, longer observation periods may be necessary to exclude the possibility of indolent lymphoma relapse completely. In this context, diagnostic accuracy metrics, including NPV, were calculated only in the suspected recurrence cohort, because the primary presentation cohort consisted solely of patients with confirmed lymphoma. Although this design limitation precluded the accuracy assessment in de novo cases, the recurrence cohort likely reflects the most common real-world clinical scenario in which EUS-guided biopsy is considered for suspected lymphoma relapse. The calculation of diagnostic accuracy in this cohort excluded nondiagnostic cases. Although this approach is conventional for statistical clarity, it may overestimate the actual NPV in real-world practice. This should be interpreted with caution, as nondiagnostic biopsies represent clinically meaningful outcomes that can influence management decisions. In the present study, nondiagnostic results accounted for 12.2% of cases and often necessitated additional testing to establish a definitive diagnosis. Importantly, these patients ultimately received an appropriate diagnosis or management without delay in clinical decision-making. Notably, all pathologic diagnoses were rendered by a team of expert hematopathologists at a large-volume tertiary referral center, which likely minimized interobserver variability and improved diagnostic confidence. Nevertheless, the absence of an external central pathology review may limit the generalizability of our findings to institutions with different pathologic expertise.

In conclusion, EUS-guided biopsy demonstrated high technical success, favorable safety, and an actionable diagnosis in most patients with suspected primary or recurrent deep-seated lymphoma. In this clinical pattern, beyond enabling definitive subtyping and detection of histologic transformation, lymphoma was reliably excluded with an NPV of 90.9%, supporting its role as a minimally invasive alternative to surgical biopsy, particularly in recurrent settings.

ETHICS STATEMENT

This study was approved by the IRB of Asan Medical Center (approval number: IRB number: 2025-1105). The requirement for informed consent was waived because of the retrospective nature of the study. The study was not a registered clinical trial, and no animal experiments were involved.

DISCLOSURE

The following authors disclosed financial relationships: J. Vargo: Advisory board for Atlas Endoscopy; a consultant for Steris Medical, Inc, Olympus America, and Boston Scientific; received research grants from Olympus America. All other authors disclosed no financial relationships. This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00435385); a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (grant number: RS-2023-00273237).

ACKNOWLEDGMENTS

The authors dedicate this work to the memory of Professor Cheolwon Suh, whose advice and encouragement greatly supported the conception and development of this study.

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Abbreviations: AE, adverse event; DLBCL, diffuse large B-cell lymphoma; EUS-TA, EUS-guided tissue acquisition; FNB, fine-needle biopsy; IHC, immunohistochemistry; IRB, Institutional Review Board; NPV, negative predictive value; OR, odds ratio; TA, tissue acquisition.

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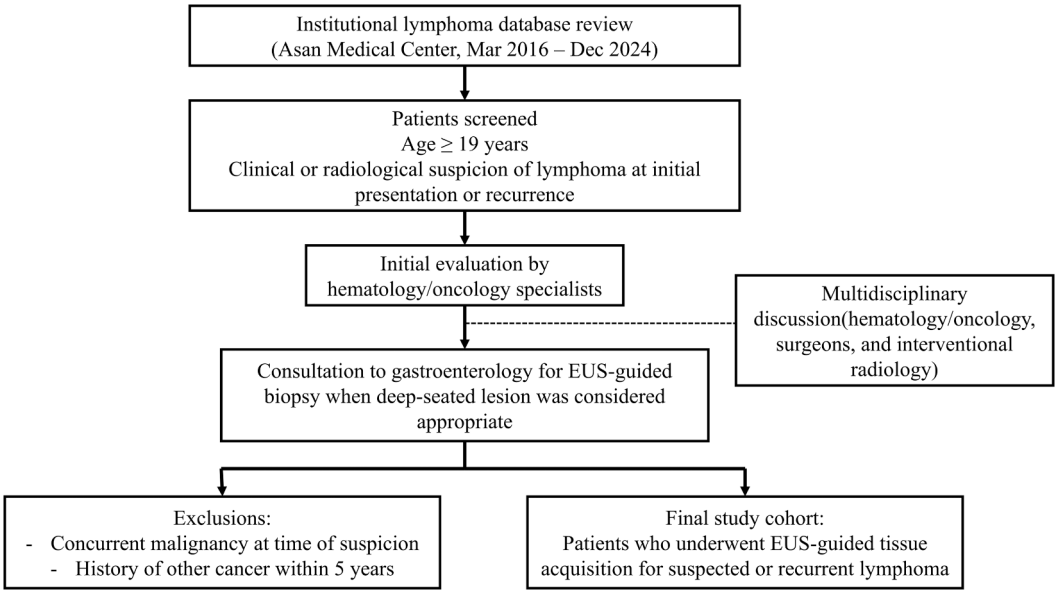
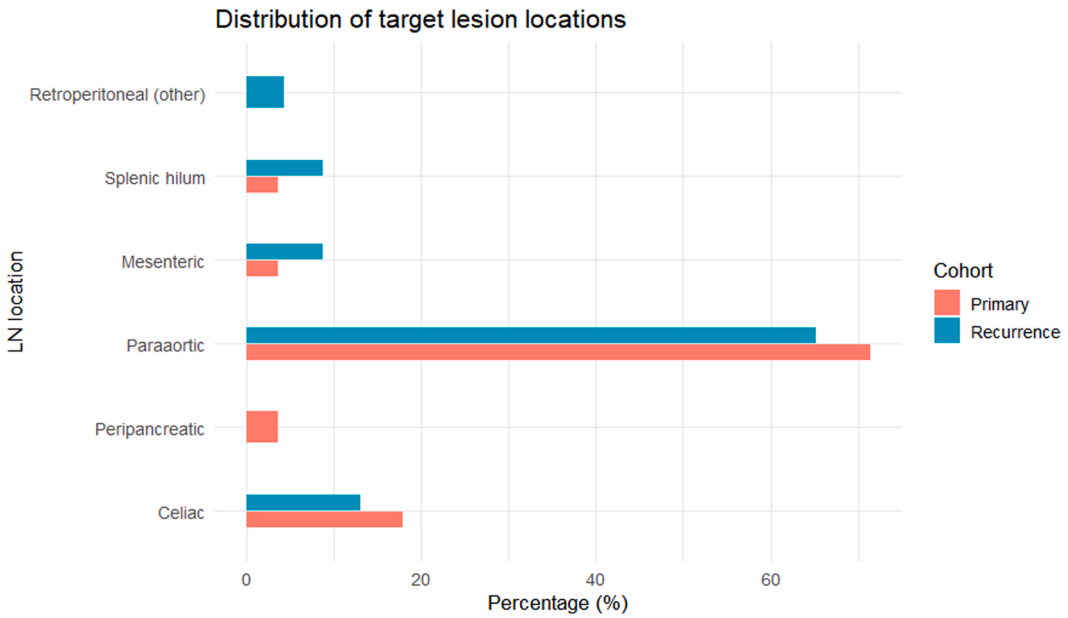
0016-5107
https://doi.org/10.1016/j.gie.2025.11.034
Received September 7, 2025. Accepted November 21, 2025.



Supplementary Figure 1. Study flow diagram. Flowchart of the patient selection process. From the institutional lymphoma database at Asan Medical Center (March 2016-December 2024), patients aged 19 years or older with clinical or radiological suspicion of lymphoma at initial presentation or recurrence were identified. All patients were initially evaluated by hematology/oncology specialists, and those with deep-seated lesions requiring tissue acquisition were referred to the gastroenterology service for EUS-guided biopsy. Patients with concurrent malignancy at the time of lymphoma suspicion or a history of another cancer within the preceding 5 years were excluded, yielding the final study cohort.



Supplementary Figure 2. Anatomical distribution of target lymph node lesions for EUS-guided biopsy in primary and recurrent lymphoma cohorts.

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SUPPLEMENTARY TABLE 1. Index diagnostic method at first presentation among the recurrence cohort

Diagnostic modality	*N* (%)
Excisional biopsy	25 (61.0)
Core needle biopsy	8 (19.5)
Endoscopic forceps biopsy	6 (14.6)
Bone marrow biopsy	2 (4.9)

SUPPLEMENTARY TABLE 2. Final histology and diagnostic modality

Histology subtype	Diagnostic modality	*N* (%)
1. Primary diagnosis cohort		
Angioimmunoblastic T-cell lymphoma	Excisional biopsy	1 (100.0)
Burkitt lymphoma	EUS-guided biopsy	2 (100.0)
Chronic lymphocytic leukemia/small lymphocytic lymphoma	EUS-guided biopsy	1 (100.0)
DLBCL	Core needle biopsy	1 (4.0)
	EUS-guided biopsy	20 (80.0)
	Excisional biopsy	4 (16.0)
Follicular lymphoma	EUS-guided biopsy	11 (91.7)
	Excisional biopsy	1 (8.3)
Mucosa-associated lymphoid tissue lymphoma	EUS-guided biopsy	3 (100.0)
Marginal zone lymphoma	EUS-guided biopsy	1 (100.0)
Peripheral T-cell lymphoma	Excisional biopsy	1 (100.0)
2. Suspected recurrence cohort		
Angioimmunoblastic T-cell lymphoma	EUS-guided biopsy	2 (100.0)
Benign	EUS-guided biopsy	10 (90.9)
	Excisional biopsy	1 (9.1)
DLBCL	Core needle biopsy	1 (6.2)
	EUS-guided biopsy	15 (93.8)
Follicular lymphoma	Clinical diagnosis (no tissue)	2 (33.3)
	EUS-guided biopsy	3 (50.0)
	Excisional biopsy	1 (16.7)
Monomorphic epitheliotropic intestinal T-cell lymphoma	EUS-guided biopsy	1 (100.0)
Mantle cell lymphoma	EUS-guided biopsy	3 (100.0)
Extranodal NK/T-cell lymphoma, nasal type	Excisional biopsy	1 (100.0)
Classical Hodgkin lymphoma	EUS-guided biopsy	1 (100.0)

Benign cases were defined as lymph node lesions with histologic findings such as reactive lymphoid hyperplasia, foam cell infiltration without evidence of malignancy, Kikuchi disease, or abscess, and confirmed by the absence of lymphoma recurrence during at least 12 months of clinical–radiological follow-up.
DLBCL, Diffuse large B-cell lymphoma; *NK*, natural killer.

SUPPLEMENTARY TABLE 3. Subsequent diagnostic or therapeutic pathways in nondiagnostic cases

Cohort	Subsequent procedure/management	Final outcome
Primary ($n = 6$)	Laparoscopic excisional biopsy	DLBCL
	Percutaneous liver biopsy	DLBCL
	Right neck excisional biopsy	MZL
	Left neck excisional biopsy	DLBCL
	Laparoscopic excisional biopsy	DLBCL
	Laparoscopic excisional biopsy	PTCL
Recurrence ($n = 5$)	Clinical diagnosis (inoperable) → RTx	Treated as a recurrence
	Laparoscopic excisional biopsy	Follicular lymphoma (grade 1-2/3)
	Laparoscopic excisional biopsy	NK/TCL
	Clinical diagnosis (inoperable) → RTx	Treated as a recurrence
	US-guided core neck LN biopsy	DLBCL

DLBCL, Diffuse large B-cell lymphoma; *LN*, lymph node; *MZL*, marginal zone lymphoma; *NK/TCL*, natural killer/T-cell lymphoma; *PTCL*, peripheral T-cell lymphoma; *RTx*, radiotherapy.

SUPPLEMENTARY TABLE 4. Diagnostic accuracy of EUS-TA for lymphoma

	Sensitivity	Specificity	PPV	NPV
Recurrence	96.2%	100.0%	100.0%	90.9%

Diagnostic accuracy was calculated on the basis of the final clinical or pathologic diagnosis.
Nondiagnostic cases were excluded from the analysis.
Sensitivity, specificity, PPV, and NPV were calculated using the Wilson method.
EUS-TA, EUS-guided tissue acquisition; *NPV*, negative predictive value; *PPV*, positive predictive value.