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Early View

Original article

Which definition of central tumour is more predictive of occult mediastinal metastasis in non-small cell lung cancer patients with radiologic N0 disease?

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Which definition of central tumour is more predictive of occult mediastinal metastasis in non-small cell lung cancer patients with radiologic N0 disease?

Running head: Definition of central tumour to predict occult N2 diseases

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List of abbreviations

ACCP = American College of Chest Physicians

CI = confidence interval

CT = computed tomography

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration

ESTS = European Society of Thoracic Surgery

EUS-FNA-B = Transoesophageal bronchoscopic ultrasound-guided fine-needle aspiration

LN = lymph node

MLND = mediastinal LN dissection

NCCN = National Comprehensive Cancer Network

NSCLC = non-small cell lung cancer

OR = odds ratio

PET-CT = integrated positron emission tomography and computed tomography

ABSTRACT

Background: Guidelines recommend invasive mediastinal staging for centrally located tumours, even in radiologic N0 non-small cell lung cancer (NSCLC). However, there is no uniform definition of central tumour which is more predictive of occult mediastinal metastasis.

Methods: A total of 1,337 consecutive patients with radiologic N0 disease underwent invasive mediastinal staging. Tumours were categorized into central and peripheral by seven different definitions.

Results: About 7% (93/1,337) of patients had occult N2 disease, and they had significantly larger tumour size, and more solid tumours on computed tomography (CT). After adjustment for patient- and tumour-related characteristics, only the central tumour definition of inner one-third of the hemithorax by concentric lines arising from the midline significantly predicted occult N2 disease (aOR, 2.13; 95% CI, 1.17–3.87; $P = 0.013$). This association was maintained after excluding patients with pure ground glass nodules (aOR, 2.54; 95% CI, 1.37–4.71; $P = 0.003$) or only including those with solid tumours (aOR, 2.30; 95% CI, 1.08–4.88; $P = 0.030$).

Conclusions: We suggest that central tumour should be defined using the inner one-third of the hemithorax adopted by drawing concentric lines from the midline. This is particularly useful for predicting occult N2 disease in patients with NSCLC.

Keywords: central tumour; lung cancer; mediastinal staging

INTRODUCTION

Accurate mediastinal staging is an essential step in the management of patients with non-small cell lung cancer (NSCLC) without distant metastases [1]. Noninvasive imaging studies including computed tomography (CT) and integrated positron emission tomography and CT (PET-CT) are initially performed to evaluate mediastinal lymph node (LN) stage. This is followed by pathologic confirmation for positive or inconclusive findings using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in most cases [1]. In the absence of mediastinal metastasis on CT or PET-CT images, invasive mediastinal staging is recommended only when there are one or more risk factors for occult mediastinal metastasis, such as N1 LN enlargement, tumour size more than 3 cm, or central location [1-3].

However, there is no uniform definition of the "central location" of tumours, even among major practice guidelines. The American College of Chest Physicians (ACCP) guidelines define tumours in the inner one-third of the hemithorax as centrally located [2], while the National Comprehensive Cancer Network (NCCN) and the European Society of Thoracic Surgery (ESTS) guidelines define those in the inner two-thirds of the hemithorax as centrally located [1, 3]. This is at least partially responsible for the inconsistent findings in many studies that investigated the association between tumour location and risk of occult N2 disease using different definitions for centrally located tumours [4-13]. Likewise, a recent survey disclosed the lack of agreement among physicians regarding the definition of central tumour [14]. Nevertheless, there are no studies comparing different definitions of central tumours, particularly when applying the definition in terms to predict occult N2 disease in patients with radiologic N0 disease.

Thus, this study aimed to evaluate the risk of occult N2 disease in patients with

NSCLC and radiologic N0 disease using seven different definitions for centrally located tumour.

METHODS

Study population and data collection

Using the Lung Cancer Surgery Registry and EBUS-TBNA Registry database at Samsung Medical Centre (a 1,979-bed referral hospital in Seoul, South Korea), patients with NSCLC and radiologic N0 disease by both CT and PET-CT were retrospectively identified from registries between January 2014 and December 2015. Radiologic N0 stage was defined as short-axis of LNs $\leq$ 1 cm in CT and maximum standardized uptake value of LNs $\leq$ 2.5 in PET-CT [15]. Patients with previous history of lung cancer, previous history of mediastinal LN dissection (MLND) due to oesophageal cancer, who underwent neoadjuvant treatment, who did not undergo standard MLND (i.e., mediastinal sampling or lung resection only), or with double primary lung cancer with different histology were excluded.

Information regarding patient- (age, sex, and smoking) and tumour-related characteristics (size, lobar location, histology) were collected from the database. The primary outcome of this study was occult mediastinal LN metastasis (occult N2 disease), which was defined as pathologically proven (either by MLND or by EBUS-TBNA) N2 or N3 disease based on the International Association for the Study of Lung Cancer LN map [16]. The Institutional Review Board of Samsung Medical Centre approved this study (IRB no. 2017-12-088-002) and waived informed consent due to its retrospective nature.

Definitions for central tumour location

Tumour locations were measured based on the inner-most part of the tumour on CT. Based on previous study [14], tumours were categorised as central and peripheral by contact with hilar structures (i.e., lobar bronchi, lobar or main pulmonary arteries, main pulmonary veins) or by location within one-third or two-thirds of the hemithorax. Lines dividing thirds of the hemithorax were drawn as follows: concentric lines arising from the hilum in both axial and coronal images, concentric lines arising from the midline in axial images, and sagittal lines arising from the midline in coronal images (**Figure 1 and 2**).

Invasive mediastinal staging

Patients with radiologic N0 disease without distant metastasis either underwent preoperative EBUS-TBNA or directly proceeded to surgical resection at the discretion of attending physicians, since there was no consistent indication for preoperative EBUS-TBNA in patients with radiologic N0 disease. EBUS-TBNA was performed with a convex probe-EBUS bronchoscope (BF-UC260F-OL8; Olympus, Tokyo, Japan) and a 22-gauge needle (NA-201SX-4022; Olympus) under moderate sedation with intravenous midazolam and fentanyl. After systematic inspection of LN station, each visible LN was sampled in the standard N3 to N2 to N1 fashion, with size cut-offs of 5mm or greater in short-axis by EBUS. We conducted three passes per node and at least two passes when core tissue was obtained [17, 18]. Transoesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-FNA-B) using EBUS bronchoscope was done in selected cases [19]. Rapid on-site cytopathological evaluation was not available. When the clinical suspicion of mediastinal metastasis remains high despite negative result in EBUS-TBNA, preoperative mediastinoscopy was performed. Otherwise, surgical resection with MLND was considered if there was no metastasis to mediastinal LNs in EBUS-TBNA.

The surgical procedures included resection of the affected lung plus LN dissection of the ipsilateral hilum and mediastinum, including all visible and palpable LNs irrespective of size [20, 21]. MLND consisted of en bloc resections of all nodes at stations 10R, 9, 8, 7, 4R, 3, and 2R for right-sided tumours and nodes at stations 10L, 9, 8, 7, 6, 5, and 4L for left-sided tumours.

Statistical analyses

Data are reported as number (%) for categorical variables and as mean (standard deviation) for continuous variables. Data were compared using Pearson χ^2 test or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Multivariable logistic regression analysis was used to adjust for potential confounding factors in the association between seven definitions for central tumour and occult N2 disease. Two models were constructed: Model 1 was adjusted for tumour size (continuous) and tumour attenuation on CT; Model 2 was additionally adjusted for age (continuous), sex, smoking history (never or ever), and lobar location (right or left) of tumour. Analyses were also performed in subgroups of patients excluding pure ground glass lesions (n = 861) and in those with solid tumours only (n = 485). All tests were two-sided, and a *P* value <0.05 was considered significant. Stata (version 14.0; Stata Corporation, College Station, TX, USA) was used for analysis.

RESULTS

Study population

During the study period, 159 patients in the EBUS-TBNA registry were suspected to

have radiologic N0 NSCLC and underwent EBUS-TBNA for N staging (**Figure 3**). Of these patients, 10 were confirmed to have N2 disease. The remaining 149 patients underwent curative resection. In the Lung Cancer Surgery Registry, 1,526 patients underwent curative resection for radiologic N0 NSCLC. After 199 patients were excluded (mediastinal sampling only [n =135], previous history of lung cancer [n = 29], lung resection without MLND [n = 12], lung resection after neoadjuvant treatment [n = 11], previous history of MLND due to oesophageal cancer [n = 7], and double primary lung cancer [n = 5]), 83 patients were confirmed to have N2 by MLND. Finally, 93 (7.0%) patients were confirmed to have occult N2 disease by EBUS-TBNA or MLND in 1,337 patients with radiologic N0 disease. Of these 93 patients with occult N2 disease, 2 also had metastases to N3 LNs. Meanwhile, there were 27 patients who received preoperative mediastinoscopy and none of them was found to have occult N2 disease.

Patient and tumour characteristics

Characteristics of the 1,337 patients are shown in **Table 1**. The mean age of patients was 62 years, 53% of patients were male, and 52% of patients were never-smokers. Tumour size was 3 cm or less in 65% of cases. CT attenuation was solid in 36% of cases, and most tumours (82%) were adenocarcinoma on histology. Baseline characteristics including age, sex, smoking history, tumour location, and tumour histology were not associated with the risk of occult N2 disease in univariate analysis. However, larger tumour size ($P < 0.001$) and increasing tumour attenuation on CT ($P = 0.001$) were significantly associated with increased risk of occult N2 disease. Time interval between PET-CT and the surgery, and the number of dissected nodes or dissected LN stations were not associated with the increased risk of occult N2 disease.

Definition of central tumour and the risk of occult N2 disease

The proportion of centrally located tumour varied widely from 9.1% to 80.3% using seven different definitions (**Table 2**). By all definitions except the inner two-thirds of the hemithorax by sagittal lines, central location was associated with increased risk of occult N2 disease in univariate analysis . However, only the central location defined as the inner one-third of the hemithorax by concentric lines arising from the midline remained statistically significant after adjustment for tumour size and attenuation on CT (adjusted odds ratio [OR], 2.05; 95% confidence interval [CI], 1.14–3.71, *P* = 0.017) and with further adjustment for age, sex, smoking history, and lobar location of tumour (adjusted OR, 2.13; 95% CI, 1.17–3.87, *P* = 0.013).

When the analyses were confined to patients excluding pure ground glass lesions (n = 861) (**Table E1-E2**) or those with solid tumours only (n = 485) (**Table E3-E4**), results were grossly unchanged. The definition of the inner one-third of the hemithorax by concentric lines arising from the midline was significantly associated with increased risk of occult N2 disease in both subgroups excluding pure ground glass lesions (adjusted OR, 2.54; 95% CI, 1.37−4.71, *P* = 0.003) and subgroups with solid tumours only (adjusted OR, 2.30; 95% CI 1.08−4.88, *P* = 0.030).

DISCUSSION

In our study, the prevalence of pathologically proven occult N2 disease in patients with NSCLC and radiologic N0 disease was 7%. Previously recognized factors including tumour size, tumour attenuation on CT, and tumour histology were again associated with risk of occult N2 disease [5, 8, 9, 11-13, 22]. After adjustment for these factors, only the central

tumours defined as located in the inner one-third of the hemithorax adopted by drawing concentric lines from the midline were associated with increased risk of occult N2 disease, among seven different definitions compared in this study. In the subgroup analyses excluding pure ground glass lesions or patients with solid tumours only, the association persisted. To the best of our knowledge, our study included the largest number of patients with NSCLC exclusively with radiologic N0 disease. In addition, this is the first study to compare different definitions of central tumours to predict occult N2 disease.

Previous studies mostly found that central tumours have higher risk of occult N2 disease in patients with radiologic N0 NSCLC, compared with peripheral tumours. However, there are considerable inconsistencies in the definitions of centrally located tumours, especially regarding the inner one-third *vs.* inner two-thirds in the hemithorax. Among studies which used inner one-third as the definition of central tumour, three studies restricted their study population to those with radiologic N0 disease [7, 10, 13]. Central location was independently associated with occult N2 disease in two studies (aOR 6.8 and 6.25, respectively, both $P < 0.001$) [10, 13] while it was not associated with occult N2 disease in a smaller study [7]. Similarly, two studies in patients with radiologic N0 disease used inner two-thirds as the definition of central tumours [5, 9]. One of these studies showed that central location was associated with occult N2 disease in a univariate analysis ($P < 0.001$) [5], and the other study also demonstrated the increased risk of occult N2 disease in patients with central tumours (aOR 3.2, $P = 0.002$) [9]. Of note, there was one study in which both definitions of inner one-third and inner two-thirds were evaluated for risk of pathologic N2 disease and revealed that neither was associated with pathologic N2 disease [11]. However, that study included a considerable number of patients with radiologic N1, N2, or even N3 disease by CT or PET-CT, which might explain the negative results. By confining the study population to radiologic N0 stage and adjusting for major confounders, our study confirmed

that location in the inner one-third by concentric lines arising from the midline is the definition of central tumour that best predicts occult N2 disease.

The most intriguing finding of our study is the difference between two types of concentric lines. Those arising from the hilum, which are the same as concentric lines used in an online survey [14], were less predictive of occult N2 disease compared to those arising from the midline. This might be explained by the presence of skip metastasis to mediastinal LNs, which is not an uncommon phenomenon in NSCLC [23, 24]. Compared to central tumours defined by concentric lines arising from the hilum, those defined by concentric lines arising from the midline are more likely to encompass tumours in apical regions or just above the diaphragm near the midline. Tumours located in those regions might directly metastasise to upper paratracheal (station 2), supraclavicular (station 1), para-oesophageal (station 8), or pulmonary ligament (station 9) LNs, and not through hilar LNs. Indeed, previous cadaveric studies found that 23.6% of segmental lymph channels drain directly into mediastinal LNs, which were more frequent from upper lobes [25], and that lymphatic vessels from the diaphragmatic pleura drained to mediastinal LNs via pulmonary ligaments [26].

Our study also compared dividing lines for the central location; concentric lines arising from the hilum in both axial and coronal images *vs.* concentric lines arising from the midline in axial images *vs.* sagittal lines in coronal images. We found that central location defined as the inner one-third of the hemithorax by sagittal lines was associated with occult N2 disease in a crude model, but significance disappeared in the adjusted model. None of the previous studies stated that they assessed tumour centrality in the sagittal plane (i.e., measurements were mostly made in axial images [5, 7, 13] or not otherwise described). Likewise, the vast majority of physicians who participated in an online survey also chose concentric lines over sagittal lines [14]. Contact with hilar structure was not recommended by any of the official guidelines and was only described in that survey, yet was chosen by 29%

of physicians [14]. In our study, central location defined as contact with hilar structure was shown to be weakly associated with occult N2 disease only in unadjusted analysis.

Although recommended indications of preoperative invasive mediastinal staging in patients with radiologic N0 are not consistent among the major clinical guidelines, guidelines from NCCN and ESTS includes tumour size criterion, as well as central tumour [1, 3]. Our study also showed the strong association of tumour size and the risk of occult N2 disease, as in the previous studies [5, 8, 9, 11, 13, 22]. The increasing odds of occult N2 disease per each centimetre again stress the importance of tumour size, and warrants further studies on optimal cut-off value of tumour size in indication of invasive mediastinal staging.

There are several limitations to this study. First, it was conducted in a single referral hospital with a comprehensive cancer centre. Second, since the study population was retrospectively recruited from two separate registries, it did not include those who underwent neither surgical resection nor EBUS-TBNA (e.g., those who received stereotactic body radiotherapy or best supportive care for radiologic N0 NSCLC). In these patients, occult mediastinal metastasis was usually diagnosed afterwards by image follow-up. Thus, the results of our study cannot be generalised to the whole population of patients with NSCLC and radiologic N0 disease. However, using EBUS-TBNA Registry data, we included patients with radiologic N0 who were confirmed to have N2 disease by EBUS-TBNA to minimise the selection bias. Third, our study determined tumour location based on the inner-most part of the tumour. Among the choices of inner-most, outer-most, or location of the majority of the tumour volume, about half of physicians in the online survey chose the inner-most part of the tumour [14], unlike many of the previous studies in which tumour locations were determined based on the “centre of the tumour” [5, 7, 9, 10, 13]. The exact centre of a lesion is difficult to define, and it is more biologically plausible to use the inner-most part of the tumour given the direction of LN metastasis. Nevertheless, no pervious study has addressed this question.

Fourth, although the definition of central tumour we suggest was associated with occult N2 disease with statistical significance, the evidence is not sufficient to use this definition as an indication for invasive mediastinal staging. Considering that the scope of surgery is curative and thus it is important not to miss N2 disease, further studies on clinical significance of false negative results, risk of the procedure, cost-effectiveness, and ultimately the effect on patients' survival are needed to determine the clinical efficacy of this definition of central tumour [27, 28].

Motivated by the apparent lack of uniformity in the definition of central tumour location [14], our study compared seven different definitions to find the definition that is most predictive of occult mediastinal metastasis. Using data from a large number of NSCLC patients without mediastinal metastasis in both CT and PET-CT, we found that central tumours defined as located in the inner one-third of the hemithorax adopted by drawing concentric lines from the midline are associated with occult mediastinal metastasis in this patient group. Our study adds to the existing body of evidence by clarifying the definition of central tumour location that is the most predictive of occult mediastinal metastasis. We suggest that this classification may constitute an indication for invasive mediastinal staging in conjunction with other known risk factors.

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Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

1 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology - Non-Small Cell Lung Cancer, version 2.2019 Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (cited Nov 21 2018).

2 Silvestri GA, Gonzalez AV, Jantz MA, *et al.* Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: e211S-e250S.

3 De Leyn P, Dooms C, Kuzdzal J, *et al.* Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014; 45: 787-798.

4 Ketchedjian A, Daly BD, Fernando HC, *et al.* Location as an important predictor of lymph node involvement for pulmonary adenocarcinoma. *J Thorac Cardiovasc Surg* 2006; 132: 544-548.

5 Lee PC, Port JL, Korst RJ, *et al.* Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007; 84: 177-181.

6 Gomez-Caro A, Garcia S, Reguart N, *et al.* Incidence of occult mediastinal node involvement in cN0 non-small-cell lung cancer patients after negative uptake of positron emission tomography/computer tomography scan. *Eur J Cardiothorac Surg* 2010; 37: 1168-1174.

7 Park HK, Jeon K, Koh WJ, *et al.* Occult nodal metastasis in patients with non-small cell lung cancer at clinical stage IA by PET/CT. *Respirology* 2010; 15: 1179-1184.

8 Kanzaki R, Higashiyama M, Fujiwara A, *et al.* Occult mediastinal lymph node metastasis in NSCLC patients diagnosed as clinical N0-1 by preoperative integrated FDG-PET/CT and CT: Risk factors, pattern, and histopathological study. *Lung Cancer* 2011; 71: 333-337.

9 Zhang Y, Sun Y, Xiang J, *et al.* A prediction model for N2 disease in T1 non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2012; 144: 1360-1364.

10 Chen K, Yang F, Jiang G, *et al.* Development and validation of a clinical prediction model for N2 lymph node metastasis in non-small cell lung cancer. *Ann Thorac Surg* 2013; 96: 1761-1768.

11 Farjah F, Lou F, Sima C, *et al.* A prediction model for pathologic N2 disease in lung cancer patients with a negative mediastinum by positron emission tomography. *J Thorac Oncol* 2013; 8: 1170-1180.

12 O'Connell OJ, Almeida FA, Simoff MJ, *et al.* A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer: HAL 2017; 195: 1651-1660.

13 Gao SJ, Kim AW, Puchalski JT, *et al.* Indications for invasive mediastinal staging in patients with early non-small cell lung cancer staged with PET-CT. *Lung Cancer* 2017; 109: 36-41.

14 Casal RF, Vial MR, Miller R, *et al.* What Exactly Is a Centrally Located Lung Tumor? Results of an Online Survey. *Ann Am Thorac Soc* 2017; 14: 118-123.

15 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.

16 Rusch VW, Asamura H, Watanabe H, *et al.* 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: 568-577.

17 Um SW, Kim HK, Jung SH, *et al.* Endobronchial ultrasound versus mediastinoscopy for mediastinal nodal staging of non-small-cell lung cancer. *J Thorac Oncol* 2015; 10: 331-337.

18 Jhun BW, Park HY, Jeon K, *et al.* Nodal stations and diagnostic performances of endobronchial ultrasound-guided transbronchial needle aspiration in patients with non-small cell lung cancer. *J Korean Med Sci* 2012; 27: 46-51.

19 Lee KJ, Suh GY, Chung MP, *et al.* Combined endobronchial and transesophageal approach of an ultrasound bronchoscope for mediastinal staging of lung cancer. *PLoS One* 2014; 9: e91893.

20 Kim D, Choi YS, Kim HK, *et al.* Heterogeneity of clinical n1 non-small cell lung cancer. *Thorac Cardiovasc Surg* 2014; 62: 103-108.

21 Kim HK, Choi YS, Kim K, *et al.* Outcomes of mediastinoscopy and surgery with or without neoadjuvant therapy in patients with non-small cell lung cancer who are N2 negative on positron emission tomography and computed tomography. *J Thorac Oncol* 2011; 6: 336-342.

22 Ong P, Grosu H, Eapen GA, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration for systematic nodal staging of lung cancer in patients with N0 disease by computed tomography and integrated positron emission tomography-computed tomography. *Ann Am Thorac Soc* 2015; 12: 415-419.

23 Riquet M, Assouad J, Bagan P, *et al.* Skip mediastinal lymph node metastasis and lung cancer: a particular N2 subgroup with a better prognosis. *Ann Thorac Surg* 2005; 79: 225-233.

24 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: 1675-1684.

25 Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the mediastinal nodes. An anatomic study on 260 adults. *J Thorac Cardiovasc Surg* 1989; 97: 623-632.
26 Okiemy G, Foucault C, Avisse C, *et al.* Lymphatic drainage of the diaphragmatic pleura to the peritracheobronchial lymph nodes. *Surg Radiol Anat* 2003; 25: 32-35.
27 Czarnecka-Kujawa K, Rochau U, Siebert U, *et al.* Cost-effectiveness of mediastinal lymph node staging in non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2017; 153: 1567-1578.
28 Navani N, Nankivell M, Lawrence DR, *et al.* Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med* 2015; 3: 282-289.

Figure Legends

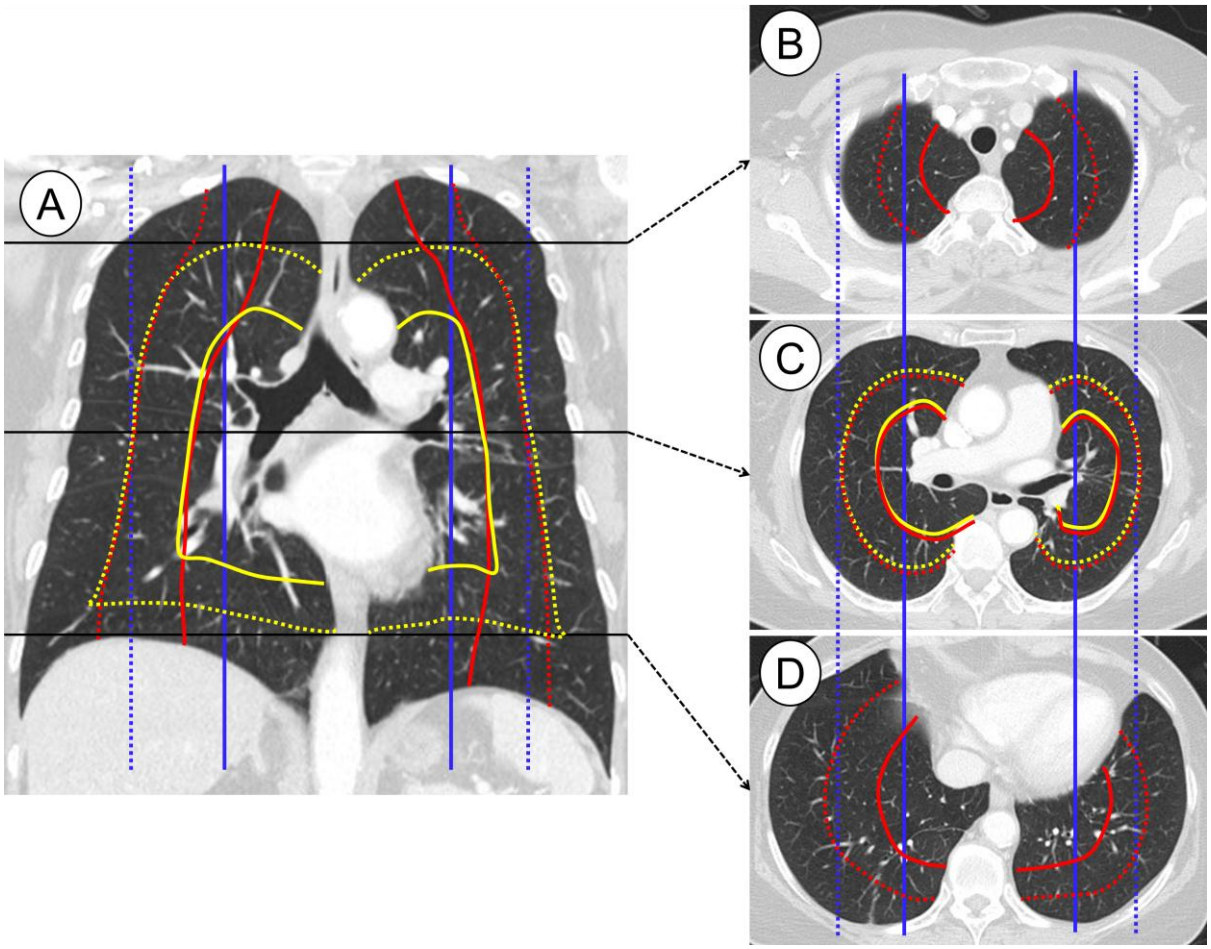
Figure 1. Definitions of each line that determine tumour location

Concentric lines arising from the hilum (yellow lines) are spherical or dumbbell shaped in three dimensions. Concentric lines arising from the midline (red lines) are cylindrical or conical in three dimensions. Sagittal lines arising from the midline (blue lines) are rectangular parallelepipeds in three dimensions. Solid lines and broken lines refer to inner one-third and two-thirds lines, respectively. (A) Coronal computed tomography (CT) at tracheal bifurcation level. (B) Axial CT image at manubrium body level. There is no yellow line because it is arising from the hilum. (C) Axial CT image at hilum level. Red lines and yellow lines are the same. (D) Axial CT image at just above diaphragm. There is no yellow line because it is arising from the hilum.

Figure 2. Conceptual three-dimensional image of (A) concentric lines arising from the hilum (corresponding yellow lines on the Figure 1A to 1D), (B) concentric lines arising from the midline (corresponding red lines on the Figure 1A to 1D), and (C) sagittal lines arising from the midline (corresponding blue lines on Figure 1A to 1D).

Figure 3. Consort diagram of the study population.

EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; NSCLC, non-small cell lung cancer; MLND, mediastinal lymph node dissection; pN, pathologic N stage.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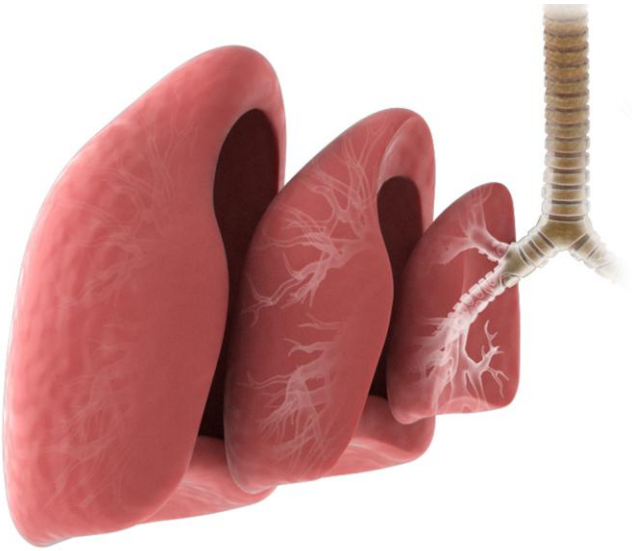

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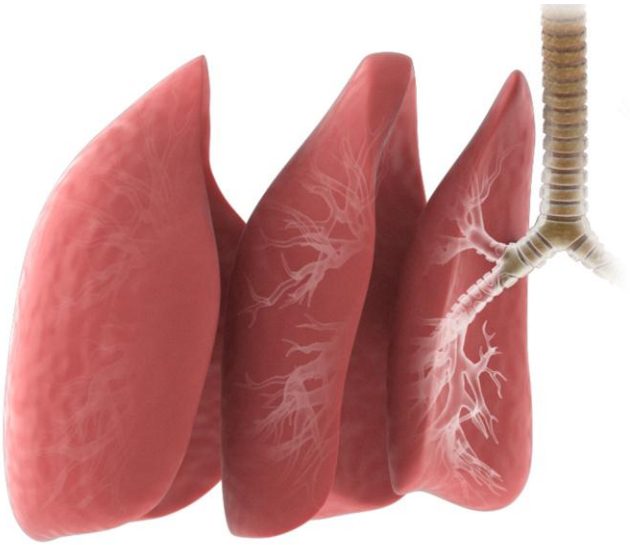

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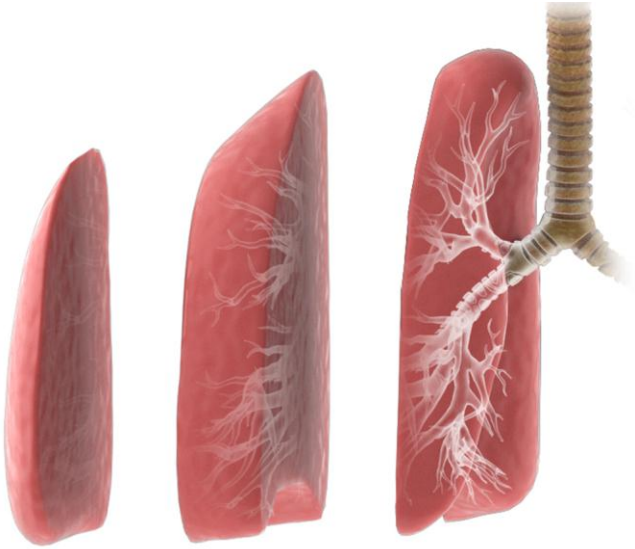

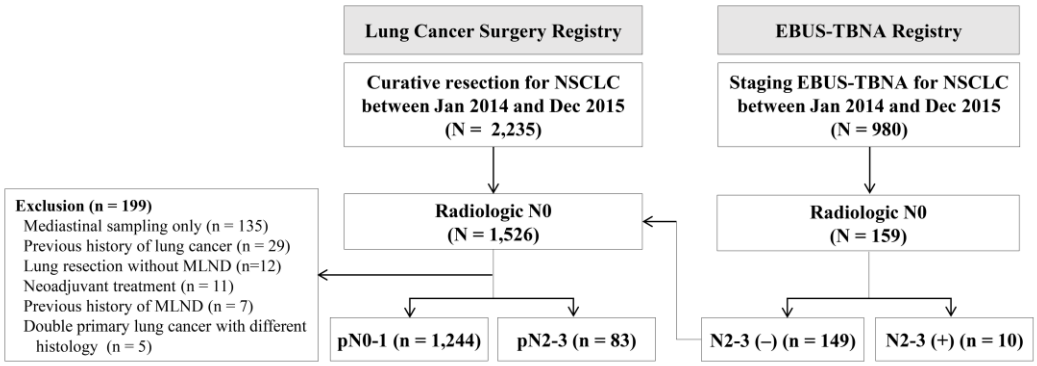
Lung Cancer Surgery Registry
EBUS-TBNA Registry
Curative resection for NSCLC between Jan 2014 and Dec 2015 (N = 2,235)
Staging EBUS-TBNA for NSCLC between Jan 2014 and Dec 2015 (N = 980)
Exclusion (n = 199)
Mediastinal sampling only (n = 135)
Previous history of lung cancer (n = 29)
Lung resection without MLND (n=12)
Neoadjuvant treatment (n = 11)
Previous history of MLND (n = 7)
Double primary lung cancer with different histology (n = 5)
Radiologic N0 (N = 1,526)
Radiologic N0 (N = 159)
pN0-1 (n = 1,244)
pN2-3 (n = 83)
N2-3 (–) (n = 149)
N2-3 (+) (n = 10)

1

Table 1 Clinical characteristics by pathologic N stage in **1,337** patients with radiologic N0 NSCLC.

	Overall (N=1,337)	**Pathologic N0 or N1 (n=1,244)**	**Pathologic N2 or N3[*] (n=93)**	***P* value[†]**	**Univariate OR (95% CI)**
Age, years	61.9 ± 9.5	61.9 ± 9.5	61.0 ± 10.3	0.366[‡]	0.99 (0.97−1.01)
Sex				0.824	
Female	633 (47.3)	590 (47.4)	43 (46.2)		1.00 (Ref)
Male	704 (52.7)	654 (52.6)	50 (53.8)		1.05 (0.69−1.60)
Smoking				0.310	
Never	693 (51.8)	645 (51.9)	48 (51.6)		1.00 (Ref)
Former	438 (32.8)	412 (33.1)	26 (28.0)		0.85 (0.52−1.39)
Current	206 (15.4)	187 (15.0)	19 (20.4)		1.36 (0.78−2.38)
Size of tumour, cm[ǁ]	2.85 ± 1.59	2.79 ± 1.55	3.70 ± 1.80	**<0.001**[‡,¶]	**1.32 (1.19–1.46)**
≤3cm	838 (62.7)	799 (64.2)	39 (41.9)		1.00 (Ref)
>3cm but ≤5cm	375 (28.0)	339 (27.3)	36 (38.7)		**2.18 (1.36−3.48)**
>5cm	124 (9.3)	106 (8.5)	18 (19.4)		**3.48 (1.92−6.30)**
Lobar location				0.176	
Right upper	423 (31.6)	394 (31.7)	29 (31.2)		1.00 (Ref)
Right middle	104 (7.8)	98 (7.9)	6 (6.5)		0.83 (0.34−2.06)
Right lower	269 (20.1)	246 (19.8)	23 (24.7)		1.27 (0.72−2.25)
Left upper	330 (24.7)	315 (25.3)	15 (16.1)		0.65 (0.34−1.23)
Left lower	211 (15.8)	191 (15.3)	20 (21.5)		1.42 (0.78−2.58)
Tumour attenuation on CT				**0.001**	
Ground glass	476 (35.6)	451 (36.3)	25 (26.9)		1.00 (Ref)
Part-solid	376 (28.1)	359 (28.9)	17 (18.3)		0.85 (0.45−1.61)
Solid	485 (36.3)	434 (34.9)	51 (54.8)		**2.12 (1.29−3.48)**
Time between PET-CT and surgery, day[+]	25.2 ± 21.2	25.4 ± 21.3	22.9 ± 20.1	0.265[‡]	0.99 (0.98–1.01)
Histology of tumour				0.097[§]	
Adenocarcinoma	1,089 (81.5)	1,010 (81.2)	79 (85.0)		1.00 (Ref)
Squamous cell carcinoma	199 (14.9)	191 (15.4)	8 (8.6)		0.54 (0.25−1.13)
Large cell carcinoma	27 (2.0)	24 (1.9)	3 (3.2)		1.60 (0.47−5.42)
Other NSCLC	22 (1.6)	19 (1.5)	3 (3.2)		2.02 (0.58−6.97)
Number of dissected nodes and					

stations during MLND[#]					
Lymph nodes	15.2 ± 8.1	15.1 ± 8.1	16.5 ± 7.9	0.142[‡]	1.02 (0.99–1.05)
Stations	4.6 ± 1.4	4.6 ± 1.4	4.7 ± 1.5	0.460[‡]	1.06 (0.90–1.25)

[*] Two patients had occult metastasis to N3 nodes as well as N2 nodes.
P values are reported by [†]chi-square test except where otherwise noted, [‡]two sample Student's t test, or [§]Fisher exact test, and are not the P values for the odds ratio reported from univariate analysis.
[‖] Size of the tumour is measured in preoperative CT scan. [¶]P values for two sample Student's t test and chi-square test are < 0.001.
[+] For 10 patients who were confirmed to have N2 disease in EBUS-TBNA, the interval between PET-CT and EBUS-TBNA were used.
[#]Analysis was done in 1,327 patients after excluding 10 patients who were confirmed to have N2 disease in EBUS-TBNA and did not undergo MLND.

NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval; CT, computed tomography; PET-CT, integrated positron emission tomography and computed tomography; MLND, mediastinal lymph node dissection.

Table 2 Risk of occult N2 disease according to each definition of centrally located tumour in patients with radiologic N0 NSCLC.s

Definition of central location	n (%)	Crude model		Model 1		Model 2	
		Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Contact with the hilar structure	122 (9.1)	**1.86 (1.02−3.40)**	**0.042**	1.16 (0.59−2.29)	0.671	1.26 (0.63−2.54)	0.510
Concentric lines arising from the hilum							
Inner one-third	216 (16.2)	**1.91 (1.17–3.11)**	**0.010**	1.29 (0.75–2.23)	0.358	1.33 (0.77–2.31)	0.311
Inner two-thirds	642 (48.0)	**1.54 (1.01–2.37)**	**0.046**	1.09 (0.68–1.73)	0.730	1.06 (0.66–1.70)	0.808
Concentric lines arising from the midline							
Inner one-third	161 (12.0)	**2.63 (1.59−4.36)**	**<0.001**	**2.05 (1.14−3.71)**	**0.017**	**2.13 (1.17−3.87)**	**0.013**
Inner two-thirds	696 (52.1)	**2.03 (1.29−3.18)**	**0.002**	1.50 (0.92−2.46)	0.104	1.48 (0.90−2.42)	0.121
Sagittal lines arising from the midline							
Inner one-third	358 (26.8)	**1.81 (1.17−2.80)**	**0.008**	1.57 (0.90−2.73)	0.113	1.59 (0.91−2.79)	0.101
Inner two-thirds	1,073 (80.3)	1.30 (0.74−2.30)	0.365	0.89 (0.49−1.63)	0.712	0.90 (0.49−1.64)	0.721

Model 1: Adjusted for tumour size (continuous) and tumour attenuation on CT. Tumour histology and number of dissected nodes and stations during MLND were not included since this information was not available preoperatively.

Model 2: Further adjusted for age (continuous), sex, smoking history (never or ever), and lobar location (right or left) of tumour.

NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval; CT, computed tomography; MLND, mediastinal lymph node dissection.

Online Supplement

Table E1 Clinical characteristics by pathologic N stage in **861** patients with radiologic N0 NSCLC after excluding pure ground-glass attenuation on CT

	Overall (N = 861)	**Pathologic N0 or N1 (n = 793)**	**Pathologic N2 or N3*** **(n = 68)**	***P* value**†	**Univariate OR (95% CI)**
Age, years	62.3 ± 9.6	62.4 ± 9.5	61.3 ± 10.9	0.349‡	0.99 (0.96−1.01)
Sex				0.598	
Female	368 (42.7)	341 (43.0)	27 (39.7)		1.00 (Ref)
Male	493 (57.3)	452 (57.0)	41 (60.3)		1.15 (0.69−1.90)
Smoking				0.748	
Never	401 (46.6)	370 (46.7)	31 (45.6)		1.00 (Ref)
Former	299 (34.7)	277 (34.9)	22 (32.3)		0.95 (0.54−1.67)
Current	161 (18.7)	146 (18.4)	15 (22.1)		1.23 (0.64−2.34)
Size of tumour, cm‖	3.12 ± 1.71	3.05 ± 1.68	3.91 ± 1.91	**< 0.001**‡,¶	**1.27 (1.12–1.43)**
≤3cm	482 (56.0)	455 (57.4)	27 (39.7)		1.00 (Ref)
>3cm but ≤5cm	272 (31.6)	245 (30.9)	27 (39.7)		**1.86 (1.07−3.24)**
>5cm	107 (12.4)	93 (11.7)	14 (20.6)		**2.54 (1.28−5.02)**
Lobar location				0.376§	
Right upper	269 (31.2)	248 (31.3)	21 (30.9)		1.00 (Ref)
Right middle	61 (7.1)	57 (7.2)	4 (5.9)		0.83 (0.27−2.51)
Right lower	182 (21.1)	168 (21.2)	14 (20.6)		0.98 (0.49−1.99)
Left upper	206 (23.9)	194 (24.5)	12 (17.6)		0.73 (0.35−1.52)
Left lower	143 (16.6)	126 (15.9)	17 (25.0)		1.59 (0.81−3.13)
Tumor density on CT				**0.001**	
Part-solid	376 (43.7)	359 (45.3)	17 (25.0)		1.00 (Ref)
Solid	485 (56.3)	434 (54.7)	51 (75.0)		**2.48 (1.41−4.37)**
Time between PET-CT and surgery, day+	24.1 ± 18.9	24.5 ± 18.9	19.6 ± 17.9	**0.038**‡	**0.98 (0.96–1.00)**
Histology of tumor				0.144§	
Adenocarcinoma	667 (77.5)	610 (76.9)	57 (83.8)		1.00 (Ref)
Squamous cell carcinoma	161 (18.7)	154 (19.4)	7 (10.3)		0.49 (0.22−1.09)
Large cell carcinoma	18 (2.1)	16 (2.0)	2 (2.9)		1.34 (0.30−5.96)
Other NSCLC	15 (1.7)	13 (1.6)	2 (2.9)		1.65 (0.36−7.48)
Number of dissected nodes and					

stations during MLND[#]					
Lymph nodes	15.8 ± 8.3	15.7 ± 8.3	16.3 ± 8.1	0.614[‡]	1.01 (0.98–1.04)
Stations	4.6 ± 1.4	4.6 ± 1.4	4.8 ± 1.6	0.277[‡]	1.11 (0.92–1.36)

[*] Two patients had occult metastasis to N3 nodes as well as N2 nodes.

P values are reported by [†]chi-square test except where otherwise noted, [‡]two sample Student's t test, or [§]Fisher exact test, and are not the P values for the odds ratio reported from univariate analysis.

[ǁ] Size of the tumour is measured in preoperative CT scan. [¶]P value for chi-square test is 0.011.

[+] For 10 patients who were confirmed to have N2 disease in EBUS-TBNA, the interval between PET-CT and EBUS-TBNA were used.

[#]Analysis was done in 851 patients after excluding 10 patients who were confirmed to have N2 disease in EBUS-TBNA and did not undergo MLND.

NSCLC, non-small cell lung cancer; CT, computed tomography; OR, odds ratio; CI, confidence interval; PET-CT, integrated positron emission tomography and computed tomography; MLND, mediastinal lymph node dissection.

Table E2 Risk of occult N2 disease according to each definition of centrally located tumour in **861** patients with radiologic N0 NSCLC after excluding pure ground-glass attenuation on CT

Definition of central location	n (%)	Crude model		Model 1		Model 2	
		Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Contact with the hilar structure	104 (12.1)	1.82 (0.96−3.47)	0.067	1.35 (0.65−2.78)	0.419	1.46 (0.69−3.08)	0.321
Concentric lines arising from the hilum							
Inner one-third	178 (20.7)	**1.95 (1.14−3.34)**	**0.015**	1.54 (0.85−2.79)	0.157	1.58 (0.86−2.88)	0.138
Inner two-thirds	482 (56.0)	1.39 (0.83−2.31)	0.211	1.04 (0.60−1.80)	0.884	1.03 (0.59−1.80)	0.907
Concentric lines arising from the midline							
Inner one-third	156 (18.1)	**2.54 (1.48−4.33)**	**0.001**	**2.41 (1.31−4.40)**	**0.004**	**2.54 (1.37−4.71)**	**0.003**
Inner two-thirds	526 (61.1)	**2.19 (1.23−3.90)**	**0.008**	1.78 (0.97−3.29)	**0.065**	1.83 (0.98−3.41)	**0.056**
Sagittal lines arising from the midline							
Inner one-third	353 (41.0)	**1.69 (1.03−2.78)**	**0.039**	**1.76 (1.00−3.10)**	**0.050**	**1.86 (1.04−3.30)**	**0.036**
Inner two-thirds	734 (85.2)	1.15 (0.55−2.37)	0.714	0.80 (0.37−1.73)	0.579	0.83 (0.38−1.80)	0.636

Model 1: Adjusted for tumour size (continuous) and tumour attenuation on CT. Tumour histology and number of dissected nodes and stations during MLND were not included since this information was not available preoperatively.

Model 2: Further adjusted for age (continuous), sex, smoking history (never or ever), and lobar location (right or left) of tumour.

NSCLC, non-small cell lung cancer; CT, computed tomography; OR, odds ratio; CI, confidence interval; MLND, mediastinal lymph node dissection.

Table E3 Clinical characteristics by pathologic N stage in **485** patients with radiologic N0 NSCLC of solid attenuation on CT

	Overall (N = 485)	**Pathologic N0 or N1 (n = 434)**	**Pathologic N2 or N3*** **(n = 51)**	***P* value†**	**Univariate OR (95% CI)**
Age, years	63.1 ± 9.8	63.3 ± 9.6	61.3 ± 11.6	0.163‡	0.98 (0.95−1.01)
Sex				0.267	
Female	177 (36.5)	162 (37.3)	15 (29.4)		1.00 (Ref)
Male	308 (63.5)	272 (62.7)	36 (70.6)		1.43 (0.76−2.69)
Smoking				0.801	
Never	188 (38.7)	170 (39.2)	28 (35.3)		1.00 (Ref)
Former	189 (39.0)	169 (38.9)	20 (39.2)		1.12 (0.57−2.19)
Current	108 (22.3)	95 (21.9)	13 (25.5)		1.29 (0.61−2.75)
Size of tumour, cm‖	3.39 ± 1.67	3.31 ± 1.61	4.07 ± 2.02	**0.002**‡, ¶	**1.26 (1.08–1.47)**
≤3cm	246 (50.7)	226 (52.1)	20 (39.2)		1.00 (Ref)
>3cm but ≤5cm	169 (34.9)	149 (34.3)	20 (39.2)		1.52 (0.79−2.92)
>5cm	70 (14.4)	59 (13.6)	11 (21.6)		2.11 (0.96−4.64)
Lobar location				0.414§	
Right upper	148 (30.5)	134 (30.9)	14 (27.5)		1.00 (Ref)
Right middle	35 (7.2)	31 (7.1)	4 (7.8)		1.24 (0.38−4.01)
Right lower	96 (19.8)	86 (19.8)	10 (19.6)		1.11 (0.47−2.62)
Left upper	118 (24.3)	109 (25.1)	9 (17.6)		0.79 (0.33−1.90)
Left lower	88 (18.1)	74 (17.1)	14 (27.5)		1.81 (0.82−4.00)
Time between PET-CT and surgery, day+	23.4 ± 20.5	24.0 ± 20.6	18.5 ± 19.2	0.072‡	0.97 (0.95–1.00)
Histology of tumour				0.087§	
Adenocarcinoma	348 (71.7)	306 (70.5)	42 (82.3)		1.00 (Ref)
Squamous cell carcinoma	116 (23.9)	110 (25.3)	6 (11.8)		**0.40 (0.16−0.96)**
Large cell carcinoma	10 (2.1)	9 (2.1)	1 (2.0)		0.81 (0.10−6.55)
Other NSCLC	11 (2.3)	9 (2.1)	2 (3.9)		1.62 (0.34−7.75)
Number of dissected nodes and stations during MLND#					
Lymph nodes	16.4 ± 8.6	16.3 ± 8.6	16.8 ± 7.8	0.768‡	1.01 (0.97–1.04)
Stations	4.5 ± 1.4	4.5 ± 1.3	4.9 ± 1.7	**0.042**‡	**1.28 (1.01–1.62)**

* There were two patients with occult metastasis to N3 nodes as well as N2 nodes.
P values are reported are for †chi-square test except where otherwise noted, ‡two sample Student's t test, or §Fisher exact test, and are not the P values for the odds ratio reported from

univariate analysis.
[|] Size of the tumour is measured in preoperative CT scan. [¶]P value for chi-square test is 0.149.
[+] For 10 patients who were confirmed to have N2 disease in EBUS-TBNA, the interval between PET-CT and EBUS-TBNA were used.
[#]Analysis was done in 475 patients after excluding 10 patients who were confirmed to have N2 disease in EBUS-TBNA and did not undergo MLND.

NSCLC, non-small cell lung cancer; CT, computed tomography; OR, odds ratio; CI, confidence interval; PET-CT, integrated positron emission tomography and computed tomography; MLND, mediastinal lymph node dissection.

Table E4 Risk of occult N2 disease according to each definition of centrally located tumour in **485** patients with radiologic N0 NSCLC of solid attenuation on CT

Definition of central location	n (%)	Crude model		Model 1		Model 2	
		Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Contact with the hilar structure	50 (10.3)	**2.40 (1.12−5.16)**	**0.025**	1.65 (0.71−3.84)	0.243	1.69 (0.72−3.97)	0.231
Concentric lines arising from the hilum							
Inner one-third	94 (19.4)	**2.09 (1.10−3.96)**	**0.024**	1.56 (0.78−3.12)	0.214	1.58 (0.78−3.20)	0.204
Inner two-thirds	279 (57.5)	1.28 (0.70−2.32)	0.426	0.99 (0.53−1.87)	0.980	0.98 (0.51−1.87)	0.951
Concentric lines arising from the midline							
Inner one-third	67 (13.8)	**3.06 (1.57−5.97)**	**0.001**	**2.31 (1.10−4.84)**	**0.027**	**2.30 (1.08−4.88)**	**0.030**
Inner two-thirds	293 (60.4)	1.84 (0.97−3.50)	0.064	1.43 (0.72−2.83)	0.302	1.48 (0.74−2.96)	0.272
Sagittal lines arising from the midline							
Inner one-third	144 (29.7)	1.77 (0.98−3.21)	0.060	1.30 (0.67−2.52)	0.437	1.30 (0.66−2.57)	0.443
Inner two-thirds	416 (85.8)	0.88 (0.39−1.96)	0.753	0.60 (0.26−1.41)	0.245	0.62 (0.26−1.47)	0.279

Model 1: Adjusted for tumour size (continuous). Tumour histology and number of dissected nodes and stations during MLND were not included since this information was not available preoperatively.

Model 2: Further adjusted for age (continuous), sex, smoking history (never or ever), and lobar location (right or left) of tumour.

NSCLC, non-small cell lung cancer; CT, computed tomography; OR, odds ratio; CI, confidence interval; MLND, mediastinal lymph node dissection.