N3 hilar sampling decision in the staging of mediastinal lung cancer

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To the Editor:

The guidelines [1–4] on invasive staging for lung cancer recommend endoscopic ultrasound-guided fine-needle aspiration over surgical staging in patients with a high suspicion of lymph node involvement, either by morphological criteria (>1 cm in short axis) on computed tomography (CT) or metabolic criteria on positron emission tomography (PET) uptake (standardised uptake value maximum (SUVmax) >2.5). This recommendation is also valid for a CT and PET negative mediastinum if there is a central tumour, N1 disease, a low uptake tumour or a T2 tumour (>3 cm). Systematic endoscopic ultrasound node assessment should include the abnormal nodes by CT or PET and a minimum of three N2 stations (4R, 7 and 4L) [1–4]. Any node >5 mm in short axis diameter at endoscopic assessment should be sampled. These recommendations are based on a number of studies that compared cervical mediastinoscopy to endobronchial ultrasound (EBUS) in surgical patients [3, 5], which means that information on N3 hilar lymph nodes (stations 10 and 11) is lacking. There are no specific statements regarding whether or not to sample hilar N3 lymph nodes [1–4]. As Murgu [6] pointed out, routinely sampling these stations may not be warranted because N3 hilar stations do not impact staging if N3 mediastinal stations are positive and because thoracic surgeons only sample N3 mediastinal stations in surgical staging. This study aims to determine the value of this extended clinical practice and to establish whether a higher SUV max cut-off point can provide better PET-CT diagnostic accuracy.

This is a retrospective descriptive study on our database, which includes 1013 patients studied by EBUS-transbronchial needle aspiration (TBNA) at the University Hospital of Bellvitge (Barcelona, Spain) from January 2012 to January 2018. We included patients with lung cancer staged by PET-CT and EBUS-TBNA who had at least one sampled N3 station hilar lymph node (contralateral 10 and 11), while a pathological report was deemed conclusive.

Previous to EBUS, all patients underwent routine ^{18}F-FDG PET-CT scans with a Discovery ST PET-CT (GE Healthcare) or a Discovery IQ PET-CT (GE Healthcare). All patients fasted for at least 6 h, and glucose levels in peripheral blood were confirmed to be $\leqslant$140 mg·dL^{-1} before administering the ^{18}F-FDG injection. Approximately 5.5 MBq·kg^{-1} of body weight of ^{18}F-FDG was administered intravenously 1 h before standard PET-CT imaging acquisition (from the base of the skull to the proximal thighs).

A single nuclear medicine expert at our Institution blindly reviewed all scans and determined the SUVmax of primary mass and every single lymph node. The analysis was performed with two cut-off points for SUVmax (2.5 and 5).

Convex EBUS-TBNA was performed with an Olympus BF-UC180F and a Fujifilm EB-530 US under general anaesthesia through a laryngeal mask (iGel, Intersurgical).

Lymph node examination was performed with a systematic approach and all nodes with a short-axis $\geqslant$5 mm were sampled with a 21-gauge needle (NA-201SX-4021, Olympus) supported by rapid on-site evaluation. Cell blocks were obtained from all punctures.

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There is insufficient evidence for the sampling of morphometabolically normal N3 hilar lymph nodes https://bit.ly/3gWcar7

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A cut-off point of ⩾10 mm in diameter in the short axis was deemed as highly suspicious of malignancy upon CT examination. In this study, measurements are exclusively based on ultrasonography since it is a more accurate and real-time approach.

The baseline characteristics of participants were described using mean±SD for continuous variables and frequencies for categorical variables. The statistical analysis was performed using Microsoft Office Excel 2007.

85 patients with a mean±SD age of 67±10.3 years met the inclusion criteria, of whom 74 (87%) were men. Pathological diagnoses were adenocarcinoma in 38 (44.7%) cases, squamous cell lung carcinoma in 34 (40%) cases, nonsmall cell lung carcinoma in eight (9.4%) cases, small cell lung carcinoma in three (3.5%) cases, sarcomatoid carcinoma in one (1.2%) case, and neuroendocrine lung cancer in one (1.2%) case.

A total of 329 lymph nodes were sampled, of which 81 were mediastinal N3 with 10 (12.3%) testing positive for malignancy, 95 were hilar N3, among which six (6.3%) were histologically positive, and 124 and 29 were N2 and N1 lymph nodes, respectively. N3 hilar lymph node results are given in table 1.

With a PET-CT cut-off point of ⩾2.5 SUVmax, none of the 44 normal N3 hilar lymph nodes tested histologically positive for lung cancer. Of the 51 patients with abnormal N3 hilar lymph nodes (39 by PET-CT, three by short-axis measured with EBUS and nine for both), malignancy was found in 11.7% (2.6% by PET-CT, 33% by EBUS and 44.4% when PET-CT and EBUS findings are combined).

If a PET-CT cut-off point was established at ⩾5 SUVmax, none of 78 normal N3 hilar lymph nodes tested histologically positive for lung cancer. Of the 17 patients with abnormal N3 hilar lymph nodes (five by PET-CT, eight by short-axis measured with EBUS, and four for both), malignancy was found in 35.3% (20% by PET-CT, 25% by EBUS, and 75% when PET-CT and EBUS findings are combined).

TABLE 1 Pathological results according to morphometabolic features in 95 hiliar N3 lymph nodes

	All lymph nodes	Histology		Malignancy %
		Malignant	Non-malignant	
Lymph nodes	95	6	89	
EBUS				
Diameter in short axis, mm				
<10	83	1	82	1.2
⩾10	12	5	7	41.7
PET-CT				
SUVmax cut-off of 2.5				
<2.5	47	1	46	2.1
⩾2.5	48	5	43	10.4
PET-CT				
SUVmax cut-off of 5				
<5	86	2	84	2.3
⩾5	9	4	5	44.4
Combined EBUS/PET-CT				
SUVmax cut-off of 2.5				
<10 mm, SUVmax <2.5	44	0	44	0.0
<10 mm, SUVmax ⩾2.5	39	1	38	2.6
⩾10 mm, SUVmax <2.5	3	1	2	33.3
⩾10 mm, SUVmax ⩾2.5	9	4	5	44.4
Combined EBUS/PET-CT				
SUVmax cut-off of 5				
<10 mm, SUVmax <5	78	0	78	0.0
<10 mm, SUVmax ⩾5	5	1	4	20.0
⩾10 mm, SUVmax <5	8	2	6	25.0
⩾10 mm, SUVmax ⩾5	4	3	1	75.0

Data are presented as n or %. EBUS: endobronchial ultrasounds; PET-CT: positron emission tomography-computed tomography; SUVmax: standardised uptake value maximum.

According to this series, normal hilar N3 lymph nodes (short axis measured by EBUS <10 mm and <5 SUVmax) should not be sampled, regardless of mediastinum N3 status. However, when hilar N3 lymph nodes present morphologically and/or metabolically abnormal features, EBUS-TBNA is mandatory, since malignancy is found in 35.3% of cases on average. A recent study [7] did not find any N3 lymph node morphologically suspicious of malignancy by EBUS when it was PET-CT metabolically negative. However, to the best of the authors' knowledge, this is the first report to focus on the value of sampling hilar N3 based on a combination of EBUS morphology data (short axis) and metabolic activity assessed by PET-CT.

In our study, we used two SUVmax cut-off points. SUVmax ⩾2.5 is considered the reference for malignancy in solid tumours, though this value can be different when applied to lymph nodes. Different authors have explored the cut-off point for lymph nodes, positing values between 4.5 and 6.2 [8–10]. We decided to apply a SUVmax cut-off of 5 as this is a mid-range value in the literature. By increasing the SUVmax cut-off point to 5, 34 samples could have been avoided (table 1).

A study limitation is the absence of patients' surgical status. However, that was not the aim of the study and the correlation reported between EBUS and surgery results for malignancy is very high [3, 11].

Our proposal to restrict EBUS sampling to morphometabolically abnormal hilar N3 would reduce procedural time, lower the risk of complications and achieve better cost-effectiveness. Furthermore, a reduction of the radiation field alone would justify this practice. Possibly, the proposal of Evison *et al*. [12] to use a stratification model combining variables of PET-CT and EBUS is the way forward.

In conclusion, morphometabolically normal N3 hilar lymph nodes (PET-CT: SUVmax<5 and EBUS <10 mm in short axis) should not be sampled, regardless of mediastinal N3 status. Using a SUVmax ⩾5 reduces the number of samples required without compromising diagnostic accuracy. A multicentre prospective study is needed to corroborate this finding.

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References

1 Travis WD, Brambilla E, Noguchi M, *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6: 244–285.
2 Silvestri GA, Gonzalez A V, Jantz MA, *et al.* Methods for staging non-small cell lung cancer. *Chest* 2013; 143: e211S-e250S.
3 Ge X, Guan W, Han F, *et al.* Comparison of endobronchial ultrasound-guided fine needle aspiration and video-assisted mediastinoscopy for mediastinal staging of lung cancer. *Lung* 2015; 193: 757–766.
4 Asamura H, Chansky K, Crowley J, *et al.* The International Association for the Study of Lung Cancer Lung Cancer Staging Project. *J Thorac Oncol* 2015; 10: 1675–1684.
5 Leong TL, Loveland PM, Gorelik A, *et al.* Preoperative staging by EBUS in cn0/n1 lung cancer: systematic review and meta-analysis. *J Bronchol Interv Pulmonol* 2019; 26: 155–165.
6 Murgu SD. Diagnosing and staging lung cancer involving the mediastinum. *Chest* 2015; 147: 1401–1412.
7 Serra P, Centeno C, Sanz-Santos J, *et al.* Is it necessary to sample the contralateral nodal stations by EBUS-TBNA in patients with lung cancer and clinical N0 / N1 on PET-CT? *Lung Cancer* 2020; 142: 9–12.
8 Bryant AS, Cerfolio RJ, Klemm KM, *et al.* Maximum standard uptake value of mediastinal lymph nodes on integrated FDG-PET-CT predicts pathology in patients with non-small cell lung cancer. *Ann Thorac Surg* 2006; 82: 413–417.
9 Kumar A, Dutta R, Kannan U, *et al.* Evaluation of mediastinal lymph nodes using F-FDG PET-CT scan and its histopathologic correlation. *Ann Thorac Med* 2011; 6: 11–16.

10 Hellwig D, Graeter TP, Ukena D, *et al.* 18F-FDG PET for mediastinal staging of lung cancer: which SUV threshold makes sense? *J Nucl Med* 2007; 48: 1761–1766.
11 Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound *versus* mediastinoscopy for non-small cell lung cancer. *J Thorac Dis* 2017; 9: S83-S97.
12 Evison M, Morris J, Martin J, *et al.* Nodal staging in lung cancer: a risk stratification model for lymph nodes classified as negative by EBUS-TBNA. *J Thorac Oncol* 2015; 10: 126–133.