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# A novel use of endobronchial ultrasound bronchoscope to biopsy supraclavicular lymph node

## Abstract

**Background**: Accurate staging for patients with lung cancer is essential for management and prognostication. Percutaneous ultrasound-guided fine needle aspiration (US FNA) of supraclavicular lymph nodes is not always performed clinically for variety of reasons. Our study explores the utility of supraclavicular lymph node biopsy using the endobronchial ultrasound (EBUS) bronchoscope at the time of a mediastinal staging procedure as a possible alternative to US FNA.

**Methods**: This study included 22 patients who underwent supraclavicular lymph node biopsy using the EBUS bronchoscope during lung cancer staging procedure from 2019 to 2021 at the University of Pennsylvania. Feasibility and safety of the procedure were reported. Descriptive statistics were performed for baseline demographics, imaging features, pathology results, tumor cellularity and adequacy for oncological testing.

**Results**: The procedures were safely performed in all patients with no safety events reported. All patients were diagnosed with malignancy and EBUS-guided supraclavicular lymph node FNA showed definitive diagnosis in 19. Of the 16 patients with the final diagnosis of non-small cell lung cancer (NSCLC), 14 had tumor seen in supraclavicular lymph node sampling and 9 were upgraded to Stage IIIB disease from lower mediastinal lymph node staging. Eleven supraclavicular lymph node samples had tumor cellularity >10%. Eight samples were sent for next generation sequencing (NGS). Three of them were the only source for NGS.

**Conclusions**: Supraclavicular lymph node biopsy using the EBUS bronchoscope is a feasible and safe procedure to perform during lung cancer staging. Sampling has significant clinical value for accurate staging and oncologic testing.

**Keywords**: supraclavicular lymph node biopsy, EBUS, lung cancer staging, cytology, tumor cellularity, NGS

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**Abbreviations:** ISACL, International Association for the study of lung cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CT, computed tomography; PET, positron emission tomography; US FNA, ultrasound-guided fine needle aspiration; EBUS, endobronchial ultrasound; NGS, next generation sequencing; FDG fluorodeoxyglucose; OR, operating room; ROSE, rapid on-site evaluation; TBNA, transbronchial needle aspiration; FB, flexible bronchoscopy; IHC, immunohistochemistry stains; STP, solid tumor panel; FTP, fusion transcription panel; IQR, interquartile range; SUVmax, maximum standardized uptake value; PD-L1, programmed death-ligand 1.

## Introduction

Lung cancer continued to be the leading cause of death in the United States in 2021.[1] Based on the International Association for the Study of Lung Cancer (IASLC) 8th edition of non-small cell lung cancer (NSCLC) staging, supraclavicular lymph nodes are classified as N3 lymph nodes.[2] N3-positive NSCLC represents inoperable Stage IIIB disease.[3] The 5-year survival rate for patients with Stage IIIB NSCLC was 24% compared with 42% for stage IIIA disease.[4] A contralateral supraclavicular lymph node upstages small cell lung cancer (SCLC) to extensive stage disease, with a 2-year survival of 5%, compared with 20-40% for limited stage.[5,6] Therefore, proper staging of lung cancer is essential for management and prognosis.

Computed tomography (CT) and positron emission tomography (PET) scans are frequently used for clinical lung cancer staging. For the diagnosis of mediastinal and hilar lymph node staging, CT and PET were found to have sensitivities of 76.9% and 80.0% respectively.[7] A meta-analysis including 698 patients showed only 52% agreement between clinical staging and pathological staging.[8] Twenty-three percent of patients were clinically under-staged and 14% were over-staged. Both scans are helpful in detecting metastasis to supraclavicular lymph nodes with reported sensitivities of 67% for CT and 71% for PET.[9] The detection of enlarged supraclavicular lymph node on CT scan increases as the mediastinal involvement becomes evident.[10] However, not all enlarged supraclavicular lymph nodes represent metastatic disease. Brantigan et al. reported that the positive yield for palpable supraclavicular lymph node was 98% but only 23.8% for non-palpable ones based on pathology findings from surgically resected lymph nodes in patients with NSCLC.[11] Therefore, it is important to obtain pathologic diagnosis of enlarged supraclavicular lymph node in patients with suspected lung cancer.

Ultrasound-guided fine needle aspiration (US FNA) has been established to be feasible and safe for supraclavicular lymph node biopsy.[12] Its clinical use varies significantly from center to center, and biopsy of an enlarged supraclavicular lymph node is not always performed. The obstacles clinicians may face when attempting to implement routine supraclavicular US-FNA in staging lung cancer

patients include the availability of equipment and staffing, training and comfort level for US-FNA, as well as timing of the biopsy under the aegis of the US department if unable to perform individually. Another concern clinicians may have, is a delay in diagnosis from a false negative. In addition, US-guided biopsy of the supraclavicular lymph node is not always feasible given the close proximity of supraclavicular lymph nodes to vessels and vital organs.

The idea of acquiring tissue from metastatic sites, such as supraclavicular nodes, is more relevant than ever, as immunotherapy and targeted therapy for advanced stage NSCLC are now available.[13] The requirements for tissue acquisition must enable molecular analysis. The value of routine supraclavicular lymph node biopsy for invasive pathologic staging and oncologic testing beyond diagnosis has yet been evaluated.

The current study explores the utility of performing supraclavicular lymph node biopsy using the endobronchial ultrasound (EBUS) bronchoscope by interventional pulmonologists at the time of a mediastinal staging procedure as a possible alternative to regular US FNA. The aim of the study is to establish feasibility and safety of the procedure. The clinical value of the supraclavicular lymph node biopsy for additional oncologic testing such as next generation sequencing (NGS) was also evaluated. Some of the results of the study were previously reported in the form of an abstract.[14]

## Material and methods

### Study cohort

This retrospective study has received exemption from the University of Pennsylvania Institutional Review Board (IRB protocol # 844679). We retrospectively reviewed all patients who underwent EBUS bronchoscope directed biopsy of supraclavicular lymphadenopathy from August, 2019 to September, 2021. Patients with suspected lung cancer were scheduled for diagnostic and staging EBUS at the Hospital of University of Pennsylvania (Philadelphia, PA). CT and/or PET scans were reviewed by an attending physician prior to EBUS procedure. If supraclavicular lymphadenopathy was evident on pre-procedure CT scan and/or was fluorodeoxyglucose (FDG)-avid on pre-procedure PET scan, it was evaluated using the EBUS bronchoscope and biopsied if feasible during the diagnostic bronchoscopy procedure in the operating room (OR). A total of 22 patients were identified and included in the study. We reviewed patient demographic information, image studies, procedure reports, as well as cytology, surgical pathology and molecular analysis reports.

### EBUS lung cancer staging

A convex probe ultrasound bronchoscope (Olympus BF-UC180F; Olympus America Inc, Central valley, PA) was used for EBUS procedures in the OR. Total intravenous general anesthesia was used for all patients with continuous infusions of propofol and remifentanil. The bronchoscope was inserted orally and a systematic nodal evaluation was done according to clinical guidelines.[2] Any lymph node that had a short axis greater than 5mm under ultrasound was sampled. Number of passes and agitations were obtained per operator's discretion with the institutional standard of care to perform 3 passes per lymph node and 30 agitations per pass. We used 22-gauge EBUS needles (NA-201SX-4022, Olympus America Inc, Central valley, PA) in most cases; while 19-gauge needles (Vizishot FLEX 19G, Olympus America Inc, Central valley, PA) were used when alternative diagnosis, such as lymphoma, was suspected. Rapid on-site evaluation (ROSE) was only used at bronchoscopist's discretion.

### Supraclavicular lymph node biopsy using EBUS bronchoscope

Supraclavicular lymph node biopsy using the EBUS bronchoscope was performed prior to mediastinal lymph node sampling as it represented the highest lymph node stage in patients with suspected lung cancer. Two operators were needed for the procedure. One operated the bronchoscope, while the other held the tip of the bronchoscope firmly on the skin to stabilize scope apposition (Figure 1). A small amount of saline was sprayed on the patient's neck to facilitate ultrasonic coupling. Once the site was identified, alcohol-based antiseptic was used to clean the skin. The EBUS bronchoscope was then placed on the skin and the operator scanned for the lymph node in the neck. FNA biopsy was performed if the short axis of the lymph node was more than 5mm. During the biopsy, one operator held the end of the bronchoscope tightly against the skin and the other operator performed the FNA in the same manner as used during mediastinal lymph node EBUS-Transbronchial needle aspiration (EBUS-TBNA).

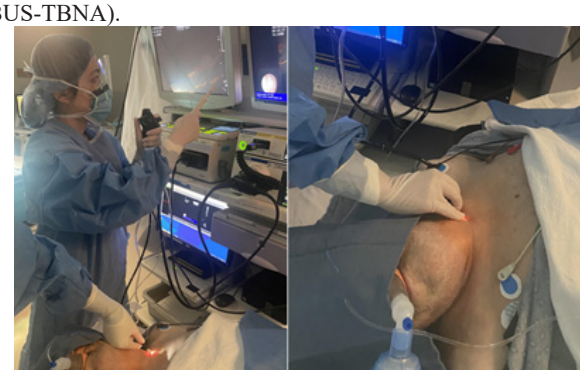

**Figure 1** Supraclavicular lymph node biopsy using EBUS bronchoscope.

### Flexible bronchoscopy (FB)

We performed FB for all patients for airway exam and biopsy of endobronchial lesion and/or peripheral lung lesion if clinically indicated.

### NGS and immunohistochemistry stains (IHC)

After the diagnosis of NSCLC was made, IHC and NGS were performed following a health system wide reflex pathway. Tissues diagnosed with adenocarcinoma or squamous cell carcinoma underwent programmed death-ligand 1 (PD-L1) staining. In cases where sufficient analyzable material was available, NGS was performed on tissues diagnosed specifically with adenocarcinoma. The solid tumor panel (STP) is a NGS assay used for DNA sequencing of 152 genes; the fusion transcription panel (FTP) was an RNA sequencing assay of 55 gene rearrangements. Both tests were performed at the Center for Personalized Diagnostics lab at the Hospital of the University of Pennsylvania. Testing was triaged according to available tissue. Assays were previously validated for cytologic and surgical pathology specimens.[15]

### Outcomes and covariates

The primary outcome of the study was the feasibility and safety of supraclavicular lymph node biopsy using EBUS bronchoscope. A final chart review was performed at the time of data entry to look for safety events. Minimum time that passed between procedure and final chart review was about 2 months. We also described the imaging characteristics and pathological diagnoses of the supraclavicular lymph node biopsied. For patients with the diagnosis of NSCLC, we further described tumor cellularity of the supraclavicular lymph node biopsied and its use for molecular analysis.

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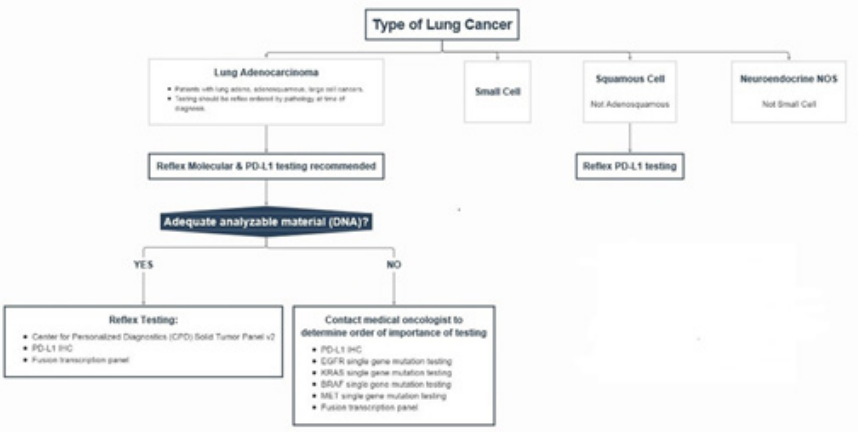


**Figure 2** NSCLC molecular analysis and IHC pathway at the hospital

PD-L1, programmed death-ligand 1; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus; BRAF, v-raf murine sarcoma viral oncogene homolog B1; MET, mesenchymal epithelial transition.

## Statistical analysis

We used descriptive statistics to evaluate patient baseline characteristics. Median and interquartile range(IQR) were used to describe continuous variables, while frequencies and percentages were used for categorical variables. All analyses were conducted using Stata/BE 17.0.

# Results

There was a total of 22 patients who underwent supraclavicular lymph node biopsy using the EBUS bronchoscope during the study period. Patient characteristics are shown in Table 1. Slightly over half of the patients were female. The median BMI was 27. Most of the patients smoked in the past with a median of 50 pack-year smoking history. Over half of the patients(N=12) were deceased at the time of data collection. NSCLC was the diagnosis most frequently made. Among those patients, the majority were found to have poorly differentiated carcinoma. Other final diagnoses include SCLC, lymphoma and poorly differentiated malignant epithelioid neoplasm.

**Table 1** Demographics and patient characteristics

| | No.(%) or Median(IQR) |
|---|---|
| **Gender** | |
| Female | 12(54.6%) |
| Male | 10(45.6%) |
| Age | 69(62-77) |
| Ethnicity | |
| Caucasian | 18(81.8%) |
| African American | 1(4.6%) |
| Asian | 1(4.6%) |
| Other | 2(9.1%) |
| BMI | 27(24-32) |
| Smoking status | |
| Current smoker | 4(18.2%) |
| Former smoker | 14(63.4%) |
| Never smoker | 4(18.2%) |
| Pack-year | 50(12-60) |
| Deceased | 12(54.6%) |
| Diagnosis | |
| NSCLC | 16(72.7%) |
| Poorly differentiated carcinoma | 14(63.6%) |
| Adenocarcinoma | 1(4.6%) |
| Squamous cell carcinoma | 1(4.6%) |
| SCLC | 4(18.2%) |
| Lymphoma | 1(4.6%) |
| Poorly differentiated malignant epithelioid neoplasm | 1(4.6%) |

NSCLC,non-small cell lung cancer; SCLC, small cell lung cancer; IQR, interquartile range

## Feasibility and safety of supraclavicular lymph node biopsy using EBUS bronchoscope

All supraclavicular lymph node biopsy using EBUS bronchoscope was successfully performed. Tissue was present for cytology or pathology exam in all cases. There were no complications reported, such as bleeding, hematoma, infection or pneumothorax.

## Characteristics of supraclavicular lymph nodes

Imaging characteristics and pathologic diagnoses of supraclavicular lymph nodes are shown in Table 2. Enlarged right-side supraclavicular lymph nodes were present in 72.7% of the patients and two had bilateral lymph nodes. The median size of the lymph node was 11x17mm. It was not documented if the lymph node was palpable or not. All of the enlarged supraclavicular lymph nodes were FDG avid on PET scan with a median maximum standardized uptake value (SUVmax) of 7.6. The majority of the cases had concordant pathology between the supraclavicular lymph node biopsy and the mediastinal lymph node samples with an overall positive rate of 86.4% (14 NSCLC, 4 SCLC, 1 lymphoma) for malignancy from supraclavicular lymph node biopsy. One sample had only atypical cells and two samples were lymphocytes only.

Among the 16 patients with NSCLC, supraclavicular lymph node biopsy upstaged more than half of the patients (N=9) from their pathologic mediastinal lymph node stages. One patient had no diagnostic sample from mediastinal lymph node biopsies and the supraclavicular lymph node biopsy was the only source for tissue diagnosis. Supraclavicular lymph node biopsy was frequently used for NGS. Only 3 samples (18.8%) were considered inadequate for NGS by using the internal cut off for tumor cellularity of > 10% to attempt the assay. NGS panels were run on supraclavicular lymph

node biopsy samples in half of the cases (N=8), and in three cases it was the sole tissue source for NGS. Comprehensive data pertaining to tumor cellularity and its suitability for NGS analysis has been elucidated in Table 3. Mutations in TP53, KRAS and STK11 were the most frequently detected.

Among the 4 patients with SCLC, 3 were found to have extensive stage disease based on mediastinal staging alone. One patient had limited stage disease with metastasis to unilateral supraclavicular lymph node, which did not upgrade his disease. Detailed clinical information on individual patient is available in Table 4.

**Table 2** Imagine characteristics and pathological diagnosis of supraclavicular lymph nodes

| | **No.(%) or Median (IQR)** |
|---|---|
| Site of enlarged supraclavicular lymphnode on image study | |
| Rightside | 16(72.7%) |
| Leftside | 4(18.2%) |
| Bilateral | 2(9.1%) |
| Size of supraclavicular lymphnode on CT scan | |
| Shortaxis | 11mm (10-19mm) |
| Longaxis | 17mm(13-23mm) |
| FD Gavidity of supraclavicular lymphnode on PET scan | 7.6(4.9-13.5) |
| Pathology diagnosis of supraclavicular lymphnodebiopsy | |
| NSCLC | |
| Poorly differentiated carcinoma | 13(59.1%) |
| Squamous cell carcinoma | 1(4.6%) |
| SCLC | 4(18.2%) |
| Lymphoma | 1(4.6%) |
| Atypicalcells | 1(4.6%) |
| Lymphocytes–nomalignantcellsseen | 2(9.1%) |

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; IQR, interquartile range

**Table 3** Tumor cellularity, NGS status and clinic significance of supraclavicular lymph node biopsy in patients with NSCLC

| | **No.(%)** |
|---|---|
| Total number of patients with NSCLC | 16 |
| NSCLC upstaged by supraclavicular lymph node biopsy | 9 (56.3%) |
| Tumor cellularity for supraclavicular lymph node | |
| <10% | 3(21.4%) |
| 10-19% | 3(21.4%) |
| 20-39% | 4(28.6%) |
| >40% | 4(28.6%) |
| NGS running on supraclavicular lymph node biopsy samples | 8 (50%) |
| FNA from supraclavicular lymph node as the sole source for NGS | 3 (18.8%) |

NSCLC, non-small cell lung cancer; NGS, next generation sequencing; FNA, fine needle aspiration

**Table 4** Clinical and oncological information

| | **Site of enlarged supraclavicular lymph node on image study** | **Final diagnosis** | **Mediastinal Stage** | **Pathology diagnosis from supraclavicular lymph node** | **Tumor Cellularity of Supraclavicular lymph node biopsy** | **NGS run on supraclavicular lymph node** | **Disease related mutations** |
|---|---|---|---|---|---|---|---|
| 1 | Right | Poorly differentiated carcinoma | N2 | Poorly differentiated carcinoma | 20-39% | Yes | TP53, KRAS, STK11 |
| 2 | Right | poorly differentiated carcinoma | N3 | poorly differentiated carcinoma | >40% | Yes | KRAS, STK11 |
| 3 | Right | Poorly differentiated carcinoma | Suspicious for malignancy only | Poorly differentiated carcinoma | 10-19% | Yes(only source) | QNS |
| 4 | Right | Poorly differentiated carcinoma | N3 | Poorly differentiated carcinoma | 20-39% | Yes | KRAS, TP53 |
| 5 | Bilateral | Hodgkin lymphoma | NA | Hodgkin lymphoma | | | |
| 6 | Right | Poorly differentiated malignant epithelioid neoplasm | NA | Few lymphocytes | | | |
| 7 | Right | SCLC | Extensive stage | SCLC | | | |
| 8 | Right | Poorly differentiated carcinoma | N2 | Poorly differentiated carcinoma | 10-19% | Yes | KRAS, TP53 |
| 9 | Right | SCLC | Extensive stage | SCLC | | | |

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Table 4 Continued....

| | Site of enlarged supraclavicular lymph node on image study | Final diagnosis | Mediastinal Stage | Pathology diagnosis from supraclavicular lymph node | Tumor Cellularity of Supraclavicular lymph node biopsy | NGS run on supraclavicular lymph node | Disease related mutations |
|---|---|---|---|---|---|---|---|
| 10 | Bilateral | SCLC | Extensive stage | SCLC | | | |
| 11 | Right | Poorly differentiated carcinoma | N3 | Poorly differentiated carcinoma | 10-19% | No | NF1, NF2, BRCA2, SETD2, MET |
| 12 | Right | Poorly differentiated carcinoma | N3 | Poorly differentiated carcinoma | <10% | No | KRAS,TP53, SMARCA4, MDM5C, BRCA2, SETD2, MET |
| 13 | Right | Poorly differentiated carcinoma | N2 | Poorly differentiated carcinoma | <10% | No | |
| 14 | Left | SCLC | Limited stage | SCLC | | | |
| 15 | Left | Poorly differentiated carcinoma | No enlarged mediastinal lymph node | Poorly differentiated carcinoma | >40% | Yes(only source) | Normal sequencing |
| 16 | Right | Poorly differentiated carcinoma | N3 | Poorly differentiated carcinoma | >40% | No | KRAS, TP53, EGFR, KMT2C |
| 17 | Right | Poorly differentiated carcinoma | N2 | Poorly differentiated carcinoma | 20-39% | No | KRAS, TP53, EGFR, KMT2C |
| 18 | Right | Adenocarcinoma | N3 | rare atypical cell | | No | STK11, NF2 |
| 19 | Right | Poorly differentiated carcinoma | N3 | Poorly differentiated carcinoma | >40% | Yes(only source) | KRAS, STK11 |
| 20 | Left | poorly differentiated carcinoma | N2 | poorly differentiated carcinoma | <10% | No | STK11, ATRX, CDKN2A, SMARCA4 |
| 21 | Left | squamous cell carcinoma | N1 | squamous cell carcinoma | 20-39% | Yes | TP53, KDM5C |
| 22 | Right | poorly differentiated carcinoma | N2 | lymphocytes | | No | TP53, MET |

## Discussion

The current study examined the feasibility of supraclavicular lymph node biopsy using the EBUS bronchoscope during bronchoscopic mediastinal staging for suspected lung cancer. All procedures were safely performed with no procedure-related adverse events reported. Pathology exam was successfully performed in all cases. Importantly, supraclavicular lymph node biopsy upstaged over half of the NSCLC cases. Tissue from supraclavicular lymph node biopsies was frequently used for NGS and served as the sole source for NGS testing in some cases.

It is well studied that clinical staging does not correlate well with pathological staging.[8,16] Therefore, invasive lymph node staging is preferred when feasible. The reported clinical practice to biopsy supraclavicular lymph nodes varies significantly. Some patients are referred to interventional radiology for US FNA;[10] some are biopsied by pulmonologists in the office setting;[17] and others probably forgo biopsy and clinical staging is used instead. The role of supraclavicular lymph node US FNA in the diagnosis of lung cancer has been studied in the past.[18, 19] It has shown to be safe and effective. However, some obstacles lung cancer clinicians face include availability of resources (e.g. staffing, equipment), personal familiarity and comfort with the procedure, and the lack of an established pathway for a consulting service with expertise to perform timely outpatient US FNA. Other concerns include possible delay in diagnosis in the case of a false negative; and percutaneous biopsy not feasible due to anatomy. For example, one prospective study that enrolled 101 patients with suspected lung cancer and enlarged supraclavicular lymph node on CT scan, only 62 had enlarged lymph nodes on ultrasound.[18] Eighty-eight patients were eventually diagnosed with cancer; however, only 44 received a diagnosis from an initial supraclavicular lymph node US FNA. All of the above reasons might have contributed to the limited use of US FNA of supraclavicular lymph nodes more routinely. Biopsy of enlarged supraclavicular lymph nodes using the EBUS bronchoscope during lung cancer staging procedures does not require extra resources, and the pulmonologist can use the equipment that she/he is familiar with for the procedure. In this small series, the procedure was easy to perform with one operator and one assistant. No major safety concerns were found. Additionally, traditional mediastinal lymph node staging via EBUS TBNA as well as biopsy of a primary lesion, if necessary, can be performed during the same procedure.

The current study showed the majority of the patients who underwent supraclavicular lymph node biopsy using the EBUS bronchoscope were diagnosed with lung cancer. Over half of the patients with NSCLC were found to have N2 or lower stage disease with traditional mediastinal staging and were upgraded to stage IIIB with a positive supraclavicular lymph node. There were two patients who did not have biopsy proven metastasis despite enlarged lymph nodes by CT scan. This is consistent with the literature - false positives

for CT and PET scans are not uncommon[20] and the diagnostic accuracy of integrated PET and CT in the detection of supraclavicular lymph node metastasis was reported to be 71%.[9] Although supraclavicular lymph node biopsy did not change disease stage for any of the patients with SCLC in our current study, its clinical use is still of value as the presence of contralateral supraclavicular lymph node is not uncommon and biopsy should be considered.

Our study supports biopsy of supraclavicular lymph nodes for more accurate pathologic lymph node staging for selected patients. Regardless of the technique used, this data suggests supraclavicular lymphadenopathy should be evaluated by FNA when it is enlarged on CT scan and/or FDG-avid on PET during diagnosing and staging suspected lung cancer. By employing rapid on-site cytology or an expedited outpatient US-FNA service, many patients could potentially skip bronchoscopy all together if the supraclavicular lymph node samples provided adequate tissue for tumor characterization and molecular analysis. Our approach is a feasible alternative to promote expedient tissue acquisition in a patient-centered fashion and to collect more specimens for all downstream analyses.

Our study showed adequate tumor cellularity from supraclavicular lymph node biopsy for NGS in the majority of cases. For about half of the NSCLC patients, the samples from the supraclavicular lymph node biopsy were determined to be the best samples for NGS by pathologists. Tissue from the supraclavicular lymph node biopsy was the sole tissue source for NGS in 18.8% of the cases. To the best of our knowledge, there was no previous research studying the use of cytology samples from supraclavicular lymph node biopsies for NGS testing. Our study shows that the sample could be invaluable for oncologic testing in certain patients.

## Limitations

The current study is a small, single-center, retrospective study. Patients with either enlarged supraclavicular lymph node on CT scan (>1cm) or increased FDG uptake in the same area on PET scan were screened. We did not evaluate patients without above features nor the ones who had above features but did not go through biopsy.

## Conclusions

The current study described a novel way to use the EBUS bronchoscope for the biopsy of supraclavicular lymph nodes as an alternative to standard US FNA. The technique can be performed by interventional pulmonologists, is safe to perform, and can add valuable information for the staging and management of lung cancer.

## Conflicts of interest

Drs Haas and DiBardino have received consulting fees from Olympus America, Inc. There is no disclosure from other authors of this manuscript.

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