

## INTRODUCTION

The introduction of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has advanced the evaluation of mediastinal lymph node (LN) lesions and increased the diagnostic capability of bronchoscopy.<sup>1</sup> Complementary use of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) has further added to the staging of lung cancer by analysis of mediastinal LN and left adrenal gland (LAG) lesions. EUS-FNA allows superior views of the paraoesophageal area, inferior mediastinum, and aorto-pulmonary window (lymph node stations 5, 8 and 9), whereas EBUS-TBNA easily accesses the paratracheal, subcarinal, and hilar lymph nodes.<sup>2-4</sup>

The combined modality approach has been established as having improved diagnostic yield and impressive safety outcomes.<sup>5-10</sup> Current guidelines support the combination of EBUS-TBNA and EUS-B-FNA.<sup>3, 11, 12</sup> In recent times, progression of bronchoscopic evaluation has extended to the application of endoscopic transoesophageal fine needle aspiration using the convex probe bronchoscope (EUS-B-FNA) without compromising the diagnostic performance seen with EUS-FNA.<sup>13-14</sup> Use of a single endobronchial ultrasound bronchoscope (EBUS) for EBUS-TBNA and EUS-B-FNA has allowed for a more comprehensive sampling and staging of non-small cell lung cancer (NSCLC),<sup>2</sup> thereby improving diagnostic precision.<sup>2, 13, 15</sup> A joint bronchoscopic and transoesophageal approach has notable diagnostic accuracy of malignant nodes between 93-100%.<sup>5, 8, 9, 15</sup>

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Lung cancer has a tendency to metastasise distantly, including the LAG. LAG assessment using a single EBUS scope has been reported as feasible and enhances complete endobronchial and esophageal mediastinal nodal staging via the same videobronchoscope.<sup>16, 17</sup>

A single-setting and proceduralist approach complementing EUS-B-FNA with EBUS-TBNA has documented and conceivable benefits, including reduced costs, sedation, procedure duration and oxygen desaturations, whilst nullifying the requisite for two procedures.<sup>2, 13, 18, 19</sup> Studies conducted by Herth *et al.* and Hwangbo *et al.* reported no complications with pulmonologist performed EUS-B-FNA.<sup>2, 13, 15</sup> EUS-B-FNA is also a more appropriate approach in those patients who experience refractory coughing and/or have reduced lung function.<sup>20-22</sup>

This is the first Australian study of pulmonologist-performed EUS-B-FNA for assessment of mediastinal LN and LAG lesions, which aims to validate international studies in the diagnostic and staging utility, feasibility and safety of such an approach.

## **METHODS**

Approval was granted by Institutional Human Research Ethics Committee to conduct this study. All patients who underwent EUS-B-FNA from the period of January 1<sup>st</sup> 2015 and June 8<sup>th</sup> 2016 were identified in prospective procedural databases from two tertiary hospitals in Melbourne, Australia.

## **Patients**

All patients who were considered for minimally invasive assessment of suspected or known lung cancer were enlisted for EUS-B-FNA. Eligible patients were those where lesions were adjacent to the oesophagus on Computed Tomography of the chest and either;

- i) not amenable to EBUS-TBNA (see figure 1), or
- ii) target lesion was deemed to be more easily accessed via transoesophageal means (eg. LAG lesions), or
- iii) where a transoesophageal approach was preferred due to anaesthetic risk

## **Performance of EUS-B-FNA**

EUS-B-FNA was performed using a flexible linear scanning transducer (BF-UC180F-OL8; Olympus, Tokyo, Japan; or EB-1970UK; Pentax, Tokyo, Japan) under conscious sedation. Local anaesthesia was applied to the pharynx, larynx, trachea and bronchi with topical lignocaine 1% or 2% in preparation for bronchoscope introduction as previously stipulated.<sup>23</sup>

The ultrasound bronchoscope was inserted to the pharynx through the mouth and guided into the oesophagus posterolateral to the arytenoid cartilage. Continuous ultrasound imaging was conducted as described by Tournoy *et al.* to confirm correct positioning of the instrument using the thyroid, trachea, aortic arch, azygous vein, pulmonary arteries, heart and descending aorta as sonographic landmarks.<sup>4</sup> Upon localization of a target lesion, a 22-gauge needle (NA-201SX-4022; Olympus, or GUS-21-18-022; Medi-Globe SonoTip II) was introduced with aspirates performed under real-time ultrasound guidance.

Aspirates were expelled onto glass slides and subject to rapid on-site examination (ROSE) using previously reported rapid Romanowsky stain (Quick Dip; POCD Scientific, Artarmon, Australia),<sup>24</sup> and processed for formal cytological analysis as previously described.<sup>25</sup>

In cases where no diagnosis was made via EUS-B-FNA, a definitive diagnosis was obtained by alternate means of tissue diagnosis. In order to establish proposed diagnostic sensitivity in this study, aspirates which were non-diagnostic were deemed a false negative procedure.

## **RESULTS**

During the period of January 1st 2015 and June 8<sup>th</sup> 2016, 61 patients underwent EUS-B-FNA, with sampling performed at 69 mediastinal LN sites. Sampling of the LAG lesion was performed in four patients. Aspirates of mediastinal LN and LAG lesions were sufficient on ROSE in 71 of 73 (97%) patients. In 21 patients, EUS-B-FNA sampling was performed at mediastinal LN and LAG sites not amenable to EBUS-TBNA (see figure 1). Particulars regarding target lesion site diagnostic information are provided in Table 1. No complications occurred in any patients.

### **Role of EUS-B-FNA in diagnostic advancement**

The addition of EUS-B-FNA increased the diagnostic and staging utility of pulmonologist performed bronchoscopy with a further diagnosis made in twelve mediastinal LN and two LAG lesions, which could not have been obtained via EBUS-TBNA (Table 1). Four patients also had

successful sampling of benign mediastinal LN lesions at sites not accessible by EBUS-TBNA, confirmed as true negative findings on subsequent surgical sampling.

Diagnostic sensitivity for malignancy in mediastinal LN lesions was 88% (51 of 58). Seven patients had surgical confirmation of benign findings. All false negative cases (n=10) reported in this cohort are either presumed or surgically confirmed, with ongoing clinical surveillance continuing in four patients, and clinical deterioration precluding further sampling in two. In those mediastinal LN lesions inaccessible to EBUS-TBNA, EUS-B-FNA demonstrated diagnostic findings in 12 of 17 (71%), with sensitivity for malignancy of 88% (15 of 17). Sampling of four patients with LAG lesions by EUS-B-FNA confirmed metastatic lung carcinoma in two.

## DISCUSSION

Our results confirm limited published international literature that pulmonologist-performed transoesophageal mediastinal assessment with a linear EBUS video-bronchoscope is a safe and feasible procedure.<sup>2, 15</sup> Our study also adds to two previous reports of successful sampling of LAG lesions via EUS-B-FNA.<sup>16, 17</sup> We have previously reported the utility of EUS-B-FNA in improving diagnostic yield from convex-probe Endobronchial ultrasound-guided sampling of parenchymal lung lesions.<sup>26</sup> [Daniel P Steinfert, Michael W Farmer, Louis B Irving, Barton R Jennings. Pulmonologist-performed per-oesophageal needle aspiration of parenchymal lung lesions using an EBUS bronchoscope: diagnostic utility and safety. *J Bronchol Intervent Pulmonol*. 2016 In Press] This report now also confirms the significantly

improved diagnostic yield in selected patients of the combined approach in mediastinal assessment, through increasing the number of mediastinal LN sites that may be accessed by the pulmonologist via EUS-B-FNA and potentially upstaging lung cancer by sampling LAG lesions.<sup>16, 17</sup>

EUS-B-FNA enables accessibility to paraoesophageal lymph nodes, and specifically at stations 5, 8 and 9, which are not amenable to EBUS-TBNA.<sup>19</sup> Illustrative cases in Figure 1 demonstrate lesions that were successfully sampled, that would not be amenable to standard EBUS sampling via the airways. In combining sonological evaluation of the mediastinum with EBUS-TBNA and EUS-B-FNA, it would negate the requisite for two procedures.<sup>19</sup> This would drastically reduce costs, and time delayed in awaiting individual procedures or repeated clinical evaluation.

**The benefits of EUS-B-FNA may also include the ability to perform sampling in patients with excessive cough or reduced lung function precluding from increased sedation.<sup>20</sup> A recent randomised study concluded that EUS-FNA, compared with EBUS-TBNA, demonstrated comparable patient tolerance with fewer doses of anesthetics and sedatives, shorter procedure time, and fewer oxygen desaturations during the procedure.<sup>18</sup> We did not record intra-procedural oxygenation in this cohort, and the utility of EUS-B-FNA in patients with excessive cough or poor lung function precluding escalation of sedation remains to be confirmed in future studies. .In addition, it can be inferred that EUS-B-FNA decreases doses of sedatives and has fewer episodes of oxygen desaturation given these results seen in EUS-FNA. Published guidelines by Vilmann *et al.* recommend combined evaluation with endobronchial (EBUS-TBNA) and oesophageal (EUS-B-FNA) ultrasound for**

sampling over either procedure alone in the diagnosis and staging of lung cancer.<sup>11</sup> Specific training requirement or minimum procedural number for competence has not been studied in EUS-B-FNA. Konge et al. demonstrated that pulmonologists with awareness of lung cancer staging and experience in bronchoscopy were able to quickly improve their EUS-FNA performance.<sup>27</sup> However, despite twenty procedures there were inconsistencies with competent performance.<sup>27</sup> Importantly, these pulmonologists were trained in bronchoscopy and not specifically in EBUS. This highlights the need for regular endoscopic intervention by trained pulmonologists, with training in both EBUS-TBNA and EUS-B-FNA in order to perform complete endoscopic staging in one session.<sup>11</sup>

Unlike EBUS-TBNA, the lack of endoluminal landmarks within the oesophagus during EUS-B-FNA identifies the requirement for trained pulmonologists to rely solely on interpretation of the sonographic image and knowledge of surrounding vascular structures.<sup>20</sup> Whilst cardiologists conduct transoesophageal echocardiograms routinely, those pulmonologists who regularly perform EBUS with needle puncture and aspiration will likely be able to transfer this skill set from EBUS-TBNA to EUS-B-FNA.

### **Limitations and future directions**

This study incorporated patients selected for EUS-B-FNA of mediastinal LN and LAG lesions where post-CT imaging, pre-procedural diagnostic potential was deemed high. Those patients who underwent evaluation via EUS-B without FNA (e.g. inability to visualise target lesion) were excluded in the study, nor have we included all consecutive patients undergoing bronchoscopic mediastinal staging including EBUS-TBNA. Our findings confirm the accuracy of

pulmonologist-performed EUS-B-FNA for staging of lung cancer. Future studies are required to confirm accuracy of EUS-B-FNA in assessment of infective<sup>28</sup> and haematologic<sup>29</sup> causes of mediastinal lymphadenopathy.

Training requirements for EUS-B-FNA are not currently established, though are likely to be reduced in pulmonologists well versed in EBUS-TBNA, due to overlapping skills in bronchoscopic dexterity, ultrasound image interpretation, and lymph node sampling.

Proceduralists in this study all had extensive experience with EBUS-TBNA, and had observed performance of EUS, prior to commencing EUS-B. Each proceduralist also undertook further self-directed learning including review of sonographic anatomy from the oesophagus,<sup>4</sup> and/or attendance at post-graduate courses in EUS-B. In addition, proceduralists undertook their initial experience with direct observation by EUS proceduralists. As EUS-B becomes more established, training is likely to be directed solely by Pulmonologists experienced in the technique.

Despite being recommended in recently published international guidelines on staging of lung cancer,<sup>11</sup> EUS-B-FNA is not to our knowledge currently formally addressed in Australian College/Society training programs or accreditation guidelines. Until this is corrected, we suggest individual pulmonologists seek support, and potentially training, from available local sources. As discussed above, this may include either pulmonology or gastroenterology colleagues with appropriate expertise. Interventional pulmonologists with experience in EBUS-TBNA may also consider seeking formal credentialing from their institution to perform this procedure.

## **CONCLUSIONS**

The utility of performing EUS-B-FNA allows higher diagnostic yield of mediastinal LN lesions and access to LAG lesions, whilst preserving patient safety. EUS-B-FNA by trained pulmonologists with awareness of surrounding anatomy augments mediastinal diagnostic potential, assists in lung cancer staging and prevents the need for surgical evaluation.

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## ABSTRACT

**BACKGROUND:** Transoesophageal endobronchial ultrasound (EBUS) video-bronchoscope insertion provides pulmonologists access to conduct endoscopic fine-needle aspiration (EUS-B-FNA) of mediastinal lymph node (LN) lesions and also assist in lung cancer staging by sampling left adrenal gland (LAG) lesions. Limited literature have described additional diagnostic value, whilst maintaining patient safety.

**METHODS:** All eligible patients with paraoesophageal lesions on thoracic computed tomography (CT) underwent pulmonologist-performed EUS-B-FNA at two tertiary centres and were included in this prospective observational cohort study.

**RESULTS:** EUS-B-FNA sampling was performed at 69 mediastinal LN lesion sites, including seventeen sites inaccessible to bronchoscopic sampling. Four LAG lesions were sampled via EUS-B-FNA. There were no complications. EBUS-TBNA was augmented by EUS-B-FNA due to accessibility of sampling lesions otherwise unamenable bronchoscopically, thereby increasing diagnostic utility. Diagnostic sensitivity of EUS-B-FNA for malignancy in mediastinal LN lesions was 88% (51 of 58). For mediastinal LN lesions not amenable to EBUS-TBNA, the sensitivity for diagnosis of malignancy via EUS-B-FNA was 88% (15 of 17). Diagnostic sensitivity of EUS-B-FNA for malignancy in LAG lesions was 50% (2 of 4).

**CONCLUSIONS:** EUS-B-FNA is a precise and safe approach in the evaluation and staging of lung cancer when performed by a pulmonologist. It complements and increases the diagnostic utility of EBUS-TBNA by further coverage of mediastinal LN stations and access to LAG lesions.

**TITLE PAGE**

Pulmonologist-performed transoesophageal sampling for lung cancer staging using an endobronchial ultrasound videobronchoscope; An Australian experience

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Combining endoscopic transoesophageal fine-needle aspiration using convex probe bronchoscope (EUS-B-FNA) and endobronchial ultrasound (EBUS) bronchoscopy enhances the diagnostic yield of mediastinal nodal staging in lung cancer, whilst maintaining safety.

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