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Is central lung tumour location really predictive for occult mediastinal nodal disease in (suspected) non-small-cell lung cancer staged cN0 on ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography?

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Abstract

OBJECTIVES: Current guidelines recommend preoperative invasive mediastinal staging in centrally located tumours with negative mediastinum on positron emission tomography–computed tomography, based on a 20–30% prevalence of occult mediastinal disease (pN2–3). However, a uniform definition of central tumour location is lacking. Our objective was to determine the best definition in predicting occult pN2–3.

METHODS: A single-institution database was queried for patients with (suspected) non-small-cell lung cancer staged cN0 after positron emission tomography–computed tomography and referred to invasive staging and/or primary surgery. We evaluated 5 definitions: inner 1/3, inner 2/3, contact with bronchovascular structures, ≤2 cm from bronchus or endobronchial visualization.

RESULTS: Between 2005 and 2015, 813 patients were eligible (cT1: 42%, cT2: 28%, cT3: 17% and cT4: 11%). Invasive mediastinal staging and resection were performed in 30% and 97% of patients, respectively. Any nodal upstaging (pN+) was found in 21% of patients, of whom pN2–3 was found in 8%. Central tumour location demonstrated 4 times higher odds for any pN+ [for inner 1/3 vs outer 2/3, odds ratio 3.90 (95% confidence interval 2.24–6.77), $P < 0.001$], whereas no significantly different odds was observed for pN2–3. The discriminative ability for pN+ was not significantly different between the several definitions.

CONCLUSIONS: The prevalence of occult pN2–3 was only 8% when modern fusion positron emission tomography–computed tomography imaging pointed at clinical N0 non-small-cell lung cancer. None of the 5 verified definitions of centrality was predictive for occult pN2–3. However, each definition of centrality was related to any pN+ at a prevalence of 21%, without significant differences in discriminative ability between definitions. These data question whether indication for preoperative invasive mediastinal staging should be based on centrality alone.

Keywords: Non-small-cell lung cancer • Central tumour • Nodal upstaging • cN0 • pN1 • pN2

INTRODUCTION

Mediastinal lymph node involvement in patients with non-small-cell lung cancer (NSCLC) is an important predictive parameter of survival, and it allocates towards appropriate therapy [1]. Several studies found an association between central location of a lung tumour and unforeseen positive mediastinal nodes (pN2–3) after negative mediastinal imaging by computed tomography (CT)

and/or positron emission tomography (PET) with a prevalence of 16–36% [2–6]. Therefore, current guidelines recommend invasive mediastinal staging by endosonography or videomediastinoscopy in patients with a centrally located tumour and negative mediastinum on PET and CT [1, 7–9].

Different definitions of central location of a lung tumour are being used in the literature. The National Comprehensive Cancer Network (NCCN) and European Society of Thoracic Surgeons (ESTS) guidelines define a lesion within the inner two-thirds of the lung as central [7, 8]. The guidelines of the American College of Chest Physicians (ACCP) consider lesions in the inner one-third as central [9]. Other definitions of central location are also used, such as endobronchial visualization by the standard bronchoscope [10, 11], contact with lobar or first segmental branches of vessels or bronchus [12] or distance of less than 2 cm from the bronchial tree [13]. An online survey showed huge variation in the definition of central lung tumour location among both pulmonologists and surgeons [14].

The objective of this study was to identify which definition of central location of the tumour would have the highest predictive value of unforeseen positive mediastinal lymph nodes in PET-CT-staged clinical N0 NSCLC.

PATIENTS AND METHODS

This is a retrospective study from a prospective single-centre database, managed by the respiratory oncology multidisciplinary team of the University Hospitals Leuven, Belgium (The Leuven Lung Cancer Group). The institutional review board's approval was obtained (S59161). Data were collected and anonymized in accordance with the International Conference on Harmonization Guidelines of Good Clinical Practice. Patients with (suspected) NSCLC, clinically node negative (cN0) on imaging with an integrated ^{18}F-fluorodeoxyglucose-PET and CT scan, resectable and referred for invasive mediastinal staging or anatomical resection were included. Our registry contains 5009 unique patient entries between 2005 and 2015. We excluded patients who did not undergo invasive mediastinal and/or surgical resection ($n = 2444$), patients with suspected positive lymph nodes on PET-CT ($n = 1385$) and patients with pretreatment diagnosis of neuroendocrine histology (carcinoid, large-cell neuroendocrine carcinoma or small-cell lung cancer) ($n = 174$), radio-occult lesions ($n = 10$), former therapy of lung cancer ($n = 114$) or without imaging for review ($n = 69$). Lymph nodes were considered radiologically suspicious if these had a short axis of more than 1 cm in CT or if these were ^{18}F-fluorodeoxyglucose-PET positive by visual qualitative assessment (uptake higher than mediastinal blood pool). The International Association for the Study of Lung Cancer (IASLC) lymph node map was used to define the lymph node stations [15]. Clinical and pathological stages were converted to the 8th edition of the Union for International Cancer Control TNM classification [16]. Radiographic size, solid versus subsolid lesion, pretreatment histology, cT, cM, side and location in upper/middle versus lower lobe were investigated together with 5 different definitions of central location of the tumour:

1. Inner 1/3 (central) vs outer 2/3 (peripheral): patients were allocated to the 'inner 1/3' group if the centre of the tumour was located in the inner 1/3 of the lung parenchyma, i.e. adjacent to the mediastinum, 1/3 radially measured from the secondary carina on transverse CT imaging [9].
2. Inner 2/3 (central) vs outer 1/3 (peripheral): equally measured according to the first definition but at 2/3 [7, 8].
3. Contact with lobar or first segmental branches of pulmonary vessels or bronchus (central) vs no contact (peripheral): patients were allocated accordingly after review of transverse CT imaging [12].
4. Tumour ≤2 cm of the bronchial tree (central) or >2 cm from the bronchial tree (peripheral): patients were allocated to the central group if the tumour reached a zone of ≤2 cm around the distal 2 cm of trachea, carina, named major lobar bronchi, up to their first bifurcation [13].
5. Visualized on the standard bronchoscopy (central) vs not visualized (peripheral): patients were allocated to the central group if the tumour was visualized by the standard bronchoscopy (typically 5–6 mm bronchoscope, i.e. not by paediatric scope or endosonography) [10, 11].

All CT scans were primarily reviewed by 1 author (H.D.C.). CT images of patients with lesions that were located in an ambiguous position (borderline central versus peripheral) were discussed in group (H.D.C., C.D. and P.D.L.). The ESTS guidelines on perioperative systematic nodal dissection were routinely followed by all involved surgeons [17].

Aims

The primary aim was to evaluate the association between each of the 5 different definitions of central tumour location and the prevalence of positive mediastinal nodal disease (pN2–3). The secondary aim was the evaluation of the association between central tumour location and any unforeseen positive nodes, i.e. pN1 and pN2–3 combined (pN+).

Statistics

Odds ratios and 95% confidence intervals (CIs) were reported from binary logistic regression models for pN2–3 upstaging (versus pN0–1) and pN+ upstaging (versus pN0, i.e. no upstaging). For each of the 5 definitions of central tumour location separately, a multivariable logistic regression model was fitted for pN+ upstaging with the following selected parameters: central tumour location, cT, pretreatment histology, lobar location (upper/lower), solid versus subsolid, cM and radiographic size. Given the low prevalence, no multivariable analyses were performed for pN2–3 upstaging. The discriminative ability has been quantified using the area under the curve (0.5 = random prediction and 1 = perfect discrimination) and compared between models using a test proposed by DeLong *et al.* [18]. The area under the curves of multivariable models were obtained after leave-one-out cross-validation. *P*-values <0.05 were considered significant. All analyses were performed using the SAS software, version 9.4 of the SAS System for Windows.

RESULTS

Patient characteristics

We identified 813 patients with (suspected) NSCLC, cN0 after PET-CT and referred for mediastinal staging and/or surgical resection after multidisciplinary team meeting between January

2005 and December 2015. Pretreatment demographics are listed in Table 1. In half of the patients, pathological tumour confirmation was absent prior to invasive staging or resection, and 4% were benign at final pathology. Subsolid lesions (semisolid or pure ground glass) were observed in 7%.

Central location

The different definitions of central tumour location resulted in different percentages of lesions being central. The most conservative definition was 'visualized by bronchoscopy' with 23% of lesions designated as being central. Location in the inner 1/3 of the lung, tumour contact with bronchovascular structures or distance ≤2 cm of the proximal bronchial tree resulted in 32–36% of lesions being central. The least selective was location in the inner 2/3 of the lung with half of the patients being central (Table 1).

Management of patients

Thirty-one percent of patients underwent invasive mediastinal nodal staging, with 93% of them diagnosed by videomediastinoscopy (Table 2). Primary resection was performed in 751 patients and in 189 patients after invasive staging. Three patients underwent explorative surgery only. Thirty-nine patients underwent induction treatment followed by surgery (Table 2). Twenty patients did not undergo resection after invasive mediastinal staging. Eleven of them had positive mediastinal nodes at invasive staging. Resections were performed using video-assisted thoracic surgery (VATS) in 42% of patients ($n = 335/790$). Central lesions (inner 1/3) were operated using VATS in 10% of the patients ($n = 24/243$). Overall, the median number of examined lymph node stations was 5 [interquartile range (IQR) of 3–6], and median number of mediastinal lymph node stations was 3 (IQR 2–4) (Table 2). We found no difference in the number of lymph node stations assessed between VATS and open surgery [5 (IQR 3–5) vs 5 (IQR 3–6), $P = 0.33$]. More stations were evaluated in case of central tumour location versus peripheral [for the inner 1/3 definition: 5 (IQR 4–6) vs 4 IQR (3–5), $P < 0.001$]. There were 324 observed deaths. The mean follow-up was 84 months. The 5-year survival was 61% (95% CI 58–64) with 258 patients at risk at 5 years.

Prevalence of nodal upstaging

Any nodal upstaging (cN0 to pN+) was found in 171 (21%) patients. This was pN1 in 106 (13%) patients and pN2–3 in 65 (8%) patients (Table 3). The negative predictive value [true negatives ($n = 748$)/all negatives ($n = 813$)] of PET-CT in the detection of positive mediastinal nodes was, therefore, 92%. Positive mediastinal nodes were detected by invasive mediastinal staging in 17 (26%) patients, by lymphadenectomy at resection after false-negative invasive staging in 9 (14%) patients and by surgery without preresection invasive mediastinal staging in 39 (60%) patients. The negative predictive value of mediastinal invasive staging was 97% [true negatives ($n = 223$)/all negatives ($n = 231$)] at a prevalence of 11% [$n = (9 + 17)/248$].

Table 1: Clinical patient characteristics of 813 patients with cN0-suspected NSCLC after FDG-PET and CT, before invasive mediastinal staging or resection

Number of patients	813
Age (years), mean ± SD	65.5 ± 8.9
Male gender, *n* (%)	567 (70)
WHO ($n = 790$), *n* (%)	
0	615 (78)
1	146 (19)
2	27 (3)
3	1
4	1
FEV_1 (%, $n = 752$), median (IQR)	83 (69–99)
VC (%, $n = 744$), median (IQR)	97 (84–112)
DLCO (%, $n = 721$), median (IQR)	73 (62–85)
BMI (kg/m^2, $n = 790$), median (IQR)	26 (23–28)
Previous malignancies ($n = 790$), *n* (%)	
Yes	187 (24)
Side, *n* (%)	
Right	456 (56)
Pretreatment histology, *n* (%)	
Unknown	416 (51)
Squamous	196 (24)
Non-squamous	201 (25)
CT: location (lobar), *n* (%)	
Upper	577 (71)
Location (central), *n* (%)	
Inner 1/3	257 (32)
Inner 2/3	412 (51)
Contact	291 (36)
≤2 cm from bronchus	281 (35)
Visualized by bronchoscopy	190 (23)
CT: characteristics, *n* (%)	
Solid	758 (93)
CT: size (cm)	
Mean (SD)	3.4 ± 2.2
Median (IQR)	2.7 (1.8–4.5)
cT, *n* (%)	
in situ	5 (1)
1a	46 (6)
1b	152 (19)
1c	144 (18)
2a	175 (22)
2b	56 (7)
3	142 (17)
4	93 (11)
cM, *n* (%)	
0	760 (93)
1a–1b	53 (7)
cStage, *n* (%)	
0	5 (1)
IA1	44 (5)
IA2	135 (17)
IA3	137 (17)
IB	169 (21)
IIA	51 (6)
IIB	129 (16)
IIIA	90 (11)
IVA	53 (7)

BMI: body mass index; CT: computed tomography; DLCO: diffusion capacity of the lung for carbon monoxide; FDG-PET: ^{18}F-fluorodeoxyglucose–positron emission tomography; FEV_1: forced expiratory volume 1; IQR: interquartile range; NSCLC: non-small-cell lung cancer; SD: standard deviation; VC: vital capacity; WHO: World Health Organization.

Table 2: Management of patients and final pStage

Management of patients, *n* (%)	
Primary resection (without invasive staging)	562 (69)
Explorative surgery	3
Invasive mediastinal staging	248 (31)
With resection	189
With neoadjuvant treatment and resection	39
Followed by CTh/ChRT (no surgery)	20
Type of invasive staging (*n* = 248), *n* (%)	
Cervical VAM	214 (86)
Endosonography	19 (8)
Endosonography and cervical VAM	15 (6)
Completeness of resection (*n* = 790), *n* (%)	
Complete (R0)	738 (93)
Highest node positive (R1)	28 (3.5)
Surgical margin positive (R1)	8 (1)
Extracapsular lymph node involvement (R1)	18 (2.3)
Macroscopic tumour left (R2)	3 (0.4)
Type of resection (*n* = 790), *n* (%)	
Lobectomy	620 (78)
RUL	229
RML	39
RLL	80
LUL	187
LLL	95
Bilobectomy	42 (5)
RUM	23
RLM	19
Pneumonectomy	73 (9)
Right	22
Left	51
Segmentectomy	36 (5)
Wedge	19 (2)
pStage (*n* = 790), *n* (%)	
IA1	68 (9)
IA2	147 (19)
IA3	126 (16)
IB	64 (8)
IIA	40 (5)
IIB	189 (24)
IIIA	86 (11)
IIIB	12 (1.5)
IV	27 (3.4)
NA (no tumour)	31 (3.9)

CTh: chemotherapy; ChRT: chemoradiotherapy; LLL: left lower lobe; LUL: left upper lobe; RLL: right lower lobe; RLM: right lower and middle lobe; RML: right middle lobe; RUL: right upper lobe; RUM right upper and middle lobe; VAM: videomediastinoscopy.

Table 3: Post-treatment characteristics

Number of patients	813
Nodal stage of all patients (*n* = 813; the highest stage after invasive staging or resection), *n* (%)	
pN0	642 (79)
pN1	106 (13)
pN2	57 (7)
pN3	8 (1)
pNx	9 (1)
NA (no tumour)	31 (4)
pN+	171 (21)
pN2/3	65 (8)
Number of lymph node stations examined (*n* = 790), median (IQR)	5 (3–6)
Number of mediastinal lymph node stations examined (*n* = 790), median (IQR)	3 (2–4)
Post-treatment histology, *n* (%)	
Squamous	317 (39)
Adenocarcinoma	393 (48)
Large cell	16 (2)
Adenosquamous	25 (3)
Sarcomatoid carcinoma	3
Neuroendocrine	28 (3.5)
Carcinoid	14
SCLC	5
LCNEC	9
Benign	29 (4)
Other	2
Sarcoma	1
Lymphoma	1

IQR: interquartile range; LCNEC: large-cell neuroendocrine carcinoma; NA: not applicable; SCLC: small-cell lung cancer.

Mediastinal nodal upstaging (pN2–3)

Univariable analysis did not demonstrate a relationship between central tumour location and unforeseen positive mediastinal nodes (pN2–3) for any of the 5 definitions of central tumour location (Table 4). The prevalence of pN2–3 was 8% overall for the complete cohort and never higher than 10% in patients with central tumour location whatever definition used (Table 4). The univariable analysis demonstrated that pretreatment non-squamous histology was predictive of mediastinal nodal disease (Table 5). Also, in none of the multivariable analyses, a significant relationship between central tumour location by any of the 5 definitions and pN2–3 upstaging was obtained. Non-squamous pretreatment histology was the only independent predictor in all 5 multivariable models.

Any nodal upstaging (pN+)

Central tumour location was related to overall nodal upstaging (from cN0 to pN+) in a univariable analysis with odds ratios between 3.36 (95% CI 2.32–4.88) and 4.21 (95% CI 2.96–5.99) depending on the definition of central tumour location (Table 4). Irrespective of the definition of centrality, pretreatment histology, centrality and tumour location in the upper lobe were significant in the multivariable model (with the exception of histology in the model with visualization by bronchoscopy as definition of central location). Table 6 summarizes the result for the model with the inner 1/3 as definition for centrality. The odds ratios for the effect of centrality equalled 3.90 (2.24–6.77), 2.99 (1.66–5.36), 4.46 (2.47–8.06), 4.21 (2.36–7.51) and 3.27 (1.79–5.97) in multivariable models with centrality definitions 1–5, respectively. The area under the curve of multivariable models ranged between 0.736 and 0.754. AUCs did not differ significantly between the 5 definitions, neither in the univariable model nor in the multivariable model ($P > 0.10$ for all pairwise comparisons).

DISCUSSION

Our main finding is that in a cohort of (suspected) NSCLC without nodal involvement after PET-CT (cN0), the prevalence of unforeseen positive mediastinal nodes was only 8%, varying between 6 and 10% according to the 5 verified definitions of central tumour location. The negative predictive value of imaging

Table 4: Univariable logistic regression

Definitions	Tumour location: central/peripheral	*n*	pN+ upstaging				pN2–3 upstaging			
			n (%)	OR (95% CI)	*P*-value	AUC (95% CI)	*n* (%)	OR (95% CI)	*P*-value	AUC (95% CI)
1	Inner 1/3 (central)	257	99 (39)	4.21 (2.96–5.99)	<0.001	0.66 (0.62–0.71)	26 (10)	1.49 (0.89–2.51)	0.13	0.55 (0.48–0.61)
	Outer 2/3	556	72 (13)				39 (7)			
2	Inner 2/3 (central)	412	125 (30)	3.36 (2.32–4.88)	<0.001	0.64 (0.60–0.68)	39 (9)	1.51 (0.90–2.53)	0.12	0.55 (0.49–0.61)
	Outer 1/3	401	46 (11)				26 (6)			
3	Contact (central)	291	105 (36)	3.90 (2.74–5.55)	<0.001	0.66 (0.62–0.70)	26 (9)	1.22 (0.72–2.04)	0.46	0.52 (0.46–0.59)
	No contact	522	66 (13)				39 (7)			
4	≤2 cm around bronchus (central)	281	103 (37)	3.95 (2.78–5.61)	<0.001	0.66 (0.62–0.70)	26 (9)	1.29 (0.77–2.17)	0.34	0.53 (0.47–0.59)
	>2 cm around bronchus	532	68 (13)				39 (7)			
5	Visualized by bronchoscopy (central)	190	79 (42)	4.11 (2.86–5.91)	<0.001	0.65 (0.60–0.69)	18 (9)	1.28 (0.73–2.27)	0.39	0.52 (0.47–0.58)
	Not visualized by bronchoscopy	623	92 (15)				47 (8)			
	Total	813	171 (21)				65 (8)			

OR with 95% CI and area under the curve of different definitions of central tumour location in relation to nodal upstaging.
AUC: area under the curve; CI: confidence interval; OR: odds ratio; pN+ upstaging: nodal upstaging from cN0 to pN1, pN2 or pN3.

with PET-CT was, therefore, 92%. A review of the historical series with CT imaging without PET demonstrated a median negative predictive value of 82% (range 55–91%) [9]. With integrated PET-CT, the mean negative predictive value increased to 90% (range 83–100%), which is in line with this study [9].

This is the first study comparing 5 definitions of central tumour location and their relationship with unforeseen mediastinal disease in patients with cN0 (suspected) NSCLC and referred to invasive mediastinal and/or surgery. We were unable to identify a definition of central tumour location with a stronger predictive value for unforeseen mediastinal disease over another. In fact, none of the 5 definitions of central tumour location were related to pN2–3 in the univariable or the multivariable analysis. We could argue that the best definition is the one that is the most reproducible and easy to obtain. Further studies would be necessary to answer this question, although the clinical impact might be small if the prevalence of unforeseen mediastinal nodes is confirmed to be under 10% in studies with modern integrated PET-CT.

Current guidelines recommend invasive mediastinal staging in case of central tumour location [1, 7–9]. Previous studies demonstrating a relationship between central tumour location and unforeseen mediastinal nodes after imaging were different from this study as they combined cN0 and cN1 patients [3] and were based on CT imaging only [4, 5] or on non-integrated CT and PET [2]. Apart from our study, 3 other studies with cN0 NSCLC patients after PET-CT failed to demonstrate a significant difference in mediastinal upstaging between central or peripheral lesions [19–21]. We thus question the prediction of unforeseen mediastinal disease in case of cN0 NSCLC solely based on central location of the tumour. To our knowledge, the only study demonstrating that central location was a predictor of pN2 disease in patients with cN0 NSCLC after integrated PET-CT was recently published by Gao *et al.* [6]. Of note, they reported a high prevalence of subsolid lesions (56% vs 7% in this study), 19% ($n = 53/284$) of patients were not referred for resection (after invasive staging) and the number of assessed lymph node stations was not recorded. It is unclear whether relative more resections with lymphadenectomy were performed in case of central lesions, and non-surgical treatment was more frequent in peripheral lesions. With this conflicting literature, we argue that guidelines should not catalogue patients with central tumours together with cN1 disease on imaging. This was the case in the ACCP guidelines due to the difficulty to assess the N1 nodes in case of central tumour location [9]. Unlike studies concerning central tumours, studies with focus on cN1 lesions have consistently demonstrated 20–30% prevalence of occult N2 disease [22].

To make a prediction on the chance of unforeseen mediastinal disease, and therefore, the usefulness of invasive mediastinal staging, a model more complex than currently used by guidelines seems to be necessary. Farjah *et al.* [23] developed a prediction model for pathological N2 disease in patients with a negative mediastinum by PET. In this model with 6 risk factors for N2 disease including central tumour location, only cN1 disease by PET was associated with pN2 disease after the multivariable analysis. These patients were not included in our study as it is clear that cN1 disease warrants invasive mediastinal staging. The rate of unforeseen pN2 is also variable according to histological grade [23]. In our practice, this factor would be only partially helpful as only half of the cN0 patients referred to surgery had known histology. Multidisciplinary discussion of patient profile and imaging resulted in the resection of benign lesions in only 8% of patients without pretreatment histology or 4% overall.

Looking at any nodal upstaging, i.e. pN1 and pN2-N3 together (pN+), all 5 definitions of central tumour location were similarly predictive. Visualization by bronchoscopy was most selective with the highest chance of unforeseen lymph node disease (42% in the central group). Area under the curve was similar for 5 definitions. The significant relationship between central tumour location and any nodal upstaging (cN0 to pN1 or pN2) is driven by cN0 to pN1 upstaging. We previously demonstrated in a multicentre retrospective study that more than a quarter of patients with a central cStage I NSCLC had unforeseen positive N1 nodes at resection [24]. As surgeons often choose an open approach for central lesions (i.e. with higher intrinsic chance of N1 upstaging), failure to include central tumour location in several retrospective studies comparing N1 upstaging between VATS and open surgery leads to a selection bias with seemingly lower N1 upstaging in the VATS group [24].

Table 5: A univariable analysis of risk factors for pN2/3 upstaging

	Total	pN2–3, *n* (%)	OR (95% CI)	*P*-value
Number of patients	813	65 (8)		
Side				
Right	456	34 (8)	0.85 (0.51–1.41)	0.52
Left	357	31 (9)	#	
Lobar location				
Upper	577	45 (8)	0.91 (0.53–1.58)	0.75
Lower	236	20 (8)	#	
Pretreatment histology				<0.001
Unknown	416	21 (5)	#	.
Squamous	196	14 (7)	1.45 (0.72–2.91)	0.30
Non-squamous	201	30 (15)	3.30 (1.84–5.93)	<0.001
CT characteristics				
Solid	758	63 (8)	2.40 (0.57–10.09)	0.23
Subsolid	55	2 (4)	#	
Radiographic size (cm)				
Linear			1.04 (0.93–1.16)	0.46
Curvilinear, quadratic				<0.001
cT				0.098
Tis-T1mi-1a	51	1 (2)	#	.
1b	152	8 (5)	2.78 (0.34–22.76)	0.34
1c	144	9 (6)	3.33 (0.41–26.98)	0.26
2a	175	20 (11)	6.45 (0.84–49.29)	0.072
2b	56	7 (13)	7.14 (0.85–60.22)	0.071
3	142	14 (10)	5.47 (0.70–42.68)	0.11
4	93	6 (6)	3.45 (0.40–29.46)	0.26
cM				
cM = 0	760	59 (8)	0.66 (0.27–1.61)	0.36
cStage				0.36
0 or IA1	49	1 (2)	#	.
IA2	135	7 (5)	2.63 (0.32–21.90)	0.37
IA3	137	6 (4)	2.20 (0.26–18.73)	0.47
IB	169	20 (12)	6.44 (0.84–49.28)	0.073
IIA	51	7 (14)	7.64 (0.90–64.57)	0.062
IIB	129	13 (10)	5.38 (0.69–42.27)	0.11
IIIA	90	5 (6)	2.82 (0.32–24.88)	0.35
IVA	53	6 (11)	6.13 (0.71–52.86)	0.099

The results for the different definitions of central location are summarized in Table 4.

CI: confidence interval; CT: computed tomography; OR: odds ratio.

Limitations

The following are limitations of this study. Except from the characteristic problems with retrospective analyses, we should be especially careful while drawing conclusions from the prevalence of mediastinal disease in subgroups, as these are based on low numbers. We did not include the primary tumour maximal standardized uptake value (SUV_{max}) as a parameter—even if 1 study suggested a relationship with unforeseen mediastinal nodal disease [25]—for several reasons, in our prospective experience, analysis with an SUV threshold was not superior to the use of visual interpretation scale, an ideal cut-off value has not been determined and the values are not standardized from centre to centre or even between scanners in the same centre [7, 26, 27]. Furthermore, a prospective study found a prevalence of only 5.6% N2 disease in cT1–2cN0 tumours with an SUV_{max} of greater than 10, i.e. presumed high-risk patients for unforeseen mediastinal disease [28]. We did not investigate potential differences in evaluation of centrality of tumours among different investigators.

Table 6: A multivariable model to assess the risk of any nodal upstaging (pN+) with central tumours defined as located in the inner 1/3 of the lung

	OR (95% CI)	*P*-value
Pretreatment histology		0.009
Unknown	#	#
Squamous	2.18 (1.19–4.00)	0.012
Non-squamous	1.00 (0.50–2.00)	0.99
cT (imaging)		0.14
1a	#	#
1b	3.76 (0.42–33.87)	0.24
1c	2.64 (0.29–24.34)	0.39
2a	4.84 (0.55–42.61)	0.15
2b	6.33 (0.63–63.48)	0.12
3	2.43 (0.23–25.12)	0.46
4	2.46 (0.20–29.77)	0.48
Location		
Lower lobe	#	#
Upper lobe	0.55 (0.34–0.89)	0.014
Radiographic size (cm)	1.11 (0.93–1.33)	0.26
CT characteristics		
Subsolid	#	#
Solid	1.92 (0.24–15.60)	0.54
cM		
0	#	#
1a and 1b	0.60 (0.19–1.87)	0.38
Side		
Left	#	#
Right	0.84 (0.53–1.33)	0.46
Inner 1/3		
Peripheral (outer 2/3)	#	#
Central (inner 1/3)	3.90 (2.24–6.77)	<0.001

CI: confidence interval; CT: computed tomography; OR: odds ratio.

'Visualized by bronchoscopy' might be an interesting parameter for large databases and studies as this is readily available in patient files, potentially less investigator dependent and causes less workload than retrospective CT analysis [11].

CONCLUSION

We found no correlation between 5 different definitions of central lung tumour location and unforeseen mediastinal nodal disease in patients with cN0 (suspected) NSCLC after imaging with contemporary PET-CT. The prevalence of N2 disease was 8%, and prevalence of any nodal upstaging (pN+) was 21%. All definitions of central tumour location were predictive for pN+. A more complex model than central location alone seems necessary to accurately predict mediastinal positive nodes when modern PET-CT demonstrates cN0 NSCLC.

Conflict of interest: none declared.

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