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Prevalence of nodal metastases in lymph node stations 8 & 9 in a large UK lung cancer surgical centre without routine pre-operative EUS nodal staging

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ABSTRACT

Introduction: Endoscopic ultrasound (EUS) allows access to the inferior mediastinal lymph node stations (8 and 9) which are beyond the reach of endobronchial ultrasound (EBUS). The addition of EUS to EBUS procedures requires cost and resource investment. This study sought to describe the prevalence of station 8/9 nodal metastases from intra-operative lymph node sampling in a UK region where routine pre-operative EUS is not available.

Methods: A retrospective review of all lung cancer resections at the University Hospital South Manchester from 2011 to 2014. Surgical variables, pre-operative PET variables and survival outcomes were collected and analysed.

Results: 1421 surgical resections were performed in the study period. Lymph node stations 8 and/or 9 were sampled in 52% (736/1421) of patients. Overall, there were 34 patients with lymph node metastases at station 8/9. This represents 2.4% of the study populations and 4.6% of patients in whom stations 8/9 were sampled intra-operatively. Of those patients with station 8/9 metastases, 65% (22/34) had multi-station N2 disease and the majority of the additional N2 disease was present in EBUS-accessible areas (lymph node stations 2, 4 and 7). Two percent (16/736) of patients in whom station 8/9 lymph nodes were sampled intra-operatively had N2 disease that was only accessible endoscopically with EUS. There was no significant difference in overall survival in patients with pathological N2 disease stratified according to whether stations 8/9 were involved or not.

Conclusions: The prevalence of lymph node metastases in stations 8/9 in this UK surgical centre where routine pre-operative EUS is not performed is low at approximately 5%. Given the identification of N2 disease in two-thirds of these patients can potentially be achieved through EBUS alone, this questions whether the resource implications of EUS are justified by the impact on patient management.

1. Introduction

The European Society of Thoracic Surgeons (ESTS) recommends that pre-operative endoscopic mediastinal staging is performed in patients with lung cancer and enlarged or metabolically active thoracic lymph nodes on computed tomography (CT) or positron emission tomography (PET) [1]. The favoured endoscopic technique within this guideline is combined endobronchial ultrasound–endoscopic ultrasound (EBUS-EUS). EUS is complimentary to EBUS allowing access to the inferior mediastinal stations via the oesophagus (stations 8 and 9: *para*-oesophageal and inferior pulmonary ligament nodal stations respectively) which are beyond the reach of EBUS. Mediastinoscopy is recommended following negative EBUS-EUS staging and this approach has been shown to be more effective at detecting N2/3 disease than mediastinoscopy alone [2]. Mediastinoscopy is also unable to access stations 8 and 9, leaving EUS as the only routine pre-operative nodal staging procedure able to sample stations 8 and 9. In the United Kingdom (UK) EBUS is widely available but combined EBUS-EUS is not. Adding EUS to EBUS staging procedures would require additional operators (likely gastroenterologists), equipment, training and costs. Respiratory physicians using the EBUS scope in the oesophagus (EUS-B) has been advocated though the scanning range and ultrasound image

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quality is less than that of a true EUS scope and additional training is required to understand the differing anatomical orientation [3]. Furthermore, if a well performed staging EBUS can provide accurate information about nodal status in the accessible nodal stations (2, 4, 7, 10 and 11), can appropriate management decisions be made without the need for sampling of stations 8 and 9 or would such an approach result in missed N2 disease that could influence management decisions? UK lung cancer physicians are therefore faced with a dilemma: are the cost and resource implications of adding EUS to EBUS for pre-operative mediastinal staging justifiable for potential improved patient benefit?

Greater Manchester Cancer is a large Cancer Network in the North West of England with a population of approximately 3 million and 2500 new lung cancer cases per year. Pre-operative nodal staging is widely available with EBUS but there is no routine use of EUS or EUS-B. There is a single Thoracic Surgery Service located at the University Hospital South Manchester. This study sought to investigate the prevalence of nodal metastases in stations 8 & 9 sampled intra-operatively during surgical resection of primary lung cancer in this region where routine pre-operative EUS is not available. Additional factors were examined to see whether pre-operative investigations could identify patients more likely to have station 8 or 9 nodal metastases and whether nodal disease at stations 8 and 9 influenced survival versus other N2 mediastinal nodal stations.

2. Methods and materials

The University Hospital of South Manchester (UHSM) is a regional Thoracic Oncology Centre in the North West of the United Kingdom. It is the sole thoracic surgical centre serving Greater Manchester Cancer. We undertook a retrospective study of the pathological outcomes from intra-operative lymph node sampling from all NSCLC resections between 01/01/2011 to 31/12/2014. Multiple surgical variables and pathological outcomes were recorded including: type of surgery (pneumonectomy, lobectomy/bilobectomy and sub-lobar resection), side of operation (right versus left), number of location of mediastinal lymph nodes sampled, pathological T-stage and pathological N-stage (including single station versus multi-station in N2 disease). In Greater Manchester PET scan results are accessible through an online web-based platform and therefore we were able to review all pre-operative PET scan results for this study population. The following variables were recorded: PET T-stage, PET N-stage and location and number of PET positive thoracic lymph nodes (including single station versus multi-station for positive N2 nodes). EBUS is performed in 5 NHS trusts across Greater Manchester with CT scans performed at all 10 NHS trusts and we were not able to consistently review pre-operative CT and EBUS results for this study cohort. Survival data was obtained from national death registries and calculated up to September 2017.

The number of resections in which stations 8 and/or 9 were sampled intra-operatively was assessed and which factors were associated with sampling of these stations was analysed using chi-square tests and multivariable logistic regression. The prevalence of station 8 and 9 metastases across the study population was analysed and whether there was any relationship between PET findings and the identification of station 8/9 nodal metastases at surgery was explored. Comparison of survival between patients with pathological N2 disease with and without station 8/9 involvement was carried out using Kaplan-Meir analysis and the log-rank test.

3. Results

There were 1421 surgical resections for primary lung cancer in the study period. The mean age at time of operation was 67.5 years old (SD: 9.2, range: 20–87). There were 715 female patients (50.3%) and 706 male patients (49.7%). The histological sub-types were: adenocarcinoma 52% (723/1421), squamous cell carcinoma 37% (523/1421), large cell carcinoma 4% (53/1421), other NSCLC 6% (85/1421) and small cell lung cancer 1% (13/1421). Lobectomy/bilobectomy was the commonest type of operation, performed in 81% (1156/1421) of cases. A total of 60% (849/1421) had right sided operations. Pathological N-stage for the study population was categorised as follows: Nx 76 (5%), N0 926 (65%), N1 213 (15%), N2 206 (15%). Of the 206 patients with pathological N2 disease 65 (32% of those with N2, 4.6% of the study population) had multi-station N2. All patient characteristics and variables are presented in Table 1.

Table 1
Patient characteristics and variables.

Variable	Categories	n (%)
Age	Mean	67.5 ± 9.2)
Gender	Male	706 (50%)
	Female	715 (50%)
Histological Sub-type	Adenocarcinoma	723 (52%)
	Squamous cell carcinoma	523 (37%)
	Large Cell NSCLC	53 (4%)
	Small cell lung Cancer	13 (1%)
	Other	85 (6%)
PET T-stage	T1	264 (19%)
	T2	444 (31%)
	T3	172 (12%)
	T4	44 (3%)
	No T-stage given	497 (35%)
PET N-stage	N0	673 (47%)
	N1	125 (9%)
	N2	174 (12%)
	N3	40 (3%)
	No N-stage given	409 (29%)
Type of Surgery	Pneumonectomy	100 (7%)
	Lobectomy/bilobectomy	1156 (81%)
	Sublobar resection	165 (12%)
Side of Operation	Right	849 (60%)
	Left	572 (40%)
Pathological T-stage	pT1a	433 (31%)
	pT1b	326 (23%)
	pT2a	212 (15%)
	pT2b	165 (12%)
	pT3	275 (19%)
Pathological N-stage	pN0	926 (65%)
	pN1	213 (15%)
	pN2	206 (15%)
	pNx	76 (5%)

Lymph node station 8 was sampled intra-operatively in 20% (283/1421) of patients and station 9 in 45% (636/1421). Overall stations 8 and/or 9 were sampled in 52% (736/1421) of patients. Overall adequacy of intra-operative lymph node sampling, assessed against the standards set out in the International Association for the Study of Lung Cancer (IASLC) staging recommendations [4], increased significantly from 14% in 2011–53% in 2014. This data has been previously published [5]. Those patients undergoing a pneumonectomy ($p < 0.001$) and left sided operations ($p < 0.001$) were more likely to have stations 8/9 sampled intra-operatively whereas those undergoing sub-lobar resections ($p < 0.001$), those with pathological T-stage pT1a ($p = 0.006$), and those with PET T-stage T1 ($p = 0.001$) were less likely to have stations 8/9 sampled intra-operatively (Table 2). A multivariable logistic regression analysis showed type of surgery, side of operation and PET T-stage were independent predictors of whether stations 8/9 were sampled intra-operatively.

Station 8 was positive for nodal metastases from intra-operative sampling in 11 patients (0.8% of study population and 3.9% of those patients in whom station was sampled). Station 9 was positive in 27 patients (1.9% of study population and 4.2% of those patients in whom station 9 was sampled). Overall, 34 patients had either/or station 8/9 positive for nodal metastases (2.4% of study population and 4.6% of those patients in whom stations 8 and/or 9 were sampled intra-operatively). In the 34 patients with station 8 and/or 9 nodal metastases, the primary tumour was located in the lower lobes in 65% (22/34). Twenty