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Prognostic Value of Cut-off of Lymph Nodes Number and Ratio in Operated Early-Stage Lung Cancer

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ABSTRACT

BACKGROUND

Mediastinal lymphadenectomy is becoming central in thoracic surgery. We evaluated the cut-off of number of resected lymph node and lymph node ratio that could have a prognostic and therapeutic value.

METHODS

We selected 550 patients with early-stage non-small cell lung cancer treated with lobectomy and mediastinal lymphadenectomy. We evaluated the cut-off for both parameters from ROC (Relative Operation Characteristic) curves.

RESULTS

The cut-off was 15 for number of removed lymph node and 0.135 for lymph node ratio. At univariate analyses, number of lymph nodes influenced disease-free survival ($p = 0.028$) and overall survival ($p = 0.017$), while lymph node ratio influenced only disease-free survival ($p < 0.001$). At multivariate analyses, the influence of lymph node ratio on disease-free survival was confirmed ($p = 0.022$). More than 15 lymph nodes showed a higher disease-free survival ($p = 0.007$) and overall survival ($p = 0.011$). Comparing less or more than 15 lymph nodes removed the rate of relapse was 25.0% and 19.3% respectively (mean time to relapse: 14.3 ± 12.4 *vs.* 24.0 ± 16.7 months); mortality rate was 14.6% and 7.0% respectively (mean time to death: 12.1 ± 10.1 *vs.* 17.6 ± 15.6 months).

Lymph node ratio less than 0.135 nodes showed a higher disease-free survival ($p < 0.001$) and overall survival ($p = 0.018$). Comparing lymph node ratio less or more than 0.135 the rate of relapse was 37.0% and 65.7% respectively (mean time to relapse: 21.7 ± 15.3 *vs.* 8.8 ± 7.5 months); the mortality rate was 21.0% and 37.3% respectively (mean time to death: 25.0 ± 19.1 *vs.* 8.9 ± 4.3 months).

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CONCLUSION

Number of lymph nodes and lymph node ratio showed a direct correlation with the patient's prognosis.

KEYWORDS

Resected lymph nodes; Lymph node ratio; Mediastinal lymphadenectomy; Non-small cell lung cancer; Lymph node metastases

INTRODUCTION

Lung cancer is estimated to be the main cause of cancer death worldwide, with about 1.8 million deaths in 2020 [1]. According to the European Society for Medical Oncology (ESMO), the anatomic surgical resection of the involved lobe together with hilar and mediastinal node dissection are the correct treatment for the early-stage non-small cell lung cancer (NSCLC) [2]. The pathological status of lymph nodal is a strong predictor of survival in patients with lung cancer. Current guidelines suggest a minimum of six lymph nodes to be resect and analyze [3].

The importance of the number of resected lymph nodes on prognosis has been already highlighted for other neoplastic disease like breast [4], colorectal [5] and gastric [6] cancer. In the last years, the interest for a quantitative analysis of lymph node is growing up also for lung cancer. The amount of resected lymph nodes should be taken into consideration, since there might be a correlation between the number of excised lymph nodes and the probability of undetected nodal metastases [7-9]. This parameter has some limitations because it could be influenced by the kind of lymphadenectomy performed, lymph node fragmentation and interindividual differences in the number of lymph nodes in the lymphatic chain [10].

The Lymph Node Ratio (LNR) is a new parameter that could overcome the limitations of number of lymph nodes. It is the ratio between the number of metastatic lymph nodes and the number of resected lymph nodes. A high LNR could reflect a more diffuse lymph node metastatic involvement, on the contrary a low LNR could be due to high number of resected lymph nodes or a minor number of metastatic lymph nodes. Different LNR value could be related to different prognosis in patients with mediastinal lymph node metastases [8, 11].

In our study, we selected a cohort of patients with cN0 that undergone pulmonary lobectomy with hilar and mediastinal lymphadenectomy. Our first goal was to find an optimal cut-off value, for both parameter number of lymph nodes and LNR, able to dichotomize patients in two groups with a significant different survival. In addition, we evaluated how the number of resected lymph nodes and LNR influenced overall survival and disease-free survival.

MATERIALS AND METHODS

Population

The retrospective review 550 patients with NSCLC with clinical early stage (Stage I/II) who underwent lobectomy with lymphadenectomy between January 2015 and December 2020. Patients with synchronous cancer or previous history of another cancer were excluded. No neo-adjuvant chemotherapy and/or radiotherapy were included.

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. Images were dated no more than 30 days. CT guided transthoracic biopsy or intraoperative frozen section was performed for the diagnosis. A lymph node was considered suspect for malignancy if diameter was greater than 10 mm in short axis [12] or standardize uptake value (SUV) max score was greater than 2.0 [13]. Endobronchial Ultrasound (EBUS) biopsy was performed in every suspected lymph node.

Negative histologic biopsies were considered cN0. Negative histologic biopsies were considered cN0. If the tissue from endobronchial biopsy were inadequate for the histological diagnosis, was shifted to invasive staging. The choice between mediastinoscopy and thoracoscopic lymph node biopsy was guided by lymph node position.

Surgical Procedure

Lobectomy with hilar and mediastinal lymphadenectomy was performed through thoracotomy (posterior or anterolateral) or Video Assisted Thoracoscopic Surgery (VATS) [14]. To allow a selective ventilation of the non-affected lung, every patient was under general anesthesia with double lumen endotracheal tube. Due to the retrospective nature of the study, we revised medical records to attribute to each patient the nodal dissection pattern performed. Systematic nodal dissection is the dissection of at least three mediastinal lymph node stations (always including station 7). If the lymphadenectomy did not fulfil the criteria of systematic nodal dissection was considered sampling. Lymph node sampling is the dissection of at least six nodes; therefore, we excluded all patients with less than six nodes removed [3]. Whenever possible, we resected lymph nodes en bloc with the surrounding fat. When a lymph node was fragmented, all parts were considered as the same node station for the histological analysis.

Mediastinal lymphadenectomy was carried out in every patient and the choice of which station to analyze was carried out considering various parameters. First, we focused on preoperative histology and radiological tumor characteristics, like prevalence of ground glass opacity (GGO) or solid part, mixed attenuation lesion, central position, and lymph nodes characteristics, like short axis at TC scan more than 1 cm, presence of necrotic core, adipose hilium or tendency to confluence). During surgery, all homolateral mediastinal stations were explored and all enlarged or suspected lymph nodes were sampled.

Histologic Evaluation and Pathological Staging

Pathological classification was based on 2015 World Health Organization Classification of Lung Cancer and pathological staging was based on the 8th edition of the lung cancer TNM (Tumor Node Metastases) [15].

The number of resected lymph node was evaluated in every patient as the number of lymph nodes located within the resected lobe and the others resected during lymphadenectomy, thereby we included both N1 and N2. The lymph node count was the sum of all lymph nodes. If lymph nodes were fragmented, each fragment was counted as another lymph nodes. Histological analysis was performed with haematoxylin-eosin stain and eventually immunohistochemical analysis. In patients with metastatic lymph nodes, Lymph Node Ratio was evaluated including both pN1 and pN2. This last parameter derived from the ratio between the number of metastatic nodes and all resected nodes.

Follow-Up

The follow-up 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

Statistical data analysis was conducted using the SPSS Statistics program version 26.0 (IBM Corp., Armonk, NY). Student's T was used for continuous variables and Pearson's chi-squared test for discontinuous variables. The threshold of significance was set at p-value = 0.050.

We calculated the cut-off for the number of the removed lymph nodes and Lymph Node Ratio from ROC (Relative Operation Characteristic). We chose the most suitable cut-off for stratifying patients in two groups with statistically significant prognostic differences: AUC (Area Under the Curves) <0.5, higher Youden's Index Figure 1.

Survival was graphically represented with Kaplan-Meier curves. Prognostic factors were then evaluated with a Cox regression model. A univariate analysis and multivariate analysis, using the backward stepwise method, was carried out with the variables that influenced the various survivals.

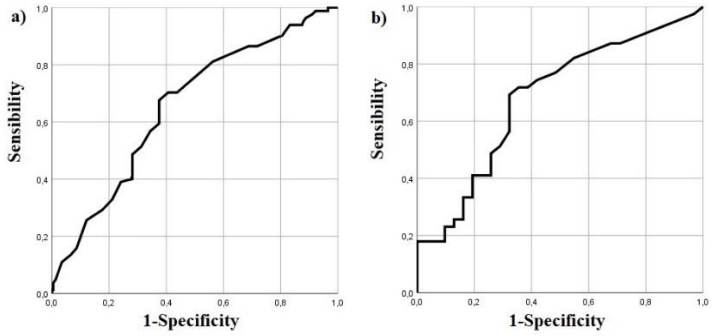

Figure 1: ROC curves for a) number of resected lymph nodes, b) lymph node ratio.

RESULTS

In a cohort of 550 patients, lymph node metastases were found in 124 patients (22.5%): 56 were N1 metastases (10.1%) and 68 were N2 metastases (12.4%).

Variables	DFS		OS	
	p-value	Odds Ratio	p-value	Odds Ratio
Age ≥ 70 years	0.941	1.018	0.192	1.573
Gender	0.219	0.732	0.103	0.534
Stage (TNM VIII Ed.)				
I Stage		1		1
II Stage	**<0.001**	3.349	0.057	2.611
III Stage	**<0.001**	10.581	**<0.001**	9.098
Tumor Diameter ≥ 2cm	**0.003**	2.594	**0.005**	5.391
Histology	0.418	1.253	**0.005**	2.597
Smoke	0.805	1.085	0.086	3.489
Open Vs. VATS	0.632	0.887	0.459	1.322
Tumor SUV max ≥5	**<0.001**	2.905	**<0.001**	7.035
N2 diameter ≥ 1cm	**<0.001**	2.768	**0.004**	2.949
N2 SUV max ≥2	**<0.001**	3.591	**0.001**	3.815
Number lymph nodes ≥20	**0.028**	0.576	**0.017**	0.398
Type of lymphadenectomy	**0.001**	0.347	**0.022**	0.324
Lymph Node Ratio≥0.135	**<0.001**	3.571	0.071	2.324

Table 1: Univariate analysis of prognostic factors for disease free survival and overall survival.
DFS: Disease Free Survival; OS: Overall Survival; TNM: Tumour Node Metastases; VATS: Video Assisted Thoracic Surgery; SUV: Standardize Uptake Value.

The median number of resected lymph nodes for each patient was 23 (interquartile range 16-31): for systematic lymph node dissection the median number was 29 (interquartile range 21-37), whereas for sampling the median number was 10 (interquartile range 6-18). The average operative time was 123 minutes (range 45-215 minutes). In particular, the average time was 125 (from 67 to 215) minutes in systematic dissection and 98 (45 to 140) minutes for sampling.

The cut-off of numbers of removed lymph node was 15 (sensitivity 0.676, specificity 0.375, AUC<0.5); the cut-off for Lymph Node Ratio was 0.135 (sensitivity 0.692, specificity 0.323, AUC< 0.5).

At Cox regression model analyses, the univariate analysis showed that the following factors influenced the disease-free survival: disease stage (p <0.001), tumor diameter more than 2 cm at CT scan (p = 0.003), tumor SUV max greater than 5 (p <0.001), N2 lymph nodes greater than 1 cm at CT (p <0.001) or SUV max greater than 2 (p <0.001), type of lymphadenectomy performed (p = 0.001), number of lymph nodes removed greater than 15 (p = 0.028) and Lymph Node Ratio greater than 0.135 (p <0.001). At univariate analyses, the overall survival was influenced by disease stage (p <0.001), tumor histology (p = 0.005), tumor diameter more than 2 cm at CT scan (p = 0.003), tumor SUV max greater than 5 (p <0.001), N2 lymph nodes greater than 1 cm at CT (p = 0.004) or SUV max greater than 2 (p = 0.001), type of lymphadenectomy (p = 0.022), number of lymph nodes removed greater than 15 (p =

0.017). The Odds Ratio (OR) for disease free survival was 0.576 when more than 15 lymph nodes has been removed and 3.571 when lymph node ratio was higher than 0.135. OR for overall survival was 0.398 when more than 15 lymph nodes have been removed and 2.324 when lymph node ratio was higher than 0.135 Table 1. At multivariate analysis, the only predictors of disease-free survival were type of lymphadenectomy (p = 0.005) resulting in a lower risk of recurrence in patients with systematic lymphadenectomy, lymph node ratio (p = 0.022) with a worse trend for patients with LNR greater than 0.135, and the disease stage (p = 0.045). Multivariate analysis also showed that the only factors influencing overall survival were the stage (p = 0.002) and histology (p = 0.023). OR for disease free survival was 2.347 when lymph node ratio was higher than 0.135 Table 2.

	DFS			OS	
	p-value	**Odds Ratio**		**p-value**	**Odds Ratio**
Stage (TNM VIII Ed.)	**0.045**	2.405	**Histology**	**0.023**	4.457
Type of lymphadenectomy	**0.005**	0.276	**Stage (TNM VIII Ed.)**	**0.002**	9.098
Lymph Node Ratio≥0.135	**0.022**	2.347	**Type of Lymphadenectomy**	0.082	0.284

Table 2: Multivariate analysis of prognostic factors for disease free survival and overall survival. DFS: Disease Free Survival; OS: Overall Survival.

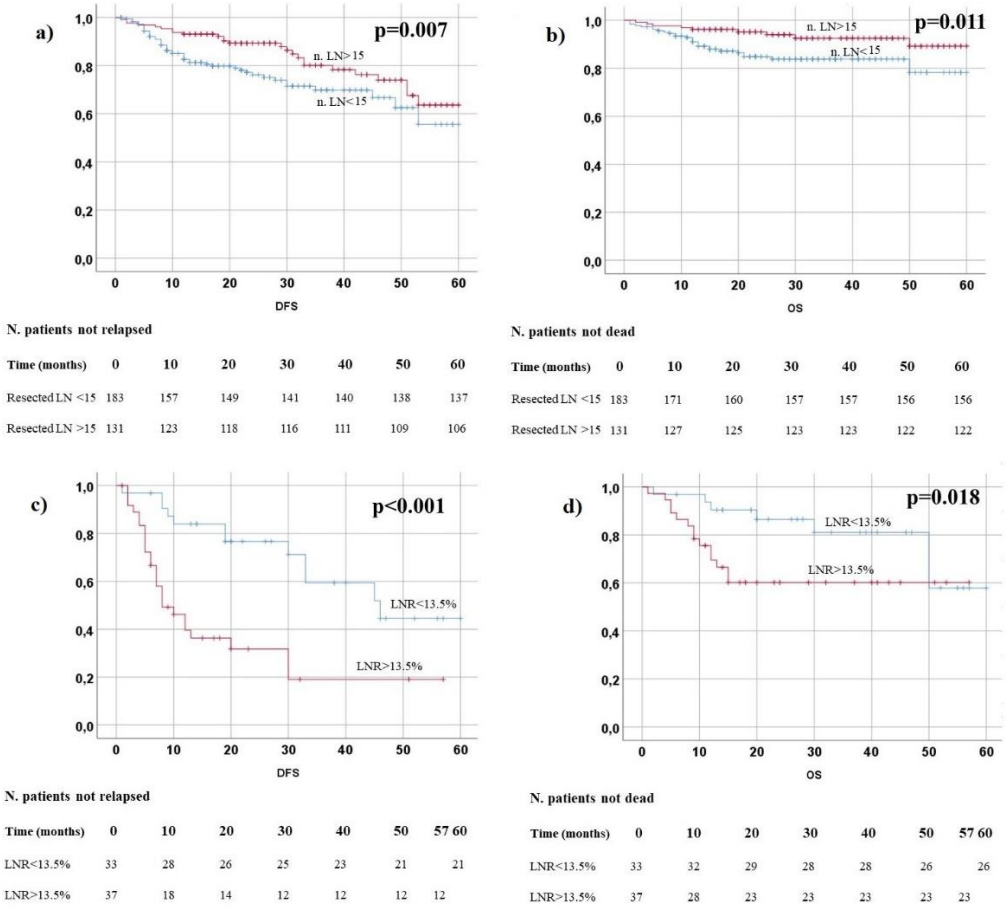

Figure 2: Kaplan Maier curves for **a)** disease free survival for number of resected lymph nodes; **b)** overall survival for number of resected lymph nodes; **c)** disease free survival for lymph node ratio; **d)** overall survival for lymph node ratio.

Less than 15 lymph nodes were removed in 58.5% of patients (322/550) while more than 15 in 41.5% (228/550). In patients with less than 15 lymph nodes removed the relapse rate was 25.0% (80/322) with a mean time to

relapse of 14.3 ± 12.4 months, the mortality rate was 14.6% (47/322) with a mean time to death of 12.1 ± 10.1 months. In patients with more than 15 lymph nodes removed the recurrence rate was 19.3% (44/228) with a mean time to relapse of 24.0 ± 16.7 months, the mortality rate was 7.0% (16/228) with a mean time to death of 17.6 ± 15.6 months Table 3. Kaplan Maier curves for number of resected lymph nodes showed that patients who have been removed more than 15 lymph nodes showed a higher disease-free survival (p = 0.007) and overall survival (p = 0.011) Figure 2.

Among patients with metastatic lymph nodes, lymph node ratio was less than 0.135 in 46% of patients (57/124) while more than 0.135 in 56% (67/124). In patients with Lymph node ratio less than 0.135 the relapse rate was 37.0% (21/57) with a mean time to relapse of 21.7 ± 15.3 months, the mortality rate was 21.0% (12/57) with a mean time to death of 25.0 ± 19.1 months. In patients with Lymph node ratio more than 0.135 the relapse rate was 65.7% (44/67) with a mean time to relapse of 8.8 ± 7.5 months, the mortality rate was 37.3% (25/67) with a mean time to death of 8.9 ± 4.3 months Table 3. Patients with LNR less than 0.135 nodes showed a higher disease-free survival (p <0.001) and overall survival (p = 0.018) Figure 2.

		DFS			OS		
	Value	Events	Mean time	p-value	Events	Mean time	p-value
Number of resected lymph nodes	< 15	92/368 (25.0%)	14.3 ± 12.4 months	0.007	54/368 (14.7%)	12.1 ± 10.1 months	0.011
	>15	50/260 (19.2%)	24.0 ± 16.7 months		18/260 (6.9%)	17.6 ± 15.6 months	
Lymph node ratio	< 0.135	24/64 (37.5%)	21.7 ± 15.3 months	<0.001	14/64 (21.9%)	25.0 ± 19.1 months	0.018
	>0.135	50/74 (65.8%)	8.8 ± 7.5 months		28/74 (36.8%)	8.9 ± 4.3 months	

Table 3: Comparison between patients with more or less than 15 lymph nodes removed and patients with more or less than 0.135 lymph node ratio about disease free survival and overall survival.

DISCUSSION

In recent years, more and more attention has been paid to the number of lymph nodes removed during lymphadenectomy. Unlike other types of neoplasia, the guidelines for lung cancer do not indicate a minimum number of lymph nodes that should be removed [4-6]. The number of resected lymph node and LNR could be calculated considering both hilar and mediastinal nodes or considering the two compartments separated. In our study we studied the number of dissected nodes in the whole population, while LNR was evaluated in patients with metastatic nodes, considering both N1 and N2.

Previous studies have shown that the number of lymph nodes removed was directly correlated to the patient's prognosis [8, 9]. The explanation could lie in the ability to obtain a correct staging of disease, in a possible therapeutic effect due to the higher probability to remove metastatic cells and, also, in the possibility of a more robust immunological response in regional lymph nodes [8].

Osarogiagbon et al. [16] showed that the probability of finding lymph node metastases was directly related to the number of lymph nodes examined, concluding that a more careful lymphadenectomy would lead to a more accurate diagnosis of the true stage of the pathology. Indeed, if the number of examined lymph node stations is low, patients may be misidentified as pN0. The correlation between number of excised lymph nodes and the impact on DFS and OS can be found in several previous studies. In Nwogu et al, as the total number of excised lymph nodes increases, both DFS and OS show progressive improvement [8]. The cut-off about the number of lymph nodes that should be removed varies in the different studies reviewed. Ludwing et al. found an improvement in survival when more than 13 lymph nodes are removed; the HR (Hazard Ratio) for OS

was 0.74 for patients with more than 13 lymph nodes removed as a reference [7]. Bria et al. set the cut-off at 10 lymph nodes because they found HR 1.95 (p <0.001) for DFS and 1.76 (p = 0.002) for OS in patients with less than 10 resected nodes [17]. Baker et al, considered the cut-off at 16 lymph nodes, finding a lower HR (0.78) value for mortality [9]. In the study of Xu et al. the number of excised lymph nodes was divided into three groups: less than 10, between 10 and 20, and greater than 15. They showed an increasing rate of 5-years disease free survival (26.9%, 58.8% and 75.0% respectively) and overall survival (53.8%, 76.5% and 78.3% respectively) [18] Table 4.

	Study	Value	Disease free survival	p-value	Overall survival	p-value
Number of resected lymph nodes	Ludwig et al. [7]*	<13 >13			1 0.74	
	Bria et al. [17]	<10 >10	1.95 1	<0.001	1.76 1	0.002
	Nwogu et al. [8]*	1-3 4-6 7-9 >10	0.94 0.85 0.79 1	0.577 0.181 0.104	1.02 0.91 0.83 1	0.838 0.364 0.125
	Xu et al. [18]**	<10 10-20 >20	26.9% 58.8% 75.0%	0.001	53.8% 76.5% 78.3%	
	Becker et al. [9]*	<16 >16			1 0.78	
Lymph node ratio	Bria et al. [17]*	<0.09 >0.09	1 2.30	0.001	1 2.02	0.01
	Wisnivesky et al. [19]*	<0.15 0.16-0.50 >0.50			1 1.26 1.92	 <0.001 <0.001
	Nwogu et al. [8]*	<0.24 0.25-0.49 >0.50	0.38 0.56 1	<0.001 0.003	0.42 0.58 1	<0.001 0.002
	Urban et al. [11]*	<0.125 0.125-0.249 0.250-0.499 >0.50			1 1.09 1.38 1.73	 0.019 <0.001 <0.001
	Chiappetta et al. [10]*	< 0.4 >0.4	1 1.90	<0.001	1 1.87	<0.001
	Han et al. 2019 [20]*	<0.36 >0.36			1 1.646	<0.001

Table 4: Different cut-offs proposed in the literature.
Note: *HR (Hazard Ratio); **Rate of 5-years Disease Free Survival (DFS) or Overall Survival (OS).

In our study, by analyzing recurrence and mortality data, we found 15 removed lymph nodes to be a significant cut-off for prognosis. When more than 15 lymph nodes were removed, the recurrence and mortality rates were lower.

Another pivotal prognostic factor for patients with occult lymph node metastases was the Lymph node ratio (LNR). This parameter is calculated as the ratio between the number of positive lymph nodes, at histological analysis, and the total number of lymph nodes removed. Some previous studies considered the total number of lymph node examined (both N1 and N2). Nwogu et al, found three ranges of LNR values (<0.24, 0.25-0.49, >0.5): when less than 0.24, the HR for both DFS and OS was 0.38 and 0.42 respectively, using >0.50 as reference [8].

With the same method, Bria et al used 0.09 as cut-off (HR for DFS 2.30 and HR for OS 2.02 when LNR >0.09) [17]. Urban et al divided four ranges and showed gradually increasing HR for OS values from LNR less than 0.125, used as reference, to values greater than 0.50 (HR 1.73) [11]. Others studied considered only N1 or N2 lymph nodes. Wisnivesky et al. considered a population with only N1 metastases and divided LNR into the three ranges (<0.15, 0.16-0.49, >0.5), finding a worse overall survival when LNR was more than 0.50 (HR1.92 considering LNR

<0.15 as reference) [19]. Other studies have done a dichotomous division of the LNR value. Han et al. used 0.36 as cut-off of LNR (HR for OS of 1.646 when >0.36) [20] Table 4. In our study, the cut-off for LNR, derived from a ROC curve, was 0.135. The analyses showed a worse prognosis in patients with LNR over this value (Odd ratio 3.571 for disease-free survival and 2,324 for overall survival).

The correlation between Lymph node ratio and prognosis, highlighted in the study, especially as regards the disease-free survival can be explained considering that high values, especially when many lymph nodes have been removed, are indicative of a more widespread disease at a local-regional level and therefore of patients more susceptible to recurrence due to difficulties in eradicating neoplastic disease.

The literature data showed a wide variability in the cut-off for the number of resected lymph nodes. There is still not a unanimous consensus on the method to count lymph nodes: some pathologists count different pieces of the same station as different nodes, while other ones as a single lymph node. The number of resected lymph nodes could be influenced by the kind of lymphadenectomy performed and by the expertise of the surgeon. The method to achieve an optimal lymphadenectomy is still a matter of debate, although guidelines suggested systematic or lobe specific dissection [21,22].

In the light of these considerations, LNR could overcome these problems because it reduces the influence of lymph node fragmentation or interindividual differences in the number of lymph nodes in the lymphatic chain as confounding factors [10]. Moreover, this ratio highlights the grade of tumor spread. A high value expresses that, out of the total number of lymph nodes removed, a high number had metastatic involvement, while a low value identifies a lower percentage of positive lymph nodes out of the total number removed. Therefore, LNR could become a parameter to stratify the prognosis and guide a tailored treatment, with eventually adjuvant therapy [11].

This study has some limitations. First, the relatively small number of patients, the retrospective design of the study and the follow-up time less than 5 years. The study included two high volume centers with possible different operating techniques that could lead to selection bias for the choice of type of lymphadenectomy. At least, we did not have a standardization on pathological analyses because different pathologist analyzed and counted the lymph nodes.

CONCLUSION

Number of lymph nodes and lymph node ratio showed a direct correlation with the patient's prognosis. These parameters could be useful to stratify the prognosis and guide a tailored treatment.

AVAILABILITY OF DATA

No other data were used in this article.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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