Standardized intrapulmonary lymph node dissection in lung cancer specimens: A national Colombian analysis

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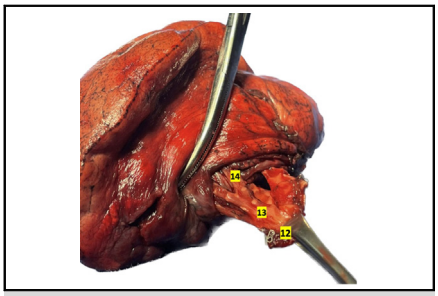
ABSTRACT

Objective: In patients with non–small cell lung cancer, lymph node assessment is essential for appropriate staging. The intrapulmonary lymph nodes (IPLNs) should be considered when assigning the N stage but are infrequently evaluated in Colombian centers, resulting in understaging that may hinder optimal treatment.

Methods: We conducted a prospective study of IPLN dissection in patients with clinical stage I or II non–small cell lung cancer who underwent surgical resection at 9 institutions in Colombia between 2021 and 2023. IPLN dissection was performed by trained surgeons who collected lymph nodes from fresh specimens after resection and before formalin fixation.

Results: One hundred patients were eligible for the analysis. Their mean age was 67 ± 10.9 years, and 76% were women. Most (74%) had adenocarcinoma, 20% had neuroendocrine tumors, and 6% had squamous cell carcinoma. Successful sampling and histopathologic analysis of at least one IPLN station was obtained in 85% of patients, 9% had upstaging due to positive N2 lymph nodes, and 5% had upstaging due to positive N1 lymph nodes. Among the patients with pN0 or pN1 disease, 3.2% (3 out of 91) were upstaged exclusively due to positive IPLNs.

Conclusions: Fresh-specimen dissection to collect IPLNs is appropriate and feasible to achieve more accurate pathological staging in Colombian lung cancer patients. In clinical N0 patients, IPLN dissection maximizes selection for adjuvant therapy. (JTCVS Open 2024;20:174-82)



Pulmonary lobe with intrapulmonary lymph node stations dissected.

CENTRAL MESSAGE

In patients with lung cancer patients with clinical No non–small cell lung cancer, harvesting intrapulmonary lymph nodes in fresh specimens is a valuable practice because it maximizes selection for adjuvant therapy.

PERSPECTIVE

Metastatic lymph nodes have been shown to negatively influence the overall survival of lung cancer patients. This study of intrapulmonary lymph node dissection, conducted across 9 institutions with experience treating cancer in Colombia, demonstrates increased pathological staging precision. Further and randomized studies are necessary to determine the need for routine implementation of this technique.

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Abbreviations and Acronyms

CT = computed tomography
IASLC = International Association for the Study of Lung Cancer
IPLNs = intrapulmonary lymph nodes
LNs = lymph nodes
NSCLC = non–small cell lung cancer
OS = overall survival
PET = positron emission tomography

Lung cancer is the second most frequent and deadliest cancer worldwide and is detected in its early stages, when surgical management can be the most beneficial, in only ~18% of patients.[1] Detecting or ruling out tumor invasion of the hilar and mediastinal lymph nodes (LNs) is among the most important components of staging and has an influence on overall survival (OS) and disease-free survival.[2] The International Association for the Study of Lung Cancer (IASLC) recommends that systematic nodal dissection or lobe-specific LN dissection should be performed during lung resection, that the minimum number of stations sampled for the nodal assessment must be 6 (3 intrapulmonary or hilar nodal stations and 3 mediastinal nodal stations), and that the subcarinal station should always be included.[3]

In the LN map proposed by the IASLC in 2009, the intrapulmonary LNs (IPLNs) correspond to stations 12, 13, and 14.[4] IPLN dissection can be performed by a surgeon, who collects the LNs from a fresh specimen after resection and before formalin fixation, or by a pathologist, who typically collects the LNs from a formalin-fixed surgical specimen 24 to 48 hours after the surgery, but can collect from fresh specimens as well. Standardized dissection techniques, such as the centrifugal technique developed by Raymond and colleagues,[5] can help maximize collection. However, despite their importance, IPLNs are either not evaluated or not documented in the pathology report in up to 90% of patients.[6] Subsegmental and segmental LN metastasis has been reported in 6.8% to 27% of patients with resected non–small cell lung cancer (NSCLC).[7,8] When LNs from these stations are not dissected, they are not evaluated by the pathologist, resulting in understaging that may prevent optimal lung cancer treatment.

There is no published information on IPLN assessment at South American centers or IPLN involvement in early-stage lung cancer in South American patients. The objective of this study was to describe the histopathological findings of IPLN dissections performed at multiple referral centers in Colombia and collected from fresh specimens by the thoracic surgeon using a standardized dissection technique. This design is particularly suited to hospitals that lack an established group of pathologists.

MATERIALS AND METHODS

Study Design

We conducted a multicenter, prospective cohort study with retrospective data analysis, enlisting 9 major lung cancer centers located in the 3 largest cities of Colombia. After the project was designed by the senior authors (P.A.U.F., S.I.M.J., and C.A.C.F.), we convened a virtual meeting to train all the participating thoracic surgeons in a fresh-specimen dissection technique for IPLN harvesting according to the IASLC LN map proposed in 2009.[4] Our aim was to standardize the procedure. The local teams consisted of thoracic surgeons with over a decade of experience in managing patients with lung cancer. For this study, we used the IPLN dissection technique proposed by Raymond and colleagues.[5] The surgeons then had to share photos or videos of the specimens dissected for the first few cases performed so 2 of the senior investigators (P.A.U.F., S.I.M.J., and C.A.C.F.) could verify the quality of the dissection. Feedback was given to the local teams accordingly.

Inclusion criteria were pathologic stage I or II NSCLC according to the TNM eighth edition staging system.[9] Patients were staged with computed tomography (CT), positron emission tomography (PET), brain magnetic resonance imaging, and invasive mediastinal staging by endobronchial ultrasound or video mediastinoscopy when clinically indicated. The study was limited to patients with early-stage lung cancer because improved LN staging has the largest influence on treatment and prognosis in these patients. Exclusion criteria were younger than age 18 years, no histological confirmation of NSCLC, centrally located tumors with bronchial infiltration that did not allow the standardized IPLN dissection, previous systemic treatment for another cancer, and the presence of another synchronous lung tumor, with an exception for nonmelanoma skin cancer managed with local therapies. Centrally located tumors were defined as lung tumors located in the inner two-thirds of the hemithorax based on CT imaging. LN count was based on whether the pathologist reported a complete LN or fragments of a LN. All fragments were counted as a single LN.

Data Collection

After defining the inclusion and exclusion criteria, we obtained approval for the study from the institutional research and ethics committee of each institution. The study was carried out in accordance with the guidelines of the Declaration of Helsinki. The informed consent was not requested by the institutional research and ethics committee of any of the participating institutions. Study data were obtained from clinical records. Data were collected between September 2021 and March 2023 and was supervised by institutional clinical monitoring groups and the head researcher (H.J.M.G.). Information was extracted from 1 of 2 databases: A proprietary database using Excel software (Microsoft) stored on a private cloud server where data for all patients was collected or a REDCap platform, which was

Informed consent: The informed consent was not requested by the Institutional Research and Ethics Committee of each institution.

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requested by 2 institutions and used exclusively for their patients. The head researcher (H.J.M.G.), who lives in Bogotá, DC, recorded the information directly from each institution to reduce the risk of bias. A convenience sample of 100 patients meeting the inclusion criteria was obtained.

Intrapulmonary LN Dissection

Systematic LN dissection was defined as dissection of all mediastinal and hilar LNs, and lobe-specific LN dissection was defined as stations 2R, 4R, and 7 for right upper and middle lobes tumors, stations 5L, 6L, and 7 for left upper lobe tumors; and stations 7, 8, and 9 for left or right lower lobe tumors. During surgical lung resection (segmentectomy, lobectomy, or bilobectomy), the dissection of the mediastinal, hilar, and interlobar LN stations was performed by the thoracic surgeon. In patients undergoing segmentectomy, the LNs of station 12 were included in the intraoperative LN harvesting. Each station was labeled individually. Once the surgical specimen was extracted and the surgery was completed, dissection and collection of the intrapulmonary LNs from the fresh specimen were performed on the back table in the same operating room (Figure 1). Briefly, traction was placed on the bronchial stump toward the surgeon. Dissection was performed following the peribronchial path with Metzenbaum scissors from the lobar or segmental bronchial stump of the specimen to the periphery. The IPLNs were collected sequentially from stations 12, 13, and 14. After the LNs were collected, they were placed, by station, in vials that had been previously marked. Once completed, the surgical specimen was sent to pathology after LN dissection.

Statistical Analysis

Categorical variables were presented in absolute values and percentages. Continuous variables were summarized using central tendency measures (mean or median) accompanied by their corresponding measures of dispersion (SD) or interquartile range (IQR). The distribution was tested using the Shapiro-Wilk test. For the analysis of categorical data with a dichotomous response, 2×2 contingency tables were constructed, and independence was evaluated with the χ^2 statistics and Fisher exact test. For nominal or ordinal variables with more than 2 response categories, multinomial logistic regression models were adjusted to determine independence between the covariates of interest. A P-value $< .05$ was considered statistically significant. Data were analyzed using SPSS Statistics for Windows, version 19.0 (IBM).

RESULTS

In this study, 100 patients with stage I to IIB lung cancer who underwent upfront surgical management with fresh-specimen dissection of IPLNs were included in the analysis; 43 (43%) had centrally located tumors without bronchial invasion that would prohibit IPLN dissection. Their mean age was 67 ± 10.9 years, and 76% were women. Of the 100 patients, 58 (58%) had a history of smoking, and 46.5% had a smoking history >20 pack-years (Table 1).

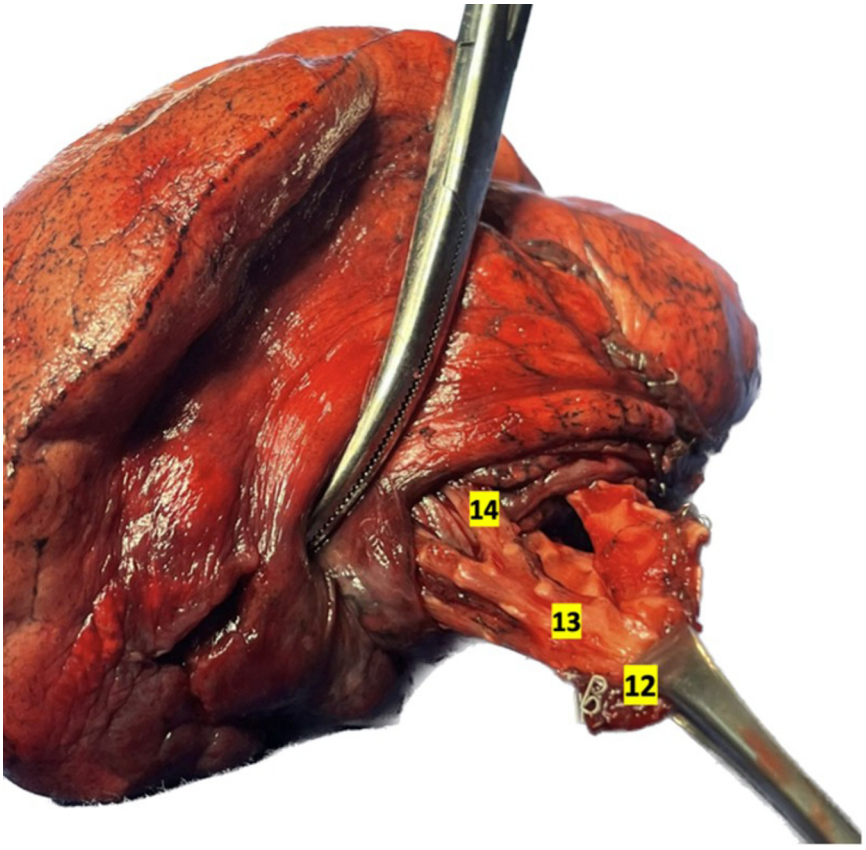


FIGURE 1. Lymph node dissection of the intrapulmonary stations in a lobectomy specimen showing the locations where the nodes of stations 12, 13, and 14 were removed.

TABLE 1. Patient (n = 100) and tumor characteristics

Characteristic	Result
Sex	
Female	76 (76)
Male	24 (24)
Age (y)	67 ± 10
Smoking history	
Yes	58 (58)
No	42 (42)
Staging modalities	
CT	100 (100)
PET	91 (91)
VM	8 (8)
EBUS	5 (5)
Clinical stage	
IA	76 (76)
IB	9 (9)
IIA	6 (6)
IIB	9 (9)
Tumor location*	
RUL	24 (24)
RML	4 (4)
RLL	31 (31)
LUL	25 (25)
LLL	16 (16)
Tumor location	
Central	43 (43)
Peripheral	57 (57)
Histologic subtype	
Adenocarcinoma	74 (74)
Squamous cell carcinoma	6 (6)
Neuroendocrine	
Typical carcinoid	15 (15)
Atypical carcinoid	5 (5)
Lung resection	
Lobectomy	91 (91)
Bilobectomy	1 (1)
Segmentectomy	8 (8)

Values are presented as n (%) or mean ± SD. *CT*, Computed tomography; *PET*, positron emission tomography; *VM*, video-mediastinoscopy; *EBUS*, endobronchial ultrasound; *RUL*, right upper lobe; *RML*, right middle lobe; *RLL*, right lower lobe; *LUL*, left upper lobe; *LLL*, left lower lobe. *Lobe.

TABLE 2. Lymph node metastases

Characteristic	Patients (n = 100)
cN	
N0	97 (97)
N1	3 (3)
pN	
N0	83 (83)
N1	8 (8)
N2	9 (9)
LN stations collected	
10	75 (75)
11	88 (88)
12	85 (85)
13	78 (78)
14	39 (39)
IPLN metastasis	10 (10)
IPLN (+) only	3 (3)
IPLN (+) and 10-11 (+)	5 (5)
IPLN (+) and pN2 (+)	2 (2)
Location of tumor with IPLN metastasis	
Central	6 (60)
Peripheral	4 (40)
Upstaging	25 (25)
N2	9 (9)
N1	5 (5)
10, 11	2 (2)
12, 13, 14	3 (3)
Other	11 (11)

cN, Clinical lymph node status; *pN*, pathological lymph node status; *LN*, lymph node; *IPLN*, intrapulmonary lymph node.

All patients included in the analysis were staged with chest CT; 91 (91%) were staged with PET/CT and 17% brain magnetic resonance imaging, 13% underwent invasive mediastinal staging (8% video mediastinoscopy and 5% endobronchial ultrasound). Most of the NSCLCs were adenocarcinomas (74%), 6% were squamous cell carcinomas, and 20% were neuroendocrine tumors (15% typical carcinoids and 5% atypical carcinoids) (Table 1). The most common type of resection was lobectomy (91%); 1 patient (1%) underwent bilobectomy, and 8% of patients underwent segmentectomy. Pathological staging revealed that 75% of the tumors were pathological stage (p)T1, with 60% of all tumors classified as pIA and 15% classified as pIB (Table 1).

Systematic LN dissection—all mediastinal tissue containing the LNs was dissected and removed systematically within anatomic landmarks, and the hilar and intrapulmonary LNs were also dissected[10]—was performed in 18% and lobe-specific LN dissection in 82% of patients. No additional, more distal, or unnumbered intrapulmonary peribronchial LNs were described within the histopathological reports. Twenty-five percent of patients had upstaging after surgical resection; 9% had upstaging due to positive mediastinal LNs (N2), 5% had upstaging due to positive N1 LNs (2 with metastases in station 10 or station 11 and 3 with metastases in the IPLNs), and 11% were upstaged due to other tumor characteristics (Table 2). Most patient and tumor characteristics were not significantly associated with pathological N stage. However, lobectomy was associated with significantly more LN involvement (N1/N2) compared with segmentectomy ($P = .018$) (Table 3), with similar LN retrieval in patients with lobectomy (median 15 nodes per patient; IQR, 5-24 nodes) and patients with segmentectomy (15 nodes per patient; IQR, 10-26 nodes). The median number of LNs collected per patient was 15

TABLE 3. Metastatic lymph nodes based on N classification

Characteristics	Lymph node involvement			*P* value	Total (n = 100)
	N0 (n = 83)	N1 (n = 8)	N2 (n = 9)		
Sex				.259	
Female	64 (84)	7 (9)	5 (7)		76
Male	19 (79)	1 (4)	4 (17)		24
Age (y)				.426	
18 to 64	32 (82)	2 (5)	5 (13)		39
65+	51 (84)	6 (10)	4 (7)		61
Smoking status				.588	
Yes	50 (86)	4 (7)	4 (7)		58
No	33 (79)	4 (10)	5 (12)		42
Size of the tumor (cm)				.070	
<1	8 (100)	0 (0)	0 (0)		8
>1-2	40 (87)	4 (9)	2 (4)		46
>2-3	19 (90)	1 (5)	1 (5)		21
>3-4	9 (69)	1 (8)	3 (23)		13
>4-5	4 (50)	1 (13)	3 (38)		8
>5-6	3 (75)	1 (25)	0 (0)		4
Lobe location				.222	
Upper	44 (90)	3 (6)	2 (4)		49
Lower	36 (77)	4 (9)	7 (15)		47
Middle	3 (75)	1 (25)	0 (0)		4
Histologic subtype				.175	
Adenocarcinoma	61 (82)	5 (7)	8 (11)		74
Squamous cell carcinoma	6 (100)	0 (0)	0 (0)		6
Neuroendocrine					
Typical carcinoid	13 (87)	1 (7)	1 (7)		15
Atypical carcinoid	3 (60)	2 (40)	0 (0)		5
Lung resection				.018	
Lobectomy	75 (82)	8 (9)	8 (9)		91
Segmentectomy	8 (100)	0 (0)	0 (0)		8
Mediastinal dissection				.872	
Systematic	15 (83)	1 (6)	2 (11)		18
Lobe-specific	68 (82)	7 (9)	7 (9)		82
Tumor location				.499	
Central	34 (79)	5 (12)	4 (9)		43
Peripheral	49 (86)	3 (5)	5 (9)		57

Values are presented as n (%).

(IQR, 9.25-25.5 LNs) in the entire cohort. The median number of LNs collected per patient was 15 (IQR, 8-24 LNs) for pN0 tumors, 13 (IQR, 10.25-26.25 LNs) for pN1 tumors, and 22 nodes (IQR, 10-26.5 LNs) for pN2 tumors.

All 3 IPLN stations were successfully sampled with histopathologic analysis in 36 (36%) of the patients, and at least 1 IPLN station was examined in 85 (85%) of patients. Despite methodical dissection, no LNs were recovered from station 12 in 15% of patients, from station 13 in 22%, and from station 14 in 61% of patients. Similarly, we found an absence of LNs from station 10 in 25% of patients and from station 11 in 12% (Table 2). In 4% of patients, the histopathological report described the presence of lung tissue with anthracosis instead of LN tissue in at least 1 IPLN station.

LN metastases in the IPLNs were confirmed histopathologically in 10 patients, and 6 of these patients (60%) had central tumors. The most frequent intrapulmonary station with histopathological confirmation of metastasis to the LNs was station 14. Two of the patients (20%) with IPLN metastases were staged as pN2 due to other positive LN stations, and 5 of the patients with IPLN metastases (50%) also had metastatic involvement in either station 10 or 11 (Table 2). Three patients (3.2%, 3/91) with LN metastases in stations 12, 13, or 14 and no positive N2 LNs were upstaged solely based on the finding of IPLN metastases.

TABLE 4. Characteristics of patients with upstaging by intrapulmonary lymph node stations metastasis alone

Patient	Sex	Age (y)	Histologic subtype	Size tumor (cm)	Location tumor (central or peripheral)	Metastases present in IPLN station	Stage without IPLN examination	Stage with IPLN examination
1	Female	59	TC	1-2	Central	12 (−), 13 (−), 14 (+)	IA	IIB
2	Female	61	ADC	1-2	Central	12 (+), 13 (−), 14 (−)	IA	IIB
3	Female	71	ADC	1-2	Peripheral	12 (−), 13 (−), 14 (+)	IA	IIB

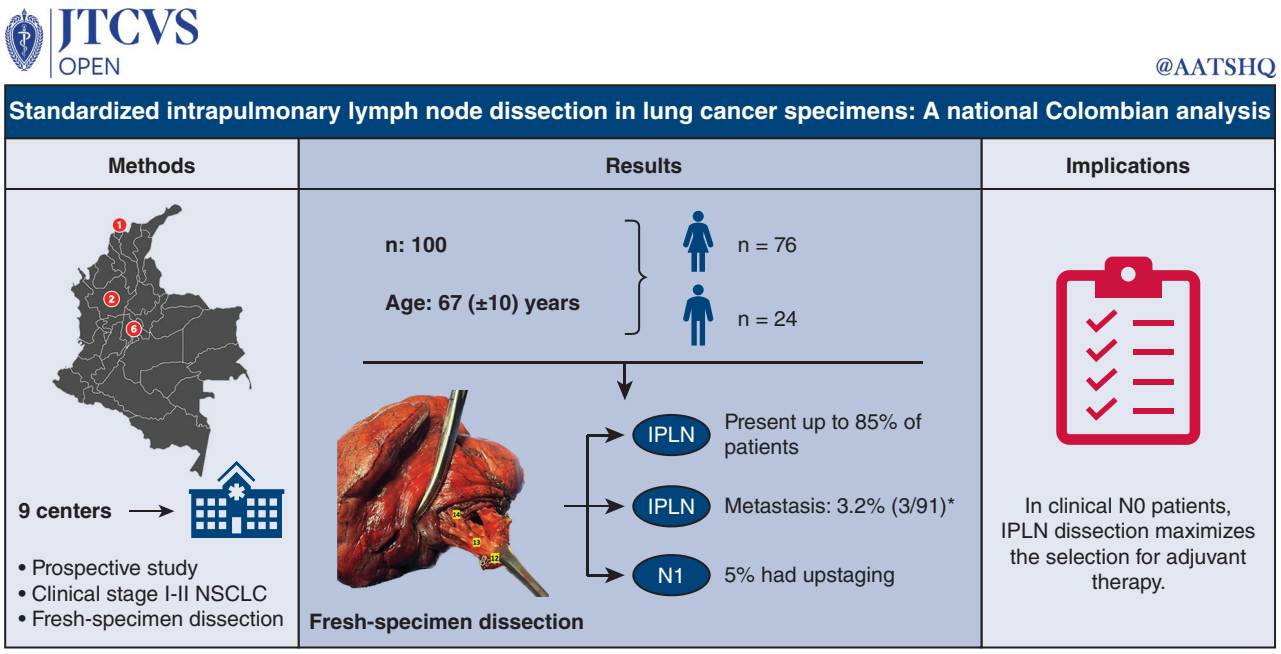
IPLN, Intrapulmonary lymph node; *TC*, typical carcinoid; *ADC*, adenocarcinoma.

The lung tumors in these 3 patients were all 1 to 2 cm in size and located in the lower lobes; 2 were centrally located (Table 4). Additionally, 2 of these patients had a preoperative PET-CT, and neither was found to have a hypermetabolic lesion other than the primary tumor.

DISCUSSION

Colombia has a population of 48 million with an estimated age-standardized incidence of lung cancer of 10.5 per 100,000 in 2020.[1] This is the first study to date examining the percentage of South American patients with lung cancer upstaged using an IPLN analysis. Pathologists do not routinely perform IPLN dissection in Colombia. Some medical centers lack onsite pathologists, and communication issues can arise with the pathologist who processes the surgical specimen. Additionally, some Colombian pathologists are not trained in lung cancer. We found that harvesting IPLN from fresh specimens is a feasible and safe procedure in Colombia when performed by experienced thoracic surgeons. Standardizing the technique for harvesting IPLNs was crucial to obtain an optimal amount of LN tissue. Osarogiagbon first described a technique for harvesting IPLNs from formalin-fixed specimens following a peribronchial route.[11] This method significantly increased the number of nodes collected, from 0 to 5 to 0 to 17 ($P < .001$). We performed IPLN collection based on the technique by Raymond and colleagues,[5] who were the first group to provide a replicable and detailed technique in fresh specimens. We identified other studies that harvested IPLN from fresh specimens, but they did not clearly detail their methodology.[7,12]

Osarogiagbon and colleagues[13] recently evaluated the impact of 2 interventions to improve pathologic nodal staging in a study of 4019 patients treated with resection for lung cancer at 12 American hospitals. One intervention was using a LN specimen collection kit by the participating surgeons and the other was a standardized protocol for pathologists to grossly dissect IPLN from lung specimens, like the methods that thoracic surgeons used on fresh specimens in our study. They found that the surgery intervention and



IPLN: IntraPulmonary Lymph Node; *metastatic N2 level excluded.

FIGURE 2. Graphical abstract depicting the main study objectives and results.

combination of the pathology and surgery interventions were superior at achieving a good LN dissection. Complete resection according to IASLC criteria was accomplished in 14% with no intervention, 21% with only the pathology intervention, 53% with only the surgery intervention, and 61% with both interventions ($P < .0001$). Additionally, nonexamined intrapulmonary LNs were found in 24% of patients treated with no intervention as compared with 17% to 18% for each intervention or the combination of the 2 ($P < .0001$). Like our study, Osarogiagbon and colleagues'[13] study demonstrates that both standardized dissection of IPLNs and the attention of thoracic surgeons to an adequate LN retrieval dramatically improve pathological nodal staging of lung cancer.

Although not all IPLN stations dissected contained LN tissue, LN tissue was recovered from stations 12, 13, and 14 in approximately one-third of our patients and from at least 1 of these IPLN stations in 85%. Rena and colleagues,[8] in a study of 596 patients with resected NSCLC, reported the absence of LN tissue collection from stations 11 or 12 in 17% of patients and from stations 13 or 14 in 32%. Wang and colleagues[12] reported an absence of LN tissue collection from stations 12, 13, and 14 in 9.7%, 1.9%, and 58.7% of patients, respectively. Our results are more similar to those of Wang and colleagues,[12] and we observed a wide range of IPLN recovery with missed IPLN stations in 15% to 61%, depending on the station assessed. The most prevalent challenge we faced was distinguishing pulmonary anthracosis from small LNs, particularly in station 14, where the presence of lung tissue was described in many pathology reports. We recommend being mindful of dissecting all segments in the specimen.

In Rena and colleagues' study,[8] the median number of examined LNs was 16 (range, 10-34) in patients staged as pN0, 17 (range, 10-32) in patients staged as pN1, and 18 (range, 11-36) in patients staged as pN2. We founded, the median number of LNs collected was similar (15 in pN0 patients, 13 in pN1 patients, and 22 in pN2 patients) and comparable with IPLN retrieval reported in the current literature. Typically, histopathological reports do not describe whether a complete LN or a LN fragment is being examined. LNs can be fragmented during dissection by either the surgeon or the pathologist. Reports with a lot of IPLNs likely reflect LN fragments rather than complete LNs. We believe that pathology reports should uniformly differentiate LN fragments from complete LNs. Our study counted fragments as 1 IPLN regardless of the number of fragments described.

We found that 3.2% of the patients with early-stage NSCLC who were not classified as N2 due to other criteria were upstaged due to IPLN involvement (Figure 2). These patients were reclassified as stage IIB rather than IA and had the opportunity to receive a more specific treatment based on international guidelines due to confirmed pN1 compromise. We included neuroendocrine tumors in our analysis because the available data on LN involvement is limited. It is notable that 1 of the 3 patients with upstaging due to intrapulmonary LN involvement had a neuroendocrine tumor, which accounted for only 20% of the sample. However, the influence of this finding is beyond the scope of this discussion. We included patients with centrally located tumors without bronchial compromise in our analysis because many studies have excluded these patients.[7,14,15] Patients with centrally located tumors had a mean tumor size of 1.5 cm and had IPLN metastases more often than patients with peripheral NSCLC, highlighting the importance of performing IPLN dissection in these patients. We believe that both the thoracic surgeon and the pathologist play important roles in achieving accurate staging, but we advocate for IPLN retrieval from fresh specimens because fresh tissues are easier to dissect. Dissection of fresh specimens has become the routine practice of the different thoracic surgery groups that participated in the study.

Lei and colleagues[7] evaluated the relationship between metastases in N1 LNs and tumor size, showing that tumors with a diameter <1 cm, 1 to 2 cm, and 2 to 3 cm presented with LN metastasis in 0%, 4.3%, and 7.6%, respectively. Deng and colleagues[16] found that tumors $\leq$1 cm, >1 but $\leq$1.5 cm, and >1.5 cm had IPLN involvement in 0%, 2.5%, and 18% of patients, respectively. Konno and colleagues[17] demonstrated that peripheral tumors $\leq$2 cm had N1 involvement in up to 14% of patients in a 239-patient study. Our study founded similar results—no IPLN metastases in patients with tumors <1 cm and N1 metastasis in 5% to 9% of patients with tumors >1 cm. Abbas and colleagues[18] reported that in patients with stage IA NSCLC, N2 involvement occurs in 4% to 7% due to skip metastasis; however, we observed this in only 1 patient.

In 2015, the IASLC reported a negative influence on OS when LNs were involved and demonstrated that patients with metastasis in a single N1 station (N1a), versus multiple N1 stations (N1b), presented OS at 5 years of 59% versus 50% ($P < .001$).[3] Smeltzer and colleagues[19] analyzed a prospective cohort of 110 patients who underwent lung resection and were treated based on the staging at that moment but who had their surgical specimens reassessed later. They found a 6% increase in N1 staging. Patients with >2 discarded intrapulmonary lymph nodes with metastasis had 4.8 times (95% CI: 2.1, 10.9) the hazard of death compared with those without missed lymph node metastasis, (unadjusted P-value = .0005). Wang and colleagues[20] conducted a study analyzing the importance of examining stations 13 and 14 in 435 patients. In 170 patients, stations 10 through 14 were routinely examined; in the 265-patient control group, only stations 10 through 12 were examined. The patients with routine examination of stations 10 through 14 had better OS (89% $\pm$ 3% vs 77% $\pm$ 4% at 5 years; $P = .027$) and better disease-free survival

(81% ± 4% vs 67% ± 4% at 5 years; $P = .021$), likely because of better staging. Patients who underwent IPLN dissection and were still classified as pN0 were truly pN0. In the same way, Yoshida and colleagues[21] reported that 5-year OS was 79.8%, 59.6%, 62.7%, and 56.9% for patients who underwent LN dissection from stations 13 or 14, 12, 11, and 10, respectively. The current management guidelines for the management of lung cancer from the National Comprehensive Cancer Network,[22] the European Society of Medical Oncology,[23] and the American Society of Clinical Oncology[24] recommend the use of chemotherapy for patients with pN1 NSCLC; however, they do not mention the IPLNs specifically. Wang and colleagues[12] compared the use of platinum-based adjuvant chemotherapy (4 cycles) versus not administering adjuvant chemotherapy in patients with IPLN metastases in whom stations 10 and 11 were negative for metastasis (n = 76; chemotherapy in 43 vs no chemotherapy in 33). The administration of adjuvant chemotherapy improved OS (57.3 ± 1.5 vs 47.1 ± 3.2 months; $P = .002$). Analysis of survival and cancer recurrence are of interest to us but were outside of the scope of this study.

The primary limitation of this study was the number of patients included, which resulted in a small number of positive IPLNs for analysis. Additionally, all IPLN harvesting was done from fresh specimens, and we did not compare the utility of these methods with formalin-fixed specimens. Due to the descriptive nature of the results, it is not possible to make comparisons with other outcomes such as survival and recurrence. This was the first multicenter study by Colombian thoracic surgeons. We faced new challenges, including getting approval from multiple ethics committees and different databases from each institution. A controlled study of the influence of systematic LN sampling from fresh surgical specimens, as established in this study, on long-term oncological outcomes is one area of interest.

CONCLUSIONS

Harvesting IPLNs is important when staging patients with early-stage lung cancer undergoing surgery. We concluded that IPLN dissection technique from fresh specimens is a feasible, replicable, and safe procedure at multiple hospitals in different cities in Colombia, and it is potentially applicable to other institutions that do not have structured thoracic pathology groups. Metastases to the IPLNs were found in 3.2% of patients treated surgically for early-stage NSCLC. IPLNs were obtained in up to 85% of patients, and station 14 was positive for metastasis most frequently. No patients with tumors <1 cm had IPLN involvement. Further analysis is needed to determine if the fresh specimen dissection is superior to the formalin-fixed specimen dissection as well as the methods for IPLN harvesting.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflict of interest.

References

1. Cardona AF, Mejía SA, Viola L, et al. Lung cancer in Colombia. *J Thorac Oncol*. 2022;17(8):953-960. https://doi.org/10.1016/j.jtho.2022.02.015
2. Kang CH, Ra YJ, Kim YT, Jheon SH, Sung SW, Kim JH. The impact of multiple metastatic nodal stations on survival in patients with resectable N1 and N2 non–small cell lung cancer. *Ann Thorac Surg*. 2008;86(4):1092-1097. https://doi.org/10.1016/j.athoracsur.2008.06.056
3. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10(12):1675-1684. https://doi.org/10.1097/JTO.0000000000000678
4. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4(5):568-577. https://doi.org/10.1097/JTO.0b013e3181a0d82e
5. Raymond C, Vieira A, Joubert P, Ugalde PA. Maximizing lymph node dissection from fresh lung cancer specimens. *Eur J Cardiothorac Surg*. 2022;63(1):ezac554. https://doi.org/10.1093/ejcts/ezac554
6. Ramirez RA, Wang CG, Miller LE, et al. Incomplete intrapulmonary lymph node retrieval after routine pathologic examination of resected lung cancer. *J Clin Oncol*. 2012;30(23):2823-2828. https://doi.org/10.1200/JCO.2011.39.2589
7. Bi L, Zhang H, Ge M, et al. Intrapulmonary lymph node (stations 13 and 14) metastasis in peripheral non-small cell lung cancer. *Medicine (Baltimore)*. 2021;100(27):e26528. https://doi.org/10.1097/MD.0000000000026528
8. Rena O, Boldorini R, Papalia E, et al. Metastasis to subsegmental and segmental lymph nodes in patients resected for non-small cell lung cancer: prognostic impact. *Ann Thorac Surg*. 2014;97(3):987-992. https://doi.org/10.1016/j.athoracsur.2013.11.051
9. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11(1):39-51. https://doi.org/10.1016/j.jtho.2015.09.009
10. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non–small cell lung cancer. *Eur J Cardiothorac Surg*. 2006;30(5):787-792. https://doi.org/10.1016/j.ejcts.2006.08.008
11. Osarogiagbon RU, Eke R, Sareen S, et al. The impact of a novel gross dissection protocol on intrapulmonary lymph node retrieval from lung cancer resection specimens. *Ann Diagn Pathol*. 2014;18(4):220-226. https://doi.org/10.1016/j.anndiagpath.2014.03.005
12. Wang X, Yan S, Wang Y, et al. Adjuvant chemotherapy may improve outcome of patients with non-small-cell lung cancer with metastasis of intrapulmonary lymph nodes after systematic dissection of N1 nodes. *Chin J Cancer Res*. 2018;30(6):588-595. https://doi.org/10.21147/j.issn.1000-9604.2018.06.03
13. Osarogiagbon RU, Ray MA, Fehnel C, et al. Two interventions on pathologic nodal staging in a population-based lung cancer resection cohort. *Ann Thorac Surgery*. 2024;117(3):576-584. https://doi.org/10.1016/j.athoracsur.2023.08.026
14. Robinson EM, Ilonen IK, Tan KS, et al. Prevalence of occult peribronchial N1 nodal metastasis in peripheral clinical N0 small (≤2 cm) non–small cell lung cancer. *Ann Thorac Surg*. 2020;109(1):270-276. https://doi.org/10.1016/j.athoracsur.2019.07.037
15. Zhang DG, Chen XC, Zhu D, et al. Intrapulmonary lymph node metastasis is common in clinically staged IA adenocarcinoma of the lung. *Thorac Cancer*. 2019;10(2):123-127. https://doi.org/10.1111/1759-7714.12908
16. Deng HY, Zhou J, Wang RL, et al. Surgical choice for clinical stage IA non-small cell lung cancer: view from regional lymph node metastasis. *Ann Thorac Surg*. 2020;109(4):1079-1085. https://doi.org/10.1016/j.athoracsur.2019.10.056
17. Konno H, Isaka M, Mizuno T, Kojima H, Ohde Y. P1.17-36 analyses of segmental and intrapulmonary lymph node metastases of small-sized peripheral solid

predominant non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2019; 14(10):S622. https://doi.org/10.1016/j.jtho.2019.08.1309

18. Abbas G, Raza B, Abbas K, Lamb J, Toker A. Segment-specific lymph node dissection and evaluation during anatomical pulmonary segmentectomy. *Video Assist Thorac Surg*. 2021;6:17. https://doi.org/10.21037/vats-2019-rcs-08
19. Smeltzer MP, Faris N, Yu X, et al. Missed intrapulmonary lymph node metastasis and survival after resection of non-small cell lung cancer. *Ann Thorac Surg*. 2016;102:448-453. https://doi.org/10.1016/j.athoracsur.2016.03.096
20. Wang X, Yan S, Lv C, et al. Impact of omission of intrapulmonary lymph node retrieval on outcome evaluation of lung cancer patients without lymph node metastasis: a propensity score matching analysis. *Clin Lung Cancer*. 2017; 18(6):e411-e416. https://doi.org/10.1016/j.cllc.2017.05.001
21. Yoshida Y, Yotsukura M, Nakagawa K, Watanabe H, Motoi N, Watanabe SI. Surgical results in pathological N1 non–small cell lung cancer. *Thorac Cardiovasc Surg*. 2021;69(4):366-372. https://doi.org/10.1055/s-0040-1713613
22. Gregory KN, Hughes MO, Aisner DL, et al. *NCCN guidelines version 3.2023 non-small cell lung cancer continue NCCN guidelines panel disclosures*; 2023.
23. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv1-iv21. https://doi.org/10.1093/annonc/mdx222
24. Pisters K, Kris MG, Gaspar LE, Ismaila N, Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA NSCLC Guideline Expert Panel. Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non–small-cell lung cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. 2022;40(10):1127-1129. https://doi.org/10.1200/JCO.22.00051

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