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Diagnostic performance of 19-gauge endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in suspected lymphoma: a prospective cohort study

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20 **Abstract**

21 **Introduction**

22 Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) represents a minimally-
23 invasive approach in the evaluation of mediastinal/hilar lymphadenopathy. Diagnostic performance of EBUS-
24 TBNA in lymphoma using standard 22-gauge (22G) needle is limited by sample volumes that are often
25 inadequate for histopathological assessment.

26 **Objectives**

27 To evaluate the diagnostic utility of 19-gauge (19G) EBUS-TBNA needle in the evaluation of suspected
28 lymphoma.

29 **Methods**

30 We prospectively collected clinical and procedural information for patients undergoing EBUS-TBNA with 19G
31 needle at Royal Melbourne Hospital for investigation of mediastinal/hilar lymphadenopathy, where lymphoma
32 was considered in the differential diagnosis. All consecutive patients between June 15, 2016 and July 10, 2019
33 were included. If definitive diagnosis was not achieved on EBUS-TBNA, final diagnosis was determined
34 through subsequent investigation or a minimum of six months radiologic surveillance.

35 **Results**

36 Thirty-nine patients underwent EBUS-TBNA using 19G needle for evaluation of suspected lymphoma. Thirteen
37 patients had a prior diagnosis of lymphoma (33%). Lymphoma was ultimately diagnosed in 23 patients (59%).
38 Of these, ten had a prior diagnosis of lymphoma (43%). 19G EBUS-TBNA demonstrated lymphoma in 19
39 patients, with a sensitivity of 83% (95%CI 66-93) for detection of lymphoma. Four patients required surgical
40 biopsy to definitively characterise lymphoma subtype. Therefore, sensitivity of 19G EBUS-TBNA for definitive
41 diagnosis of lymphoma was 65% (95%CI 45-81). In patients with a prior diagnosis of lymphoma, sensitivity
42 for definitive diagnosis of lymphoma was 80% (95%CI 48-95).

43

44 **Conclusion**

45 Diagnostic performance of 19G EBUS-TBNA appears similar to standard 22G needle in detection and definitive
46 diagnosis of lymphoma. Further invasive testing remains necessary following non-diagnostic EBUS-TBNA
47 procedures.

48

49 **Abstract word count:** 248

50 **Keywords:** Lymphoproliferative disorders; Lymphoma; Bronchoscopy; EBUS-TBNA; Ultrasound

51

52 **Introduction**

53 Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) represents a minimally-
54 invasive approach in the evaluation of mediastinal and/or hilar lymphadenopathy. EBUS-TBNA is well-
55 established as an effective modality in lung cancer staging,^{1,2} demonstrating superior safety and diagnostic
56 performance to mediastinoscopy. Meta-analyses estimate its sensitivity to be 88-93%.³⁻⁵ Recent literature has
57 explored the diagnostic utility of EBUS-TBNA in other conditions, including lymphoma.

58 Previous studies utilising EBUS-TBNA have reported highly variable sensitivities of 32-90% in the diagnosis
59 of lymphoma,⁶⁻⁸ with a recent meta-analysis reporting a pooled sensitivity of 66%.⁹ The diagnostic performance
60 of EBUS-TBNA in suspected lymphoma is variable, due to the need for histologic specimens to classify certain
61 lymphoma subtypes. Owing to this variance between cytologic and histologic specimens,¹⁰ the utility of EBUS-
62 TBNA for definitive diagnosis of lymphoma remains uncertain.

63 19-gauge (19G) EBUS-TBNA needle has been shown to safely provide larger volumetric tissue samples than
64 standard 22G EBUS-TBNA needle.^{11,12} Despite this, there is paucity of data regarding the use and diagnostic
65 utility of 19G needle in lymphoma. We have utilised 19G needle for sampling in patients with suspected
66 lymphoma, hypothesising that the larger volumetric tissue samples procured by 19G needle will lead to
67 improved diagnostic performance. In this report, we present our experience of 19G EBUS-TBNA for the
68 evaluation of suspected lymphoma.

69 **Methods**

70 Institutional Review Board approval was granted for performance of this study (QA#2014087). We
71 prospectively collected demographic, clinical, and procedural information for patients undergoing 19G EBUS-
72 TBNA at Royal Melbourne Hospital for investigation of mediastinal/hilar lymphadenopathy, where lymphoma
73 was considered in the differential diagnosis. All consecutive patients between June 15, 2016 and July 10, 2019
74 were included in this cohort. Recorded data included principal indication for performance of EBUS-TBNA,
75 previous history of lymphoma, final pathologic diagnosis, further diagnostic procedures, and details of treatment

76 (if applicable). This study is presented in accordance with the CONSORT 2010 statement¹³ and STROBE
77 guidelines¹⁴.

78 **Performance of EBUS-TBNA**

79 EBUS-TBNA was performed by consultant respiratory physicians experienced in performance of EBUS-
80 TBNA. A dedicated convex array bronchoscope (BF-UC180F-OL8, Olympus, Tokyo, Japan) was used to
81 visualize pathologic lymph nodes (LNs), as directed by CT chest findings, before performance of EBUS-TBNA
82 using a 19-gauge needle (ViziShot 2 FLEX 19G, Olympus, Tokyo, Japan). A minimum of three needle passes
83 were performed with initial material transferred to the slides for rapid on-site cytologic evaluation (ROSE) and
84 subsequent material placed in formalin solution to allow the preparation of a cell block for histologic evaluation
85 and immunocytochemical analysis. The majority of tissue samples were sent for flow cytometry (59%).
86 Immunohistochemical analysis was performed at the discretion of the reporting pathologist.

87 A diagnosis was considered a true positive diagnosis if the reviewing pathologist was able to establish a
88 definitive diagnosis of lymphoma on the basis of the specimen obtained at EBUS-TBNA, and the treating
89 clinician felt no further specimen was required before commencement of therapy. A true negative diagnosis was
90 represented by an EBUS-TBNA specimen negative for lymphoma with an alternate definitive diagnosis
91 established, or subsequent surgical biopsy confirming the absence of lymphoma, or stability or regression of
92 lymphadenopathy during a minimum follow-up duration of six months. Flow cytometry was considered
93 abnormal if an abnormal lymphoid population was identified, or if results were suggestive of lymphoma
94 warranting further biopsy.

95 Summary statistics were used to report demographic and procedural data. Sensitivity and specificity were
96 calculated to evaluate performance of 19G EBUS-TBNA in the detection and definitive diagnosis of lymphoma.
97 Associated 95% confidence intervals were reported using the modified Wald method. The diagnostic
98 performance of 19G EBUS-TBNA in de novo and recurrent disease was compared using Fisher's exact test
99 (two-tailed) for categorical variables. Statistical analysis was performed using GraphPad QuickCalcs.¹⁵

100 **Results**

101 Between June 15, 2016 and July 10, 2019, 39 patients underwent EBUS-TBNA using 19G needle for evaluation
102 of suspected lymphoma. Cohort demographics and procedural details are provided in Table 1. Thirteen patients
103 had a prior diagnosis of lymphoma (33%) and had presented with suspected recurrent disease. No complications
104 from the procedure were noted amongst our cohort.

105 Final pathologic diagnoses are recorded in Table 2. A final pathologic diagnosis of lymphoma was made in 23
106 patients (59%). Of these, ten had a prior diagnosis of lymphoma (43%). EBUS-TBNA yielded tissue
107 demonstrating lymphoma in 19 patients. One patient required repeat EBUS-TBNA and four patients required
108 surgical biopsy to definitively characterise lymphoma subtype for management purposes (Figure 1). A further
109 four patients with non-diagnostic EBUS-TBNA underwent surgical biopsy to establish a diagnosis of
110 lymphoma. One patient with non-diagnostic EBUS-TBNA was diagnosed with recurrent T-cell lymphoma
111 based on subsequent imaging studies, and was considered a false negative result for the purpose of this study.
112 One patient with non-diagnostic EBUS-TBNA underwent surgical biopsy which confirmed a diagnosis of
113 sarcoidosis. Two patients diagnosed with reactive lymphadenopathy underwent clinical and radiological follow-
114 up for a minimum of six months, with no alternate diagnoses made in these patients.

115 Sensitivity and specificity for detection of lymphoma using 19G EBUS-TBNA were 83% (95% CI 66-93) and
116 100% (95% CI 77-100) respectively. Sensitivity for definitive diagnosis of lymphoma using 19G needle was
117 65% (95% CI 45-81). In patients with a prior diagnosis of lymphoma, sensitivity for definitive diagnosis of
118 lymphoma was 80% (95% CI 48-95). Rates of definitive diagnosis in de novo and recurrent disease were not
119 significantly different ($p=0.197$). Overall, the negative predictive value (NPV) for detection of lymphoma was
120 80% (95% CI 58-93). The NPV for detection of lymphoma was 87% (95% CI 61-98) in de novo diagnosis and
121 60% (95% CI 23-88) in patients with a prior history of lymphoma.

122 EBUS-TBNA samples were sent for flow cytometry in 23 patients (59%). Of these, 14 (61%) had a final
123 diagnosis of lymphoma. Among these patients, abnormal flow cytometry was detected in eight samples (57%),
124 including two cases where lymphoma was not otherwise demonstrated on cytology. Flow cytometry results for

patients with a final diagnosis of lymphoma are recorded in Table 3. Excluding cases of Hodgkin's lymphoma, which classically demonstrates normal flow cytometry,^{10,16} sensitivity and specificity of abnormal flow cytometry for detection of lymphoma was 78% (95% CI 44-95) and 100% (95% CI 66-100) respectively. The positive predictive value (PPV) of abnormal flow cytometry for lymphoma was 100% (95% CI 63-100).

Discussion

Recent meta-analysis of 21G/22G EBUS-TBNA identified a pooled sensitivity and specificity of 66% and 99% for definitive diagnosis of lymphoma.⁹ This is largely due to difficulties in diagnosing particular lymphoma subtypes on cytologic specimens. Given the larger tissue yields obtained by 19G TBNA needle, we hypothesised that their use would improve diagnostic performance. Our experience demonstrates that the diagnostic performance of 19G EBUS-TBNA for diagnosis of lymphoma is not different to previously published reports utilising smaller needle sizes.

Sensitivity and specificity of 19G EBUS-TBNA for the detection of lymphoma was 83% (95% CI 66-93) and 100% (95% CI 77-100) respectively. The sensitivity for definitive diagnosis of lymphoma was 65% (95% CI 45-81). In patients with a previous history of lymphoma, the sensitivity for definitive diagnosis of lymphoma was 80% (95% CI 48-95). The increased rate of definitive diagnosis in this subpopulation likely reflects a reduced diagnostic threshold for recurrent disease, although we note that the rates of definitive diagnosis in de novo and recurrent disease were not significantly different.

Use of flow cytometry is associated with improved sensitivity of EBUS-TBNA in the diagnosis of lymphoma.⁹ Within our cohort, abnormal flow cytometry demonstrated a sensitivity of 78% (95% CI 44-95) for the detection of non-Hodgkin lymphoma. Abnormal flow cytometry is strongly predictive for lymphoma, and should reinforce the need for further biopsy when cytology is non-diagnostic. Increasing use of fluorescence in-situ hybridisation (FISH) and polymerase chain reaction (PCR) in the diagnosis, classification and prognostication of lymphoma may serve to further increase the utility of EBUS-TBNA in future.^{17,18}

Definitive diagnosis of specific lymphoma subtypes using EBUS-TBNA remains challenging despite the use of 19G needle and flow cytometry. These include hypocellular variants of Hodgkin's lymphoma such as nodular

sclerosing disease. Needle aspirates of such subtypes often yield few Reed-Sternberg cells against a background of reactive cells: false-negative results may occur if only reactive cells are aspirated. All patients with nodular sclerosing variants required surgical biopsy to establish a definitive diagnosis, representing a significant proportion (38%) of patients requiring further surgical biopsy. A previous study detailing our experience with 22G needle in the evaluation of lymphoma similarly noted that surgical biopsy was required to establish a diagnosis of lymphoma in such patients.⁸

Our findings reinforce the utility of EBUS-TBNA as a safe, effective, minimally-invasive modality for assessment of suspected lymphoma. Nearly two-thirds of patients with lymphoma achieved definitive diagnosis without invasive surgical biopsy. The morbidity and mortality of mediastinoscopy (2.5% and 0.2%, respectively)^{19,20} is greater than that of EBUS-TBNA (1.2%, 0.01%),²¹ and includes a number of rare but catastrophic complications, including vocal cord palsy and injury to major mediastinal vessels.²² Furthermore, previous cost-benefit analyses have estimated that initial use of EBUS-TBNA in NSCLC diagnosis results in cost savings of \$5700 per patient compared with mediastinoscopy alone, primarily through reduced staffing and equipment costs.²³ Surgical risks are further increased in patients who have previously undergone mediastinoscopy or mediastinal radiotherapy.^{24,25} By reducing the need for invasive surgical biopsy in the evaluation of suspected lymphoma, initial assessment with EBUS-TBNA obviates the significant harm and financial cost associated with such procedures.

Strengths and limitations

There is paucity of data regarding the use of 19G needle in suspected lymphoma. This study represents the largest documented series of 19G EBUS-TBNA in the evaluation of lymphoma. Our cohort consists of a wide range of lymphoma subtypes across 23 patients, in comparison to previous 19G studies containing four or fewer patients with lymphoma.^{12,26-29} However, this series is limited by its nature as a single-centre study. The ability of our centre to facilitate ROSE of small-volume specimens by experienced pathologists mean that our results may not be generalisable to other institutions. Furthermore, a sizeable proportion of patients with a final diagnosis of lymphoma had a prior history of lymphoma (43%). As the sensitivity of EBUS-TBNA is higher in

diagnosing recurrent lymphoma compared to de novo diagnosis,^{30,31} this may overestimate its overall diagnostic performance within our cohort.

Conclusion

Our findings confirm the utility of EBUS-TBNA for evaluation of mediastinal and/or hilar lymphadenopathy in patients with suspected lymphoma. The diagnostic performance of 19G EBUS-TBNA for detection and definitive diagnosis of lymphoma appears similar to that of 22G needle. Diagnosis of hypocellular variants on EBUS-TBNA remains challenging. Abnormal flow cytometry is strongly predictive for lymphoma, and demonstrated a sensitivity of 78% (95% CI 44-95) for detection of non-Hodgkin lymphoma. Further invasive testing remains necessary following non-diagnostic EBUS-TBNA procedures.

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	<i>Patients referred for evaluation of lymphoma (n=39)</i>
Age (years) (mean $\pm$ SD)	53.5 $\pm$ 19.8
Male sex – no. (%)	21 (54%)
Female sex – no. (%)	18 (46%)
Nodal stations sampled (%)	
2	3 (8%)
4	18 (46%)
7	18 (46%)
10/11	8 (21%)
12	1 (3%)
Lung mass	
Endobronchial lesion	3 (8%)
Paratracheal mass	3 (8%)
Hilar mass	2 (5%)
Left lower lobe	2 (5%)
Left upper lobe	1 (3%)
Lingula	1 (3%)
Mediastinal mass	1 (3%)
Right middle lobe	1 (3%)

<i>Final diagnosis</i>	<i>Number of patients referred for evaluation of lymphoma (N=39)</i>
Lymphoma	
Classical Hodgkin's lymphoma	6
Follicular lymphoma	4
B-cell lymphoma not otherwise specified	3
Nodular sclerosing classical Hodgkin's lymphoma	3
Diffuse large B-cell lymphoma	2
Large B-cell lymphoma	2
Peripheral T-cell lymphoma	2
Small B-cell lymphoma	1
Sarcoidosis	7
Non-small cell lung cancer	2
Reactive lymphoid tissue	2
Chronic necrotising inflammation	1
<i>Cryptococcus neoformans</i>	1
Mesothelioma	1
Renal cell carcinoma	1
Small cell carcinoma	1

272 **Table 3.** Flow cytometry results, listed according to lymphoma subtype.

Final diagnosis
Classical Hodgkin's lymphoma (N=3) <ul style="list-style-type: none">• No abnormal lymphoid population detected• No abnormal lymphoid population detected, slight T-helper cell predominance• No abnormal lymphoid population was detected
Follicular lymphoma (N=4) <ul style="list-style-type: none">• CD5-/CD10+ clonal B-cell population consistent with follicular lymphoma*• CD10+ clonal B-cell population identified, most suggestive of follicular lymphoma*• CD10+/CD19+ monoclonal B-cell population*• Abnormal T and B lymphoid populations identified*
B-cell lymphoma not otherwise specified (N=2) <ul style="list-style-type: none">• No abnormal lymphoid population detected• The lymphoid immunophenotype is not conclusive and demonstrates predominance of helper T cells and a small population of CD10+ B cells.
Nodular sclerosing classical Hodgkin's lymphoma (N=2) <ul style="list-style-type: none">• Small population of lymphocytes with CD5 co-expression along with possible light chain restriction*• No abnormal lymphoid population was detected
Diffuse large B-cell lymphoma (N=1) <ul style="list-style-type: none">• Features diagnostic of B-cell lymphoproliferative disorder and most typical of a CD5-/C10+ non-Hodgkin lymphoma*
Large B-cell lymphoma (N=1) <ul style="list-style-type: none">• Features diagnostic of a B-cell lymphoproliferative disorder and most typical of a CD5-negative B-cell non-Hodgkin lymphoma*
Peripheral T-cell lymphoma (N=1) <ul style="list-style-type: none">• Atypical antigenic expression patterns noted, including CD4+/CD8+(dim) and a large proportion (85%) of CD4+/CD26- cells suggestive of a T-cell lymphoproliferative disorder*

273 *Asterisks denote an abnormal flow cytometry result.

275 **Figure 1.** CONSORT flow diagram illustrating method of diagnosis for patients ultimately diagnosed with
276 lymphoma. Diagnoses grouped by utility of EBUS-TBNA for each patient. Asterisks denote a diagnosis of
277 recurrent lymphoma.

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