

# Nodal size ranking as a predictor of mediastinal involvement in clinical early-stage non-small cell lung cancer

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## Abstract

In non-small cell lung cancer (NSCLC) patients, the recommended minimum requirement for an endoscopy-based mediastinal staging procedure is sampling the largest lymph node (LN) in right and left inferior paratracheal, and subcarinal stations. We aimed to analyze the percentage of cases where the largest LN in each mediastinal station was malignant in a cohort of NSCLC patients with mediastinal metastases diagnosed in the lymphadenectomy specimen. Furthermore, we investigated the sensitivity of a preoperative staging procedure in a hypothetical scenario where only the largest LN of each station would have been sampled.

Prospective data of patients with mediastinal nodal metastases diagnosed in the lymphadenectomy specimens were retrospectively analyzed. The long-axis diameter of the maximal cut surface of all LNs was measured on hematoxylin and eosin-stained sections.

Seven hundred seventy five patients underwent operation and 49 (6%) with mediastinal nodal disease were included. A total of 713 LNs were resected and 119 were involved. Sixty seven nodal stations revealed malignant LNs: in these, the largest LN was malignant in 39 (58%). In a “per patient” analysis, a preoperative staging procedure that sampled only the largest LN would have attained a sensitivity of 0.67; and if the largest and the second largest were sampled, sensitivity would be 0.87.

In patients with NSCLC, nodal size ranking is not reliable enough to predict malignancy. In clinical practice, regardless of the preoperative staging method, systematic thorough sampling of all visible LNs is to be recommended over selective random samplings.

**Abbreviations:** CT = computer tomography, ESTS = European Society of Thoracic Surgeons, H-E = hematoxylin and eosin, IQR = interquartile range, LN = lymph node, NSCLC = non-small cell lung cancer, PET = positron emission tomography, SD = standard deviation, SND = systematic nodal dissection, VAMLA = video-assisted mediastinoscopic lymphadenectomy.

**Keywords:** early-stage, mediastinum, nodal size, non-small cell lung cancer, staging

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## 1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.<sup>[1]</sup> In non-small cell lung cancer (NSCLC) an accurate evaluation of regional lymph node (LN) involvement is crucial to determine prognosis of the disease and choice of treatment. Assuming that malignant LNs are larger than benign ones, non-invasive mediastinal staging methods have been traditionally based on nodal size criterion as a predictor of malignancy. In computer tomography (CT), LNs with a short axis diameter longer than 10mm are considered abnormally enlarged. However, several studies have demonstrated that this size criterion is not reliable enough<sup>[2–4]</sup> and the reported sensitivity of CT in lung cancer staging is very low.<sup>[5]</sup> The introduction of positron emission tomography (PET), which considers the metabolic behavior rather than the nodal size, has increased the diagnostic yield in mediastinal staging compared with CT alone.<sup>[6]</sup> However, PET and PET/CT could also be influenced by the nodal size because malignant LNs with short axis less than 10 mm may pass unnoticed. Following this concern, the current staging guidelines for preoperative mediastinal staging for NSCLC promulgated by the European Society of Thoracic Surgeons (ESTS)<sup>[7]</sup> recommends to proceed to an invasive staging method not only when PET/CT and/or CT shows mediastinal involvement but also in many cases after a normal PET/CT. In

this setting, the ESTS recommended minimum requirement for an endoscopy-based mediastinal staging procedure is sampling the largest LN in the right and left inferior paratracheal (#4R and #4L, respectively) and subcarinal (#7) stations,<sup>[8]</sup> as well as PET positive LNs within each of these stations.<sup>[7]</sup> Although the ESTS guidelines have been properly validated with mediastinoscopy<sup>[9]</sup> and video-assisted mediastinoscopic lymphadenectomy (VAMLA),<sup>[10]</sup> with reported negative predictive value for mediastinal nodal disease of 0.94 for both studies, this minimum requirement of sampling the largest LN in stations 4L#, 4#, and 7 has never been validated.

In daily practice, it is commonly noticed that malignant LNs are not restricted to the largest of each nodal station, especially stations #7 and #4R. Studies performed on autopsy specimens as well as “in vivo” have demonstrated that LNs from these stations are larger than those from other mediastinal stations, either in patients with lung cancer<sup>[11]</sup> or with non-neoplastic conditions.<sup>[12–14]</sup> Some previous studies have compared the size of malignant mediastinal LNs with non-malignant mediastinal LNs in resected lung cancer specimens.<sup>[3–4,15–17]</sup> However, only 2 studies have analyzed the value of nodal size ranking as a predictor of malignancy.<sup>[18–19]</sup>

The objectives of our study were:

1. to analyze the percentage of cases where the largest LN in each mediastinal station was malignant in a cohort of patients with NSCLC with mediastinal nodal metastases diagnosed in the lymphadenectomy specimen obtained by VAMLA at clinical staging or by systematic nodal dissection (SND) at the time of lung resection;
2. to compare the size of malignant mediastinal LNs with that of non-malignant mediastinal LNs; and
3. to investigate the sensitivity of an endoscopic preoperative staging procedure in a hypothetical scenario where only the largest LN of each station was sampled.

## 2. Material and methods

### 2.1. Patients

The clinical data of patients with mediastinal nodal metastases diagnosed in the surgical specimens after VAMLA or SND from January 2010 to December 2017 in our Institution were prospectively entered in a database and retrospectively analyzed. Nodal stations were defined using the International Association for the Study of Lung Cancer lymph node chart.<sup>[8]</sup> Patients with a mediastinoscopy performed previous to the SND were not included. Patients who underwent induction chemotherapy were excluded from the study. The study was approved by the Internal Review Board (Comité Étí Hospital Universitari Mútua Terrassa, reference number: 05201804). Surgical techniques were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all participant patients.

### 2.2. Surgery

Video-assisted mediastinoscopic lymphadenectomy (VAMLA):

VAMLA was indicated for invasive mediastinal staging in patients with normal mediastinum after PET/CT mainly in the following situations: central tumors, clinical N1 on CT or PET and tumors >3 cm.<sup>[20]</sup>

VAMLA has been described elsewhere<sup>[21]</sup> In brief, first, the subcarinal nodal station (#7) was completely excised along the main bronchi, the pulmonary artery, and the esophagus. This

dissection often included the upper part of the paraesophageal nodes (#8). Next, the superior vena cava and mediastinal pleura were exposed caudal to the innominate artery, and the right inferior paratracheal nodes (#4R), including the fatty tissue, were completely removed down to the azygos vein and right main bronchus. Finally, the left inferior paratracheal LNs (#4L) were carefully dissected and removed individually after identification of the left recurrent laryngeal nerve. In most cases, VAMLA was extended to the right and left hilar LNs (#10R and #10L, respectively). For left lung cancers, extended cervical video-mediastinoscopy was added to explore the subaortic (#5) and para-aortic (#6) LNs.

Systematic nodal dissection (SND) at the time of lung resection:

SND implied the excision en bloc, whenever possible, of the LNs and fatty tissue of the upper mediastinum, the subcarinal space, and the lower mediastinum, as well as the hilar and the intrapulmonary LNs. At least, 6 LNs had to be removed, 3 from 3 mediastinal nodal stations (including always the subcarinal) and 3 from the hilar and intrapulmonary nodal stations.<sup>[22]</sup> This type of lymphadenectomy was a condition needed to define complete resection, together with the integrity of the resection margins, of the nodal capsule and of the highest mediastinal LN.<sup>[23]</sup>

One whole LN or all fragments of 1 LN were kept in 1 container to facilitate the counting of removed and involved LNs, and the quantification of nodal disease. The containers were labeled with the name of the nodal station.

### 2.3. Pathology

Each LN was placed in a separate cassette, fixed in 10% formalin for at least 24 hours and embedded in paraffin. After fixation, every dissected LN was longitudinally bisected on a plane parallel to the longest axis length. Thin sections (5 μm) were cut and stained with hematoxylin and eosin (H-E). LNs were evaluated by a pathologist following the current guidelines.<sup>[24]</sup> Deposits of tumor not associated with any structure recognizable as a LN node (capsule, subcapsular sinus, and lymphoid follicles) were not counted as LN metastasis. In case of fragmented LNs the parts were put together and considered as a whole, following current recommendations. The long-axis diameter of the maximal cut surface of all LNs was measured on HE-stained sections.

### 2.4. Statistical analysis

Data were entered into a database and analyzed using Stata software [StataCorp. 2014. Stata Statistical Software: Release 13. College Station, TX: StataCorp LLC]. Categorical variables were expressed as absolute and relative frequencies, continuous variables as means and standard deviations (SD), and non-normally distributed data as medians and interquartile ranges (IQR) (25%–75%). Size of malignant and non-malignant LNs was compared through Mann–Whitney *U* test. Differences between percentage of cases where the largest LN was malignant and nodal station location were calculated by exact Fisher exact test. *P* value <.05 was considered as significant. A “per patient” analysis was performed and the sensitivity of a preoperative staging procedure that would have sampled only the largest LN of each nodal station was calculated. False negative cases were considered those patients with all of the malignant LN not being the largest of each nodal station. Sensitivity was calculated using standard formula.

Table 1	
Patients' characteristics (Number: 49).	
Sex Number (%)	Male 38 (77.6)
Age mean (SD)	64.3 years (±9.9)
Pathology Number (%)	
Adenocarcinoma	29 (59.2)
Squamous-cell carcinoma	13 (26.5)
Large cell carcinoma	3 (6.1)
Non-small cell lung cancer not otherwise specified	2 (4.1)
Atypic carcinoid	2 (4.1)
Surgical procedure Number (%)	
Video assisted mediastinal lymphadenectomy	39 (79.6)
Lung resection with systematic nodal dissection	10 (20.4)
Number of LN dissected mean (SD)	14.5 (±5.7)
Number of nodal stations dissected mean (SD)	3.8 (±1)

### 3. Results

Five hundred thirty four patients underwent lung resection surgery with SND and 241 patients underwent VAMLA from January 2010 to December 2017. Forty nine (6.3%) patients presented mediastinal metastases and were included in the study. The main characteristics of the patients are described in Table 1.

A total of 713 LNs were resected, 119 were malignant. Sixty seven nodal stations revealed malignant LNs (Table 2). In these, the largest LN was found to be malignant in 39 (58.2%) cases: no differences were found between nodal station location ( $P < .6$ ). Among malignant nodal stations with the largest LN being non-malignant, in 16 (23.8%) cases the second largest LN was malignant, while in 12 (17.9%) cases neither the largest nor the second largest were found to be malignant. Focusing on the nodal stations included in the ESTS recommendations (#4R, #4L, and #7), the largest LN was malignant in 31 (54%) cases.

The median long axis diameter of overall mediastinal LNs was 10 mm (7–15). There were differences between the median long axis diameter of malignant LNs (15 mm (10–20)), and non-malignant LNs (10 mm (7–17)) ( $P < .001$ ) (Fig. 1). In malignant

Table 2	
Malignant nodal stations (Number: 67).	
Number of LNs per station mean (SD)	4.5 (±3.1).
Number of malignant LN Number (%)	One 44 (65.7)
Two or more	23 (34.3)
Size ranking of the largest malignant LN Number (%)	
1 <sup>st</sup> Largest	39 (58.2)
2 <sup>nd</sup> Largest	16 (23.9)
3 <sup>rd</sup> Largest	7 (10.4)
4 <sup>th</sup> Largest	2 (3)
5 <sup>th</sup> Largest	2 (3)
6 <sup>th</sup> Largest	1 (1.5)

mediastinal nodal stations the median long axis diameter of the largest malignant LN was 17 mm (10–22), and the median long axis diameter of the largest non-malignant LN was 18 mm (13–22). No differences were found between both groups ( $P < .62$ ) (Fig. 2).

In a “per patient” analysis, in a hypothetical scenario where only the largest LN of each nodal station had been sampled in a preoperative staging procedure, this sampling strategy would have attained a sensitivity of 0.67. If the largest and the second largest LN of each station had been sampled, the sensitivity would have increased up to 0.87. Focusing on patients with malignant LNs in stations #4R, #4L, and #7, a sampling strategy following the ESTS minimum requirements for a preoperative staging procedure, would have attained a sensitivity of 0.63. Extending the sampling to the largest and the second largest LN of these stations would have meant an increment of the sensitivity up to 0.87 (Fig. 3).

### 4. Discussion and conclusions

In our series, the largest LN of a malignant nodal station was not essentially malignant in many cases. Although, overall, the size of malignant LNs was larger than that of non-malignant LNs, in malignant nodal stations there were no differences between the

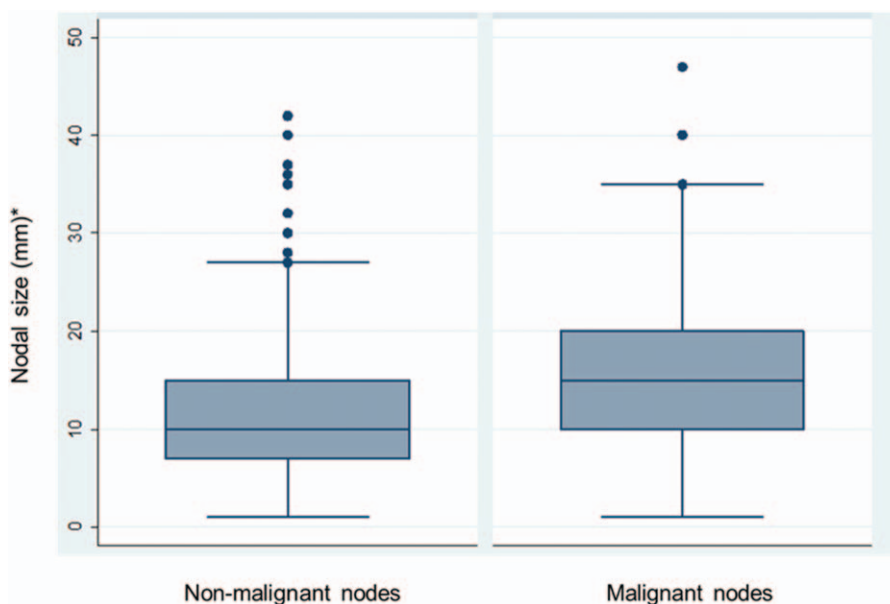
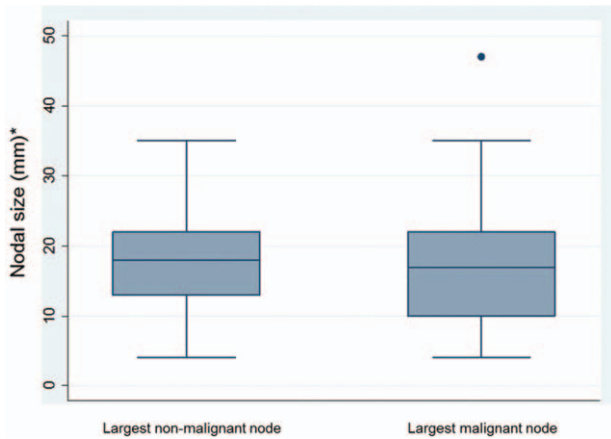


Figure 1. Median size of non-malignant mediastinal nodes (10 (7–15)) compared with median size of malignant mediastinal nodes (15 (10–20)) (Mann–Whitney  $P < .001$ ). \*Long-axis diameter.



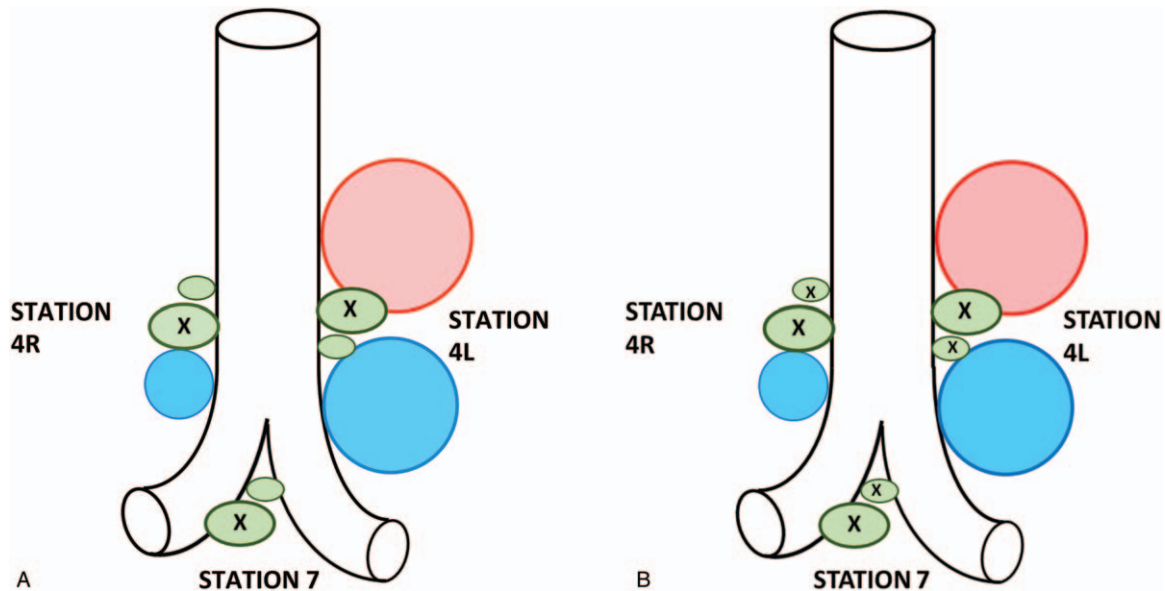
**Figure 2.** Median size of the largest non-malignant node (18mm (13–22)) compared with median size of the largest malignant node (17 mm (10–22)) of each malignant nodal station. No differences were found between both groups (Mann–Whitney test  $P < .62$ ). \*Long-axis diameter.

median size of the largest malignant LN and the median size of the largest non-malignant LN. In our study, a hypothetical preoperative staging procedure that sampled only the largest LN of each mediastinal station would have attained a low sensitivity. Following the minimum requirements of the ESTS in patients with LN metastases involving stations #4R, #4L, and #7, would mean even lower sensitivity. These figures reinforce the idea that, regardless of the preoperative staging method, a thorough sampling of all visible LNs should be prioritized over arbitrary samplings.

It is known for more than 30 years that the size criterion used to distinguish between malignant and non-malignant LNs in CT staging is not reliable enough.<sup>[3–4,15]</sup> Therefore, the strategy of

sampling only the largest LN in each mediastinal station does not seem to be an accurate approach. Only 2 studies have investigated the relation between nodal size ranking and malignancy. Suemitsu et al, in a series of 371 patients who underwent lung resection with nodal dissection of more than 6 LNs, found that the largest LN (based on short-axis diameter) contained metastases in only 27.4% of cases in adenocarcinoma patients and 25% in squamous cell carcinoma patients. This study has 2 points of criticism: firstly, lack of differentiation between hilar and mediastinal stations (that were analyzed together); secondly, measuring the LNs by the surgeons through direct assessment of the fresh surgical specimens. The latter can potentially lead to misinterpretation as the diameter of some LNs could be overrated due to presence of fatty tissue, and non-lymphatic samples also could be accidentally included. In this setting, several authors have demonstrated that specimens previously labeled as LN during nodal dissection or at gross inspection are revealed to be non-lymphatic on histological examination in up to one third of the cases.<sup>[14,25]</sup> In our study all nodal long-axis diameters were measured on HE-stained sections of histologically confirmed LNs.

The other study that investigated nodal size ranking was conducted by Ikeda et al and included 25 patients with N2 disease in lung resection specimens. One hundred fourteen mediastinal LN stations were resected. Of these, 47 had metastases. Among the 47 malignant stations there were 137 malignant LNs and 122 non-malignant LNs. The largest LN node had metastases in 44 of the 47 malignant stations (94%). However, it should be considered that the rate between malignant and non-malignant LNs in these stations was high (52.8%) and the likelihood for a single LN (including the largest) to be malignant was increased just as a matter of probability. The number of LNs per nodal station in normal circumstances and in lung cancer<sup>[11,25]</sup> varies among individuals. However, studies performed in autopsy series of patients without thoracic disorders, showed that mediastinal



**Figure 3.** In patients with malignant LNs in stations #4R, #4L, and/or #7, a sampling strategy following the ESTS minimum requirements for a preoperative staging procedure (sampling the largest LN per station), would have attained a sensitivity of 0.63 (Fig. 3a). Extending the sampling to the largest and the second largest LN of these stations would have meant an increment of the sensitivity up to 0.87 (Fig. 3b).

stations #4R and #7 usually have more LNs per station in comparison with other stations. In our series, most of the malignant nodal stations presented 1 single malignant LN and the median number of overall LNs per station was 4.5. Thereby, a random sampling of 1 single LN, regardless of the size criteria, would have obtained an overall likelihood of malignancy of 22%.

In the study of Ikeda et al, all the malignant nodal stations presented a malignant LN as the largest or the second largest. Thus, the authors affirmed that a staging approach that included sampling of the 2 largest LNs would attain a sensitivity of 100%. Similarly, in the study of Suemitsu et al in stations were the largest and the second largest LNs had no metastasis, the likelihood of metastasis in the third largest or smaller ones was 6.0% in adenocarcinoma patients and 11.4% in squamous cell carcinoma patients. Our results are in agreement with these studies. In our series 82.1% of malignant nodal stations presented a malignant LN as the largest or the second largest. Furthermore, in a “per patient” analysis the sensitivity of a staging procedure that sampled the 2 largest LNs of every station would increase the sensitivity significantly compared with sampling only the largest (from 0.67 to 0.87).

Another concern about the studies of Suemitsu et al and Ikeda et al is that there was no mention whether the patients who underwent lung resection had undergone a mediastinoscopy (that could have bisected some of the non-malignant LNs) prior to surgery. In our study, none of the 10 patients with mediastinal LN metastases identified in the SND specimen had undergone mediastinoscopy before resection.

One limitation that our study shares with those of Ikeda et al and Suemitsu et al is that most of the included patients had NSCLC in early clinical stage, otherwise they would have not been eligible for surgery. Accordingly, our results have to be considered in the clinical early stage, where tumors are not associated with large LNs on CT or positive LNs on PET or PET/CT. However, what can be considered as an inclusion bias is also an advantage by virtue of 2 reasons: First, the methodology followed in the study is the most accurate for nodal measurement and comparison between LNs because size is measured on H-E stained slides of completely dissected LNs and all the LNs were completely retrieved from each nodal station. This method could only be obtained by means of nodal resection. Second, it is actually in this clinical early stage setting were sampling the largest LN loses meaning and is much needed to be validated. The recommendations for sampling at least 1 node from stations #4R, #4L, and #7 as a minimum requirement were established before the introduction of PET/CT. At this time, invasive preoperative staging of patients with normal mediastinum on CT was highly uncommon and mediastinoscopy was usually reserved for patients with enlarged LNs. Even with lack of evidence, it was logical that, if the minimum requirement was sampling 1 LN per station, in patients with abnormal mediastinum, the chosen LN should be the largest. Over the last years, there have been plenty of evidences showing that patients with normal mediastinum on PET/CT can have occult mediastinal metastases. Thus, increasingly, many patients with NSCLC and normal mediastinum on PET/CT undergo preoperative invasive staging.<sup>[26]</sup> And, as affirmed previously, it is in this clinical setting where this recommendation loses meaning.

In summary, in patients with clinical early-stage NSCLC, nodal size ranking is not reliable enough to predict malignancy. A

preoperative staging strategy that includes sampling the largest LN of each nodal station attains poor sensitivity. In clinical practice, regardless of the preoperative staging method, systematic thorough sampling of all visible LNs is to be recommended over selective random samplings.

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