Original Article

Central location and risk of imaging occult mediastinal lymph node involvement in cN0T2-4 non-small cell lung cancer

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Background: Appropriate pre-operative staging is a cornerstone in the treatment of non-small cell lung cancer (NSCLC). Central location and size greater than 3 cm are amongst indications for pre-operative invasive mediastinal staging but the quality of the evidence behind this recommendation is low.

Methods: We retrospectively reviewed all cases of cT2-4N0M0 NSCLCL after CT and TEP-CT which underwent surgical resection with lymph node dissection or had a positive invasive pre-operative mediastinal staging in our institution from 2014 to 2018.

Results: Three hundred and ten patients met inclusion criteria, 79 (25.5%) central and 231 (74.5%) peripheral tumors. Central tumor location was associated with a higher prevalence of pN2-3 disease (17.7% *vs.* 6.1%, P<0.001). In a multivariate analysis, central tumor location remained the only factor statistically associated with imaging occult mediastinal disease (OR 3.23, 95% CI: 1.45–7.18). NPV of PET-CT for occult mediastinal disease was 0.83 (95% CI: 0.72–0.90) in central and 0.94 (95% CI: 0.90–0.97) in peripheral tumor. Central location was also associated with a higher prevalence of occult N1 to N3 disease (43.0% *vs.* 15.2%, P<0.001).

Conclusions: This study suggests that invasive mediastinal staging is required in central cT2-4N0 NSCLC but can be questioned in peripheral one, especially in cT2N2 subgroup if the patient is a candidate for lobar resection.

Keywords: Lung cancer; mediastinal staging; tumor location; occult mediastinal disease

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Introduction

Appropriate pre-operative staging is a cornerstone in the treatment of non-small cell lung cancer (NSCLC). Identifying patients with imaging occult mediastinal nodal involvement prior to surgery is important to prevent futile thoracoscopies. Factors which increase the risk of imaging occult mediastinal disease have been identified and their presence is used to decide on the need for preoperative invasive mediastinal staging by endoscopic needle techniques or mediastinoscopy. However, there are discrepancies between different guidelines on the characteristics which should lead to invasive mediastinal staging. The European Society of Thoracic Surgeons (ESTS) (1) and National Comprehensive Cancer Network (NCCN) (2) recommend invasive mediastinal staging in all tumors larger than 3 cm while the American College of Chest Physicians (ACCP) (3) does not consider tumor size in their recommendations. When examining the evidence cited by the ESTS and NCCN guidelines, only two studies

demonstrating a low negative predictive value of integrated positron emission tomography (PET-CT) to detect occult mediastinal disease in this population are cited (4,5). Another characteristic cited by all three above mentioned guidelines is central tumor location. Although all guidelines cite central tumor location as an indication for invasive mediastinal staging, the definition of a central tumor remained elusive until recently. This was well highlighted by a survey published by Casal *et al.* (6) demonstrating large discrepancies between physicians in what was considered a central tumor. Since this survey, Shin *et al.* (7) explored different definitions of central tumor location in a large cohort of radiologically N0 NSCLC and found only one definition which was significantly associated with the presence of occult mediastinal disease : a lesion located within the inner one-third of the hemithorax delimited by concentric lines arising from the midline. In another study, Casal *et al.* (8) also identified two definitions associated with upstaging to any N in T1N0M0 patients but the association did not remain when focusing on N2/3 disease. Larger tumors have a greater chance of having a central portion due to their size, hence of being considered central, this may explain the relationship between tumor size and imaging occult mediastinal disease. Tumor size could also be a predictor of occult mediastinal disease, independently from tumor location.

Given this background, we conducted a retrospective study to compare the prevalence of occult mediastinal disease in central and peripheral radiological N0 NSCLC larger than 3 cm. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1565).

Methods

Study population

Using the prospectively maintained database of the lung cancer investigation clinic of the Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), we retrospectively identified all patients with radiological N0 NSCLC which were investigated in our institution from 01/01/2014 to 31/12/2018. The study was approved by local Research Ethics Board (CRIUCPQ, 2019-3070), and informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

All patients with resectable cT2-4N0 NSCLC who underwent surgical lymph node (LN) dissection or invasive mediastinal staging demonstrating N2/3 disease were included. All surgical resections were performed by video-assisted thoracic surgery (VATS) or thoracotomy with systematic mediastinal nodal dissection.

Patients who did not undergo confirmatory surgical lymph nodes dissection after a negative invasive staging procedure, with synchronous lung tumors, previous history of lung cancer and final pathology of small cell lung cancer, carcinoid tumor or pulmonary metastasis from another organ were excluded. Patients who did not undergo CT and PET-CT or for whom radiology reports of CT and PET-CT were not available were excluded.

Imaging

A lymph node was considered abnormal on imaging if its short axis was greater or equal to 10mm on computed tomography (CT) scan or its maximum standardized uptake value (SUV) was greater or equal to 2.5 on integrated positron emission tomography (PET-CT).

Tumor location was determined from axial, sagittal and coronal images if a CT was available. If CT images were not available, axial images from PET-CT were used. Location was defined based on the most central portion of the tumor. Central tumor was defined as located in the inner one-third of the hemithorax adopted by drawing concentric lines from the midline, based on a recent study (7).

All images were blindly reviewed by MF and JG. If location reported by MF and JG differed, a senior radiologist reviewed images and made the final decision. All tumor sizes were measured based on their long axis on CT. Tumors were classified according to 8th TNM classification (9). For T3 and T4 NSCLC based on the presence of multiple lesions in the same lung, we measured the largest lesion to determine tumor size.

Objectives

Our primary objective was to compare the prevalence of occult mediastinal disease in central and peripheral radiological N0 NSCLC larger than 3 cm. Our secondary objectives were to assess the impact of tumor size and location on the prevalence of any occult nodal disease (pN1-3) and the negative predictive value of PET-CT for pN1-3 and pN2/N3 disease according to tumor location.

Statistics

Data was compared using the Chi-square or Fisher tests for categorical variables, and the *t*-test or Mann-Whitney test for continuous variables depending on the Gaussian distribution of the variables. OR and 95% confidence intervals (CIs) were calculated from binary logistic regression models for pN1-3 upstaging (versus pN0) and pN2/N3 upstaging (versus pN0/N1). A multivariate logistic regression analysis was used to adjust for potential confounding factors in the association between central tumour and occult N2 disease. All statistical results were 2-sided and a P value <0.05 was considered significant. All analysis were performed with the Prism software (GraphPad Software Inc., California, United States) and SAS software (version 9.4 of the SAS System for Windows).

Results

Patient and tumors characteristics

Three hundred and ten cT2-4N0 NSCLC staged with a CT and PET-CT who met inclusion criteria were found in our local lung cancer investigation clinic database for the January 2014 to December 2018 period. Patient and tumor characteristics are listed in *Table 1*. Mean age was 66.8 years and 54.8% of patients were females. Most tumors were T2 (cIB–IIA; n=203, 65.5%). Within T3/T4 subgroup (cIIB–IIIA), 13 (12.1%) were classified as T3/T4 invasion and 12 (11.2) as T3/T4 ipsilateral nodule. CT scan images were available for axial, coronal and sagittal image review to determine tumor location in 251 patients (81.3%). Seventy-nine (25.5%) tumors were classified as central and 231 (74.5%) were peripheral.

Surgical characteristics

One hundred and eighty-three patients (59.0%) underwent invasive mediastinal staging prior to surgery, mainly by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (72.1%) (*Table 2*). Centrally located tumors were associated with an increased rate of invasive mediastinal staging (78.5% *vs.* 52.4%), and confirmatory mediastinoscopy after a negative EBUS staging (43.7% *vs.* 12.5%). Two occult N2 metastases were found after EBUS staging and these two patients were not operated. All other patients underwent surgical mediastinal nodal dissections (*Table 2*). The mean number of dissected nodal stations was 4.3±1.4, including 2.5±1.1 mediastinal nodal stations. No differences in the number of nodal stations assessed during the surgery were reported between central and peripheral tumors.

Risk factors for imaging occult mediastinal disease (N2-3)

The prevalence of imaging occult mediastinal disease was 9.9% (n=28). Age, lesion SUV, histology and tumor size were not associated with a higher prevalence of pN2-3 disease (*Table 1*). Female sex was associated with a lower prevalence of pN2-3 disease [10/170 (5.9%) *vs.* 18/140 (12.9%), P=0.045] while central tumor location was associated with a higher prevalence of pN2 disease [14/79 (17.7%) *vs.* 14/231 (6.1%), P<0.001]. The risk of nodal upstaging according to the clinical stage and the location of the tumor is detailed in *Figure 1*. Amongst cIB-IIA tumors, 17.1% of central and 5.4% of peripheral tumors were upstaged to stage pIIIA while amongst cIIB-IIIA tumors, 18.2% of central and 7.9% of peripheral tumors were upstaged to stage pIIIB.

In a multivariate analysis, tumor central location remained the only factor statistically associated with imaging occult mediastinal disease (adjusted OR 3.23, 95% CI: 1.45-7.18, P=0.001) (*Table 3*). NPV of PET-CT for occult mediastinal disease was 0.83 (95% CI: 0.72–0.90) in central and 0.94 (95% CI: 0.90–0.97) in peripheral tumor (*Table 4*).

Risk factors for imaging any occult nodal disease (N1-3)

The prevalence of any imaging occult nodal disease was 22.3% (n=69). Prevalence was 43% (n=34) in central tumors and 15.2% (n=35) in peripheral tumors.

In a multivariate analysis, tumor central location was statistically associated with imaging occult nodal disease (adjusted OR 5.0; 95% CI: 2.59–9.62, P<0.001) (*Table 3*). NPV of PET-CT for any occult nodal disease was 0.57 (95% CI: 0.45–0.68) in central and 0.80 (95% CI: 0.73–0.82) in peripheral tumor (*Table 4*).

Discussion

In this retrospective study, the overall prevalence of occult mediastinal disease in cT2-4N0M0 NSCLC was 9%, with a significantly lower prevalence in peripheral *vs.* central tumors (6.1 *vs.* 17.7%). Tumor size was not significantly associated with the prevalence of occult mediastinal disease in this population. This questions the need to have

Table 1 Patient and tumor characteristics

Characteristics	All patients	pN2	pN0/N1	P
Patients, n	310	28	282	
Age (years), mean ± SD	66.8±7.3	67.2±7.4	67±8.4	0.85
Sex, n (%)				0.045
Male	170 (54.8)	10 (35.7)	160 (56.7)	
Female	140 (45.2)	18 (64.3)	122 (43.3)	
Smoking history (pack-years), mean ± SD	36±19	38.4±17.5	36.7±19.7	0.55
Location (lobar), n (%)				0.23
RUL	115 (37.1)	7 (25)	108 (38.3)	
RML	17 (5.4)	0	17 (6.1)	
RLL	60 (19.4)	6 (21.4)	54 (19.1)	
LUL	87 (28.1)	10 (35.7)	77 (27.3)	
LLL	31 (10.0)	5 (17.9)	26 (9.2)	
CT tumor size (mm), mean ± SD	44.5±16.5	47.4±22.6	44.2±15.8	0.47
Tumor SUV, mean ± SD	9.5±5.9	9.9±5.6	9.4±6	0.51
Tumour location				<0.001
Central	79 (25.5)	14 (50.0)	65 (23)	
Peripheral	231 (74.4)	14 (50.0)	217 (77)	
Clinical stage, n (%)				0.21
IB–IIA (T2N0M0)	203 (65.5)	15 (53.6)	188 (66.7)	
IIB–IIIA (T3-4N0M0)	107 (34.5)	13 (46.4)	94 (33.3)	
Invasion	13	2	11	
Satellite/ipsilateral node	12	2	10	
Histology, n (%)				0.97
Adenocarcinoma	216 (69.7)	19 (67.9)	197 (69.9)	
SCC	84 (27.1)	8 (28.6)	76 (26.9)	
Other NSCLC	10 (3.2)	1 (96.5)	9 (3.2)	

SD, standard deviation; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; CT, computed tomography; SUV, standard uptake value; SCC, squamous cell carcinoma.

"tumor larger than 3 cm" amongst indications for invasive mediastinal staging as if larger tumors are peripheral, their prevalence of occult mediastinal disease remains relatively low irrespective of their size.

Guidelines provided by the ESTS and the NCCN include tumor size above 3 cm as an indication for invasive mediastinal staging. This recommendation is based on the results of two studies. The first is a meta-analysis which reported a 89% NPV for PET-CT to detect any nodal upstaging in NSCLC larger than 3 cm while the NPV was 94% in NSCLC smaller than 3 cm (4). Tumor location was not considered in this meta-analysis. One could speculate that larger tumors are more likely to be central due to their size which could have driven the findings. The second is a smaller single center study limited to 153 peripheral tumors which found a NPV for PET-CT to detect mediastinal disease of 85% in peripheral NSCLC larger than 3 cm while the NPV was 92% in peripheral NSCLC smaller than

Table 2 Staging and procedure characteristics

Characteristics	All patients (n=310)	Central (n=79)	Peripheral (n=231)	P
Invasive staging, n (%)	183 (59)	62 (78.5)	121 (52.4)	<0.001
EBUS	132 (72.1)	43 (69.4)	89 (73.6)	0.6
Mediastinoscopy	51 (27.9)	19 (30.6)	32 (26.4)	0.6
Confirmatory mediastinoscopy	31 (23.8)	17 (41.5)	14 (15.7)	0.003
N2 nodes detected after invasive staging, n (%)	2 (1.1)	2 (3.2)	0	
Surgical nodal dissection, n (%)	308 (99.4)	77 (97.5)	231 (100)	0.06
Surgical resection, n (%)	305 (98.4)	76 (96.2)	229 (99.1)	0.1
Type of surgery				<0.001
Lobectomy	276 (90.5)	59 (77.6)	217 (94.8)	
Pneumonectomy	17 (5.6)	15 (19.7)	2 (0.8)	
Segmentectomy or wedge resection	12 (3.9)	2 (2.7)	10 (4.4)	
Mediastinal nodal stations dissected, mean ± SD	2.5±1.1	2.5±1.1	2.5±1	0.9
Nodal stations dissected, mean ± SD	4.3±1.4	4.2±1.6	4.4±1.3	0.3
N2 nodes detected after nodal dissection, n (%)	26 (8.4)	12 (15.2)	14 (6.1)	0.016

EBUS, endobronchial ultrasound; SD, standard deviation.

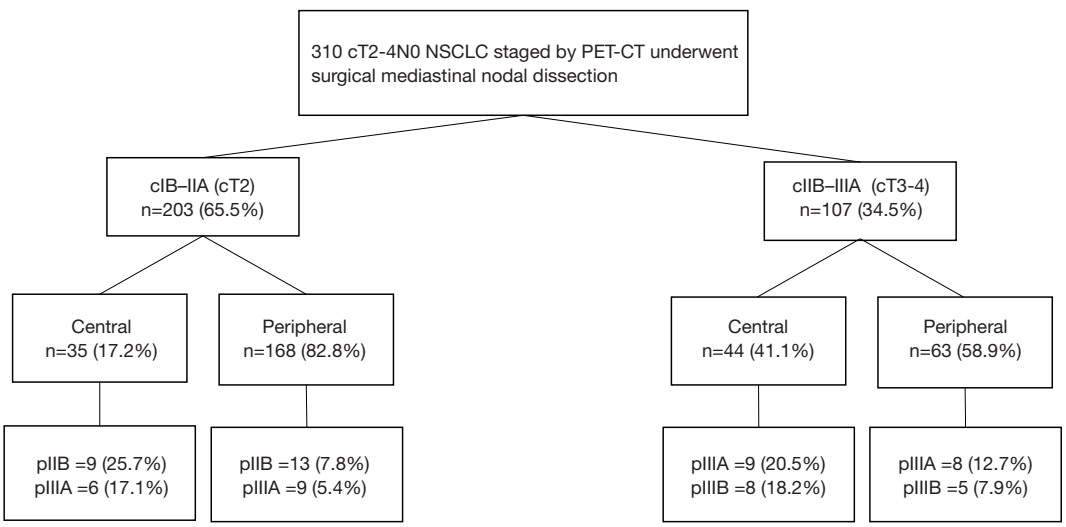

Figure 1 Risk of nodal upstaging according to the clinical T stage and the location of the tumour. NSCLC, non-small cell lung cancer.

3 cm (5). Tumor centrality was defined by the absence of contact with the intrapulmonary main bronchi, pulmonary artery, pulmonary veins, or the origin of the first segmental branches. This definition never proved to be associated with occult mediastinal disease in subsequent studies and may have misclassified certain tumors as peripheral thus decreasing the NPV of PET in peripheral tumors.

Since the publication of these guidelines, studies attempting to define tumor centrality have been published to reconciliate previous studies which yielded variable conclusions as to the relationship between central tumor location and occult mediastinal disease. Casal *et al.* focused on cT1N0M0 patients and failed to identify a definition of central tumor associated with an increased prevalence of

Table 3 Multivariate analysis of nodal upstaging risk factors

Tumour location	Patients, n	pN+ upstaging			pN2 upstaging		
		N (%)	Adjusted OR (95% CI)	P	N (%)	Adjusted OR (95% CI)	P
Central	79	34 (43.0)	4.99 (2.59–9.62)	<0.001	14 (17.7)	3.23 (1.45–7.18)	0.001
Peripheral	231	35 (15.2)	–		14 (6.1)	–	
Total	310	69 (22.3)	–		28 (9.0)	–	

Our model was adjusted for age, tumor size, sex, and SUV.

Table 4 Negative predictive value of PET-CT for occult nodal disease

Tumour location	Patients, n	pN+		pN2	
		NPV	95% CI	NPV	95% CI
Central	79	0.57	0.45–0.68	0.83	0.72–0.90
Peripheral	231	0.85	0.80–0.89	0.94	0.90–0.97
Total	310	0.78	0.73–0.82	0.91	0.87–0.94

NPV, negative predictive value; CI, confidence interval.

occult N2/N3 disease despite a robust 607 patients study exploring 8 different definitions (8). Decaluwé *et al.* did not limit themselves to T1 lesions but again were not able to find a definition of central tumor associated with an increased prevalence of occult N2/N3 disease (10). Both studies did find an association between tumor centrality and upstaging to any N. In a third study, Shin *et al.* included tumors irrespective of size and found only one definition which predicted occult N2 disease: a lesion located within the inner one-third of the hemithorax delimited by concentric lines arising from the midline. They hypothesize that this definition, which they were the only group to study, may have been associated with occult mediastinal disease due to skip metastasis to the mediastinum from apical tumors which are not considered central according to the more commonly used definitions which are based on concentric circles arising from the hilums or contact with central structures. As this study focused on defining tumor centrality, the impact of other factors, such as tumor size, on the prevalence of occult disease mediastinal was not explored after adjustment for tumor location. Univariate analysis did demonstrate a significant relationship between tumor size and occult mediastinal disease. The fact that we did not find this relationship in our cohort may be explained by the exclusion of smaller tumors. Yang *et al.* (11) previously demonstrated that the relationship between tumor size and occult mediastinal disease dissipates for further increase in tumor size above 3 cm. Likewise, tumor location was determined by physicians. However, all images were blindly and independently reviewed by two pulmonologists, and in case of divergence by a senior radiologist. Moreover, most of tumor location were defined from a CT scan using axial, coronal and sagittal views and not only from axial images, in order to obtain the most relevant classification.

The prevalence of occult mediastinal disease in peripheral cT2N0 remains low in our study (5.4%) but others, such as Gao *et al.* (12), obtained higher prevalences in their population. However, Gao *et al.* (12) did not focus on this subgroup and included only 48 solid cT2N0 but obtained a prevalence of 18% in peripheral cT2N0 cancer. The specific prevalence of occult mediastinal disease for the peripheral cT2N0 subgroup is not available for most studies, but Gómez-Caro *et al.* (5) and Decaluwé *et al.* reported respectively only 9.2% and 11.7% for the cT2N0 subgroup including peripheral tumors.

We elected to limit our study to cN0 patients as cN1 patients already have a well demonstrated indication for invasive mediastinal staging with a 25% prevalence of occult mediastinal disease regardless the location of the tumor (13,14). We also excluded cT1N0M0 tumors as our team and Casal *et al.* (8) have previously demonstrated that despite being central, cT1N0M0 tumors remain at low prevalence of occult mediastinal disease.

Preoperative knowledge of N1 disease may modify management if radiation therapy or a sublobar resection

are the planned treatment and this should be considered when staging a patient if these treatments are planned. CT and PET CT were associated with an 80% negative predictive value for detecting N1-3 disease in peripheral cT2-4N0 NSCLC hence further staging is necessary in this population prior to radiation therapy or sublobar resection. If the patient is a lobar resection candidate, occult N1 disease discovered at surgery will modify postoperative but not intraoperative or preoperative management. Because of the heterogeneity of patients with locally advanced stage III NSCLC, making an optimal decision for management of these patients is complex. Surgery has long been considered as the optimal treatment for resectable disease. It should be emphasized that multi-modality therapy combining chemotherapy and radiation therapies in addition to surgery (either as neo-ajuvant or adjuvant) improve outcomes compared to surgery alone (15). For unresectable stage III disease, concurrent chemoradiation is the preferred treatment and consolidation with durvalumab reported good outcomes in term of progression free survival (16).

Conclusions

This retrospective study suggests that invasive mediastinal staging is required in central cT2-4N0 NSCLC but can be questioned in peripheral one, especially in cT2N) subgroup if the patient is a candidate for lobar resection. Further larger prospective studies to validate this finding are necessary.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by local Research Ethics Board (CRIUCPQ, 2019-3070), and informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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