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Non-Lobe Specific Metastases in Occult N2 after Lobectomy for Clinical N0 Non-Small Cell Lung Cancer

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ABSTRACT

OBJECTIVES

Non-small cell lung cancer can spread into lobe specific stations and non-lobe-specific mediastinal lymph nodes. We evaluated frequency and features of non-lobe specific nodal metastases, focusing especially on the prognostic value of only non-lobe specific N2-metastases after lobectomy.

METHODS

We performed a retrospective review of 550 patients with non-small cell lung cancer with clinical N0, undergoing lobectomy and systematic or lobe specific node dissection. We evaluated disease free and overall survival rates using Kaplan-Meier method and significance was tested by log-rank test.

RESULT

Occult N2 disease was detected in 68 patients (8.1%), 26 of them (38.2%) had metastases in non-lobe specific stations. Comparing patients with lobe and non-lobe specific lymph node metastases, 3-years DFS rate was 44.4% *vs.* 20.0% (p-value = 0.009), while 3-years OS rate was 87.3% *vs*. 26.7% (p-value <0.001). Among patients with non-lobe specific metastases 16 of them (61.5%) had only non-lobe specific metastases, the remaining 10 patients (38.5%) had metastatic lymph node at the same time in non-lobe specific station but also in lobe-specific stations. Comparing post-operative survival between patients with only non-lobe specific metastases and synchronous lobe and non-lobe specific metastases, 3-years DFS rate was 12.5% *vs.* 41.3% respectively (p-value = 0.03), and 3-years OS rate was 12.5% vs 76.7% (p-value = 0.002).

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CONCLUSION

In patients with occult N2 disease, the finding of a metastatic lymph node in a non-lobe specific station relates with significant lower survival rate. The subset of patients who presented only non-lobe specific node metastases showed a significant lower survival rate compared to the remaining occult N2.

KEYWORDS

Lung cancer; Non-lobe specific metastases; Systematic lymphadenectomy; Lobe specific lymphadenectomy

INTRODUCTION

According to the European Society for Medical Oncology (ESMO), the treatment for the early stage (I-II) non-small cell lung cancer (NSCLC) is the anatomic surgical resection of the involved lobe together with systematic node dissection [1]. This last expression entails the resection of at least three mediastinal stations always including the subcarinal one [1]. Other studies have demonstrated that each lobe spreads tumor cells according to a preferential lymphatic route [2,3]. According to this last theory, a dissection limited to lobe-specific nodes might be yet equally effective technique of lymphadenectomy. However, the ability of NSCLC to spread metastatic cells outside of the preferential lymphatic drainage route is common, as observed by Rouvière for the first time in 1929 [4].

The impact of the two different methods of lymph node dissection on survival has been largely evaluated in literature [5-7]. Most of the studies reported an insignificant difference in survival whatever the type of lymphadenectomy especially among earlier stages and small size tumors [8-10]. However, the lobe specific node dissection could miss a noteworthy amount of non-lobe specific metastases, thus potentially affecting the prognosis [11-13]. On the contrary, the routine adoption of a systematic node dissection did not have influence on surgery duration and postoperative morbidity [8,14].

In the present paper, we evaluated the frequency and features of lobe specific metastases (LSM) and non-lobe specific metastases (non-LSM) as well as long-term outcomes. Patients selected for the study were homogeneous for type of surgery (i.e., lobectomy) but differentiated for type of lymphadenectomy (systematic *vs*. lobe specific), chosen depending on pre-operative features and intra-operative findings. Our purpose was to investigate whether the discovery of non-lobe specific metastases might affect the prognosis of the operated patients.

MATERIAL AND METHODS

Population

We performed a retrospective review of 550 patients with NSCLC who underwent lobectomy with lymphadenectomy between January 2015 and December 2020. We selected patients with primary NSCLC with clinical early stage (Stage I/II). The eligibility criteria included no neo-adjuvant chemotherapy and/or radiotherapy as well as absence of synchronous cancer or previous history of another cancer. All patients had undergone a systematic or lobe-specific node dissection [1]. The type of lymphadenectomy performed has been extrapolated from surgery reports.

Pre-Operative Evaluation

Pre-operative staging was performed by thoracic computed tomography (CT) scan and synchronized CT with 18-fluorodeoxyglucose-positron emission tomography (18FDG-PET/CT) scanning. No images older than 30 days were considered. Solid composition of the tumor was evaluated as well as the rate of ground glass opacity (GGO). Clinical N status was evaluated, according to

previous evidence, with CT scan and 18FDG-PET/CT. Significant metabolic activity was set at a standardize uptake value (SUV) max score greater than 2.0 [15]. Lymph node size was calculated by the CT scan, considering suspect for malignancy a diameter greater than 10mm in short axis [16]. All suspected lymph nodes underwent histologic confirmation by Endobronchial Ultrasound (EBUS) biopsy. Negative histologic biopsies were considered cN0. If the tissue from endobronchial biopsy were inadequate for the histological diagnosis, was shifted to invasive staging. Mediastinoscopy or thoracoscopic lymph node biopsy depending on the lymph node position.

Surgical Procedure

Surgical procedures were performed through either lateral thoracotomy or Video Assisted Thoracoscopic Surgery (VATS) [17]. Every patient was under general anesthesia with double lumen endotracheal tube to allow a selective ventilation of the non-affected lung. Mediastinal lymphadenectomy was carried out in every patient, we excluded all patients with less than 6 nodes removed [18]. To achieve mediastinal lymphadenectomy the surgeon examined preoperative radiological characteristics of the tumor (prevalence of GGO or solid part, mixed attenuation lesion, central position) and of the lymph nodes (short axis at TC scan more than 1cm, presence of necrotic core). During surgery, all homolateral mediastinal stations were explored and all enlarged or suspected lymph nodes were resected. When possible, lymph nodes were resected *en bloc* with the surrounding fat. Systematic lymph node dissection (SLND) is the dissection of at least 3 mediastinal lymph node stations (always including station 7). Lymphadenectomy can be defined "non-lobe specific", if at least one station dissected lies outside the lymphatic drainage of the affected lobe, or "lobe specific" if all dissected nodes lie on lymphatic route of the lobe. The preferential lymphatic drainage from the affected lobe in case of tumors sited in the right upper lobe and middle lobe consisted in nodal stations 2 and 4; right lower lobe 7, 8 and 9; left upper lobe 2, 4, 5 and 6; left lower lobe 7, 8 and 9.

Histologic Evaluation and Pathological Staging

Tumors were classified according to the 2015 World Health Organization Classification of Lung Cancer. Moreover, tumor grade of differentiation, size and position were assessed [19]. The pathological stage (pTNM) was based on the 8th edition of the lung cancer TNM [20].

The number of examined lymph node was evaluated in every patient and derived from lymph nodes located within the resected lobe and mediastinal lymph nodes. The count was the sum of entire lymph nodes and each fragment of lymph nodes.

Histological analysis was performed with haematoxylin-eosin stain and eventually immunohistochemical analysis. The group of patients with pN2 disease was classified as "lobe specific" when nodal metastases were found only along the lobe specific lymphatic drainage. On the contrary, "non-lobe specific" were defined those with at least one non-lobe specific station involved but they could have simultaneous lobe specific metastases. Furthermore, in "non-lobe specific" group, we split those with non-lobe specific stations as unique site of metastatic involvement from those with both lobe and non-lobe specific metastases.

Follow-Up

For the follow-up our program included CT scan every 6 months for the first 2 years, then annually. 18FDG-PET/CT was requested in suspected lesions appeared at CT scan. The median time for follow up was 27 months (range 12-72).

Statistical Analysis

Due to the dimension of the sample and the normal distribution of the patients, data were expressed as mean ±

standard deviation. Statistical analysis of the data was conducted using the SPSS Statistics program version 26.0 (IBM Corp., Armonk, NY). Student's t-test for continuous variables and Pearson's quadratic test for discontinuous variables were used as significance tests. In the case of a comparison between three continuous variables, the ANOVA test was used with subsequent post-hoc tests in the case of a statistically significant difference. A p-value <0.05 was considered statistically significant. The survival curve was estimated with Kaplan Meier method. Disease Free Survival (DFS) was calculated from the day of surgery to the demonstration of local or distant relapse. Recurrence was considered local if it involved the ipsilateral hemithorax and mediastinum, distant if it was in any other side. Overall survival (OS) was calculated from the day of surgery to the death of the patients or last available follow-up.

RESULTS

In a cohort of 550 patients, 426 were pN0 (77.5%), 56 were pN1 (10.2%), while 68 had occult mediastinal nodal involvement was detected in 68 patients (12.4%): For 42 of them (42/68, 61.8%) lymph node involvement was found only in the lobe specific stations while for the other 26 patients (26/68, 38.2%) non-lobe specific stations were involved. The groups of patients with non-lobe specific metastases were composed of 16 patients (61.5%) with only non-lobe specific metastases and 10 patients (38.5%) with synchronous lobe and non-lobe specific metastases.

Clinical and pathological characteristics of the two groups (lobe specific *vs.* non-lobe specific lymph node metastases) have been evaluated (Table 1).

Variable	***Tot (n=68)***	***LSM (n=42)***	***Non-LSM (n=26)***	***p-value***
Age	69.8±8.3	69.4±8.2	73.2± 7.1	0.14
Gender				
Male	44 (64.7%)	24 (57.1%)	19 (73.3%)	0.34
Female	24 (35.3%)	18 (42.9%)	7 (26.7%)	
Smoking Status				
Never	12 (17.6%)	10 (23.8%)	2 (7.6%)	0.15
Former and Current	56 (82.4%)	32 (76.2%)	24 (92.4%)	
Approach				
Thoracotomy	23 (33.8%)	11 (26.2%)	12 (46.2%)	0.16
VATS	45 (66.2%)	31 (73.8%)	14 (53.8%)	
Lymphadenectomy				
SLND	49 (72.0%)	23 (54.7%)	26 (100.0%)	<0.001
LSLND	19 (28.0%)	19 (45.3%)	0 (0.0%)	
Pathologic T				
pT1	26 (38.2%)	21 (50.0%)	5 (19.3%)	
pT2	33 (48.5%)	15 (35.7%)	18 (69.2%)	0.20
pT3	7 (10.3%)	4 (9.5%)	3 (11.5%)	
pT4	2 (3.0%)	2 (4.8%)	0 (0.0%)	
pN Subgroups				
2 a2	39 (57.4%)	34 (80.1%)	5 (19.2%)	<0.001
2 a1	15 (22.0%)	2 (4.7%)	13 (50.0%)	
2b	14 (20.6%)	6 (14.2%)	8 (30.8%)	
Tumor Dimension (CT)				
< 2cm	14 (20.6%)	10 (23.8%)	4 (15.4%)	0.04
> 2cm	54 (79.4%)	32 (76.2%)	22 (84.6%)	
Tumor SUVmax (18FDG-PET/CT)				
< 5	7 (10.3%)	7 (16.7%)	0 (0.0%)	<0.001
> 5	61 (89.7%)	35 (83.3%)	26 (100.0%)	
Histology				
Adenocarcinoma	59 (86.7%)	38 (90.5%)	21 (80.8%)	0.29
Squamous Cell Carcinoma	9 (13.2%)	4 (9.5%)	5 (19.2%)	
Differentiation				
Well	7 (10.3%)	7 (16.7%)	0 (0.0%)	0.02
Moderate	33 (48.5%)	24 (57.1%)	9 (34.6%)	
Poor	28 (41.2%)	11 (26.2%)	17 (65.4%)	
Consistency				
Prevalence Solid	51 (75.0%)	26 (62.0%)	25 (96.2%)	0.03
Prevalence GGO	17 (25.0%)	16 (38.0%)	1 (3.8%)	

Lobe Primary Tumour				
RUL	24 (35.3%)	16 (38.0%)	8 (30.8%)	0.13
RML	4 (5.9%)	0 (0.0%)	4 (15.4%)	
RLL	17 (25.0%)	14 (33.3%)	3 (11.5%)	
LUL	16 (23.5%)	7 (16.7%)	9 (34.6%)	
LLL	7 (10.3%)	5 (12.0%)	2 (7.7%)	
Position Primary Tumor				
Central	47 (69.1%)	23 (54.7%)	24 (92.3%)	0.01
Peripheral	21 (30.9%)	19 (45.3%)	2 (7.7%)	
Removed lymph nodes				
<15	40 (59.0%)	26 (61.9%)	14 (53.8%)	0.57
>15	28 (41.0%)	16 (38.1%)	12 (46.2%)	

Table 1: Clinicopathologic characteristics of patients with lobe specific metastases (LSM) and non-lobe specific metastases (non-LSM) in mediastinal lymph node.

18FDG-PET/CT: 18-Fluorodeoxyglucose- Positron Emission Tomography/Computed Tomography; CT: Computed Tomography; GGO: Ground Glass Opacity; LLL: Left Lower Lobe; LSLND: Lobe Specific Lymph Node Dissection; LSM: Lobe Specific Metastases; LUL: Left Upper Lobe; RML: Right Middle Lobe; RLL: Right Lower Lobe; RUL: Right Upper Lobe; VATS: Video Assisted Thoracoscopic Surgery

Type of lymphadenectomy, between lobe specific and non-lobe specific metastases, showed statistical significance (p-value <0.001) since non-lobe specific metastases are detectable only with a systematic dissection. The incidence of non-LSM was also associated with the subclassification of the N status (p-value <0.001), since non-LSM was found on 50.0% of patients with skip metastasis (pN2a1). Tumor dimension at CT scan bigger than 2 cm was found in 84.6% (22/26) of non-LSM (p-value = 0.04), also SUV_{max} more than 5 was found in 100% (26/26) of non-LSM (p-value <0.001). Moreover, tumors with poor grade of differentiation were more frequent in the non-lobe specific metastases group (p-value = 0.02), as well as a solid radiologic pattern (p-value = 0.03), and a central position of lung nodule (p-value = 0.01). No significant difference was found in age, gender, smoking status, surgical approach, histology, affected lobe and number of removed lymph nodes.

At topographic analysis, among all patients with mediastinal metastases, right upper lobe was the most common location of the primary tumor (24/68: 35.3%) followed by right lower lobe (17/68: 25.0%) and left lower lobe (16/68: 23.5%) (Table 2).

Lymph Node Station	RUL	RML	RLL	LUL (n=9)	LLL (n=4)
2	7 (29.2%)	-	-	-	2 (28.6%)
3	-	-	-	-	-
4	9 (37.5%)	-	3 (17.7%)	2 (12.5%)	-
5	-	-	-	3 (18.7%)	-
6	-	-	-	2 (12.5%)	-
7	-	-	3 (17.7%)	-	2 (28.6%)
8	3 (12.5%)	-	4 (23.5%)	4 (25.0%)	-
9	5 (20.8%)	4 (100%)	7 (41.1%)	5 (31.3%)	3 (42.8%)
TOTAL	24	4	17	16	7
Lobe Specific	16 (66.6%)	-	14 (82.3%)	7 (43.8%)	5 (71.4%)
Non-Lobe specific	8 (33.4%)	4 (100%)	3 (17.7%)	9 (56.2%)	2 (28.6%)

Table 2: Distribution of lymph node metastases and division between lobe specific and non-lobe specific ones basing on affected lobe.

LLL: Left Lower Lobe; LUL: Left Upper Lobe; RLL: Right Lower Lobe; RML: Right Middle Lobe; RUL: Right Upper Lobe.

Right middle lobe gave only non-lobe specific metastases (4/4 100%), the lymph node station involved was the subcarinal (9). Left upper lobe had prevalence of non-lobe specific metastases (9/16: 56.2%), the most frequent involved station was 8 (4/17: 23.5%) and 9 (7/17: 41.1%). Lobe-specific metastases were found more frequently in right upper lobe (16/24: 66.6%), right lower lobe (14/17: 82.3%) and left lower lobe (5/7: 71.4%). The most common involved lymph node stations were 2 (7/24: 29.2%) and 4 (9/24: 37.5%) for the right upper lobe, 9 (7/17: 41.1%) and 8 (4/17: 23.5%) for right lower lobe, and station 9 (3/7: 42.8%) for left lower lobe.

In the group of non-LSM, 16 patients (16/26: 61.5%) had metastases only in non-lobe specific lymph node station,

while in 10 patients (10/26: 38.5%) metastases was found at the same time in non-lobe specific and lobe specific stations. Right upper lobe had 50.0% (4/8) of only non-LSM and the metastases was found in station 9 in each patient. Right middle lobe had 100% of non-LSM in station 9. For right lower lobe 2 only non-LSM (2/3) 66.7% was found in station 4, while one patient had metastases in station 4 and 9 (1/3: 33.3%). Only non-LSM for the left upper lobe were 6 (6/9: 66.7%), 4 of them in station 9 and the other 2 in station 8; for the remaining 3 patients, one had simultaneous metastases in stations 9 and 5 and two patients in station 8 and 4. Left lower lobe did not give only non-LSM but involved at the same time stations 2 and 9 in 100% of patients (Table 3).

Non-LSM Sub-groups	RUL (n=8)	RML (n=4)	RLL (n=3)	LUL (n=9)	LLL (n=2)
Only Non-LSM n=16 (16/26: 61.5%)	n=4 (50.0%)	n=4(100%)	n=2 (66.7%)	n=6 (66.7%)	n=0 (0.0%)
	Only station 9	Only station 9	Only station 4	Station 9 (n=4) Station 8 (n=2)	-
Synchronous LSM+Non-LSM n=10 (10/26: 38.5%)	n=4 (50.0%)	n=0(0.0%)	n=1 (33.3%)	n=3 (33.3%)	n=2 (100%)
	Stations 8+4 (n=2) Stations 9+2 (n=1) Stations 8+4 (n=1)	-	Stations 4+9	Stations 9+5 (n=1) Stations 8+4 (n=2)	Stations 2+9 (n=2)

Table 3: Involved lymph node stations basing on affected lobe in the two sub-groups of non-LSM.
LLL: Left Lower Lobe; LUL: Left Upper Lobe; LSM: Lobe Specific Metastases; RLL: Right Lower Lobe; RML: Right Middle Lobe; RUL: Right Upper Lobe

We compared post-operative survival between patients with lobe specific metastases and those with non-lobe specific ones (Table 4). In the lobe-specific metastases group, 17 patients (17/42, 40.4%) relapsed, with a 3-years DFS rate of 44.4% and a mean time to relapse of 12.7 ± 14.6 months, and 5 (5/42, 11.9%) died, with a 3-years OS rate of 87.3% and a mean time to death of 16.5 ± 15.6 months. On the other hand, in the non-lobe specific metastases one, 24 patients relapsed (24/26, 92.3%) and 23 died (23/26, 88.5%).

This set had a 3-years DFS rate of 20.0%, with a mean time to relapse of 10.3 ± 8.6 months, and a 3-years OS rate of 26.7%, with a mean time to death of 5.8 ± 4.5 months.

Group	N.	Recurrence	3Y-DFS	Mean time to relapse	Mortality	3Y-OS	Mean time to death
				Months ± SD			Months ± SD
LSM	42	17 (40.4%)	44.4%	12.7 ± 14.6	5 (11.9%)	87.3%	16.5 ± 15.6
non-LSM	26	24 (92.3%)	20.0%	10.3 ± 8.6	23 (88.5%)	26.7%	5.7 ± 4.5
Total	68	42 (61.8%)	34.8%	11.7 ± 12.3	28 (41.2%)	61.9%	14.4 ± 14.7

Table 4: Comparison of survival analyses between LSM and non-LSM.
3Y-DFS: 3-Years Disease Free Survival Rate; 3Y-OS: 3-Years Overall Survival Rate; LSM: Lobe-Specific Metastases; SD: Standard Deviation

The analysis of survival rates estimation using Kaplan-Meier method showed a statistically significant difference between the two groups for DFS (p-value = 0.009) and OS (p-value <0.001) (Figure 1A and Figure 1B).

Comparison of post-operative survival in the two sub-groups of non-lobe specific lymph node metastases (only non-LSM and synchronous lobe and non-LSM). Patients with only non-LSM showed a worse prognosis if compared to the other group. The recurrence was 75.0% (12/16) for only non-LSM and 60.0% (6/10) for patients with synchronous LSM and non-LSM. The mortality was 75.0% (12/16) for only non-LSM and 40.0% (4/10) for patients with synchronous LSM and non-LSM. Patients with only non-LSM had both a lower 3-years DFS (12.5% *vs.* 41.3%) and OS (12.5% *vs.* 76.7%) rate, with a shorter time to relapse (6.9 ± 2.8 *vs.* 13.7 ± 14.1 months) and time to death (12.0 ± 4.7 *vs.* 16.3 ± 19.5 months), and a significant difference for both DFS (p-value = 0.03) and OS (p-value = 0.002) (Table 5).

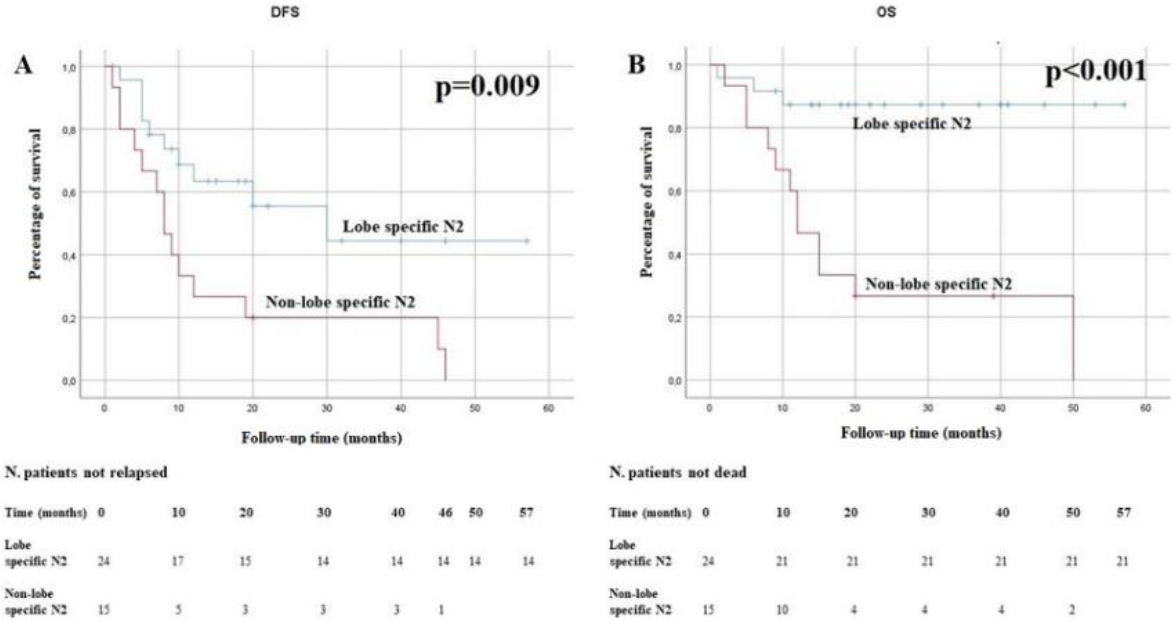

Figure 1: Kaplan-Meier survival curves of disease-free survival (A) and overall survival (B) between patients with only lobe specific lymph node metastases and patients with non-lobe specific ones.

Group	N.	Recurrence	3Y-DFS	Mean Time to Relapse Months ± SD	Mortality	3Y-OS	Mean Time to Death Months ± SD
Only non-LSM	16	12 (75.0%)	12.5%	6.9 ± 2.8	12 (75.0%)	12.5%	12.0 ± 4.7
Synchronous LSM + non-LSM	10	6 (60.0%)	41.3%	13.7 ± 14.1	4 (40.0%)	76.7%	16.3 ± 19.5
Total	26	18 (69.2%)	34.8%	11.7 ± 12.3	17 (65.4%)	61.9%	14.4 ± 14.7

Table 5: Comparison of survival analyses between the two sub-groups of non-LSM.
3Y-DFS: 3-Years Disease Free Survival Rate; 3Y-OS: 3-Years Overall Survival Rate; LSM: Lobe-Specific Metastases; SD: Standard Deviation

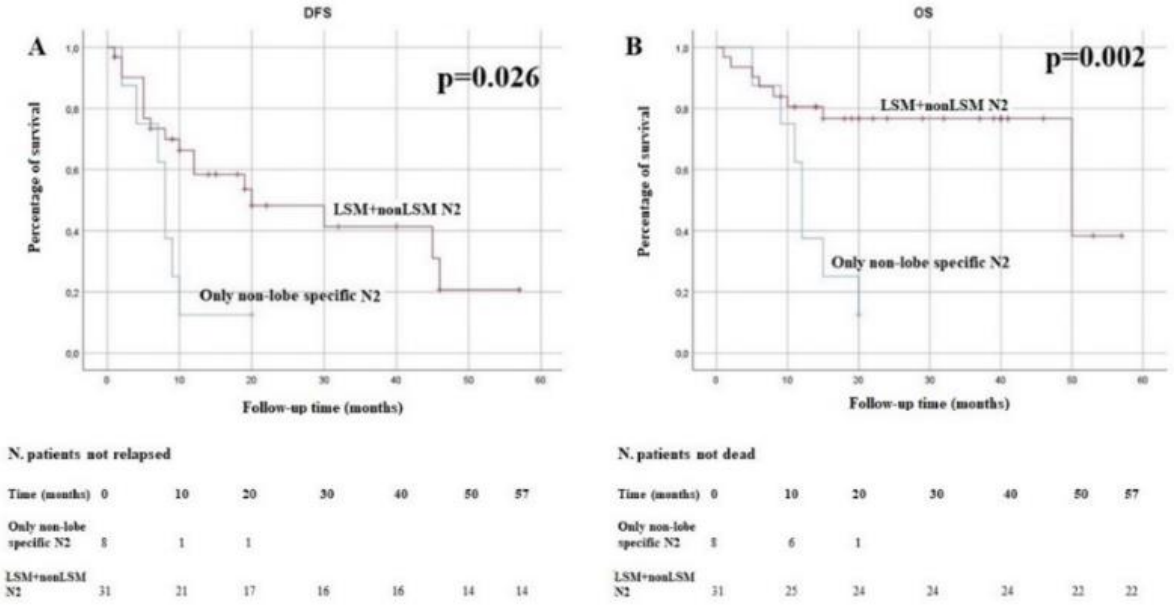

Figure 2: Kaplan-Meier survival curves of disease-free survival (A) and overall survival (B) between patients with only non-lobe specific lymph node metastases and patients with synchronous lobe specific and non-lobe specific metastases.

The analysis of survival rates estimation using Kaplan-Meier method showed a statistically significant difference between the two groups for DFS (p-value = 0.03) and OS (p-value = 0.002) (Figure 2A and Figure 2B).

DISCUSSION

The possibility of detecting non-lobe specific N2 metastases is consistent [12] and the impact on prognosis is relevant. Their frequency ranges from 5.1% to 14.3% [20] but reaches 25.6% in other experiences [12]. Similarly, presence of non-lobe specific metastases appears to be a significant bad prognosticator [13]. In Sun et al, non-lobe specific region metastases have a significant worse OS rate compared to lobe specific ones (11.7% *vs.* 27.5%, respectively) [13]. According to these considerations systematic mediastinal node dissection appears, whenever feasible, more appropriate [21,22], despite the demonstrated impact on operative time and postoperative morbidity [8,14].

In our paper, the detection of non-lobe specific metastases was more common in patients with a low grade of differentiation and a presence of solid morphology. Hence, we could deduct that a more aggressive tumor tends to spread outside the preferential lymphatic drainage, indeed, we found than the half of non-LSM was skip N1. Moreover, the central position of the primary tumor is related to a higher probability of non-lobe specific metastases. This might be due to a more straightforward way of lymphatic drainage towards the mediastinum [23]. Non-LSM were more frequently associated with tumor bigger than 2 cm or tumor SUVmax more than 5.

Notably, non-lobe specific metastases had a higher prevalence (9/15, 60.0%) in tumors located in the right hemithorax. Moreover, right middle lobe (2/2, 100%) and left upper lobe (5/9, 55.6%) tumors showed more non-lobe specific metastases than lobe-specific ones. We did not find in literature a clear prevalence of this metastatic distribution or a standardized metastatic pattern. Riquet et al., in a population of 1,779 patients, found a relatively greater prevalence of non-lobe specific metastases in the left hemithorax [24]. Fang et al described the presence of metastases in non-lobe specific lymph nodes especially from the left lower lobes [21]. On the contrary, Ndiaye et al had already reported a right-sided prevalence of non-lobe specific metastases. They described, in 65 patients, a complex variation in lymphatics pathway in the right lung [25]. Topol et al., studying the lymphatic pathway on 96 cadavers, discovered that non-lobe specific lymph node metastases can be due to the presence of lymphatic vessels crossing the segmental or lobar borders [26]. These anatomical variations might explain the ability of the primary tumor to spread metastatic cell in uncommon lymphatic stations.

Focusing on the distribution of mediastinal lymph node involvement, we found that a significant number of patients with non-lobe specific metastases had only non-lobe specific ones (7/15, 46.7%). Therefore, we deduced that lobe specific nodal involvement was not a condition favoring the onset of non-lobe specific metastases. On the contrary, Zhang et al. found that clinical presence of lobe specific nodal metastases was the only independent predictor of non-lobe specific metastases [11].

The presence of only non-lobe specific metastases showed a more severe prognosis compared to the other groups. The extremely high relapse rate in those patients may be due to the greater aggressiveness of the primary tumor. This implies an increased ability of spreading metastases far from its localization, trespassing the preferential lymphatic drainage route.

The presence of metastases in a non-lobe specific station suggests the possibility of a more complex communication

in the mediastinal lymphatic drain route. A more aggressive tumor with a stronger metastatic potential could justify the worse prognosis. Indeed, most of tumors with only non-lobe specific nodal metastases were adenocarcinomas and had a poor grade of differentiation.

This study has some limitations. First of all, the relatively small number of patients if compared with other studies that have enlisted thousands of patients [9,10]. Other limitations are the retrospective design of the study and the follow-up time less than 5 years. Anyway, so far there are no prospective studies regarding this argument in literature. All patients received pre-operative 18 FDG-PET/CT but this exam has been performed in different diagnostic centers, so the evaluation of clinical staging could be not homogeneous. The points of strength of the study are the strict inclusion and exclusion criteria that resulted in a homogeneity of diagnostic and therapeutic procedures; moreover, we paid attention for the first time on only non-lobe specific metastases finding a group of patients with a worse prognosis.

CONCLUSION

We observed that primary tumor can spread into mediastinal lymph nodes in both lobe specific and non-lobe-specific region sites is a not negligible percentage. In patients with clinically occult N2 disease, the finding of a metastatic lymph node in a non-lobe specific region represents an important indicator of a worse prognosis, especially when the localization is found only in non-lobe specific nodes with a more than halved survival rate.

Among patients with non-lobe specific metastases, we found that almost one half of patients presented only non-lobe specific ones and this condition is related with a significant lower survival rate both for DFS and OS.

So far, the pathway of lymphatic spread is still unpredictable. A systematic lymph node dissection could be the only method to analyze both lobe and non-lobe specific stations, so this technique could better stage the disease and stratify patient's prognosis. In this way, future prospective could be to assess a role for preoperative evaluation of the lymphatic pathway, finding sentinel node for each primitive lung nodule localization [27].

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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