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Research Article

Evaluation of the Diagnostic Value of Electromagnetic Navigational Guided Targeted-Bronchoalveolar Lavage in the Diagnosis of Lung Cancer

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Abstract

Background: Electromagnetic Navigation Bronchoscopy (ENB) is recommended for the evaluation of Peripheral Pulmonary Nodules (PPNs). Current diagnostic bronchoscopy and pulmonary nodule evaluation guidelines do not establish recommendations regarding the role of individual tissue acquisition techniques, the ideal combination or sequence of executing them to optimize diagnostic yield. Anecdotally, Targeted-Bronchoalveolar Lavages (T-BAL) are performed through the Extended Working Channel (EWC) to increase yield. To our knowledge this is the first prospective study aiming to define the role of site-directed T-BAL in the diagnosis of malignancy while further examining the clinical utility of individual tissue acquisition techniques routinely employed via ENB.

Methods: Institutional Board Review approved (IRB authorization 00006557) prospective observational study of patients undergoing ENB evaluation of PPNs. Sampling procedures performed via a standardized protocol with forceps biopsy, triple needle brushings and Core Biopsy (CBS) followed by T-BAL and Bronchoalveolar Lavage (BAL). Positive results were based on identification of malignancy on cytology and/or pathology.

Results: Sixty-seven consecutive patients were included. Two patients excluded due to sampling errors; 4 patients had 2 nodules sampled. From the 69 remaining data points, there were 38 biopsy proven cases of malignancy. Thirty-one of these were detected by ENB, for a sensitivity of 81.6%. CBS was the most sensitive technique at 68.4%. T-BAL's sensitivity was 42.1%.

Conclusion: Our data suggests that the clinical utility of T-BAL is limited in the diagnosis of malignancy when compared to other tissue acquisition tools, providing no added benefit. Its potential value can be re-evaluated as newer advanced bronchoscopic technologies become available.

Keywords: Core biopsy system; Extended working channel; Lung cancer; Peripheral pulmonary nodules

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Abbreviations

PPNs: Peripheral Pulmonary Nodules
ENB: Electromagnetic Navigational Bronchoscopy
RP-EBUS: Radial Probe Endobronchial Ultrasound
T-BAL: Targeted Bronchoalveolar Lavage
BAL: Bronchoalveolar Lavage
EWC: Extended Working Channel
CBS: Core Biopsy System
TTNA: Transthoracic Needle Aspiration
ACCP: American College of Chest Physicians
AQuiRE: ACCP Quality Improvement Registry, Evaluation, and Education

Introduction

The World Health Organization lists lung cancer as one of the most common and most fatal cancers in the world [1]. The National Institutes of Health estimate that in 2018 there will be 230,00 new cases of lung and bronchus cancer with 150,000 deaths in the United States [2]. Given the significant disease burden and high mortality associated with lung cancer, there have been ongoing technological innovations to assist in the evaluation of pulmonary nodules in an effort to increase diagnostic yield.

Approved for use in 2004, Electromagnetic Navigational Bronchoscopy (ENB) was developed as a method to evaluate Peripheral Pulmonary Nodules (PPNs) that are inaccessible to traditional bronchoscopes [3]. After placement of the primary bronchoscope, an Extended Working Channel (EWC) is deployed that follows a predetermined route, previously plotted through 3D reconstruction from high resolution CT imaging, to perform site directed sampling deep in the tracheobronchial tree. Often Radial-Probe Endobronchial Ultrasound (RP-EBUS) is utilized to confirm EWC positioning prior to sampling, with a noted increase in diagnostic yield [4,5]. Once positioning is confirmed, multiple diagnostic tests may be performed through the EWC.

The 2013 guidelines by the American College of Chest Physicians (ACCP) recommend using ENB to evaluate PPNs in order to avoid more invasive studies [6]. More recently, however, it has been noted that the overall diagnostic yield of ENB has plateaued. It was therefore not alarming when the ACCP Quality Improvement Registry, Evaluation, and Education (AQuIRE) Registry reported an overall yield of 53.7% with ENB [7]. Regardless, navigational bronchoscopy remains the current recommended diagnostic approach for PPNs until enhanced and/or complimentary technologies are proven to substantially increase diagnostic yield.

Navigational bronchoscopy employs a variety of tissue acquisition tools including forceps biopsy, needle aspiration, core biopsy, needle brushings, and conventional Bronchoalveolar Lavage (BAL). Which sampling methods are utilized is variable between institutions as existing guidelines do not establish procedural recommendations regarding which technique, combination of techniques, or the order that sampling should be performed [6,8-10].

Site directed BAL through the EWC is anecdotally performed to theoretically increase diagnostic yield. To our knowledge, the actual clinical utility of this has not been studied in a prospective manner. At our institution performing a EWC guided target-site directed lavage is referred to as a Targeted-Bronchoalveolar Lavage (T-BAL) and is routinely performed during ENB studies. The objective of our study is to define the role of T-BAL in the diagnosis of malignancy as well as further assessing the clinical utility of the individual tissue acquisition techniques routinely employed during ENB.

Materials and Methods

Institutional Review Board approval was obtained for a prospective observational study of patients undergoing ENB guided, RP-EBUS, and fluoroscopy assisted, evaluation of PPNs. All patients referred for ENB due to suspicious PPNs noted on CT imaging that appeared inaccessible by conventional bronchoscopy were included in the study. The only exclusion criteria were pediatric patients as defined as being under the age of 18 and those with contraindications to radiographic studies. Data collection occurred over a period of 12 months from 06/2017 through 06/2018 and included all relevant ENB studies performed at the study institution. Patients' clinical courses were followed via chart review until 3 months after completion of data acquisition. Informed consent was not required as the diagnostic procedure was not altered from the standard of care.

Data collected on each patient included age, gender, volume instilled and aspirated by T-BAL, volume instilled and aspirated by BAL, pathology results for forceps biopsy, triple needle brushing, core biopsy, T-BAL, and BAL, presence of bronchus sign, size and characteristics of the nodule on imaging. Procedure notes, pathology reports, microbiology data, and office notes were obtained and reviewed.

Procedural Standardization

The superDimension™ navigation system was utilized for all procedures with standard planning, registration, and navigation phases. RP-EBUS was utilized to confirm lesion location prior to tissue sampling. All procedures were performed by board certified interventional pulmonologists.

Planning phase with 3D reconstruction was performed prior to the procedure date. Upon arrival to the endoscopic suite, patients were synchronized to the superDimension™ software through the registration phase. Patients received general anesthesia and underwent endotracheal intubation before initiation of the navigation phase, wherein the bronchoscope was advanced following the predetermined pathway with deployment of the EWC to the site of interest. RP-EBUS was then used to attempt confirmation of successful navigation to the target lesion by either demonstrating a concentric or eccentric image of the lesion prior to performing EWC directed sampling under real-time fluoroscopic guidance.

To encourage reproducibility, sampling was carried out in a protocolized, sequential fashion. Diagnostic tests were carried out in the following order for all ENB studies:

- Forceps Biopsy (FBx) (Covidien SDBF1000)
- Triple Needle Brushings (TNB) (Covidien SDTNB1000)
- Core Biopsy (CBS) using the using the GenCut™ core biopsy system (Covidien SDCT01), was used in place of fine needle aspiration.

Samples from each diagnostic method were collected in their own individually labelled containers.

Upon completion of the CBS, T-BAL was then performed followed by segmental BAL in a protocolized manner. T-BAL was performed via a 60cc syringe with an initial lavage of 35 cc of normal saline followed by a 5-cc air bolus to flush the channel. Negative pressure was applied for 15 seconds with a goal aspirate volume of 5 cc. If 5 cc was not obtained then an additional 20 cc of normal saline was instilled, followed by a 5-cc air bolus, and with an additional 15 seconds of negative pressure applied. The EWC was then withdrawn from the inner channel of the bronchoscope.

Upon withdrawal of the EWC, the bronchoscope remained fixed and segmental BAL was performed utilizing 20 cc normal saline lavages. This was continued until 25 cc of aspirate was obtained or after instilling a total of 150 cc between the T-BAL and BAL.

All patients underwent full diagnostic evaluation with FBx, TNB, CBS, T-BAL, and BAL. The collected samples were sent for culture, cytology, and chemistry. If ENB evaluation was nondiagnostic then the case was discussed at thoracic oncology multidisciplinary conference to assess the need for further diagnostic evaluation with possible Transthoracic Needle Aspiration (TTNA) or wedge resection, consideration for empiric stereotactic body radiation therapy after tri-modality staging, or continued monitoring with serial CT imaging of the chest. Patients were followed for 3 months after completion of data acquisition to ensure definitive diagnosis and to monitor clinical course based on thoracic oncology multidisciplinary consensus.

Results

Patient demographics and lesion characteristics

A total of 67 patients were evaluated during this study (Table 1). Two results were excluded due to errors in sample handling. Four patients had two nodules evaluated yielding a total of 69 data points from the remaining 65 patients. Of the included 65 patients 31 were male and 34 were female; mean age was 69.8 years.

Total patients	67
Excluded patients	2
Patients with two nodules sampled	4
Total data points	69
Female gender	34
Male gender	31
Malignancy diagnosed	38
Diagnosis obtained via ENB	31
Average patient age (years)	69.8 +/- 10.5
Average lesion size (mm)	19.1 +/- 8.5
Overall presence of bronchus sign	16
Bronchus sign associated with malignancy	11

Table 1: Patient Demographics and Lesion Characteristics.

Lesion size was highly variable with the mean average size being 19.1 mm with a standard deviation of 8.5 mm. The largest dimensions measured were 43 mm with the smallest being 4 mm. Lesions were characterized as most commonly spiculated, but also included cavitary, ground glass, and solid.

In total 38 out of the 69 data points were considered positive. Cases were considered positive if there was confirmed malignancy on biopsy. ENB diagnosed 31 out of 38 cases. Seven additional cases were diagnosed through TTNA or wedge resection after undergoing nondiagnostic ENB. With 38 total cases, the overall sensitivity for ENB came to 81.6% with a negative likelihood ratio of 0.18 when evaluating for malignancy.

Thirty-one data points were considered negative (Table 2). Each of these cases underwent review by multi-disciplinary thoracic tumor board to determine consensus treatment plans. Of these 31 cases, 9 were noted to have oropharyngeal flora and 3 had evidence of chronic inflammation. 10 of these patients are being followed with serial imaging, while 2 were lost to follow-up. BAL did diagnose infectious causes for PPNs in 7 patients, which included gram positive, fungal, yeast, and mycobacterium growth. 9 data points did not reveal any of the above results and were considered non-diagnostic.

Total malignancies	38	Additional Results	31
Adenocarcinoma	19	Oropharyngeal flora	9
Squamous cell carcinoma	10	Infectious	7
Non-small cell carcinoma	3	Chronic inflammation	3
Small cell carcinoma	2	Granuloma	2
Urothelial carcinoma	2	Adenomatous hyperplasia	1
Lymphoma	1	Non-diagnostic	9
Cholangiocarcinoma	1		

Table 2: Diagnostic results.

In the 38 cases that were considered positive, there was significant overlap between the testing modalities, with multiple diagnostic techniques providing positive results from a single ENB procedure. For example, one study may have been positive via FBx, CBS, and T-BAL, while another would be positive via TNB and BAL. However, there were instances where only one of the three invasive techniques; either FBx, TNB, or CBS, had a positive result.

Diagnostic yield

The sensitivity of the individual sampling methods along with the exact Clopper-Pearson 95% confidence interval were calculated (Table 3).

	Positive results	Sensitivity	Confidence intervals
Overall ENB	31	81.6%	65.7%,92.3%
Individual Tissue Acquisition Techniques			
Forceps Biopsy	19	50%	33.4%,66.7%
Triple Needle Brush	21	55.3%	38.3%,71.4%
Core Biopsy System	26	68.4%	51.4%,82.5%
Targeted-Bronchoalveolar Lavage	16	42.1%	26.3%,59.2%
BAL	18	47.3%	31.0%,64.2%

Table 3: Results by diagnostic method.

T-BAL and BAL performed similarly in the diagnosis of cancer. BAL still provided some additional diagnostic value in determining nonmalignant causes of lung nodules such as infection or inflammation (Table 2). There was no instance where malignancy was detected by T-BAL or BAL that was not detected by one of the 3 invasive methods utilized.

The mean volume instilled during T-BAL was 49.7 cc with an aspirated volume of 5.3 cc, achieving the goal of 5 cc (Table 4). The mean volume instilled with BAL was 61.9 cc with an aspirated volume of 21 cc, not achieving the goal volume of 25 cc over the course of the study.

T-BAL volume instilled (cc)	49.7 +/- 9
T-BAL volume aspirated (cc)	5.3 +/- 3.8
BAL volume instilled (cc)	61.9 +/- 19.6
BAL volume aspirated (cc)	21 +/- 5.6

Table 4: Average volumes instilled and aspirated for all patients.

In patients with malignancy the instilled volume with T-BAL was similar at 47.9 cc but was slightly higher in volume aspirated at 6.6 cc (Table 5). Instilled and aspirated volumes for segmental BAL were similar as in the overall patient population.

T-BAL volume instilled (cc)	47.9 +/- 7.9
T-BAL volume aspirated (cc)	6.6 +/- 4.3
BAL volume instilled (cc)	60 +/- 20.5
BAL volume aspirated (cc)	21.5 +/- 5.9

Table 5: Average volumes instilled and aspirated for patients with malignancy.

Complications and management

Throughout the data collection period one symptomatic pneumothorax (1.5%) occurred that required intervention. Manual aspiration was performed and succeeded in obtaining full pulmonary re-expansion, avoiding small-bore chest tube placement and hospitalization. No other ENB related complications were documented.

Discussion

With the development of dedicated lung cancer screening guidelines leading to increased screening tests, the need for accurate and minimally invasive diagnostic techniques continues to grow [11]. The diagnostic yield of ENB for the evaluation of PPNs seems to have plateaued, highlighting that it is not a standalone technology. Multiple factors may impact procedural results including CT-body divergence, dislodgement of sampling instruments after accurate placement of EWC, and concentric versus eccentric location of the PPN in relation to the airways.

Enhanced navigational, complimentary confirmatory imaging, and tissue acquisition technologies are being introduced to support an era of optimal diagnostic confidence that may potentially set the stage for future endoscopic therapeutic platforms. In the meantime, we continue our efforts to improve our diagnostic yields with the existing navigational bronchoscopy technology and tissue acquisition tools by augmenting these studies with validated imaging tools such as fluoroscopy and RP-EBUS [12].

Choosing which sampling procedures to use, and the sequence in which these are performed, have primarily been provider dependent as no consensus guideline directed protocol to provide optimal diagnostic yield is available [13]. The most commonly employed techniques include bronchial washes, brushes and biopsies, though prior reports have suggested that transbronchial needle aspiration and BAL may augment results [7,14].

The primary role for BAL lies in assessing for opportunistic infections in immunocompromised patients receiving chemotherapy [15]. There may be an extended role in the detection of hematological malignancies, metastatic breast cancer, and bronchogenic adenocarcinoma in-situ [16]. However, its role in diagnosing primary lung cancer remains limited [17,18]. Our data supports this as BAL did not provide a malignant diagnosis that was not also detected by some other method. However, it remained useful in determining nonmalignant etiologies for pulmonary nodules, most commonly those of infectious origin.

Our overall ENB yield was 81.6%. Of the individual techniques employed CBS utilizing the GenCut^{tm} system demonstrated the highest rate of detection of malignancy at 68.4%. The GenCut^{tm} system utilizes a 15-gauge rotating cutting blade that theoretically allows it to obtain tissue from eccentric lesions, wherein the lesion appears adjacent to the sampling site trajectory when visualized by RP-EBUS. This is in contrast to the concentric approach, where the EWC's trajectory is within the lesion when visualized by RP-EBUS, as is ideally required for optimal sampling via needle aspiration.

Based on prior studies CBS does appear to perform as well as needle aspiration, and it did outperform all other techniques performed during this study. A direct head to head comparison of CBS to the other diagnostic techniques utilized is beyond the scope of this study, however, our findings of this aspiration technique does support the findings of the AQuIRE registry which demonstrated peripheral transbronchial needle aspiration's improved yield over transbronchial biopsy [7].

A recent retrospective analysis examined the individual techniques employed through ENB and noted that in patients in which multiple diagnostic techniques were performed, transbronchial biopsy had a sensitivity of 75% with EWC guided lavage having a sensitivity of 30% when assessing for malignancy [19]. In this analysis however, RP-EBUS was not utilized and only a single 10 cc lavage was performed through the EWC. A prospective study in 2009 noted that performing site directed catheter suctioning with forceps biopsy increased the diagnostic yield for all diagnoses when compared to forceps biopsy alone [5].

These studies inspired the sequence for our testing, with the goal of creating a reproducible protocolized algorithm. In order to theoretically increase diagnostic yield, T-BAL was performed after the more invasive sampling methods, hypothesizing that these initial techniques exposed or disrupted the target tissue at the sampling site.

We found no additional benefit from performing ENB guided T-BAL when evaluating PPNs for malignancy. With a diagnostic yield of 42.1% it performed below even that of BAL, and neither method detected malignancy that was not otherwise detected by another diagnostic method. However, BAL did detect additional causes of PPNs other than malignancy, supporting its continued used during ENB and other bronchoscopic procedures.

The volume instilled and aspirated during T-BAL and BAL does not appear to have a significant impact on diagnostic yield as both were overall low. The American Thoracic Society recommends retrieving at least 5% of the instilled volume, ideal volumes being greater than 30% for the diagnostic evaluation of interstitial lung diseases; however, no consensus recommendation exists for malignancy [20]. The minimum volume was aspirated for both T-BAL and BAL, and the ideal volume was aspirated for BAL, however the diagnostic yield was still less than 50% in cases where malignancy was otherwise diagnosed.

Conclusion

As we enter an era of hopeful technological advances in diagnostic bronchoscopy and targeted therapies, new tissue acquisition tools will not only be evaluated for their capabilities to provide specimens for cytology and histology but also for immunohistochemical and genotype analysis. In the meantime, our rudimentary tests continue to hold diagnostic value and we aim to optimize their yield.

To our knowledge, this is the first study evaluating the potential role of ENB guided T-BAL in the diagnostic evaluation of PPNs. We demonstrate that while performing T-BAL is a simple and safe procedure, it confers no additional benefit as it does not improve the diagnostic yield. The yield of ENB was the highest when multiple tissue sampling techniques were employed, with CBS resulting in the highest individual yield.

Conflicts of Interest

Dr. Ismael Matus: No conflicts of interest. Dr. Timothy Roedder: No conflicts of interest. Dr. Avalon Mertens: No conflicts of interest. Dr. Haroon Raja: No conflicts of interest.

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