ORIGINAL ARTICLE

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for the Evaluation of Suspected Lymphoma

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Background: Evidence regarding the utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the assessment of isolated mediastinal lymphadenopathy (IMLN) is evolving. Its diagnostic accuracy in the evaluation of suspected lymphoma remains uncertain.

Methods: We reviewed a prospectively recorded database of consecutive patients with suspected lymphoma who underwent EBUS-TBNA to evaluate IMLN. Patients in whom EBUS-TBNA was nondiagnostic subsequently underwent surgical biopsy or a minimum of 6 months radiologic surveillance.

Results: Ninety-eight patients underwent EBUS-TBNA for evaluation of IMLN. Clinicoradiologic features suggested sarcoidosis as the likely diagnosis in 43 patients. In the remaining 55 patients, EBUS-TBNA achieved definitive diagnosis in 42 patients (76%; 95% confidence interval [CI] 55–90). Lymphoma was ultimately diagnosed in 21 of 55 patients (38%). EBUS-TBNA demonstrated lymphoma in 16 (76%) patients; however, four patients required further surgical biopsy to completely characterize lymphoma subtypes. Surgical biopsy was required to diagnose specific lymphoma subtypes not readily amenable to diagnosis with low volume specimens. Sensitivity and specificity for definitive diagnosis of lymphoma were 57% (95% CI 37–76) and 100% (95% CI 91–100), respectively.

Conclusions: Although the diagnostic accuracy of EBUS-TBNA for lymphoma is lower than that for the lung cancer staging, the procedure is an appropriate investigative technique for the patients with IMLN because of the low incidence of lymphoma in this population, and the significant proportion of such patients (76%) in whom surgical biopsy is obviated.

Key Words: Bronchoscopy, Cytology, Lymphadenopathy, Lymphoma, Small volume specimens.

(*J Thorac Oncol.* 2010;5: 804–809)

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was first developed to allow minimally invasive mediastinal staging of patients with non-small cell lung cancer (NSCLC), and there is now extensive literature confirming both the diagnostic accuracy and the safety of the procedure for this indication.[1,2] Diagnostic sensitivity in mediastinal staging of NSCLC is at least equivalent to mediastinoscopy and significantly higher for certain lymph node (LN) stations.[3] Meta-analyses estimate the diagnostic sensitivity to be 0.92.[1,2] In addition, the morbidity and mortality of EBUS-TBNA (0.15% and 0%, respectively) compares favorably with mediastinoscopy (2–5% and 0.2%, respectively).[4–6]

Evidence regarding the utility of EBUS-TBNA in the assessment of mediastinal lymphadenopathy in other conditions is evolving. Several authors have described the high diagnostic yield of EBUS-TBNA in sarcoidosis,[7–10] and small case series indicate that EBUS-TBNA is also useful in the evaluation of suspected tuberculosis.[11,12] To date, there is only a single retrospective study examining the performance of EBUS-TBNA in the diagnosis of lymphoma.[13]

There is considerable controversy regarding the role of small volume diagnostic specimens in lymphoma, with studies suggesting a high rate of discordance between cytologic and histologic specimens in patients.[14] As treatment regimens for both Hodgkin and non-Hodgkin lymphoma (NHL) generally dependent on the specific subtype and histologic grade, many centers are reluctant to rely on small volume diagnostic specimens. The ability of the 22-gauge EBUS-TBNA needle currently in use to provide accurate diagnostic information has yet to be determined. In a recent meta-analysis, it was concluded that there was insufficient evidence to recommend EBUS-TBNA for the evaluation of suspected lymphoma and that further studies investigating the performance of this technique for the evaluation of lymphoma are required.[2]

In our centers, we have performed EBUS-TBNA for initial evaluation of mediastinal lymphadenopathy when lymphoma is a suspected diagnosis given the potential benefit of establishing this diagnosis using a minimally invasive technique. This is weighed against the possibility that a second invasive surgical procedure may be required to definitively establish the diagnosis. In this report, we present our experience of EBUS-TBNA for the diagnosis of lymphoma.

METHODS

Patients

From the time of inception of EBUS-TBNA at our two tertiary referral centers, we have prospectively recorded demographic and detailed clinical information for all completed procedures. Clinical data include principal indication for performance of EBUS-TBNA, any previous history of carcinoma or lymphoma, pattern of lymphadenopathy, suspected preprocedure diagnosis, and final pathologic diagnosis. We have previously noted that the patients with isolated (i.e., in the absence of a parenchymal lung lesion) mediastinal lymphadenopathy (IMLN) or hilar lymphadenopathy undergoing EBUS-TBNA may be separated into two groups[15]—patients with typical clinicoradiologic features of sarcoidosis[16] and patients in whom sarcoidosis is unlikely to be the cause of IMLN. Lymphoma is extremely rare in the first group[4]; however, it should be suspected as a possible cause of lymphadenopathy in the latter group.

We aimed to determine the diagnostic sensitivity and specificity of EBUS-TBNA in the evaluation of suspected lymphoma in the patients with IMLN. Therefore, we performed a retrospective review of our prospectively recorded database to identify all patients undergoing EBUS-TBNA for evaluation of IMLN. Those with typical clinicoradiologic features of sarcoidosis were excluded from the study.

Performance of EBUS-TBNA

EBUS-TBNA was performed by consultant respiratory physicians experienced in performance of EBUS-TBNA (D.P.S. and M.C.). A dedicated linear array bronchoscope (BF-UC180F-OL8, Olympus, Tokyo, Japan) was used to visualize pathologic LNs, as directed by CT chest findings, before performance of EBUS-TBNA using a 22-gauge needle (NA-201SX-4022, Olympus, Tokyo, Japan). A minimum of three needle passes were performed with initial material transferred to the slides for rapid on-site cytologic evaluation and subsequent material placed in formalin solution to allow the preparation of a cell block for histologic evaluation and immunocytochemical analysis. Immunohistochemical analyses were performed at the discretion of the reporting pathologist.

A diagnosis was considered a true positive diagnosis if the reviewing pathologist was able to make a definitive diagnosis on the basis of the specimen obtained at EBUS-TBNA and the treating clinician felt no further LN specimen was required before commencement of therapy. A true negative diagnosis was represented by any of EBUS-TBNA specimen negative for lymphoma with an alternate definitive diagnosis established, or subsequent surgical biopsy confirming the absence of lymphoma, or either stability or regression of lymphadenopathy during follow-up of a minimum 6 months duration.

Statistical Methods

Summary statistics were used to report the performance characteristics of EBUS-TBNA. Sensitivity and specificity were calculated for performance of this technique for the diagnosis of lymphoma. Statistical analysis was performed using GraphPad Instat 3 for Macintosh (GraphPad Software,

TABLE 1. Results Demonstrated by EBUS-TBNA

Lymphoma	16
Diffuse large B-cell lymphoma	5
Hodgkin lymphoma (classic)	2
Small lymphocytic lymphoma	2
B-cell lymphoma NOS	2
Large cell lymphoma	1
T-cell lymphoma	1
Lymphoma NOS	1
Anaplastic large cell lymphoma	1
Lymphomatous cells, suggestive of HL	1
Metastatic carcinoma	6
Breast carcinoma	3
Renal cell carcinoma	2
Melanoma	1
NSCLC	5
Small cell lung cancer	3
Metastatic sarcoma	3
Osteosarcoma	2
Ewings sarcoma	1
Amyloid tumour	1
Normal lymphoid tissue	8
Sarcoidal granulomas	3
Mycobacterium tuberculosis	2
Bronchogenic cyst	1
Inadequate specimen	7

NOS, not otherwise specified; NSCLC, non-small cell lung carcinoma; HL, Hodgkin lymphoma; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

La Jolla, CA). Institutional review board approval was granted for the performance of this study.

RESULTS

Between October 1, 2008 and September 30, 2009, 55 patients underwent EBUS-TBNA for the evaluation of IMLN. Eight patients had a previous history of carcinoma or sarcoma, and eight patients had a previous history of lymphoma. During this period, surgical biopsies to evaluate IMLN were performed only if EBUS-TBNA was not diagnostic. No complications from the procedure were noted among our cohort.

Overall, 48 of 55 (87%) procedures yielded adequate tissue for cytopathologic evaluation, and definitive diagnosis was achieved for 42 (76%). Diagnoses resulting from EBUS-TBNA are recorded in Table 1. Overall, lymphoma was found to be the cause of IMLN in 21 patients (38%). Only two of these patients had a previous history of lymphoma. EBUS-TBNA provided tissue enabling demonstration of lymphoma in 16 patients (76%), and 12 of these patients required no further LN tissue to guide management (Figure 1*A*). Three patients in whom EBUS-TBNA demonstrated lymphoma required further surgical biopsy to subtype their disease sufficiently to guide subsequent treatment (Figure 1*B*), and one patient underwent confirmatory biopsy to enable subclassification of Hodgkin lymphoma (HL). A further four patients with nondiagnostic EBUS-TBNA required a surgical
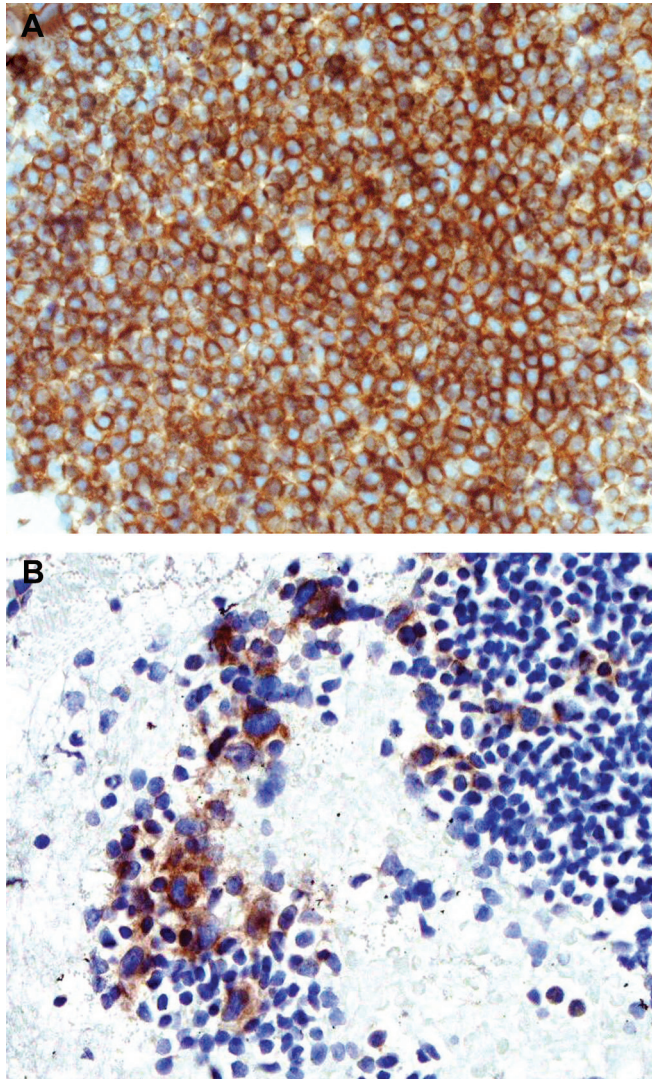
FIGURE 1. *A*, EBUS-TBNA specimen demonstrating a uniform population of small lymphocytes. Immunohistochemical staining was positive for CD 20 (pictured), CD 5, and CD23 confirming small lymphocytic lymphoma. *B*, EBUS-TBNA specimen demonstrating malignant cells in a background of lymphoid cells. Immunohistochemistry showed positive staining with CD 30 (pictured) and negative staining for epithelial markers. EBUS-TBNA specimens suggested anaplastic large cell lymphoma. Surgical biopsy confirmed the presence of anaplastic large cell lymphoma. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

FIGURE 2. Flow diagram illustrating the method by which diagnosis was achieved in all patients ultimately diagnosed with lymphoma. Final diagnoses are grouped according to the utility of EBUS-TBNA for each patient. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; IMLN, isolated mediastinal lymphadenopathy; HL, Hodgkin lymphoma; LN, lymph node.

procedure to diagnose lymphoma, and one patient, with a previous history of lymphoma, refused further surgical biopsies after a nondiagnostic EBUS-TBNA and has been assumed to have had a false negative biopsy for the purpose of this analysis. Figure 2 records all patients with lymphoma according to whether EBUS-TBNA was able to demonstrate a definitive diagnosis.

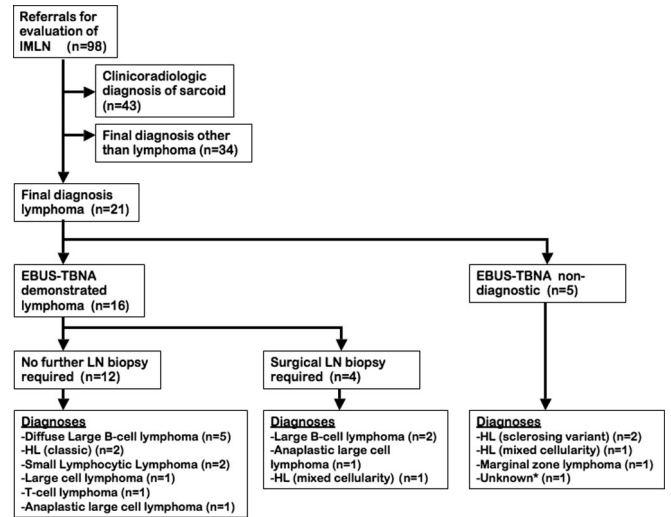Of the patients in whom EBUS-TBNA failed to obtain adequate tissue for cytopathologic evaluation, three were diagnosed with lymphoma after surgical biopsy. A further two patients underwent surgical biopsy to demonstrate benign causes for IMLN, and two patients remain well during ongoing clinical and radiologic follow-up. Lymphoma was the final diagnosis in two of eight patients in whom EBUS-TBNA demonstrated normal lymphocytes. The remaining six patients have undergone clinical and radiologic follow-up for a minimum of 6 months, and no alternate diagnoses has been made for these patients.

The diagnostic sensitivity for detection of lymphoma by EBUS-TBNA was 76% (95% confidence interval [CI] 55–90). However, in four patients in whom EBUS-TBNA indicated a diagnosis of lymphoma, further surgical biopsy was required to definitively confirm the diagnosis, and thus, we believe the diagnostic sensitivity is more accurately reported as 57% (95% CI 37–76). Specificity and negative predictive value (NPV) for the detection of lymphoma were 100% (95% CI 91–100) and 87% (95% CI 72–95), respectively.

DISCUSSION

Our findings demonstrate that EBUS-TBNA is a safe method for the evaluation of suspected lymphoma. Although lymphoma was the cause of IMLN in only 38% of patients, definitive diagnosis was achieved by EBUS-TBNA in 76% of all patients with IMLN, allowing all these patients to avoid invasive surgical biopsy, and the attendant risks. Sensitivity of EBUS-TBNA for the detection of lymphoma was 76%, and the sensitivity for the definitive diagnosis of lymphoma was 57%. Although sensitivity is reduced, compared with sensitivity of EBUS-TBNA for the detection of NSCLC metastases,[1,2] we still noted a NPV of 87%.

Patients with lymphoma in whom definitive diagnosis was not demonstrated by EBUS-TBNA seemed to have particular disease subtypes that may explain the difficulties in achieving this. Our findings reflect those of a previous study demonstrating that specific subtypes of lymphoma, such as small lymphocytic lymphoma, are relatively readily diagnosed on low-volume tissue specimens, whereas others, such as marginal zone and follicular lymphomas, are difficult to definitively diagnose on low volume specimens.[17] Patients in our study required subsequent surgical procedures to diagnose hypocellular variants of HL, marginal zone lymphoma, or to fully classify demonstrated B-cell NHL.

The diagnosis of lymphoma requires the evaluation of individual cell morphology (cytology), immunophenotype, and the overall architecture of the malignant tissue (histology).[18] Samples may also be sent for molecular analysis (to identify certain oncogenes) and immunophenotyping (to characterize the malignant lymphocyte, determine the presence of a malignant clone and subclassify NHL). Management of NHL may range from observation alone (small lymphocytic lymphoma and some follicular lymphoma) to conventional chemotherapy (for example, follicular or marginal zone lymphoma) or even autologous stem-cell transplantation (mantle cell lymphoma). Thus, obtaining sufficient tissue to facilitate an accurate diagnosis of a B-cell lymphoma subtype is of great importance to the patient and clinician.

Diagnosis of HL by cytologic specimens poses unique challenges to the pathologist, as cytologic samples are often hypocellular (especially in nodular sclerosising disease). There is often a marked paucity of Reed-Sternberg cells in needle aspirates, and the variants are often present in a background of reactive cells. False negative results may arise if only reactive cells are aspirated by TBNA.[19] Finally, evaluation of the overall background architecture is important in the diagnosis of HL.[20,21] The recently developed 21-gauge EBUS-TBNA may overcome these limitations to the use of EBUS-TBNA in the diagnosis of HL, and this should be the subject of future studies.

There are recognized situations when EBUS-TBNA may be preferred, because the risks of surgical mediastinoscopy are greater than in published series, for example, superior vena caval obstruction or mediastinal collateral vessel formation (Figure 3). Another potential application of EBUS-TBNA is in the assessment of patients with relapsed lymphoma. It is recognized that repeat mediastinoscopy or mediastinoscopy after mediastinal radiotherapy is associated with reduced sensitivity and increased rate of major complications.[22–24] In this situation, EBUS-TBNA offers a safer and effective alternative to the more invasive mediastinoscopy.

Previous studies have emphasized that low-volume tissue samples may avoid the need for surgical diagnosis in lymphoma.[25–27] Our results suggest the use of EBUS-TBNA inpatients with undifferentiated lymphadenopathy when lymphoma is a suspected diagnosis is reasonable, despite the necessity to proceed to a surgical diagnosis in a proportion of patients. It is likely that EBUS-TBNA may avoid both the morbidity and the financial costs associated with more invasive surgical procedures although it should be undertaken
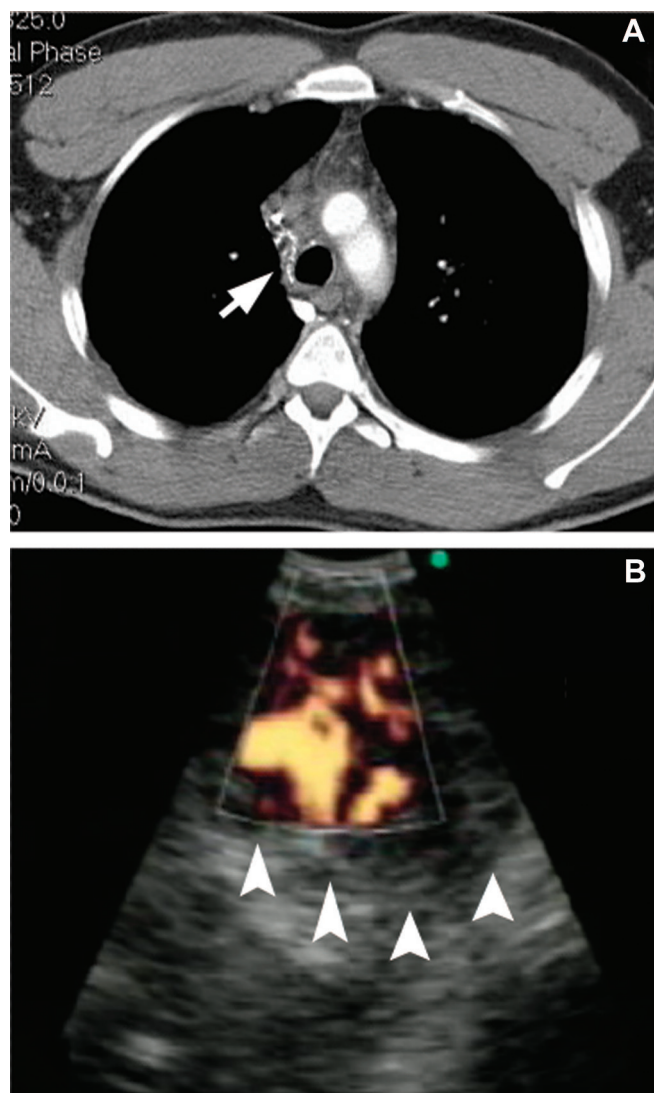

FIGURE 3. *A*, Axial contrast-enhanced computed tomography chest image from patient with clinical superior vena cava (SVC) obstruction demonstrating prominent right paratracheal lymphadenopathy causing significant narrowing of the SVC. Large collateral vessels in the right paratracheal region may be seen posterior to the narrowed SVC (*arrow*). *B*, Endobronchial ultrasound image of right paratracheal region of patient in (*A*). Doppler mode demonstrates large vessels within a poorly defined lymph node mass (*arrowheads*).

with the patient's understanding that further morphologic characterization of their disease by invasive surgical biopsy may be required.

It is not possible to determine a priori if patients will have a neoplasm not amenable to diagnosis by EBUS-TBNA and whether a surgical biopsy will, therefore, ultimately be required. Our experience indicates that EBUS-TBNA may obviate surgical biopsy in a larger majority of patients with suspected lymphoma, on the basis of IMLN (76%), as only a minority of such patients will ultimately be demonstrated to have lymphoma (38%).

The only other published analysis of the performance of EBUS-TBNA, by Kennedy et al.,[13] reported a diagnostic sensitivity of 90.0% in the evaluation of lymphoma, significantly higher than our observed sensitivity. On closer examination, however, two patients in their cohort required surgical biopsy to subclassify their lymphoma. We believe that the goal of EBUS-TBNA in these patients is to obviate invasive surgical biopsy, and if mediastinoscopy is required to provide further pathologic information to guide definitive therapy, then this goal has not been achieved. Based on the criteria applied to our series, the diagnostic sensitivity of EBUS-TBNA in the study by Kennedy et al. would be 72.7% (8 of 11 patients), more comparable to our experience. The cohort described by Kennedy et al. comprised patients predominantly with either HL or small lymphocytic lymphoma, two subtypes more easily diagnosed on low-volume specimens,[13] which provides another possible explanation for the higher observed sensitivity in their report. Consistent with this observation, four patients among our cohort in whom EBUS-TBNA was not diagnostic had hypocellular subtypes of lymphoma (sclerosing HL and marginal zone lymphoma), and three required surgical biopsy to demonstrate tumor architecture after demonstration of B-cell lymphomas by EBUS-TBNA.

In addition, over half of the cohort described by Kennedy et al. had a previous history of lymphoma. In contrast, just two patients diagnosed with lymphoma in our cohort had a previous disease history. The need for specific subtyping may not be as important in patients with a past history of lymphoma, because demonstration of a malignant clone of lymphocytes may be adequate to guide management in these patients. Finally, unlike Kennedy et al., we have excluded patients with probable sarcoidosis from our analysis. The rates of alternate diagnoses to sarcoidosis (such as lymphoma) in those with typical clinicoradiologic features have been reported as <0.05%[4]; therefore, it seems appropriate to remove such patients from calculations when assessing the diagnostic accuracy of EBUS-TBNA in the evaluation of suspected lymphoma. Exclusion of sarcoid cases from the cohort reported by Kennedy et al. leaves a NPV of 83%, rather than the reported 92.9%.

Strengths and Limitations

Our series is the largest report describing the use of EBUS-TBNA in the evaluation of suspected lymphoma. Our cohort consists of a wide variety of lymphoma subtypes and excludes patients with likely sarcoidosis, which provides a more accurate representation of NPV of the procedure.

We did not routinely use flow cytometry in the evaluation of specimens; however, immunocytochemistry was performed as required on diagnostic specimens, enabling the identification of the diagnostic immunophenotype. Nevertheless, we were able to establish a definitive diagnosis in at least 57% of patients with lymphoma using immunocytochemistry and morphology alone. False negative results for flow cytometry are highest for B-cell lymphomas,[28] and the exact group in whom morphologic or architectural interpretation requirements makes EBUS-TBNA of potentially limited utility. Fortunately, low-volume specimens may be more amenable

for other studies, such as fluorescent in situ hybridization for the detection of cytogenetic rearrangements.[29]

Finally, the role of an experienced pathologist with an interest in hematopathology and expertise in cytologic evaluation of these specimens cannot be underestimated. We believe that the utility of EBUS-TBNA depends strongly on the ability of the reviewing pathologist to interpret small volume specimens. Institutions without such expertise should not expect to be able to replicate our findings or those of Kennedy et al. Conversely, diagnostic sensitivity may improve further in future as pathologists gain greater experience in interpreting specimens obtained by EBUS-TBNA.

CONCLUSION

In conclusion, our findings indicate that EBUS-TBNA is a safe and effective procedure for the assessment of patients with mediastinal lymphadenopathy because of suspected lymphoma. The diagnostic sensitivity for the evaluation of lymphoma is lower than that for lung cancer staging, largely because of the difficulties of confirming the diagnosis of lymphoma on a small volume specimen in some disease subtypes, such as marginal zone lymphomas, or hypocellular variants of Hodgkin disease. EBUS-TBNA may still be considered as the initial investigative technique of suspected lymphoma as it may obviate the need for more invasive surgical biopsy in the majority of such patients.

ACKNOWLEDGMENTS

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