

LYMPH NODE UPSTAGING AFTER SURGERY IN PATIENTS WITH NEGATIVE MEDIASTINAL STAGING BY EBUS

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Abstract

Introduction: Mediastinal staging is a hot topic in thoracic oncology. According to the guidelines, and besides other criteria, in the presence of a primary lung cancer with increased mediastinal lymph node uptake on PET-CT, a negative result after lymph node sampling by Endobronchial Ultrasound (EBUS) is not enough to rule out mediastinal lymph node involvement, demanding a cervical mediastinoscopy to vouch for the results.

Methods and Objectives: In order to study the percentage of lymph node surgical upstaging in patients with negative mediastinal node staging by EBUS and evaluate the role of mediastinoscopy in these patients, we conducted a search in our department's database using the key-word EBUS in the period concerned between January 2014 and August 2020. A total of 302 patients were found. After applying defined criteria, we obtained 42 cases.

Results: Lymph node surgical upstaging occurred in 11 (26%) patients, of which 8 were upstaged to N2 and 3 to N1. Most of the cases were single station. Only in 5 (12% of the total) of the 11 patients, the upstaging was related to lymph node stations previously sampled by EBUS. Upstaging was more frequent among males and lower lobe tumours.

Discussion and Conclusions: Regarding the 8 upstage cases for N2, 5 were single station. Of these 8 cases, only 5 would be approachable by cervical mediastinoscopy. Furthermore, 2 of them were single station, eligible for upfront surgery. Then, only in 3 (7%) of the 42 cases cervical mediastinoscopy would be of foremost importance.

Keywords: EBUS, Mediastinal Staging

INTRODUCTION

During the last 100 years lung cancer has progressed from an uncommon and obscure disease to the most common cancer in the world and the most common cause of death from cancer¹.

Mediastinal staging is nowadays a hot topic in thoracic oncology. According to the guidelines, and besides other criteria, in the presence of a primary lung cancer with increased mediastinal lymph node uptake on

PET-CT, a negative result after lymph node sampling by Endobronchial Ultrasound (EBUS) is not enough to rule out mediastinal lymph node involvement, demanding a cervical mediastinoscopy to vouch for the results.²⁻⁵

Over the last two decades EBUS became the first-line choice to sample mediastinal lymph nodes with good results and a low rate of complications.⁶⁻⁸

Previous studies showed mixed results when comparing EBUS and mediastinoscopy. One of these, by Yasufuku et al, enrolled 153 patients that underwent EBUS

followed by mediastinoscopy in the same procedure, obtaining similar results for mediastinal staging of lung cancer.^{9,10}

Objective: Evaluate the impact of cervical mediastinoscopy in the upstaged cases.

Primary endpoint: Total percentage of lymph node surgical upstaging in patients with negative mediastinal node staging by EBUS.

Secondary endpoint: Percentage of lymph node surgical upstaging on the node stations previously sampled by EBUS.

METHODS AND STATISTIC

We conducted a search in our department's database using the key-word EBUS in the period concerned between January 2014 and August 2020. A total of 302 patients were found. We selected 42 cases after applying the following criteria:

- Inclusion:
 - o Primary lung cancer.
 - o Increased lymph node uptake on PET-CT.
 - o Negative EBUS.
 - o All patients were submitted to surgery.
 - o At least one of the lymph node stations sampled by EBUS explored in surgery.
- Exclusion:
 - o EBUS without diagnostic yield.
 - o Neoadjuvant chemotherapy.

Statistical analysis was carried out with IBM SPSS, version 26 for Windows (IBM Corp. Released 2018). Student's t-test (continuous variables) and Fisher's exact test (categorical variables) were used. A multiple logistic regression model was used to study the impact of each variable in lymph node surgical upstaging.

SAMPLE

The sample consists of 30 (71.4%) males and 12 (28.6%) females, comprised between 49 and 85 years old (Mean = 67.8, SD = 7.8), mostly belonging to the age group of 60-74 years (69.0%) (Table 1).

DESCRIPTIVE ANALYSIS

Histology: Adenocarcinoma was the most prevalent tumour – present in 66.7% of the 42 cases. Squamous cell carcinoma was present in 23.8%, large cell carcinoma (non-neuroendocrine) in 7.1% and atypical carcinoid tumour in 2.4% (Table 2).

Tumour location: The right lung (66.7%) was involved in the majority of the cases: 40.5% in the right upper lobe (RUL), 23.8% in the right lower lobe (RLL), and 2.4% in the middle lobe (ML). The left lung was affected in 33.3% of the cases: 19.0% in the left lower lobe (LLL) and 14.3% in the left upper lobe (LUL).

EBUS timing and tumour size (T): The time between EBUS and surgery ranged from 14 to 210 days (Mean = 80.3, SD = 45.1) and the Tumour size T from 1.0 cm to 19.0 cm (Mean = 3.9, SD = 3.0).

Upstaging: Lymph node surgical upstaging occurred in 11 (26.2%) patients. Among these, upstaging to N1 occurred in 3 (7.1%) patients and to N2 in 8 (19.0%) patients. Of the 11 cases with lymph node surgical upstaging, 7 (63.6%) were single station.

Only in 5 (45.5%) cases the upstaging was related to lymph node stations previously sampled by EBUS.

According to the PET-FDG results, 35 (83.3%) patients were staged as N2 (45.5%). However, in only 5 of the 11 upstaged patients, the involved lymph node stations were previously positive on PET-FDG (Table 3).

Table 1

Sample characteristics – gender and age (N = 42)

Variables		N	%	
Gender	Male	30	71.4%	
	Female	12	28.6%	
Age (years)	< 55	1	2.4%	
	Minimum - maximum: 49 - 85	55 – 59	4	9.5%
	Median: 68.0	60 – 64	10	23.8%
	Mean: 67.8	65 – 69	10	23.8%
	Standard Deviation: 7.8	70 – 74	9	21.4%
		75 – 79	4	9.5%
		80 – 85	4	9.5%

Table 2

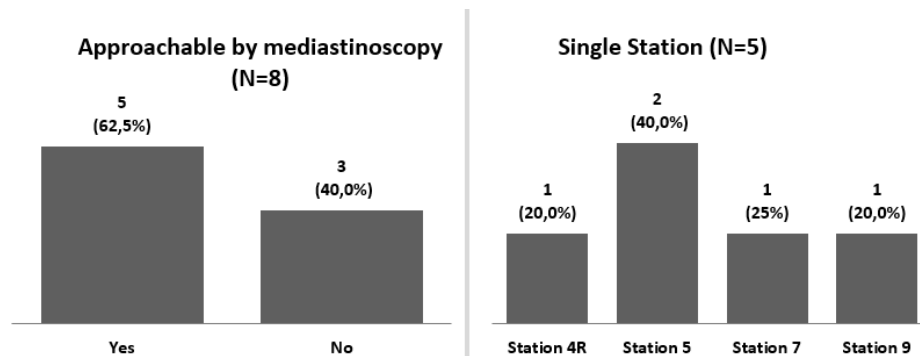
Descriptive analysis concerning histology, location, tumour size and time between EBUS and surgery (N = 42).

Variables		N	%
Histology	Adenocarcinoma	28	66.7%
	Squamous cell	10	23.8%
	Large cell carcinoma	3	7.1%
	Atypical carcinoid	1	2.4%
Location	LLL	8	19.0%
	LUL	6	14.3%
	RLL	10	23.8%
	RUL	17	40.5%
	ML	1	2.4%
Size (cm)	Minimum: 1.0, Maximum: 19.0, Median: 3.5, Mean: 3.9, SD: 3.0		
Time between EBUS and surgery (days)	Minimum: 14.0, Maximum: 210.0, Median: 71.5, Mean: 80.3, SD: 45.1		

Table 3

Descriptive analysis concerning lymph node surgical upstaging (N = 42).

Variables		N	%
N Upstaging	No	31	73.8%
	Yes	11	26.2%
Stage	N0	31	73.8%
	N1	3	7.1%
	N2	8	19.0%
Stage according to PET-FDG	N1	7	16,7%
	N2	35	83,3%
Single station upstaging (within the 11 cases with node surgical upstaging)	No	4	36.4%
	Yes	7	63.6%
Upstage on lymph nodes sampled by EBUS (within the 11 cases with node surgical upstaging)	No	6	54.5%
	Yes	5	45.5%
Upstaging stations previously positive on PET-FDG (within the 11 cases with node surgical upstaging)	No	6	54.5%
	Yes	5	45.5%


Figure 1

N2 upstage group (N=8).

Table 4
Association with lymph node surgical upstaging – (N = 42).

	Lymph node surgical upstaging		p - value
	No (n=31)	Yes (n=11)	
Gender			
Male (n=30)	20 (66.7%)	10 (33.3%)	0.097 ⁽¹⁾
Female (n=12)	11 (91.7%)	1 (8.3%)	
Age (years)			0.771 ⁽²⁾
Mean (SD)	67.6 (8.0)	68.5 (7.4)	
Histology			
Adenocarcinoma (n=28)	23 (82.1%)	5 (17.9%)	0.128 ⁽¹⁾
Squamous cell (n=10)	6 (60.0%)	4 (40.0%)	
Large Cell (n=3)	1 (33.3%)	2 (66.7%)	
Atypic carcinoid (n=1)	1 (100.0%)	0 (0.0%)	
Location			
Left Lower Lobe (n=8)	4 (50.0%)	4 (50.0%)	0.500 ⁽¹⁾
Left Upper Lobe (n=6)	5 (83.3%)	1 (16.7%)	
Right Lower Lobe (n=10)	7 (70.0%)	3 (30.0%)	
Right Upper Lobe (n=17)	14 (82.4%)	3 (17.6%)	
Middle Lobe (n=1)	1 (100.0%)	0 (0.0%)	
Location (left/right)			
Left Lobes (n=14)	9 (64.3%)	5 (35.7%)	0.264 ⁽¹⁾
Right Lobes (n=28)	22 (78.6%)	6 (21.4%)	
Location (lower/upper/middle)			
Lower Lobes (n=18)	11 (61.1%)	7 (38.9%)	0.244 ⁽¹⁾
Upper Lobes (n=23)	19 (82.6%)	4 (17.4%)	
Middle lobe (n=1)	1 (100.0%)	0 (0.0%)	
Size (cm)⁽³⁾			
Mean (SD)	3.5 (1.8)	3.8 (1.7)	0.535 ⁽²⁾
Time between EBUS and surgery (days)			0.631 ⁽²⁾
Mean (SD)	82.3 (49.4)	74.5 (31.3)	

⁽¹⁾ Fisher's exact test, ⁽²⁾ Student's t-test, ⁽³⁾ one outlier excluded.

Table 5

Logistic regression model for lymph node surgical upstaging (N = 37).

Independent variables	Odds Ratio (CI95%)	p - value
Gender (male vs. female)	7.24 (0.62, 85.07)	0.115
Age (years)	1.00 (0.87, 1.14)	0.952
Size (cm)	0.88 (0.63, 1.22)	0.430
Time between EBUS and surgery (days)	0.99 (0.96, 1.01)	0.232
Histology (squamous cell vs. adenocarcinoma)	5.08 (0.60, 43.04)	0.136
Local (lower lobe vs. upper lobe)	4.39 (0.71, 27.19)	0.112
Local (left lung vs. right lung)	1.07 (0.14, 8.27)	0.951
Nagelkerke R Square: 0.315		

Notes: 1) dependent variable: lymph node surgical upstaging (0=No, 1=Yes); 2) five cases were not included in the analysis due to small category numbers: Large cell (n=3), atypical carcinoid (n=1), middle Lobe (n=1).

ASSOCIATION WITH LYMPH NODE SURGICAL UPSTAGING

Lymph node surgical upstaging was more prevalent among males (33.3%) than among females (8.3%) ($p = 0.097$). Regarding age, no significant differences were found between patients with ($M = 68.5$, $SD = 7.4$) and without ($M = 67.6$, $SD = 8.0$) upstaging ($p = 0.771$).

Lymph node upstaging occurred in 17.9% of the adenocarcinoma tumours, in 40.0% of the squamous cell tumours, and in 66.7% of the large cell tumours (non-neuroendocrine). However, the differences were not statistically significant ($p = 0.128$).

Regarding the location of the tumour, upstaging occurred in 50% of the patients with tumours located in the left lower lobe. The upstaging was more frequent in left lung tumours (35.7%) than in the right lung (21.4%). Although, the differences were not statistically significant ($p > 0.05$), the tendency was even clearer when comparing lower lobes (38.9%) with the upper lobes (17.4%). ($p = 0.244$).

No significant differences were found regarding the size of the tumour ($p = 0.535$) and the time between EBUS and surgery ($p = 0.631$) (Table 4).

A logistic regression model with lymph node surgical upstaging (0=No, 1=Yes) as dependent variable was performed. It showed that none of the independent variables were significantly associated with the upstaging ($p > 0.05$).

Despite the non-significance, it is worth noting the higher odds ratio of upstaging for males when compared to females (OR = 7.24), for lower lobe tumours when compared to upper lobe tumours (OR = 4.39) and for squamous cell tumours when compared to adenocarcinoma tumours (OR = 5.08). Large cell carcinoma (non-neuroendocrine) was not included in this analysis due to the small number of cases (Table 5).

DISCUSSION AND STUDY LIMITATIONS

Of the 11 upstaged patients, as previously noted, 3 were upstaged for N1 and 8 for N2.

Regarding the N2 cases, 5 were single station N2, including station 4R, 7 and 9R in 1 case each, and station 5 in 2 cases. The remaining 3 cases were multi station N2. Knowing that station 5 and 9 are not approachable by cervical mediastinoscopy, it would be helpful in only 5 cases. However, of these 5 cases, 2 were single station N2, that could be considered for upfront surgery after discussion in a multidisciplinary meeting (Figure 1).

According to our results, only in 3 (7%) of the 42 cases, cervical mediastinoscopy would be of foremost importance. Other options, as the association of trans-oesophageal endoscopic ultrasound (EUS) to EBUS or lymph node sampling by video-assisted thoracoscopic surgery (VATS) could help to overcome the difficulties related to stations 5 and 9 sampling.^{5,9}

The fact that the differences in the proportions of upstaging (by gender, histology or tumour location) were not statistically significant does not necessarily mean that there are no differences. Several trends were obtained and the non-significance may be due to the small sample size that did not allow detecting significant differences.

CONCLUSIONS

Although the total number of upstaged patients is substantial (26,2%), we realize that only 12% was related to lymph node stations previously sampled by EBUS. Furthermore, only in 3 (7%) cases cervical mediastinoscopy would be essential. Both EUS and VATS might be very helpful in a large number of cases. Further studies with a larger sample would be of utmost importance to ascertain our study results.

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