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The Role of Endobronchial Ultrasound in Early-Stage Non-Small Cell Lung Cancer

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Aim
The aim of this study is to assess the impact of EBUS on the concordance of clinical and pathological NSCLC staging in our center.

Methods
Data was collected retrospectively from the hospital database regarding patients who underwent surgical resection for early stage NSCLC between 2012 and 2017.

Results
A total of 251 patients were included. The mean age was 67 (±9), 55% (n=137) were male and 83% (n=209) were current/former smokers. In group A (n=154, 61%) clinical nodal stage (cN) was established from a combination of CT, PET CT and mediastinoscopy. Group B underwent additional EBUS (n=97, 39%). cN and pathological nodal staging (pN) were concordant in 78% (n=120) in group A versus 62% (n=60) in group B (p=0.009).

Conclusion
This study demonstrated higher rates of nodal discordance in patients who underwent EBUS which contrasts existing data that demonstrates improved concordance with EBUS. We describe these findings and potential explanations further in this study.

Keywords:
Endobronchial ultrasound; Nonsmall cell lung cancer; Mediastinal staging

Introduction

Lung cancer is a devastating illness, that accounted for over 2 million deaths globally in 2018[1]. Due to the frequent lack of symptoms in early stage disease and until recently, the absence of an effective screening program, lung cancer often presents at an advanced stage. Consequently, accurate clinical staging is essential to appropriately select patients for surgical resection.[2] Depending on regional availability and expertise, conventional clinical staging modalities include non-invasive methods such as CT, PET CT and invasive techniques such as EBUS, endoscopic ultrasound (EUS) and mediastinoscopy. Accurate mediastinal nodal staging is essential in early-stage non-small cell lung cancer (NSCLC) to appropriately select patients for surgical resection. The introduction of endobronchial ultrasound (EBUS) has revolutionized mediastinal staging and is now the recommended mode of lymph node

assessment in patients with suspected early stage NSCLC and radiological evidence of lymph node enlargement greater than 10mm, PET avid lymph nodes, central tumors, tumors with low FDG uptake or advanced tumor size.[3-5] Surgical pathological stage is considered the gold standard and guides decisions regarding adjuvant treatment, postoperative surveillance and prognosis. Current evidence suggests that the correlation between clinical and pathological staging remains poor, with an accuracy ranging from 47 to 91%.[6-8] The aim of this study is to assess the impact of EBUS on the concordance of clinical and pathological NSCLC staging in our center.

Methods

This study received ethical approval from Galway University Hospital institutional review board. A retrospective search of the hospital database was performed to identify patients who underwent surgical resection of early stage NSCLC between 2012 and 2017. Data regarding patient demographics, radiological investigations including CT thorax and PET CT and invasive clinical staging techniques including mediastinoscopy and EBUS were collected from the hospital electronic database and electronic patient records. Cases were excluded from further analysis if there was inadequate available data or if patients received neoadjuvant therapy, as this would interfere with the interpretation of pathological nodal staging. Benign disease or malignant disease other than NSCLC were also excluded. Patients who underwent clinical staging using CT, PET CT and/or mediastinoscopy were allocated to Group A. Patients who underwent additional EBUS were designated group B.

EBUS-transbronchial needle aspiration (TBNA) was performed using a convex probe-EBUS bronchoscope (Pentax EB-1970UK; Pentax Medical, Hamburg, Germany). All procedures were performed under conscious sedation using a combination of intravenous midazolam and alfentanyl. EBUS inspection was performed systematically as per ERS guidelines and visible lymph node stations sampled from N3 nodes to N1 to prevent cross contamination.[9] TBNA samples were placed in formalin and sent to the hospital laboratory for examination. The pathologist defined adequacy by the presence of lymphoid tissue or tumor cells.

Intraoperative lymph node sampling techniques included systematic sampling and block lymph node dissection, depending on the surgical procedure and operator preference. Latency was defined as the time from lung cancer multidisciplinary team (MDT) decision for surgical resection, to the operation day. Pathological specimens were classified using the seventh TNM lung cancer staging system.

Statistical analysis was performed using GraphPad online statistical software. Fisher's exact test was employed to assess the statistical significance for categorical variables and t-test was used to calculate significance between means. A value < 0.05 was considered statistically significant ($P < 0.05$).

Results

Patient characteristics

276 cases of early stage NSCLC underwent surgical resection between 2012 and 2017 and were selected for further analysis. A total of 25 cases were excluded; 17 due to inadequate clinical data and 8 due to neoadjuvant therapy. 251 cases were included in the final analysis. The mean age of study participants was 67 (±9), 55% (n=137) were male and 83% (n=209) were current or former smokers. 154 patients underwent clinical staging using a combination of CT, PET CT and mediastinoscopy in Group A and 97 underwent additional EBUS in Group B.

Clinical stage

Table 1 demonstrates results in Group A and Group B. The median age in Group A and B was 67. There was a male preponderance in Group B at 61% (n=61) (p=0.038). Group B demonstrated higher smoking rates at 92% (n=89) compared to 78% (n=120) in Group A (p<0.001). Adenocarcinoma was the predominant histology in both groups at 57% (n=88) in Group A and 43% (n=42) in Group B.

Clinical T and N stage differed between the two groups as illustrated in Table 1. Patients in Group A demonstrated a lower initial clinical T stage, as 54% (n=84) had T1 disease versus 36% (n=35) in Group B (p=0.006), and a lower clinical nodal stage, with 94% (n=145) demonstrating N0 disease versus 78% (n=76) in Group B (p<0.001).

Table 1. includes a detailed breakdown of patient demographics and clinical and pathological staging in Group A and Group B. Information regarding clinical and pathological lymph node concordance in displayed in the two separate Groups.

	Group A n (%)	**Group B** n (%)
Total	154 (100%)	97 (100%)
Age (Mean, SD)	67 (±10)	67 (±8)
Male sex	76 (49%)	61 (63%)
Current or former smoker	120 (78%)	89 (92%)
Pre operative investigations		
CT	154 (100%)	97 (100%)
PET CT	137 (89%)	97 (100%)
Mediastinoscopy	1 (1%)	4 (4%)
EBUS	0	97 (100%)
Clinical tumour stage		
T1a	58 (37%)	24 (25%)
T1b	26 (17%)	11 (11%)
T2a	41 (26%)	29 (30%)
T2b	1 (1%)	10 (10%)
T3	24 (16%)	20 (21%)
T4	3 (2%)	2 (2%)
TX	1 (1%)	1 (1%)
Clinical nodal stage		
cN0	145 (94%)	76 (78%)
cN1	9 (6%)	17 (18%)
cN2	0	4 (4%)
Tumour histology		
Squamous	35 (23%)	35 (36%)
Adenocarcinoma	88 (57%)	42 (43%)
Carcinoid (typical)	8 (5%)	3 (3%)
Carcinoid (atypical)	1 (1%)	0
Large cell neuroendocrine	3 (2%)	1 (1%)
Other	19 (12%)	16 (17%)
Lung cancer surgery		
Lobectomy	135 (88%)	74 (76%)
Bilobectomy	12 (8%)	13 (14%)
Pneumonectomy	7 (4%)	10 (10%)
Pathological tumour stage		
pT1a	38 (25%)	12 (12%)
pT1b	34 (22%)	17 (18%)
pT2a	56 (37%)	36 (37%)
pT2b	8 (5%)	13 (13%)
pT3	16 (10%)	16 (17%)
pT4	2 (1%)	3 (3%)
pTX	0	0
Pathological nodal stage		
pN0	116 (75%)	46 (47%)
pN1	24 (16%)	27 (28%)
pN2	14 (9%)	24 (25%)
Resection margins		
R0	146 (95%)	80 (83%)
R1	3 (2%)	7 (7%)
R2	4 (2%)	9 (9%)
RX	1 (1%)	1 (1%)
Latency (days)		
Mean (**±**SD)	49 (± 26)	45 (±19)
Nodal staging (clinical vs pathological)		
Nodal downstaging		
• One nodal station (-N1)	2 (2%)	0
• Two nodal stations (-N2)	0	0
No change (cN=pN)	120 (78%)	60 (62%)
Nodal upstaging		
• One nodal station (+N1)	19 (12%)	24 (25%)
• Two nodal stations (+N2)	13 (8%)	13 (13%)

EBUS-TBNA adequacy

A total of 97 patients underwent EBUS for mediastinal staging in Group B. The indications for EBUS included lymphadenopathy greater than 10mm (n=50, 52%), FDG avid lymph nodes with a suvMAX ≥2.5 (n=51, 53%), primary tumour size greater than 3cm (n=45, 46%) and central tumours (n=28, 29%). In 7 cases the indications were subcentimeter lymphadenopathy and multiple pulmonary nodules. The indication was not specified in 2 cases. TBNA was performed in 86 of the 97 cases (89%). Regarding lymph node stations sampled, one station was sampled in 38 cases (44%), two lymph node stations in 37 cases (43%) and three stations in the remaining 11 cases (13%). Total EBUS-TBNA adequacy was 87% (Table 2).

Table 2. Describes the adequacy of EBUS-TBNA samples in the 86 cases that underwent EBUS in Group B. This is analyzed per lymph node stations N1, N2 and N3.

EBUS Nodal stations	EBUS-TBNA (n=86):	Adequate n (%)	Inadequate n (%)
N1	52	44 (85%)	8 (15%)
N2	66	57 (86%)	9 (14%)
N3	27	25 (93%)	2 (7%)

Pathological stage

Pathological T and N stages are described in Table 1. The mean waiting time from referral to surgery was not significantly different between groups. (p=0.19).

Lymph node concordance

Clinical nodal stage (cN) and pathological nodal staging (pN) were concordant in 78% (n=120) in Group A versus 62% (n=60) in Group B (p=0.009). Two patients in Group A were downstaged a lymph node station following analysis of surgical specimens. 20% (n=32) in Group A and 38% (n=37) in Group B were upstaged post operatively (p=0.003) (Figure 1).

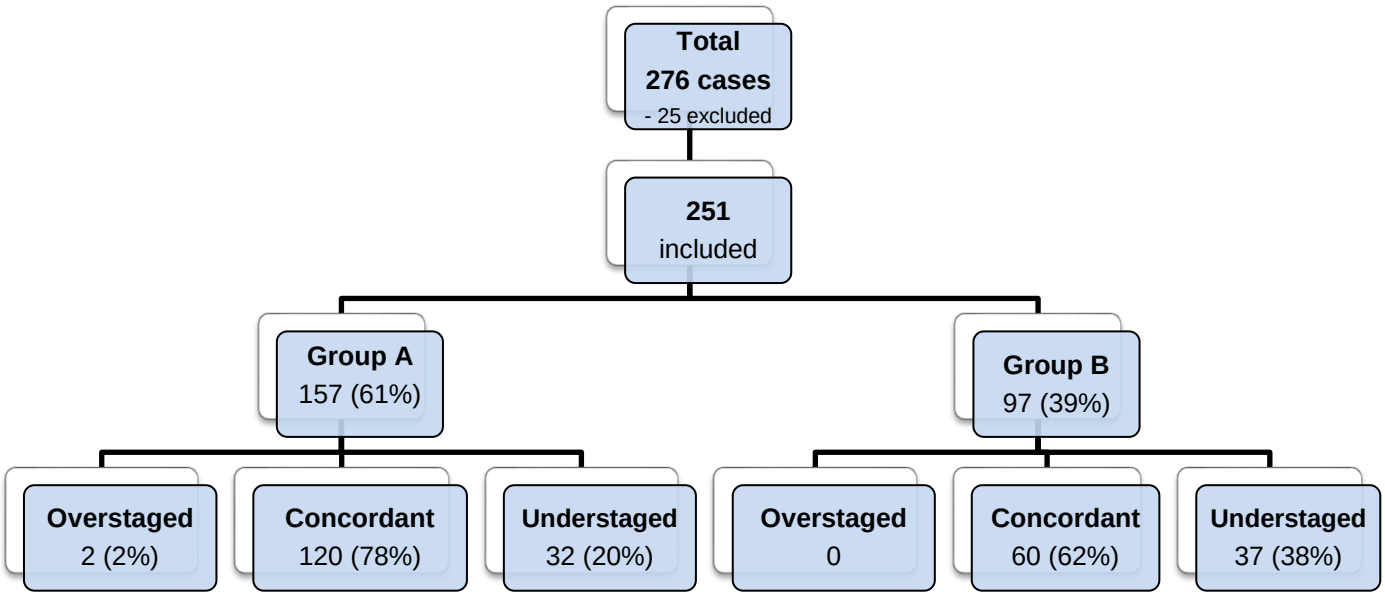

Figure 1. This flowchart illustrates the 276 patients included in the original analysis. 25 cases were subsequently excluded; 17 as there was inadequate available data and 8 as the patients underwent neoadjuvant chemotherapy which would interfere with subsequent nodal station interpretation. 251 cases were included in the final analysis: patients in Group A underwent a combination of CT, PET CT and/or mediastinoscopy, while patients in Group B underwent additional EBUS. 'Overstaged' refers to a situation where clinical lymph node staging indicated a higher lymph node stage when compared to the final pathological lymph node stage, 'Understaged' refers to the opposite situation where pathological nodal staging exceeded original clinical lymph node staging and 'concordant' refers to a situation where clinical and pathological lymph node stages were the same.

In total 37 patients (38%) had evidence of nodal upstaging in Group B post operatively, 19% (n=7) of these cases were not accessible by conventional EBUS; as 11% (n=4) were peribronchial lymph nodes and 8% (n=3) were a combination of stations 5, 8 and 9 respectively. Of these 37 patients, the total number of unexpected N2 disease was 54% (n=20) (Figure 2). Thirty eight percent (n=5) of N2 nodes had no evidence of N1 disease and were defined as 'skip lesions'.

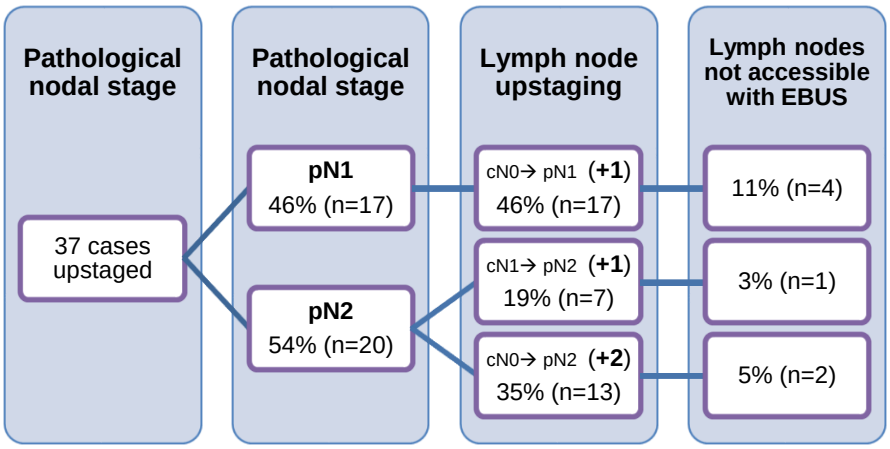

Figure 2. illustrates the 37 cases of nodal upstaging in patients who underwent EBUS in Group B. **pN1** refers to pathological upstaging of one nodal stage and **pN2** refers to pathological upstaging of two nodal stations. Similarly, **+1** indicates a single nodal station upstage and **+2** refers to upstaging of two lymph node stations.

Discussion

Current evidence suggests that the correlation between clinical and pathological staging is poor, with an accuracy that ranges from 47 to 91%.[6-8] Overall clinical and pathological lymph node concordance was 72% (n=180) in this study, reflecting the complex interplay of diagnostic, therapeutic and individual patient factors.

CT and PET CT are important clinical staging modalities; however, the sensitivity is highly dependent on lymph node size. The sensitivity of PET-CT approximates 0.85 for nodes $\geq$ 10 mm in diameter but can drop to 0.32 for nodes less than 10 mm and therefore this modality can potentially miss micrometastases to lymph nodes which do not meet this critical size criteria.[10] Furthermore PET CT can be associated with false positives and though the rates of overstaging were low in this study at 1% (n=2) and occurred in patients who did not undergo invasive mediastinal staging, this should be avoided as it could inappropriately exclude patients from curative treatment.[8]

Convex probe EBUS was developed in 2002 and incorporated into European Society of Thoracic Surgeons (ESTS) and American College of Chest Physicians (ACCP) guidelines for mediastinal staging in 2007.[3,4] EBUS was introduced in our center in 2012 and is currently the recommended initial invasive mode of mediastinal lymph node assessment in patients with suspected early stage NSCLC and suspicion of malignant nodal disease based on aforementioned criteria.[3,5] In this study the rates of nodal discordance were higher in patients who underwent additional EBUS, however interpretation of this finding is difficult in light of potential selection bias, as by definition, patients in group B were inherently more likely to have larger, more central tumors or imaging suggestive of nodal disease. In this study we found that patients in the EBUS cohort were more likely to be male and demonstrated significantly higher smoking rates, initial tumor and nodal stage. Prior studies have reported that a higher cT stage, adenocarcinoma histology and a longer waiting time to surgery are risk factors for upstaging, however they offer inconsistent findings regarding the risk gender poses.[8,10-12]

All EBUS in this study were systematic sampling procedures, performed by an experienced interventional pulmonologist. No formal auditing process exist for EBUS-TBNA in Ireland, however the British Thoracic Society Quality Statement for EBUS-TBNA in 2014 recommend a minimum diagnostic sensitivity of 88% for lung cancer staging.[13] In this study the diagnostic adequacy was 93%, 86% and 85% for N3, N2 and N1 nodes respectively. Sensitivity of N2 and N3 nodes is below the suggested 88% and could reflect numerous factors including increasing patient arousal as the procedure progresses. The limitations of EBUS in mediastinal staging must also be considered when analysing clinical and pathological concordance. EBUS-TBNA typically cannot sample ATS 5, 6, 8 and 9.[10,14] These lymph node stations accounted for 3 (8%) of the 37 cases that were understaged in this study and highlights the utility of EUS guided fine

needle aspirate (FNA) as a complementary mediastinal staging tool, as demonstrated by Zhang et al (2013) and recommended in current guidelines.[15,16]

In this study a total of 2% (n=5) of patients underwent mediastinoscopy as part of their clinical assessment. Surgical mediastinal staging techniques should be considered post EBUS/EUS if suspicion of mediastinal node involvement persists. A recent meta-analysis performed by Bousema et al suggests that the rates of unexpected N2 disease are similar in patients who do and do not undergo confirmatory mediastinoscopy following a negative endosonography, if followed by immediate lung cancer resection, suggesting that local availability and surgical waiting lists should also be factored in to clinical decision making.[17] Authors such as Fujiwara et al and Evison et al have developed risk prediction models that incorporate EBUS lymph node sonographic morphology to predict lymph node metastases.[18,19] These models could also be employed to aid clinical decision-making regarding the need for diagnostic mediastinoscopy.

Latency did not differ significantly between the two groups in this study, indicating that additional EBUS did not significantly alter diagnostic evaluation times or contribute to the higher rates of upstaging in Group B. Current standards recommend treatment to commence within 31 days of MDT clinical decision to treat, and therefore these results are noncompliant with national and international standards, with an average waiting time of 47.5 days. [20]

This study has some limitations, particularly in its retrospective observation nature, however the advantages of such data is that it represents daily practice, rather than selected populations in specialized centers. These findings also highlight the utility of surgical resection as an important staging tool in NSCLC, to provide an accurate final lung cancer stage, guide adjuvant therapy and subsequent prognostication. This is increasingly relevant as alterative curative options such as stereotactic radiation are increasingly utilized in early stage NSCLC.

This study confirms poor concordance between clinical and pathological NSCLC staging, despite advances in mediastinal staging. This is likely multifactorial and reflects a combination of diagnostic, therapeutic and individual patient factors. Additional mediastinal staging modalities, such as EUS and mediasinoscopy, and clinical prediction models based on sonographic features should be considered in a timely fashion following a negative EBUS if persistent clinical suspicion of nodal metastases exists.

Declaration of Conflicts of Interest and funding sources:
None to declare.

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