The utility of endobronchial ultrasound-guided transbronchial needle aspiration in a community with a high HIV and tuberculosis burden

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Background. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become the gold standard in diagnosing and performing nodal staging in patients with suspected lung cancer and diagnosing other malignant and benign diseases. Studies from countries with low tuberculosis (TB) incidence suggest that it has a sensitivity of 90 - 95% and a specificity of 100%.
Objectives. To investigate the utility of EBUS-TBNA in a community with a high HIV and TB burden.
Methods. We retrospectively reviewed all patients who underwent EBUS-TBNA to confirm a tissue diagnosis during a 2-year period from January 2017 - December 2018. Only patients with complete medical, pathology and radiology records and follow-up were included.
Results. During the 2 years, a total of 201 patients underwent EBUS-TBNA. Some patients (n=19) had incomplete notes or follow-up and 104 cases were ultimately diagnosed with benign nodal disease. In the 182 patients who were ultimately included in the present study, EBUS-TBNA had a sensitivity of 95.1% (95% confidence interval (CI) 88.6 - 98.2), specificity of 100% (95% CI 94.20 - 100), positive predictive value (PPV) of 100.00% (95% CI 95.3 - 100) and negative predictive value (NPV) of 94.1% (95% CI 86.0 - 97.8) for all diagnoses. The overall diagnostic accuracy was 97.3% (95% CI 93.9 - 99.2). Out of the 64 patients who had lung cancer, EBUS-TBNA had a sensitivity of 95.2% (95% CI 86.7 - 99.0), specificity of 100% (95% CI 5.5 - 100), PPV of 100.0% and NPV of 58.3% (95% CI 31.7 - 80.9). The overall diagnostic accuracy for lung cancer was 95.5% (95% CI 87.2 - 99.1%).
Conclusion. EBUS-TBNA has high diagnostic accuracy, even in a population with a high HIV and TB burden.
Keywords. lung cancer; endobronchial ultrasound; transbronchial needle aspiration.

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Many procedures have been used for the assessment of mediastinal and hilar lymphadenopathy in patients with suspected lung cancer and other pathologies.[1] Until recently, mediastinoscopy was regarded as the gold standard for cytological/histological diagnoses of mediastinal and hilar lymphadenopathy.[1] However, mediastinoscopy does not allow access to all lymph nodes and the morbidity associated with this invasive procedure is significant.[2-4]

Over the past few decades, more minimally invasive procedures for assessment of intrathoracic lymphadenopathy have been developed. One such procedure is endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), which incorporates ultrasound to guide tissue sampling and can be done in an outpatient setting. It has a sensitivity of 90 - 95% and specificity of 100%, with its accuracy rate reported to be 97.02% in a study by Ye *et al.*[2] This modality, in comparison with mediastinoscopy, has the added benefits of better accessibility to different lymph node stations, being less invasive, with less morbidity, and the possibility of repeating the procedure several times.[2,4] For these reasons, EBUS-TBNA has become an indispensable tool in the diagnosis and staging of lung cancer and the National Institute for Health and Care Excellence (NICE) has recommended its use as an initial investigation in patients with mediastinal lymphadenopathy.[5] Moreover, EBUS-TBNA is more frequently being used in the diagnosis of other pathologies including tuberculosis (TB).[3,6]

The utilisation of EBUS-TBNA to evaluate TB lymphadenitis has been reported to have a higher diagnostic accuracy and lower morbidity and mortality compared with conventional mediastinoscopy.[3]

Given its high diagnostic accuracy combined with its superior safety profile, EBUS-TBNA has been suggested by Madan *et al.*[7] as the procedure of choice for patients with TB. A recent study by Sanchez-Cabral *et al.*[8] established that the diagnostic yield of TB was particularly higher when combined with transbronchial biopsy and they suggested that EBUS-TBNA should be considered the first-line investigatory tool when evaluating HIV-positive patients with mediastinal lymphadenopathy.[7]

Our institution provides a tertiary service to the Western Cape Province of South Africa (SA), a community with one of the highest incidences of TB in the world as well as a high HIV prevalence.[8] We therefore aimed to investigate the utility of EBUS-TBNA in the diagnosis and staging of lung cancer, specifically in a population with a high HIV and TB burden.

Methods

This retrospective descriptive study was conducted at Tygerberg

Hospital, Cape Town, SA. Ethical approval was granted by the Stellenbosch University Research Ethics Committee (ref. no. HEA-2018-7911). Tygerberg Hospital is an academic tertiary public hospital with a 1 380-bed capacity serving ~3 million people, of whom 5.2% are currently HIV infected.[9] The local incidence of pulmonary TB was 1 000 per 100 000 in 2016.[10]

The respiratory unit at Tygerberg Hospital has a bronchoscopy theatre performing more than 30 EBUS-TBNA procedures monthly. The EBUS-TBNA service has been offered at this unit since 2012. This study included all patients who had undergone EBUS-TBNA from1 January 2017 - 31 December 2018.

Patient details were obtained from an existing theatre registry used for clinical governance purposes. All adult patients (>18 years old) who underwent EBUS-TBNA for diagnostic purposes with complete clinical, procedural details and follow-up were included in the study. Patients with incomplete medical records and who were lost to follow-up (to the point where no final diagnosis could be established) were excluded. For those with suspected lung cancer, only patients with complete follow-up, which included positron emission tomography – computed tomography (PET/CT) scanning, and where appropriate, mediastinoscopy and/or surgical resection were included to allow for the distinction between 'true negatives' and 'false negatives'.

Data that were collected included patients' demographic data, HIV status, procedure variables (indication for the procedure), the results of the rapid-on-site-evaluation (ROSE) of aspirates as well as the final cytology and microbiology results.

All descriptive numerical data with a normal distribution were described using means and standard deviation (SD), whereas non-normal data were described using median and interquartile ranges (IQR). Categorical data were described using frequency and percentages. Statistical analysis was performed using STATA, version 15 (StataCorp., USA) to calculate the indices of diagnostic accuracy.

Results

A total of 201 patients underwent EBUS-TBNA, of whom 19 were excluded due to incomplete records or follow-up. The remaining 182 patients (*n*=87 males and *n*=95 females) had a mean (SD) age of 57 (13) years and were included, of whom 10% (*n*=19) were HIV positive.

Less than half of the patients (43%; *n*=78) had malignancy, of whom the majority had lung cancer (82%; *n*=64). The majority had adenocarcinoma (Table 1). The final diagnoses were benign disease in 57% (*n*=104) of the patients. None of the patients with reactive lymphocytes was eventually diagnosed with lung cancer (Table 2).

Overall, EBUS-TBNA had a sensitivity of 95.1%, specificity of 100%, positive predictive value (PPV) of 100.00% and negative predictive value (NPV) of 94.1% (Table 3) The overall diagnostic accuracy was 97.3% (95% confidence interval (CI) 93.9 - 99.2). Out of the 64 patients who had lung cancer, EBUS-TBNA had a sensitivity of 95.2%, specificity of 100.0%, PPV of 100.0% and NPV of 58.3%. The overall diagnostic accuracy for lung cancer was 95.5%.

Discussion

In our present study population with a high burden of TB and HIV, we found that EBUS-TBNA had a very high specificity (100%) and sensitivity (95.2%) for lung cancer, with an overall diagnostic accuracy of 97%.

EBUS-TBNA is a minimally-invasive procedure that has been shown to have excellent accuracy in diagnosing malignancy in multiple international studies.[2-6,11] Our findings are similar to a study by Yasufuku *et al.*[13] where they showed a sensitivity, specificity and accuracy of EBUS-TBNA in diagnosing malignant conditions of 95.7%, 100% and 97.1%, respectively. A subsequent study by Yasufuku *et al.*[12] yielded similar findings, with a sensitivity, specificity, PPV and NPV of 94.6%, 100%, 100% and 89.5%, respectively. Comparable values were reported in a meta-analysis by Adams *et al.*,[4] with both a sensitivity and specificity of 95%.

EBUS-TBNA allows for rapid diagnosis and can potentially spare patients from procedures that carry higher expense and risk such as mediastinoscopy, CT-guided biopsy and conventional TBNA. The diagnostic sensitivity of cervical mediastinoscopy has been reported to be as low as 78 - 81% in two systematic reviews, showing that this modality that has traditionally been the 'gold standard' for diagnosing mediastinal lymphadenopathy, is in fact inferior to EBUS-TBNA in sensitivity and morbidity.[2]

Our present study results are also comparable to a large meta-analysis conducted by Chandra *et al.*[14] that assessed the diagnostic accuracy of EBUS-TBNA in over 1 500 patients from 8 different countries, mostly including studies conducted in the developed countries.[12] They found high diagnostic yield in patients with malignant and non-malignant conditions, with a specificity of 100% (95% CI 90 - 100) and sensitivity of 92% (95% CI 91 - 93).[14] The diagnostic accuracy was independent of ROSE and the needle size utilised.

In the only report to date from a tertiary institution in SA, it was observed that the diagnostic accuracy of EBUS-TBNA, regardless of the indication, was 68.7% (95% CI 57.7 - 75.7), had a PPV of

Table 1. Final diagnoses in patients with malignant nodal involvement (*n*=78)

Cancer type	*n*
Lung cancer	64
Non-small-cell lung cancer	
Adenocarcinoma	33
Squamous cell carcinoma	11
Large cell/poorly differentiated	9
Small-cell lung cancer	10
Other	
Carcinoid tumour	1
Pulmonary metastases	14
Breast	5
Lymphoma	4
Oesophageal cancer	2
ENT malignancies	3

ENT = ear, nose and throat.

Table 2. Final diagnoses in patients with benign nodal disease (*n*=104)

Reactive lymph nodes	78
Tuberculosis	14
Sarcoidosis	10
Unspecified granulomata	2

Table 3. Utility of endobronchial ultrasound-guided transbronchial needle aspiration for the diagnosis of all pathologies (*N*=182)

	All diagnoses (*N*=182), % (95% CI)	Lung cancer (*n*=64), % (95% CI)	All malignancies (*n*=78), % (95% CI)	Benign diseases (*n*=104), % (95% CI)
Sensitivity	95.1 (88.6 - 98.2)	95.2 (86.7 - 99.0)	95.8 (87.5 - 98.9)	93.5 (77.2 - 98.9)
Specificity	100 (94.2 - 100)	100 (5.5 - 100)	100 (51.7 - 100)	100 (93.8 - 100)
PPV	100 (95.3 - 100)	100 (92.5 - 100)	100 (93.42 - 100)	100 (85.43 - 100)
NPV	94.1 (86.0 - 97.8)	58.3 (31.7 - 80.8)	66.7 (30.9 - 91.0)	97.3 (89.8 - 99.5)
Diagnostic accuracy	97.3 (93.9 - 99.2)	95.5 (87.0 - 99.1)	96.2 (89.4 -99.3)	98.1 (93.4 - 99.8)

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

100% (95% CI 94.7 - 100), and NPV of 63.9% (95% CI 52.1 - 71.9). Malignant disease was diagnosed in 72.2% (*n*=39/54) of patients.[15] False-negative results were obtained in 20% (*n*=31) of patients, of whom 15 had malignancy. Our population had far less malignancies missed, in keeping with data from the developed countries.

Owing to the high burden of TB and HIV in SA, EBUS-TBNA will play an important role in diagnosing non-malignant conditions, particularly TB, sarcoidosis and lymphoma. Our present study diagnosed TB in 7% of the study population. A study conducted by Madan *et al.*[7] revealed that EBUS-TBNA had a diagnostic accuracy of 84.8% for diagnosing TB. A potential benefit associated with conducting EBUS-TBNA for the diagnosis of TB is the addition of broncho-alveolar lavage (BAL) with MTB Gene Xpert testing for rapid diagnosis and sensitivity testing for TB. A study analysing the utility of EBUS-TBNA in HIV infected patients showed a combined yield of BAL with TBNA of 86%, with an even higher diagnostic accuracy with transbronchial biopsy (TBB) and EBUS-TBNA of 97%.[7] Fortunately, the majority of patients with suspected TB are easily diagnosed with less invasive sputum analysis, reserving EBUS-TBNA for diagnosis and staging of lung cancer for the majority of patients in our resource-limited setting.

Study strengths and limitations

Our present study included a fairly large study population, of whom around 80 had malignant disease, allowing for a fair assessment of the utility of EBUS-TBNA for lung cancer in our local population. A potential limitation is the retrospective nature of our study, and the fact that patients with incomplete medical records or follow-up had to be excluded.

Conclusion

In conclusion, we found that EBUS-TBNA has a high diagnostic accuracy, even in a population with a high HIV and TB burden.

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Author contributions. SE, CFNK, TJJ and SMB initiated the study, analysed the data, and wrote the manuscript. All authors contributed to the study design, data collection and editing the manuscript. CFNK critically reviewed the data and final draft of the manuscript. All authors approved the final version of the manuscript for publication.

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