Original Article

Diagnostic Yield of the Virtual Bronchoscopic Navigation System Guided Sampling of Peripheral Lung Lesions using Ultrathin Bronchoscope and Protected Bronchial Brush

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Abstract

OBJECTIVES: The use of an ultrathin bronchoscope (UB) to diagnose peripheral pulmonary lesions is described. A virtual bronchoscopic navigation system was used to direct the ultrathin scope to the nodule. One of the constraints of this technique was the inability to confirm the target lesion position during biopsy by using a conventional linear endobronchial ultrasound probe, since the probe does not fit into a 1.2 mm working channel of this bronchoscope. The aim of the study was to review our institutional experience with the use of a UB for sampling peripheral pulmonary lesions using the transbronchial brush guided by virtual bronchoscopy. We describe a technique wherein we attempt to brush all the visible bronchial sub-segments once the bronchoscope has reached close to the nodule.

MATERIALS AND METHODS: In total, 52 patients underwent the procedure between 2010 and 2017. A multiplanar computed tomography (CT) scan of the chest was obtained and subsequently uploaded to the Lung Point Virtual bronchoscopy navigation software. The UB was parked close to the lesion. All visible airway branches were then brushed using a protected bronchial brush. The data were retrospectively abstracted from the electronic medical records using standardized forms.

RESULTS: A total of 52 lesions (40 solid, 8 part-solid, 3 cavitary, and 1 ground-glass) were sampled using a transbronchial brush (median, 2; range, 1-8). Twenty-four lesions were under 2 cm in size. The overall success rates were 67.3%. The average diameter of nodules was 2.7±1.01 cm; 65% lesions were in the outer-third of the lungs. The cancer-specific sensitivity was 72.5%. The presence of bronchus sign; location of the lesion; and the characteristics, size, and stage of cancer did not have any impact on the diagnostic yield.

CONCLUSION: Virtual bronchoscopy-guided ultrathin bronchoscopy with bronchial brushing is safe and has a diagnostic yield comparable to other described techniques for evaluating peripheral pulmonary nodules.

KEYWORDS: Lung nodule, ultrathin bronchoscopy, virtual bronchoscopy, lung cancer, bronchial brush

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INTRODUCTION

The National Cancer Institute-sponsored National Lung Screening Trial (NLST) reported a greater than 25% incidence of suspicious lung lesions among patients undergoing a lowdose computed tomography (CT) scan of the chest [1]. Although the prevalence of cancer among non-calcified nodules has been variably reported to be between 2% and 82% [2], the NLST [1] reported that 3.6% of the nodules detected were indeed malignant. Currently, 7 million Americans meet the NLST screening criteria [3]. Even if only one-fourth of those eligible are screened, a possible 680,000 new nodules could be discovered over 3 years [4]. An earlier diagnosis of lung cancer translates into improved 5-year survival rates [5,6], and surgical resection can provide a greater than 70% chance of survival for patients with early cancers [7]. The guidelines offer recommendations for the practitioners at a risk of stratifying the nodules and then choosing the best management option, including watchful waiting, tissue diagnosis via transthoracic/bronchoscopic modalities, and surgical excision of the nodule [8].

When biopsy is chosen as a management path for the nodule, bronchoscopic biopsies are usually preferred over transthoracic biopsies as the complication rates are lower [8,9]. However, the yield of bronchoscopy for peripheral pulmonary nodules continues to remain around 50% despite the significant advancement in technology including radial endobronchial ultrasound (r-EBUS) and electromagnetic navigation (EMN) [10]. A metaanalysis of all guided bronchoscopic strategies showed that the yield ranged between 46% and 86.2% [11]. One factor accounting for the lower yield of the conventional transbronchial biopsy is that the selection of bronchial pathways to the lesion based on solely CT scans is likely to be inaccurate beyond the third or fourth generation bronchus and that bronchoscopes are typically not able to reach the peripheral lung lesions [10].

An ultrathin bronchoscope (UB, outer diameter, <3 mm) was developed to circumvent the problem arising from the difficulty in accessing peripheral lung nodules with conventional bronchoscopes [12-15]. They are easier to negotiate through the difficult pathways to the target lesions and may be used for small peripheral lesions [13,16-18]. The diagnostic yields of UBs have varied between 48.7% and 81.6% [11,12,14,17,19-21]. The utility of using the UB has been most obvious when placement into a higher generation of bronchus is possible [22]. The combined use of virtual bronchoscopy with UB has been demonstrated to have a diagnostic yield of 75% [23]. The bronchial brush has previously been reported to have a lower diagnostic yield when used with the UB (29.4%) [12] compared to the brushing obtained when using a conventional bronchoscope (37.8%) [9]. However, other studies have demonstrated a significantly higher yield of transbronchial brushings (82.9%) with an incremental yield by using the brush over transbronchial forceps biopsy [20]. An additional consideration for using the UB is the ability to navigate into the airways following the map generated by the virtual bronchoscopic navigation (VBN) software. Asano et al. [21] reported that the bronchoscope could be advanced under direct visualization to the target bronchus in 94.7% cases. Despite the high number, there are difficulties navigating the complicated bronchial anatomy. The same authors have reported that in 6% of cases, the bronchoscope was advanced into a wrong segment in a different study even after using the VBN technology [18].

In the current study, we report our institutional experience of utilizing a UB and transbronchial brushing with a virtual bronchoscopy guidance for peripheral lung nodules. We also describe a unique technique of brushing all visible airways once the target lesion has been approximated.

MATERIALS AND METHODS

Subjects
Between January 2010 and January 2017, 52 patients (aged >20 years of age) with 52 lung lesions suspected to be malignant underwent UB with protected endobronchial brushings. Virtual bronchoscopy images were used for navigation of the UB. All patients were detailed about the nature of the procedure and the risks associated with it. The UB brush technique was offered by a single practitioner at the center and other cases where r-EBUS was used or fluoroscopic transbronchial biopsies were obtained were excluded from analysis.

Study Design
This was a retrospective analysis of all patients who underwent this combination of virtual bronchoscopic approach to a peripheral lung lesion using an UB and transbronchial brushings as a mode of obtaining a diagnosis. The institutional review board at the North Florida/South Georgia Veteran Affairs Hospital reviewed the study and approved the study protocol (IRB201700375). An approval from the ethics committee was obtained. Details of patient's age, sex, and outcomes were recorded. Details of each nodule, size, characteristics (solid/ground glass/cavitary), location within the lungs (outer third/middle third/inner third), lobar location, shape of the lesion (round/spiculated/lobulated/elongated/irregular), pathological diagnosis (benign/malignant including subtypes), presence or absence of a bronchus sign, success of the procedure (diagnostic/non-diagnostic), the stage of cancer (if a cancer diagnosis was made), types of complications, number of brushes used, and procedure duration were collected. Table 1 enumerates the inclusion and exclusion criteria for the study.

Study Procedure
All patients underwent multidetector chest CT (16- or 64-row; slice width, 0.5-1.0 mm) before bronchoscopy. Individual CT were transferred to a workstation on which a VBN software, LungPoint™ Virtual Bronchoscopic Navigation System (Broncus Technologies, Inc., Mountain View, CA), was used to create a computer-assisted image-based virtual pathway to the target lesion. The pathways are calculated to reach the points closest to the target. Three-dimensional images of the airway tree and target as well as the virtual bronchoscopic animation enabled assessment of the calculated pathways. Moderate sedation was used for all bronchoscopic procedures; the choice of medications and doses were left to the bronchoscopist's discretion. A UB (type XP160F; outer diameter, 2.8 mm; working channel diameter, 1.2 mm; Olympus Medical Systems, Tokyo, Japan) was navigated to the target bronchus using the VBN system. The bronchoscope was introduced as far as possible to approximate the lesion and was parked at the same position. Bronchial brushing was performed in all the segments that were visible at this position with a 1.2 mm cytology brush (Olympus 1.2 mm; BC-203D-2006). Different brushes were used for each of the individual segments that were visible at this position. More than one brush could be used in the same segment and left to the proceduralist's discretion. Fluoroscopy or radial probe guidance was not used to localize of the lesion.

Table 1. Inclusion and exclusion criteria for the study are enumerated above

Inclusion criteria	Exclusion criteria
1. Patients underwent bronchoscopy at the bronchoscopy suit in the VA hospital at Gainesville.	1. All cases where r-EBUS were performed will be excluded.
2. They underwent bronchoscopy to evaluate for suspected malignant lung nodules.	2. All cases that underwent blind transbronchial biopsies will be excluded.
3. Virtual bronchoscopy was performed to determine the best approach to the lung nodules.	3. All cases where fluoroscopy was used were excluded.
4. An ultrathin bronchoscope with a 2.8 mm was used for the procedure along with a 1.2 mm transbronchial brush.	
5. These cases were performed by a single proceduralist.	

Follow-up

If a diagnosis was not achieved after the procedure, we advised the patient to undergo other diagnostic procedures, such as conventional transbronchial biopsy using a conventional bronchoscope with or without r-EBUS guidance, CT-guided transthoracic needle aspiration, or surgical intervention. If a patient with an undiagnosed lesion refused further intervention, a radiological follow-up for 2 years was the performed. Lesions that disappeared or decreased in size during the observation period were deemed to be inflammatory in nature. Lesions that did not have a clear diagnosis on biopsy and patients who could not complete the 2-year follow-up until January 2017 were also excluded from the final analysis.

Statistical Analysis

A two-sided Chi-square test was used to analyze for the diagnostic yield of the procedure among different sub groups. All p values were two-sided. A p value of less than 0.05 was considered to indicate a statistically significant difference. We systematically studied the effects of nodule size, location, presence of bronchus sign, nodule shape, imaging characteristic of the nodule (solid versus non-solid), histology-malignant versus benign, effect of the number of brushes used, and location within the lungs (central versus peripheral).

RESULTS

The procedure was successfully completed for all 52 patients. No procedural complication was reported. Diagnostic material was obtained in 67.3% (35/52) patients overall, and the cancerspecific diagnostic yield was 72.5% (29/40). The diagnostic yield for a benign diagnosis was 50.0% (6/12). The difference in the yield was non-significant (p=0.12). The mean age of the patients was 65.3±9.4 years. Forty-seven males and 5 females were included in the final analysis. The patients were all veterans, which is justified by the high proportion of males in the group. Table 2 describes the patient characteristics. Fifty-two lesions (40 solid, 8 part-solid, 3 cavitary, and 1 ground-glass) were biopsied using a transbronchial brush (median 2; range 1-8). The diagnostic yield for solid nodules was 65% (26/40) compared to 75% for non-solid nodules (9/12). This difference was statistically insignificant (p=0.4). The average diameter was 2.7±1.01 cm. The average procedure duration was 22.1±9.7 minutes. Most lesions were in the right upper lobe (RUL, 21) followed by the left lower lobe (LLL, 13), left upper lobe (LUL, 8), right middle lobe (RML, 6), and right lower lobe (RLL, 4). The diagnostic yield for was 81%, 61%, 37%, 66%, and 75% for the RUL, LLL, LUL, RML, and RLL. A lesion in the RUL was more likely to have a diagnosis (17/21; 81%) in contrast to all other lobes combined (18/31; 58%). This difference was statistically insignificant (p=0.08). Thirty-three of the 52 (63.4%) lesions were in the outer-third of the lungs; 69.3% (36/52) of all lesions had a bronchus sign. Twenty-four lesions (46%) were less than 2 cm in size. The location of the nodule in the peripheral third compared to inner twothirds did not impact the yield from the procedure (63.6% vs 73.6%; p=0.3). Forty nodules were found to be malignant and 12 were benign. Of the nonmalignant nodules, exact diagnoses were established in 6 cases. There were 3 cases of nontuberculous mycobacteria, one each of *Moraxella* and *Pneumococcus* and one *Aspergillus* pneumonia. Among the

Table 2. Summary of the patient characteristics and factors associated with the result

Number of patients included in the analysis	52
Mean age	65.3 years
Male gender	47/52 (90.3%)
Median procedure duration	22.1±9.7 minutes
Median number of brushes	2 (1-8)
Average number of brushes used in peripheral one-third of the lung	2.5
Average number of brushes used in central two-third of the lung	2.1
Average diameter of nodules	2.7±1.01 cm
Lesions <20 mm in size	24 (46%)
Successful biopsy rate for lesions <20 mm	13/24 (54.1%)
Successful biopsy rate for lesions >20 mm	22/28 (78.5%)
Bronchus sign	36/52 (69.3%)
Successful procedure with a bronchus sign present	26/36 (72.2%)
Successful procedure with a negative bronchus sign	9/16 (56.2%)
Median generation of bronchi	6 (4-10)
Malignant nodule	40
Diagnostic yield for malignant nodule	29/40
Benign nodule	12
Diagnostic yield for benign nodule	6/12 (50%)
Lesions in the outer-third of the lung	33/52 (63.4%)
Diagnostic yield for nodules in the outer third of the lungs	21/33 (63.6%)
Diagnostic yield for nodules in the inner two-third of the lungs	14/19 (73.6%)
Early stage cancer (Stage I, II, limited)	37
Diagnostic yield in early stage cancer	20/37 (54%)
Late stage cancers (Stage III, IV, extensive)	15
Diagnostic yield in late stage cancer	9/15 (60%)
Solid nodules	40
Diagnostic yield for solid nodules	26/40 (65%)
Non-solid nodules	9
Diagnostic yield for non-solid nodules	9/12 (75%)
Nodules in the right upper lobe	21/52 (40%)
Diagnostic yield of the right upper lobe	17/21 (81%)
Nodules in other locations	31/52 (59%)
Diagnostic yield from nodules in other locations	18/31 (58%)

non-small cell cancers, there were 17 stage I (46%), 6 stage II (17%), 5 stage III (13.5%), and 9 stage IV (24.5%) cancers. Three patients had small cell pathology (2 limited and 1 extensive stage). The nature of the remaining 6 nodules was not diagnosed, since the patients refused further diagnostic testing, and the nodules disappeared on a followup examination. There were 17 cases of adenocarcinoma and squamous cell cancer each, 3 cases of small cell cancer, 2 cases of carcinoid

tumor, and 1 metastatic cancer with colonic primary. The diagnostic yield was independent of the histology subtype. The procedure was successful in 12 of the 17 cases with adenocarcinoma, 13 of the 17 patients with squamous cell cancer, 2 of the three 3 with small cell cancer, and both patients with carcinoid cancer. The procedure was unsuccessful in providing a diagnosis for the patient with metastatic adenocarcinoma of the colon, and it was diagnosed on a subsequent visit when the nodule had enlarged further and was biopsied using conventional transbronchial biopsy forceps under fluoroscopy combined with EBUS transbronchial needle aspiration of the mediastinal lymph node. Among those with an unsuccessful procedure, 4 patients with adenocarcinoma and 3 with squamous cell cancer underwent a surgery leading to the final diagnosis. Transthoracic needle biopsy under CT guidance was performed by interventional radiology to diagnose the remaining patients with adenocarcinoma and squamous cell carcinoma. One patient with small cell cancer was eventually diagnosed using EBUS-guided transbronchial needle biopsy of the ipsilateral hilar lymph node after it had shown interval enlargement. The success of the procedure also did not depend on the presence of a bronchus sign on CT scans, solid versus non-solid lesions, or the location of the tumor. A tumor size greater than 2 cm was the only factor that was found to indicate higher chances of yield on this diagnostic procedure but failed to achieve statistical significance (p=0.06). The diagnostic yield was 54.1% (13/24) for lesions less than 2 cm and 78.5% (22/28) for larger than 2 cm lesions. The bronchus sign was more commonly observed with a successful procedure, but this was not statistically significant (72.2% vs 56.2%, p=0.3). Interestingly, when the nodule was further subcategorized based on size (less/greater than 2 cm), the presence of a bronchus sign was associated with a significantly higher yield (p=0.04) for nodules less than 2 cm in size (10/14; 71% vs 3/10; 30%). This relationship was not seen for nodules greater than 2 cm. The chances of success were also noted to be higher for nodules located in the outer third of the lung when more than one transbronchial brush was used (71% vs 44%, p=0.2). Surprisingly, when more proximal lesions were analyzed, it was noted that all lesions biopsied using one transbronchial brush showed a positive diagnosis. The yield for cases utilizing more than one transbronchial brush in the inner two-third of the lung was 67%. It was also noted that more brushes per nodule were utilized for lesions located in the outer third compared to those more proximally located (2.5 brushes per nodules in the outer-third of the lung versus 2.1 brushes per nodule in the inner two-third of the lung). The UB was introduced up to the ninth-generation bronchus, and the location of the lesions varied between the fourth to tenth generation bronchus (Table 2). The diagnostic yield of the procedure was higher for round nodules (21/27; 78%) compared to nodules shaped differently (spiculated, 5/12; lobulated, 3/6; elongated, 4/5; and irregular 2/2). The yield was noted to be higher for rounded than for non-rounded nodules (14/25, 56%) although statistically insignificant (p=0.09).

DISCUSSION

We have demonstrated the successful application of virtual bronchoscopy guided ultrathin bronchoscopy in sampling peripheral lung lesions. We utilized a 1.2 mm bronchial brush to obtain samples. The procedure is efficient, safe and does not need EMN or radial ultrasound guidance. The procedure can be performed in a reasonable duration [24,25]. The overall sensitivity of this procedure was 72.5% for cancers and specificity was 100%. Multiple characteristics (size - greater or smaller than 2 cm, location, histology - malignant versus benign, presence of bronchus sign, solid *vs* non-solid lesion, stage of cancer) were tested for their impact on the yield and diagnostic sensitivity; however, only size of the nodule seemed to impact the diagnostic accuracy. This relationship was not found to be statistically significant (p=0.06). The results also indicate that the absence of a bronchus sign does not reduce the diagnostic yield of the procedure if the nodule size is larger than 2 cm. For nodules sized less than 2 cm, the presence of a bronchus sign is associated with significantly higher positive diagnosis using this technique (71% vs 30%; p<0.05). It was interesting to find that the presence of a bronchus sign was more likely to be associated with a diagnostic test when we limited the analysis for nodules sized less than 2 cm. This leads us to hypothesize that for small lesions (<2 cm), the presence of a bronchus in the lesion increased the likelihood of a successful procedure even if we performed brushing of all visible subsegments leading to the nodule.

Our findings are different from previous reports that have reported the lesion size [19,26], proximity to the hilum, presence of bronchus sign [27-29], location of the nodule (lower yield for lesions in the LLL superior sub-segment) [22], CT-pulmonary artery sign [22] to impact diagnostic yields. These could be the result of a small sample size, or a result of the unique biopsy technique utilized in this study. It was also noted that a greater proportion of patients in the bronchus sign negative group (87.5% compared to 72.2% in the bronchus sign positive group) had a malignant nodule. The diagnostic yield of a malignant nodule was much higher than a benign nodule with our technique and may have impacted the analysis to an extent. The yield of technique described in this article falls toward the upper end of the spectrum of diagnostic yields obtained by an UB [11,12,14,17,19-21]. This is despite using a bronchial brush, which has been suggested by some authors to be associated with a lower diagnostic yield compared to the transbronchial forceps [12]. Our yields with the brush are higher compared to other studies using the brush through a regular flexible bronchoscope (41%) [30] or using the brush without any guidance software (16.5%) [31]. Results from the AQuIRE registry indicate a yield of 37.8% using the transbronchial brush technique and 19.3% from bronchoalveolar lavage [9]. We believe the higher yield in this current study is a direct result of the novel technique we have described here. Our technique differs sufficiently from the conventional method because we brush all the sub-segments visible after the bronchoscope has been maneuvered as far as possible toward the target. We have occasionally used multiple brushes (for 4 airways) for the same segment, which might have provided additional cells contributing to the yield. Some lung lesions are not in the center of the airway but rather are eccentrically placed in relation to the airway and partially involving the bronchial wall. These lesions may involve multiple airways instead of one. A navigational software will lead us through one of these airways, and with the extended working channel,

a tissue can be obtained from that location only. We avoid this limitation inherent to navigation-based biopsy techniques by using multiple brushes and from all visible airways that lead to the lesion. Virtual navigation-assisted ultrathin bronchoscopy techniques have been compared to an operator-driven CT scan-assisted biopsy through an UB [32]. The results of this study failed to show any benefit of the VBN-assisted technique. It is interesting to note that the authors had a success rate of 45.5% using the VBN-assisted technique. Whether the superior yield noted in our study can be explained by the novelty (accessing all visible segments rather than a single airway indicated by the VBN software) of our technique is a question worth asking. With our technique, the operator depends on the virtual bronchoscopic system to determine the best path to the lesion. Once close to the lesion, the operator will brush every small airway near the lesion. We believe that this allows for better sampling by accounting for any error that may have been introduced because of any inaccuracies in the road map generated by the virtual bronchoscopic system. It is well known that the forcep arrival rates and diagnosis rate vary depending on whether the involved bronchus is clearly delineated or not [21]. Our technique possibly excludes that factor by sampling every visible sub-segmental bronchus leading to the lesion once the bronchoscope is parked close to the lesion itself. Indeed, the bronchial brush has been reported to provide an 82.9% diagnostic yield for peripheral lung lesions using virtual bronchoscopy [20]. Some lesions may not invade the mucosa and only distort (Tsuboi III, IV type lesions) [33] the bronchial wall. In this case, biopsies may only obtain normal bronchial epithelium. Brushing different areas in these types of lesions will reduce the chances of sampling errors and may allow for a higher diagnostic yield. One of the notable benefits of using a brush was the lack of any adverse events in our study. In comparison to other studies where the rate of procedurerelated pneumothorax has been reported to be around 6% [24] and 2.2% [9], the lack of any complication with this technique is definitely one of the highlights of this technique.

The small number of cases is the limitation of this study. About one-third (37%) of nodules were in the inner two third of the lung field. It is unclear if this had a role to play in modifying the overall diagnostic yield in this case.

CONCLUSION

In summary, this study does not suggest that a UB should replace the conventional bronchoscope with r-EBUS and navigational techniques but rather supports the use of the ultrathin scope as an adjunct to other techniques for the evaluation of peripheral lung lesions. It provides evidence to add this potent tool to the bronchoscopist's armamentarium.

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