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RESEARCH ARTICLE

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Lymphadenectomy for lung carcinoids: Which factors may predict nodal upstaging? A multi centric, retrospective study

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Abstract

Objective: To investigate risk factors for nodal upstaging in patients with lung carcinoids and to understand which type of lymphadenectomy is most appropriate.

Methods: Data regarding patients with lung carcinoids, who underwent surgical resection and lymphadenectomy in five institutions from January 1, 2005 to December 31, 2019, were collected and retrospectively analyzed. Clinical and pathological tumor characteristics were correlated to analyze lymph node upstaging.

Results: The analysis was conducted on 283 patients. Pathology showed 230 typical and 53 atypical carcinoids. Nodal and mediastinal upstaging occurred in 33 (11.6%) and 16 (5.6%) patients, respectively. At the univariable analysis, nodal upstaging was significantly correlated with central location ($p = 0.003$), atypical histology ($p < 0.001$), pT dimension ($p = 0.004$), and advanced age ($p = 0.043$). The multivariable analysis confirmed atypical histology (odds ratio [OR]: 11.030; 95% confidence interval [CI]: 4.837–25.153, $p < 0.001$) and central location (OR: 3.295; 95% CI: 1.440–7.540, $p = 0.005$) as independent prognostic factors for nodal upstaging. Atypical histology ($p < 0.001$), pT dimension ($p = 0.036$), number of harvested lymph node stations ($p = 0.047$), and type of lymphadenectomy ($p < 0.001$) correlated significantly with mediastinal upstaging. The multivariable analysis confirmed atypical histology (OR: 5.408; 95% CI: 1.391–21.020, $p = 0.015$) and pT (OR: 1.052; 95% CI: 1.021–1.084, $p = 0.001$) as independent prognostic factors.

Conclusion: Atypical histology, dimension, and central location are associated with a high-risk for occult hilo-mediastinal metastases, and mediastinal radical dissection may predict nodal upstaging. Thus, we suggest radical mediastinal lymph node dissection in high-risk tumors, reserving sampling, or lobe-specific dissection in peripheral, small typical carcinoids.

KEYWORDS

lung carcinoid, lymphadenectomy, lymphnodes, upstaging

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1 | INTRODUCTION

Lung carcinoids (LC) are tumors that arise from Kulchitsky's cells; even though they are still considered rare tumors, their incidence and prevalence are progressively increasing.[1–3] They are classified as typical carcinoids (TC) and atypical carcinoids (AC) based on histological features, a classification indicating different clinical behaviors. Indeed, AC have a greater likelihood of nodal and distant metastases, therefore a worse prognosis than TC.[4,5] Surgery is the treatment of choice in view of TCs clinical behavior and limited availability of chemo- or radiotherapy options.[3,4] Among surgical alternatives, lobectomy seems to be the most appropriate option, demonstrating better long term survival compared to wedge resection, even if segmentectomy may be a reasonable choice in selected patients with TC.[3,6,7]

Lymph node involvement in carcinoids is considered to be rare, but the presence of nodal metastases appeared to be one of the most important prognostic factors, which was shown to be even independent from histology in some studies.[5,8–10] Indeed, Cusumano et al.[10] reported a hazard ratio of approximately three for overall survival and five for disease free survival in case of nodal involvement, while Cardillo et al.[8] did not report any disease-related deaths in node negative patients, while 5 year overall survival was 84% in N1 patients and 22% in N2 patients (only AC). Finally. Kneuerts et al.[5] reported a significant survival difference in TC > 2 cm and AC in case of nodal metastases. For these reasons, nodal involvement seems to be as strong prognosticator in these patients, and correct nodal staging may lead to an appropriate prognosis stratification and better definition of patients who may benefit from postoperative treatments.

However, despite the prognostic importance of nodal involvement, specific indications regarding appropriate lymphadenectomy are still missing. In particular, recent studies reported a 20% increase in nodal involvement when an appropriate lymph node assessment was performed, suggesting that a high number of harvested lymph nodes determines a survival advantage.[5] Based on previous considerations, identifying the appropriate type of lymphadenectomy seems to be an important objective toward managing these patients as well as identifying lymph node involvement.

The aims of this study were to identify factors associated to lymph node upstaging in patients who underwent surgical treatment for LC and to identify the most appropriate type of lymphadenctomy to use in these tumors.

2 | METHODS

The ethics committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS approved the protocol (ID1089-04.12.2020). Data regarding patients who underwent, surgery for LC in five different high volume centers for lung cancer management and surgical treatment between January 1, 2005 to Decemeber 31, 2019 were collected and retrospectively reviewed. The inclusion criteria for patients included: age >18 years, absence of distant metastases or contralateral nodal disease, pathological diagnosis of LC, information regarding the preoperative and postoperative nodal status.

A histological diagnosis for discriminating between TC and AC was conducted using immunohistochemistry, and verifying the presence of necrosis and mitotic activity.[11] TC are highly organized carcinoid architectures with less than two mitoses/10 high-power fields (HPFs). Instead, ACs are characterized by greater mitotic activity (2–10/10 HPF) and focal or discrete necrosis. The tumor location was considered central, when the tumor was directly visualized during bronchoscopy, and peripheral when the lesion was not observed during the bronchoscopy and was judged resectable with a wedge resection.

The preoperative workup was similar among the different centers consisting in preoperative computed tomography (CT) brain-thorax-abdomen scan with contrast, while a 18FDG-PET or PET with somatostatin analogs (dotanoc-, dotatoc-, or dotatate-PET) was performed if indicated, after it became available, as already reported.[12] Following the development of minimally invasive staging technologies, EBUS with selective biopsy were performed in suspected mediastinal nodal involvement (lymphonode with short axis >1 cm or with uptake at 18FDG-PET or PET with somatostatin analogs), and in suspected nodal stations, especially in regard to differential diagnosis with non-small cell lung cancer (NSCLC). Surgery was indicated following preoperative histological diagnosis, the presence of a tumor 18FDG-PET and/or somatostatin analog PET uptake, or after multidisciplinary discussion based on CT nodule characteristics and malignancy risk. A multidisciplinary team, consisting of oncologists and surgeons, managed pre- and postoperative treatments planning follow-up schedules and adjuvant treatments based on the final pathological reports, histology, and nodal status.

2.1 | Surgery and lymph node assessment

Despite some unavoidable variability regarding the surgical technique, surgical strategies, and clinical practice were substantially similar in all centers, and oncological outcomes (in particular the aim to perform curative surgery) were respected in every case. Patients were evaluated based on their pulmonary function before surgery and can tolerate lung resection. When planning the extension of pulmonary resection, the following assumptions were considered: (1) sublobar resection (wedge resection or segmentectomy) was considered in selected (peripheral node-negative) TCs with a dimension less than 2 cm and in ACs only in case of poor pulmonary function; (2) lobectomy was indicated in all remaining cases, including those without a preoperative diagnosis or when a clear histological distinction between AC and TC was not feasible at frozen section evaluation. In particular, suspected TC was considered in low grade tumors (when preoperative/intraoperative biopsy was present), with low/absent FDG uptake or somatostatin analog uptake. Frozen section was usually performed to distinguish between neoplasms from benign nodules, and not for differentiating TC from atypical

ones. Certified thoracic surgeons, performed all surgical procedures and bronchoplastic procedures were preferred whenever feasible avoiding pneumonectomy where possible. Lymph node stations were identified in accordance with the International association for the study of lung cancer lymph-node map[13] while lymphadenectomy was planned in reference to the European association of cardio-thoracic surgeons guidelines[14]:

- Node sampling: removal of one or more lymph nodes thought to be representative, was guided by preoperative or intraoperative findings.
- Lobe-specific systematic node dissection: the mediastinal tissue, containing specific lymph node stations, was excised depending on the lobar location of the primary tumor.
- Radical nodal dissection: the entire mediastinal tissue, containing lymph nodes, was dissected and systematically removed within anatomical landmarks.

Lobe-specific dissection was defined as follows: right upper lobe stations 2–3A-3P-4, middle lobe stations 4–7, left upper lobe stations 4–5–6, left and right lower lobe stations 7–8–9.

For the retrospective nature of the study, the surgeon decided on type of resection and extent of lymphadenectomy to adopt based on their own experience, tumor location, histology, and dimension.

Pathological data were mainly collected from reports, however a center pathological review was performed in case of doubt or incomplete information to adapt histological and staging information to actual systems.[11,15] As indicated in current guidelines, LC has been clinically and pathologically staged according to the 8th Tumor Node Metastasis Edition for Lung Cancer.[15] Nodal upstaging was defined as the presence of pathological lymph node involvement in clinical N0 patients (resulting with N1, N2, or N1–N2 metastases), while mediastinal upstaging was defined as the presence of N2 involvement in patients clinically staged as N0. Patients with clinical N1 involvement (at CT, PET, or after EBUS) were not considered for N2 upstaging because of their high risk of occult mediastinal involvement. Clinical and pathological characteristics such as type of lymphadenectomy, tumor location (central vs. peripheral), histology, clinical N status, clinical and pathological T status, and number of resected nodes, were correlated with the presence of nodal and mediastinal upstaging.

3 | RESULTS

Data from 332 patients were finally collected: 2 patients were excluded for the presence of distant metastases, 7 patients for incomplete data regarding clinical and pathological nodal status, and 40 patients because mediastinal lymph node assessment was not performed. The final analysis was conducted on 283 patients. Clinical and pathological characteristics are reported in Table 1.

A preoperative histological diagnosis was carried out on 153 patients, which was obtained with a bronchoscopy in central lesions

TABLE 1 Clinical and pathological characteristics of the entire cohort

Male/female	112/171
Age	57 (17)
Histology	
Typical carcinoid	230 (81.2%)
Atypical carcinoid	53 (18.8%)
Location	
Central	114 (40.2%)
Peripheral	169 (59.8%)
Clinical stage	
I	230 (81.2%)
II	36 (12.6%)
III	16 (5.5%)
Missing	2 (0.7%)
Clinical N	
0	246 (86.9%)
1	26 (9.1%)
2	11 (4.0%)
Surgery	
Wedge	12 (4.2%)
Segmentectomy	21 (7.4%)
Lobectomy	218 (77.2%)
Bilobectomy	24 (8.4%)
Pneumonectomy	8 (2.8%)
Pathological T stage	
T1	227 (80.2%)
T2	41 (14.4%)
T3	16 (5.5%)
Pathological stage	
I	229 (81.2%)
II	33 (12.4%)
III	21 (7.4%)
Lymphadenectomy	
Mediastinal radical node dissection	215 (75.9%)
Lobe-specific	15 (5.3%)
Sampling	53 (18.8%)
Nodal upstaging	
Yes	33 (11.6%)
No	250 (88.4%)
Mediastinal (N2)	16 (5.6%)
Typical carcinoid	

TABLE 1 (Continued)

Male/female	112/171
Nodal upstaging	13 (4.9%)
Mediastinal upstaging	6 (2.2%)
Atypical carcinoid	
Nodal upstaging	20 (35.0%)
Mediastinal upstaging	10 (17.5%)

or with a transparietal fine needle ago-biopsy in peripheral tumors for histological and cytological evaluation. In particular, 7 cases had a preoperative diagnosis of typical or low grade neuroendocrine tumor, 4 cases were diagnosed with atypical carcinoid while the remaining 142 cases were diagnosed with an unspecified carcinoid tumor. A PET carried out with somatostatin analogs or Gallium was performed in 38 cases where an increased uptake was revealed in 18 cases. A FDG-PET was performed in 119 patients showing an increased uptake in 67 of them. Patients without preoperative diagnosis and negative PET with somatostatin analogs or Gallium underwent intraoperative frozen section analysis for histological assessment whenever possible to confirm the presence of NSCLC independent from the histology and to exclude benign nodules. In particular, a frozen section analysis was performed in 23 patients where the pathologists reported a carcinoid tumor diagnosis in 19 cases and of typical carcinoid in 4 patients. Thirty-seven patients presented suspicious nodal involvement. N2 involvement was suspected in six cases at the somatostatin analogs or Gallium PET, in three cases at the FDG-PET and in five cases due enlarged nodes at the CT scan.

N1 disease was clinically suspected in 28 cases: in three cases at somatostatin analogs or Gallium PET, seven cases at the FDG-PET, and 18 cases due enlarged nodes at the CT scan. EBUS was performed in six cases of suspected N2 involvement: N2 involvement was confirmed in three cases, and excluded in three cases (two cases with concomitant suspected N1 involvement). EBUS excluded N1 disease in two cases.

In 271 (95.8%) cases, surgery consisted in anatomic resections. Most patients underwent a lobectomy (218 cases), while a wedge resection was performed in 12 (4.8%) cases (Table 1). Lymphadenectomy consisted in radical nodal dissection in 215 patients, lobe-specific systematic node dissection in 15 patients, and node sampling in 53 patients. The mean number of resected lymph nodes resulted to be 9[7] and the median number of harvested nodal stations resulted to be 3 (interquartile range 3). In particular, the median number of resected nodes and resected stations was 5 and 1.5 in sampling/lobe-specific dissections versus 10 ($p < 0.001$) and 4 ($p < 0.001$) in radical dissections. Only 13% of patients who underwent node sampling or lobe-specific dissection had more than 10 resected nodes compared with 55.6% in patients who underwent radical node dissection ($p < 0.001$). Similarly, only 10.3% of patients who underwent sampling/lobe-specific dissection had more than 3 harvested stations compared to only 10% of patients with more than 10 resected nodes in the sampling group versus 51.3% of patients who underwent radical lymphadenectomy ($p < 0.001$). Nodal upstaging was detected in 33 (11.6%) patients, while mediastinal (N2) upstaging occurred in 16 (5.6%) patients.

The nodal upstaging occurred from cN0 to pN1 in 17 cases, while in the 16 pN2 patients it occurred in 5 cases from cN1 and in 11 from cN0. In eight cases the pStage resulted with concomitant pN1 and pN2 involvement, while skip metastases occurred in eight cases (Supplemental Information: Table).

Nodal downstaging occurred in 13 patients, 9 from cN1 to pN0, 3 from cN2 to pN0, and 1 from cN2 to pN1 and in regard to lymphadenectomy, 11 patients underwent nodal downstaging in the radical mediastinal dissection group (5.1%) versus 2 in the other lymphadenectomy group (2.9%).

Pathological staging was confirmed in 235 patients: Stage I in 207, Stage II in 20, and Stage III in 8 patients, with N1 involvement confirmed in 2 patients (IIb) and N2 involvement confirmed in 3 (pT1-2N2) patients, respectively.

3.1 | Nodal upstaging

In the univariable analysis (Table 2), central location ($p = 0.003$), atypical histology ($p < 0.001$) (Figure 1A), pT dimension ($p = 0.004$)-(Figure 1B), and advanced age ($p = 0.043$) all significantly correlated with nodal upstaging. Regarding lymphadenectomy, the number of harvested stations ($p = 0.06$), and radical nodal dissection ($p = 0.08$) were not statistically significant.

The multivariable analysis confirmed atypical histology (odd ratio [OR]: 11.030; 95% confidence interval [CI]: 4.837–25.153, $p < 0.001$) and central location (OR: 3.295; 95% CI: 1.440–7.540, $p = 0.005$) and are independently associated with nodal upstaging.

3.2 | Mediastinal upstaging

In the univariable analysis (Table 2), atypical histology ($p < 0.001$) -(Figure 2A), pT dimension ($p = 0.036$) (Figure 2B), number of harvested lymph node stations ($p = 0.047$), and radical nodal dissection ($p < 0.001$) (Figure 3) all significantly correlated with mediastinal upstaging. In particular, mediastinal upstaging occurred in 16% of patients who underwent radical nodal dissection while no mediastinal upstaging was detected in patients who underwent other types of lymphadenectomies. Considering the number of resected lymph nodes, mediastinal upstaging occurred in 3.1% of patients with <10 resected nodes versus 9.7% of patients >10 resected nodes ($p < 0.001$) (Figure 2C).

The multivariable analysis confirmed atypical histology (OR: 5.408; 95% CI: 1.391–21.020, $p = 0.015$) and pT dimensions (OR: 1.052; 95% CI: 1.021–1.084, $p = 0.001$) as independently associated with mediastinal upstaging; type of lymphadenctomy was not considered in the multivariable analysis due the absence of cases within other lymphadenectomy groups.

TABLE 2 Risk factors for upstaging

	Upstaging					Mediastinal upstaging				
	No (%)	Yes (%)	*p*	OR	95% CI	No (%)	Yes (%)	*p*	OR	95% CI
Sex			0.89	1.054	0.499–2.227			0.78	1.164	0.405–3.341
Male	90.1	9.9				91.7	8.3			
Female	89.6	10.4				92.8	7.2			
Location			**0.003**	2.964	1.413–6.215			0.42	1.545	0.539–4.424
Central	82.8	17.2				93.7	6.3			
Peripheral	93.4	6.6				90.6	9.4			
Dimension		14.8	0.34	1.522	0.643–3.601			0.17	2.173	0.706–6.683
T > 3	85.2	10.3				86.5	13.5			
T < 3	89.7					93.3	6.7			
Histology			**<0.001**	10.520	4.828–22.922			**<0.001**	**8.385**	**2.845–24.713**
Typical	95.1	4.9				96.4	3.6			
Atypical	64.9	35.1				76.2	23.8			
No. of dissected lymph nodes			0.66	1.197	0.544–2.637			**<0.001**	**3.365**	**0.950–11.917**
>10	86.8	13.2				90.3	9.7			
<10	88.7	11.3				96.9	3.1			
Type of lymph nodes dissection			0.08	1.980	0.917–4.271			**0.001**		
Radical dissection	90.2	9.8				86	14			
Sampling/lobe-specific	88.7	11.3				100	0			
Age[a]			**0.043**	1.026	0.999–1.054			0.39	1.016	0.978–1.056
Dimension cT[a]			0.062	1.015	0.993–1.038			**0.034**	**1.029**	**1.002–1.056**
Dimension pT			**0.010**	1.026	1.006–1.046			**0.04**	**1.041**	**1.017–1.066**
No. of lymph nodes dissected[a]			0.341	1.021	0.971–1.074			0.105	1.036	0.963–1.114
No. of lymph nodes stations dissected[a]			0.60	1.190	0.997–1.419			**0.047**	**1.126**	**1.006–1.596**

Note: Bold values indicates statistically significant.
Abbreviations: CI, confidence Interval; OR, odds ratio.
[a]Continuous variables.

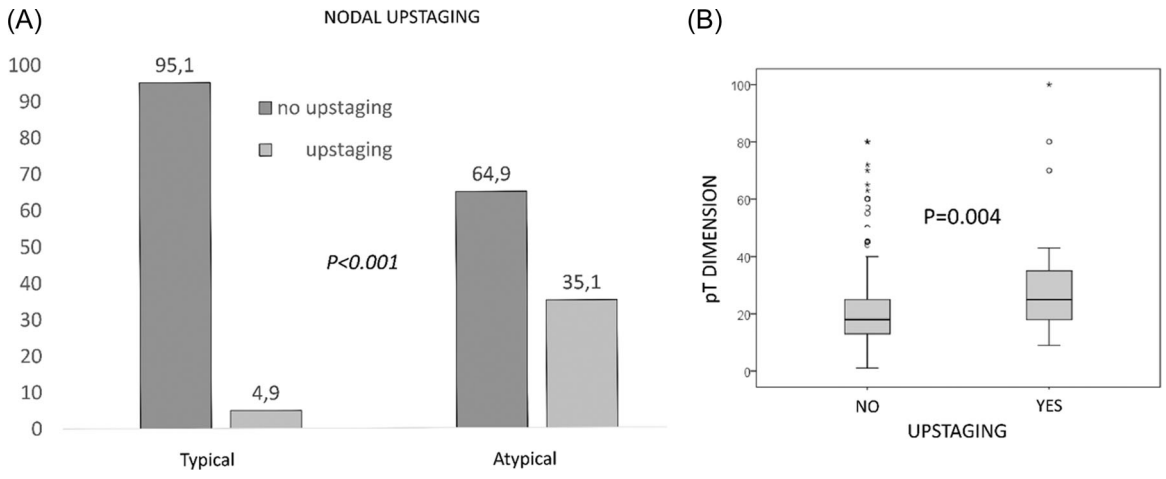

FIGURE 1 Nodal upstaging rate according to histology (A) and pT dimension (B).

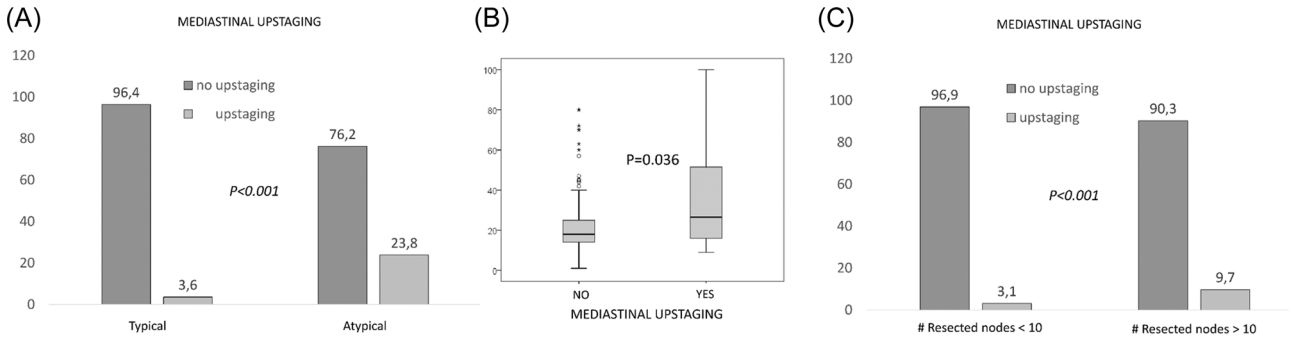

FIGURE 2 Mediastinal upstaging according to histology (A), pT dimension (B), and number of resected nodes (C).

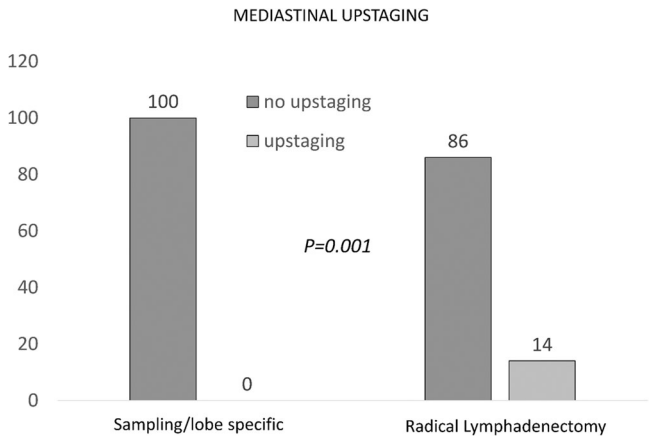

FIGURE 3 Incidence of mediastinal upstaging related to kind of lymphadenectomy occurred only in case of radical lymphadenectomy.

3.3 | TC (230 patients)

Dividing by histology, the univariable analysis (Table 3) showed that central location ($p = 0.01$) (Figure 4A), radical nodal dissection ($p = 0.01$) (Figure 4B), and pT dimension correlated with nodal upstaging in TC, but no other variables resulted to be an independent factor at the multivariable analysis.

The univariable analysis showed that cT dimension >3 cm ($p = 0.02$) (Figure 5A), pT dimension ($p = 0.008$), and radical mediastinal lymph node dissection ($p = 0.03$) correlated with mediastinal upstaging, which occurred only in patients who underwent radical mediastinal dissection: 7.2% versus 0% in patients who underwent node sampling or lobe-specific dissection. The multivariable analysis confirmed pT dimension (OR: 1.052; 95% CI: 1.016–1.090, $p = 0.004$) as independent factor; type of lymphadenectomy was not considered in the multivariable analysis due the absence of cases in other lymphadenectomies groups.

3.4 | AC (53 patients)

None of the analyzed factors significantly correlated with nodal upstaging, even if nodal upstaging occurred in 25% of peripheral tumors and 52.4% of central tumors ($p = 0.08$) (Table 3). Conversely, type of lymphadenectomy was the only prognostic factor for mediastinal upstaging ($p = 0.04$): 33.3% in radical lymphadenectomy versus 0% in other lymphadenectomy groups (Figure 5B).

4 | DISCUSSION

Our study revealed a remarkable rate of nodal upstaging (overall 11.6% [33/283] and 5.6% for mediastinal upstaging) with predominant cases of AC. Our results are in agreement with recent findings suggesting that the extent of lymphadenectomy is fundamental to improve staging in LC.[5,10] It is interesting to note that our upstaging rate is similar to nodal upstaging in NSCLC, which ranges from 10% to 14%,[16,17] while mediastinal upstaging ranges from 5% to 13% after accurate preoperative assessment.[17,18] Moreover, our upstaging rate is similar to the rate reported by Kneuertz et al.[5] showing a nodal upstaging in 13% of LC, 11% in TC, and 24% in AC patients. The authors analyzed a national cohort selecting patients with more than 10 resected lymph nodes concluding that an appropriate lymph node assessment allows a more accurate staging with a significant percentage of detected nodal metastases. Similarly, Brown et al.[19] proposed 10 resected lymph nodes as a prognostic value for TC.

Even though the extent of lymphadenectomy may improve staging and the number of resected nodes plays a prognostic role in NSCLC, there is lacking indications and guidelines for lymph node assessment concerning LC in the literature. Data from a European multicenter registry, which reproduces a real world experience regarding different lymphadenectomy approaches in LC patients, confirms that a significant upstaging detection was present when 10 lymph nodes were harvested. In particular, we noticed a significant difference comparing lymphadenectomy approaches, where we found more than 10 resected nodes in the 55% of patients who underwent radical dissection compared to 13% of patients who underwent other types of lymphadenectomies. Moreover, we analyzed the different lymphadenectomy approaches confirming that the mediastinal radical dissection is only associated with mediastinal upstaging. This should be carefully considered because the presence of lymph node involvement may significantly affect prognosis in these tumors. Indeed, LC, and in particular TC, are tumors with

TABLE 3 Risk factors for upstaging divided by histology.

	Typical						Atypical					
	Mediastinal upstaging			Upstaging			Mediastinal upstaging			Upstaging		
	No (%)	Yes (%)	*p*	No (%)	Yes (%)	*p*	No (%)	Yes (%)	*p*	No (%)	Yes (%)	*p*
Sex			0.88			0.74			0.79			0.41
Male	96.1	3.9		95.7	4.3		81	19		71.4	28.6	
Female	96.6	3.4		94.8	5.2		71.4	28.6		58.6	41.4	
Location			0.13			**0.01**			0.99			0.08
Central	98.6	1.4		90.5	9.5		75	25		47.6	52.4	
Peripheral	94.1	5.9		97.5	2.5		76.2	23.8		74.3	25.7	
Dimension			**0.02**			0.17			0.45			0.53
T > 3	88	12		90.0	10		83.3	16.7		71.4	28.6	
T < 3	97.8	2.2		95.4	4.6		69.2	30.8		59.5	40.5	
No. of lymph nodes dissected			0.99			0.67			0.07			0.75
>10	96.4	3.6		94.4	5.6		68.8	31.3		57.9	42.1	
<10	97.2	2.8		92.9	7.1		95.2	4.8		66.7	33.3	
Type of lymph nodes dissection			**0.03**			**0.01**			**0.004**			0.47
Radical dissection	92.8	7.2		87.9	12.1		66.7	33.3		65.1	34.9	
Sampling/lobe-specific	100	0		96.5	3.5		100	0		50	50	
Age[a]			0.111			0.725			0.262			0.100
Dimension cT[a]			**0.041**			0.106			0.538			0.795
Dimension pT[a]			**0.008**			**0.015**			0.543			0.524
No. of lymph nodes dissected[a]			0.331			0.293			0.281			0.478
No. of lymph nodes stations dissected[a]			0.765			0.646			0.792			0.434

Note: Bold values indicates statistically significant.
[a]Continuous variables.

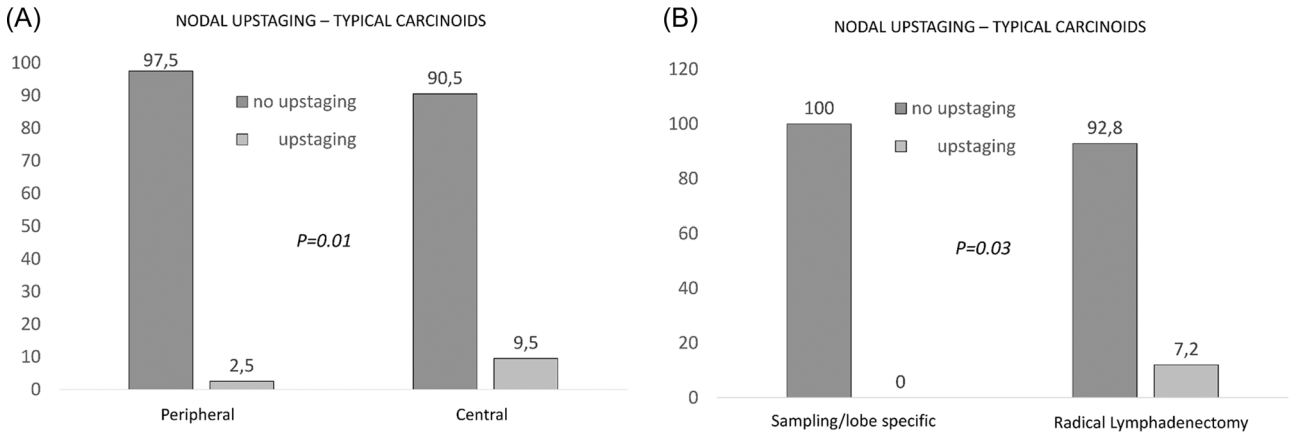

FIGURE 4 Typical carcinoids: nodal upstaging according to location (A) and kind of lymphadenectomy (B).

favorable outcomes and optimal survival rates after surgical resection. However, the presence of nodal involvement remains one of the most important prognostic factors. Indeed, nodal metastases, independently from hilar or mediastinal involvement, significantly affect the prognosis in these patients with a significantly decreased survival rate in case of nodal metastases a 5-year survival of about 90% in N0 versus 75% in pN+ TC and 85% in pN0 versus 60% in pN+ AC.[20,21] Moreover, for these kinds of tumors and specifically for AC,

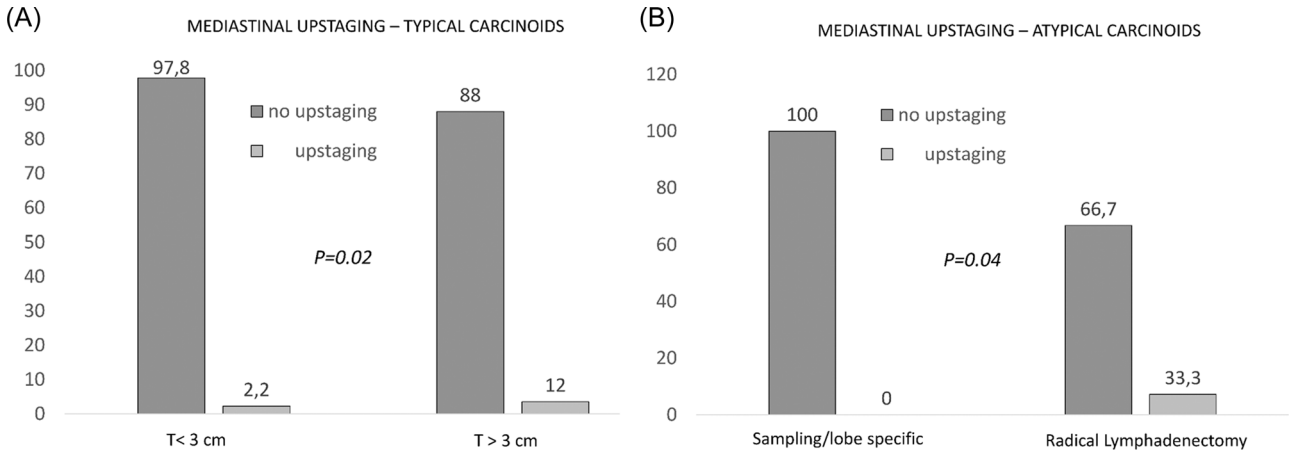

FIGURE 5 Mediastinal upstaging: according to tumor dimension in typical carcinoids (A) and kind of lymphadenectomy in atypical carcinoids (B).

which are characterized by more aggressive behavior and poorer prognosis compared to TC, the role of adjuvant therapies is still under debated. In particular, no clear advantages after administrating adjuvant therapy are described in literature.[22,23] Instead, other studies reported a worse outcome when lymph nodes were not or partially resected examined[19,24] suggesting the possibility that metastatic node resection may have a curative/prognostic role. In particular, Chen et al.[24] analyzed the survival outcome in a large cohort of AC, reporting a significant worse prognosis in patients without lymph node assessment. These results opened an intriguing question, suggesting a possible curative role of lymphadenectomy in LC, a crucial point that should be carefully evaluated. In fact, the lack of prospective studies limits the possibility to verify this theory, and stating that actual survival rates especially in AC limits the possibility of performing a lymphadenectomy in these patients is not acceptable. However, considering the little data available, the not negligible upstaging rate and the validated prognostic role of the nodal involvement, a lymph node assessment may be considered mandatory in these patients not only for staging purposes, but also for curative intent. This is an interesting hypothesis considering limited data availability regarding the role of adjuvant therapy and the nodal involvement rate in AC above 50% in large tumors.[5] Additionally, an appropriate lymph node assessment may be an important factor for a better prognosis definition based on different parameters, but it could lead to regrouping of a specific subset of patients. Moreover, adjuvant protocols based on platinum therapy or dacarbazine/Temozolomide ± radiotherapy do not support survival improvement when adjuvant therapy is administered, with actual guidelines not recommending adjuvant therapy after carcinoid surgical resection.[25] However, this result may be also due to the heterogeneity of the cohort and the difficulties in identifying patients that may genuinely have a survival advantage. For these reasons, mediastinal radical dissection may be indicated in most patients with LC, hoping that in the imminent future, specific adjuvant protocols will be available for these patients.

In particular, the ratio between metastatic and harvested lymph nodes (node ratio) seems to be a promising prognosticator for these patients[23,26] because it indicates the nodal spreading of the tumor and may be considered for adjuvant therapy administration.[23]

At the multivariable analysis the tumor dimension was observed to significantly correlate with nodal upstaging considering the entire population and in TC alone, while in AC the difference was not statistically significant. Despite some discordances between clinical and pathological dimensions, this parameter may indicate the most appropriate lymphadenctomy to adopt in TC. Indeed, in our experience, mediastinal upstaging occurred in 2%[6] of patients, and only two patients with cT1 tumors. Moreover, Kneuerts et al.[5] did not report different prognosis in TC < 2 cm with or without nodal involvement, so, it is possible that in these patients may undergo limited lymphadenectomy considering the very low possibility of unexpected nodal involvement, even if prospective studies are needed to validate this hypothesis.

In our opinion, considering the higher upstaging rate in central tumors, mediastinal radical dissection should be mandatory in case of centrally located tumors independently from their dimension and histology.

Our study confirms the increased tendency of nodal spreading in AC, independently from dimension and location, even if a statistical trend comparing central located tumors with peripheral tumors was present ($p = 0.08$). This difference may be related to the relatively low number of AC patients included in our cohort. However, as reported above, radical mediastinal dissection seems to be mandatory due to the high risk of nodal involvement, its prognostic role, in addition to its curative intent as well as to select patients who may benefit from adjuvant therapy based on platinum, dacarbazine/Temozolomide ± radiotherapy or future drugs, given the effort placed in identifying patients that may truly benefit form adjuvant therapy administration.[23]

One of the main criticisms concerning LC management regards the discrimination between TC and AC before surgery. Sometimes

large tissue biopsies (achieved by endoscopic procedures) may give the pathologist a certain confidence to formulate a definitive diagnosis but in most cases, it is extremely hard to distinguish between TC and AC. Moreover, morphologic radiological findings are often similar in both subtypes.[27] On the other hand, FDG-PET and somatostatin analogs may help evaluate and provide a sort of "nonsurgical" pre-op biopsy. Indeed, TCs usually present low FDG uptake and increased somatostatin analog uptake, while ACs present an inverse appearance.[28] The evolution of medico-nuclear technology and a better understanding of its results will be very useful in the near future toward guiding the management of LC, and associating biopsy information (low grade tumors vs. high grade) which may provide the surgeon with a complete picture and facilitate decision making in regard to the extent of resection and type of lymphadenectomy to adopt. Finally, out of 153 preoperative diagnoses, it was possible to identify typical or AC in 11 cases, thus a radical mediastinal lymph node dissection may be considered the mandatory approach in case of "carcinoid tumor" diagnosis to reduce the risk of incomplete nodal assessment especially in AC.

LC diagnoses are on the increase and an appropriate nodal assessment to locate nodal involvement may represent a fundamental part of the therapeutic strategy. Indeed, a correct lymphadenectomy permits to discover more lymph node metastases.

Finally, a consideration regarding the results in TC and AC. We tried to limit bias due to the retrospective nature of the study and the surgeon's decision-making regarding the extent of resection by analyzing the different histology (typical and atypical) and through performing a multivariable analysis to assess the value of tumor dimension. Indeed, in some cases subgroup analyses (if not prospectively planned) can detect spurious associations just by chance (for every 20 subgroup comparisons, it is possible to detect one statistically significant association). For this reason, we also considered the results in each subgroup setting the level of significance at $p \leq 0.02$. Also in this manner, the results were confirmed in the majority of variables, with a significant correlation between mediastinal upstaging and radical dissection in AC. Similarly, in AC, the association between the mediastinal upstaging with pathological tumor dimension and the connection between nodal upstaging with pathological dimension and type of lymph node dissection maintained the statistical significance.

4.1 | Limitations

This study presents some limitations due to its retrospective nature that does not allow for a proper reconstruction of the preoperative workup in all the cases involved. In some patients, a preoperative histological diagnosis was not present, however patients underwent intraoperative frozen sections to demonstrate the presence of a tumor, thus performing an adequate resection and lymphadenectomy. In particular, even tumor location may present a limitation for preoperative diagnosis due to the dimension or peripheral location, reducing the possibility of carrying out fine needle transparietal biopsies or bronchoscopy if the tumor is not identifiable in the bronchial tree.[29,30] Another limitation regarding the type of lymphadenectomy performed, has to do with the great difficulties faced when having to reconstruct the choice between node sampling, lobe-specific or mediastinal radical lymph node dissection, especially in large and central tumors. Given the retrospective nature of the study, there is also a lack of existing guidelines for surgeons, who made decisions based on their own experience regarding the extent of resection and the type of lymphadenectomy to adopt, with the impossibility of reconstructing a homogeneous and clear decision making process.

To reduce this bias, we implemented a statistical analysis performing a separate histology analysis together with a multivariable model to accurately assess the role factors play such as tumor dimension and reducing confounding factors.

Even though the preoperative workup may differ, the preoperative policy adopted was similar among the different centers involved. It always consisted in carrying out a CT scan of brain-thorax-abdomen for staging and using other technologies when necessary. In fact, EBUS or PETs were not performed in every patient due the advent of these technologies during the study period, however it is also important to note that surgical indication for LC is present independently from nodal involvement owing to the absence of valid alternatives[25] and neoadjuvant protocols. Similarly, also the number of resected nodes may be influenced by fragmentation and in some cases should be carefully considered. For this reason, one of the selection criteria for the participant centers regarded the lymph node count, which we performed as follow:

If one or more lymph node fragments were detected, each fragment was counted as another lymph node reducing the fragmentation bias. Finally, any specific preoperative or intraoperative guideline for LC is actually present, where one of aims is to describe effective nodal involvement in LC to guide future considerations and guidelines pertinent to this topic.

5 | CONCLUSION

Lymph node upstaging was found in about 10% of cases. Atypical histology, tumor dimension, and central location seem to be significant risk factors for nodal and mediastinal upstaging.

Only radical nodal dissection allows the identification of unexpected N2 disease suggesting that this type of lymphadenectomy should be performed for an appropriate pathological staging in LCs, limiting sampling/lobe-specific dissection in case of certain small peripheral TC.

6 | STATISTICAL ANALYSIS

Descriptive statistics were used to describe patient characteristics. Normality of continuous variables was investigated with the Kolmogorov–Smirnov's test. Normal continuous variables were

expressed with mean (SD), whereas non normal variables were expressed using median (interquartile interval). Categorical variables were expressed using frequencies. The Pearson's χ^2 or the Fisher's exact test, when appropriate, was used to test the association between categorical variables. The Mann–Whitney *U* and *t*-tests were used to compare quantitative variables. The OR and 95% CI were estimated using the logistic regression model. At the univariable analysis, baseline demographic and clinical characteristics were evaluated: age (continuous), sex (continuous), tumor location (central vs. peripheral), histology (typical vs. atypical), number of resected lymphnodes (continuous, less or more 10), clinical and pathological tumor dimension (continuous, more or less 3 cm), number of resected lymph node stations (continuous), and kind of lymphadenectomy (radical node dissection vs. other). The correlation between all the above-mentioned variables and the presence of nodal and mediastinal upstaging was investigated in the entire cohort, considering also typical and AC. The level of significance was set at $p \leq 0.05$. Variables testing significant at the univariable analysis were entered into multivariable analysis. A multivariable logistic regression model was developed using the stepwise regression analysis (forward selection) to compare the predictive power of different factors. Enter limit and remove limit were $p = 0.10$ and $p = 0.15$, respectively. The SPSS (v. 21.0; SPSS Inc.) statistical program was used for all analyses.

AUTHOR CONTRIBUTIONS

Dr. Marco Chiappetta and Dr. Filippo Lococo did study design, methods, interpretation results, and writing. Dr. Filippo Lococo and Giacomo Cusumano did interpretation results and writing. Dr. Isabella Sperduti did statistical analysis. Dr. Ludovic Fournel, Francesco Tabacco, Samanta Nicosia, Francesco Guerrera, Filippo Gallina, did data curation and recruitment. Dr. Francesco Facciolo, PierLuigi Filosso, Marco Alifano, Alberto Terminella, and Stefano Margaritora did supervision and revision of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of inerest.

DATA AVAILABILITY STATEMENT

Data are property of Institutions and can be shared after request evaluation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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