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"Centrally-located lung cancer and risk of occult nodal disease: an objective evaluation of multiple definitions of tumor centrality with a dedicated imaging software."

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ABSTRACT

Introduction: Current guidelines recommend invasive mediastinal staging in patients with centrally located radiographic stage T1N0M0 non-small cell lung cancer. The lack of a specific definition of central tumor has resulted in discrepancies among guidelines and heterogeneity in practice patterns.

Methods: Our objective was to study specific definitions of tumor centrality and their association with occult nodal disease. Pre-operative chest CT scans from patients with cT1N0M0 NSCLC were processed with a dedicated software that divides the lungs in thirds following vertical and concentric lines. This software accurately assigns tumors to a specific third based both on the location of the center of the tumor and its most medial aspect, creating 8 possible definitions of central tumors.

Results: 607 patients were included in our study. Surgery was performed for 596 tumors (98%). The overall pN disease was: 504 (83%) N0, 56 (9%) N1, 47 (8%) N2, and no N3. The prevalence of N2 disease remained relatively low regardless of tumor location. Central tumors were associated with upstaging from cN0 to any N (pN1, 2). Two definitions were associated with upstaging to any N: concentric lines, inner 1/3, center of the tumor (OR 3.91, 95% CI 1.85-8.26; p< 0.001); and concentric lines, inner 2/3, most medial aspect of the tumor (OR 1.9, 95% CI 1.23-2.97; p=0.004).

Conclusions: We objectively identified two specific definitions of central tumors. While the rate of occult mediastinal disease was relatively low regardless of tumor location, central tumors were associated with upstaging from cN0 to any N.

INTRODUCTION

Accurate mediastinal staging is crucial in the management of patients with lung cancer. It defines prognosis, dictates treatment, and it allows for meaningful comparisons among different therapeutic strategies in clinical trials. Techniques for mediastinal staging can be divided in two broad categories: non-invasive (radiographic) and invasive. In the context of a radiographically normal mediastinum, current guidelines suggest that invasive mediastinal staging should be performed for patients with radiographic N1 disease, tumors greater than 3 cm, and for patients with "centrally located" T1 N0 M0 lung cancer (1-3). Unfortunately, the definition of "centrally located" tumors for this latter group is not clear. While the American College of Chest Physicians (ACCP) guidelines define central tumors as those located within the inner "one-third" of the lung, the National Comprehensive Cancer Network (NCCN) and the European Society of Thoracic Surgery (ESTS) guidelines define central tumors as those within the inner "two-thirds" of the lung (1-3). Data to support one definition or the other is scant and inconsistent (4-10). In addition, methods to delineate the three thirds of the lung or to classify a tumor that crosses a boundary (i.e. between a third that is considered central and one that is considered peripheral) have not been defined. Most studies evaluating tumor centrality informing the above guidelines were retrospective in nature, with non-specific definitions, and with inherent subjectivity given by the individuals assessing images to classify tumors as central or peripheral (4-10). A recent on-line survey performed by our group demonstrated heterogeneous practice patterns arising from the lack of a uniform, clear, objective, and evidence-based definition of central tumors (11).

The purpose of this study is to objectively evaluate different definitions of tumor centrality for patients with cT1N0M0 tumors and their association with occult nodal disease in order to better inform future lung cancer practice guidelines.

METHODS

The study was conducted at The University of Texas MD Anderson Cancer Center where pertinent Institutional Review Board approval was obtained (PA16-1061). Prospectively collected data-bases of thoracic surgical cases and cytology samples of endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) were queried between the January 1st 2009 and December 31st 2016. Patients with radiographic T1N0M0 non-small cell lung cancer (NSCLC) who underwent surgical resection or who underwent EBUS-TBNA that upstaged them to N2-3 disease preventing upfront surgical resection were included in this study. The 8th edition of TNM was utilized with T1 defined as tumors of up to 3 cm in longest dimension (12). Radiographic N0 was defined as both mediastinal and hilar lymph nodes of up to 1 cm in short axis by CT and SUV of < 2.5 by PET or PET-CT. Only patients with guideline- consistent nodal dissection during surgery were included (2). The prevalence of nodal disease was determined by the pathology results of nodal dissection or by the positive results of EBUS-TBNA (when N2-3 disease was found preventing surgical resection). EBUS-TBNA was performed in N3-N2-N1 fashion with on-site cytology examination, sampling all LN of 5 mm or greater in short-axis.

A dedicated imaging-software system (VIDA Lung Zones, VIDA Diagnostics, Iowa, USA) was designed for this study (see on-line supplemental material for more details). The software automatically divides each lung into thirds (inner, middle, outer) following 2 patterns: "vertical" and "concentric". The "vertical" pattern consists of straight lines that divide the lung in the sagittal plane, while the "concentric" pattern consists of lines that follow the contour of the lung (Figure 1). Next, the operator needs to manually selectboth the most medial (closer to the hilum) aspect of the tumor and the tumor center in order to assign it to a specific third (in cases

of semi-solid tumors the solid component was utilized). This is performed while viewing simultaneously axial, coronal and sagittal CT cuts (see on-line supplemental material). This last feature (selecting center and medial aspect of tumor) was designed to solve the problem of tumors that cross a boundary (a line dividing 2 thirds) raising the question of which third they belong to (most medial one or the third where the center of the tumor is located in). Based on the above, 8 definitions of central tumors were created (Table 1). Pre-operative chest CT scans from all patients were processed with our dedicated software. The operators who processed the scans were "blind" to pathology results. The task of these operators was to identify the nodule in the CT scan and mark both the center of the tumor and its most medial aspect. The software would then automatically assign the tumor to a specific third following the vertical and concentric patterns, and utilizing both the most medial aspect of the tumor and the center of the tumor as described above.

The primary objective was to evaluate the association between each of the different definitions of central tumors (Table 1) and the presence of occult nodal disease. Nodal disease was analyzed as mediastinal disease (N2-3) or "any" nodal disease (N1-2-3). The highest N stage was utilized for each patient. Univariate logistic regression was applied to predict the odds of nodal disease by using each of the 8 definitions of tumor centrality. Odds ratios and 95% Confidence Intervals (CI) were reported from binary regression models for both mediastinal and any nodal disease. Multivariate analysis was run for the definitions that achieved statistical significance (at alpha 0.05 level) in univariate analysis controlling for multiple covariates: tumor histology, tumor differentiation, anatomic tumor location, radiographic T descriptor, nodule type (solid, semisolid, ground-glass), and FDG avidity. As part of a secondary analysis, the same process was repeated after excluding patients with ground glass and carcinoid tumors (due to the

expected low prevalence of occult nodal disease) and after excluding patients who did not have a PET or PET-CT (since PET-CT is currently the standard of care for staging). When more than one definition was found to be associated with the outcome, the strength of association among the different definitions and outcome was compared utilizing the difference in log odds ratios between the definitions calculated with 95% CI from non-parametric bootstrap with the use of Monte Carlo sampling. Analysis was performed with STATA 15 (College Station).

RESULTS

A total of 607 cT1N0M0 patients were included in our study and their pre-operative chest CT scans were analyzed with our dedicated software. Surgery was performed for 596 tumors (98%). EBUS-TBNA for nodal staging was performed in 121 patients (20%) with only 11 tumors being upstaged to N2 disease thereby preventing surgery. Pre-operative PET or PET-CT was available in 481 patients (80%). The overall pathologic N disease was as follows: 504 (83%) N0, 56 (9%) N1, 47 (8%) N2, and no N3. Baseline characteristics of patients and tumors are depicted in Table 2.

All patients

Univariate analysis did not demonstrate a firm relationship between any of the proposed 8 definitions of tumor centrality and the presence of occult pN2-3 disease (Table 3). There was a relationship between definition 2 ("concentric" lines, inner 2/3, medial aspect of the tumor) and occult pN2-3 disease with an OR of 1.88 (95% CI 1-3.51; p=0.049), but this did not reach statistical significance in multivariate analysis. Central tumor location was, however, associated with upstaging to any N (from cN0 to pN1-2-3). The definitions with the strongest relationship were number 2 ("concentric" lines, inner 2/3, medial aspect of the tumor) and 3 ("concentric"

lines, inner 1/3, center of the tumor) (Table 4). Both of them were tested in multivariate analysis against multiple confounders and they remained statistically significant (Table E1a and E1b, on-line supplemental material). The difference in log odds ratio between definitions 3 and 1 was 0.679 (95% CI 0.218, 1.141) indicating that definition 3 is significantly better than definition 1 in terms of its association with the outcome (upstage to pN1-2-3). However, we failed to demonstrate a difference between definitions 2 and 3.

Excluding patients without pre-operative staging PET-CT

Univariate analysis did not demonstrate a firm relationship between any of the proposed 8 definitions of tumor centrality and the presence of occult pN2-3 disease (Table 5). Central tumor location was associated with upstaging to any N (from cN0 to pN1-2-3). The definitions with the strongest relationship were number 2 ("concentric" lines, inner 2/3, medial aspect of the tumor) and 3 ("concentric" lines, inner 1/3, center of the tumor) (Table 6). Both definitions was tested in multivariate analysis and they remained statistically significant (Table E2a and E2b, on-line supplemental material). We failed to demonstrate a difference in log odds ratio between definitions 2 and 3.

Excluding patients with ground-glass opacities and patients with carcinoid tumors

Univariate analysis demonstrated relationship between definition 2 ("concentric" lines, inner 2/3, medial aspect of the tumor) and occult pN2-3 disease with an OR of 1.95 (95% CI 1.03-3.71; p=0.041), but this did not reach statistical significance in multivariate analysis (Table E3a and E3b). Central tumor location was associated with upstaging to any N (from cN0 to pN1-2-3). Definitions 1, 2, and 3 were associated with this outcome in univariate analysis (Table 7), but only definitions 2 and 3 remained statistically significant in multivariate analysis (Table E4a

and E4b, on-line supplemental material). Again, we failed to demonstrate a difference in log odds ratio between definitions 2 and 3.

Excluding patients with ground-glass opacities, carcinoid tumors and those without pre-operative staging PET-CT

Univariate analysis did not demonstrate a firm relationship between any of the proposed 8 definitions of tumor centrality and the presence of occult pN2-3 disease (Table E5, on-line supplemental material). Central tumor location was associated with upstaging to any N (from cN0 to pN1-2-3). The definitions with the strongest relationship were number 2 ("concentric" lines, inner 2/3, medial aspect of the tumor) and 3 ("concentric" lines, inner 1/3, center of the tumor) (Table E6, on-line supplemental material). Both definitions was tested in multivariate analysis and they remained statistically significant (Table E7a and E7b, on-line supplemental material). We failed to demonstrate a difference in log odds ratio between definitions 2 and 3.

DISCUSSION

Our study suggests that in cT1N0M0 non-small cell lung cancer the overall prevalence of occult "mediastinal" disease is relatively low regardless of tumor location. However, central location is associated with substantial risk of having occult nodal disease in any station (pN1-2-3), which is of outmost importance for non-surgical candidates with early lung cancer. This is the first study to objectively evaluate multiple definitions of tumor centrality with a dedicated software system. We identified two definitions associated with an increased probability of any occult nodal disease. Both entailed dividing the lungs into thirds following "concentric lines". One definition utilized the inner one-third of the lung (based on the center of the tumor) while the other utilized the inner two-thirds of the lung (based on the most medial aspect of the tumor).

Accurate mediastinal staging is key in the management of lung cancer. In the context of patients with cT1N0M0 disease, current guidelines suggest that invasive mediastinal staging should be performed only for patients with "centrally located" tumors (1-3). However, definitions of centrally located tumors are non-specific, there is a large discrepancy among different guidelines and, as a result, there is heterogeneity in practice patterns (11). Data supporting tumor centrality as a risk factor for occult mediastinal disease in lung cancer is scant, mostly retrospective, and inconsistent (4-10). A potential explanation for the inconsistency observed among the above studies could be differences in the definitions of tumor centrality as well as inconsistency in their application. Of note, each study evaluated a single definition of central tumors. In addition, most of these studies did not specify methods to delineate the three thirds of the lung and methods to classify a tumor that crosses a boundary (i.e. between a third that is considered central and one that is considered peripheral) introducing a large amount of subjectivity and bias. We have only identified one study which has evaluated different definitions of central tumors. In this recent study, Decaluwé and coworkers retrospectively studied 813 patients with cN0 disease (by CT and PET-CT) of which 42% were cT1, 28% were cT2, 17% cT3, and 11% cT4. 97% of patients underwent surgery (13). They evaluated 5 definitions of tumor centrality: inner one third of the lung (measured by the location of the tumor center, radially measured from the secondary carina on transverse CT image); inner two thirds (measured as the prior definition); in contact with lobar or segmental branches of pulmonary vessels or bronchi; within 2 cm of the central bronchial tree; and visualized during bronchoscopy. They studied the association of each of these definitions with the prevalence of pN2-3, and that of pN1-2-3. Any nodal upstage (pN1-2-3) was found in 21% of the cases, but pN2-3 was found in only 8%. Similarly to our study, they found no association between tumor

centrality and occult pN2-3 disease but they did find association of tumor centrality with any pN

upstage (N1-2-3). However, unlike our study, all their 5 definitions of tumor centrality were

associated with an increased odd of having any pN upstage (N1-2-3), with no particular

definition having a stronger association. It is important to note that this study differs from ours in

many ways but particularly in their population, and, of course, their methods. One of the most

relevant differences in their population is that 58% of their patients had tumors > 3cm. We did

not include these patients because invasive mediastinal staging would be already indicated based

on tumor size (as indicated in all guidelines), making a classification of central vs. peripheral less

relevant. The authors do not report a secondary analysis including only patients with cT1 tumors,

making a comparison with our study results more difficult. It is also not clear how many patients

with tumors of > 3 cm were in a central location for each of the 5 definitions, possibly

introducing a bias. With regards to methods, in addition to testing different definitions, most of

their CT scans were evaluated by a single reader, while we processed the CT scans with a

dedicated software system to accurately determine the location of the tumor and to minimize

subjectivity or human error.

In contrast to our study and that of Decaluwé and coworkers, a study by Gao and

colleagues of risk factors for occult mediastinal disease in patients with early lung cancer staged

with PET-CT reported a greater prevalence of occult pN2 disease in centrally located lesions

(14). This was a retrospective study that included patients with cT1-2 and utilized the center of

the tumor and the inner one third of the lungs (measured as the radial distance from the hilum to

the periphery of the lung) to define central tumors. The study does not report who reviewed the

images, or if there was a single or multiple chest CT readers. It included 165 patients with cT1

tumors with 23 of those being central. The overall prevalence of occult pN2 disease in cT1

tumors was 3.6% and in cT2 tumors 11.8%. The prevalence of occult pN2 disease for cT1 tumors was reported separately for solid tumors (n=71) and semi-solid (n=93). For solid cT1 tumors, it was 21.4% when central (3/24) vs. 1.8% (1/57) when peripheral (p= 0.022). For semi-solid cT1 tumors, it was 11.1% when central (1/9) vs. 1.2% (1/84) when peripheral (p= 0.185). In our study we combined solid and semi-solid tumors since the latter have a solid component that indicates invasiveness, and we only performed a separate analysis excluding purely ground-glass lesions, which are known to be less invasive.

It is important to be aware that there are other definitions of central/peripheral lung tumors that were created with different purposes, unrelated to the prevalence of occult mediastinal disease. The most popular definition is likely the one created by radiation oncologists, who define central tumors as those located within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures (15, 16). This definition was developed to evaluate the safety of stereotactic body radiation therapy in central versus peripheral tumors, and it is commonly used to adjust radiation doses. However, its ability of to predict occult N2 disease was never tested, and, hence, it should not be employed to decide whether or not invasive mediastinal staging is indicated.

One of the limitations of our study is that it was performed in a single institution. Our study population had a large proportion of patients with adenocarcinomas (73%). Although we expected this characteristic of our population to increase the prevalence of occult nodal disease, the effect may have been mitigated by the significant prevalence of semisolid lesions and ground-glass opacities which may, in fact, confer a protective effect (see table 2, e1a, and e1b). Another limitation was the low prevalence of occult mediastinal disease in our population which may have prevented us from demonstrating a significant difference between some of the

proposed definitions of central tumor. Our inability to detect a difference among the definitions of tumor centrality that were associated with occult disease may be, indeed, due to a lack of power. Also, the objective classification of tumors as central or peripheral provided by our dedicated software may not be reproducible when performed by physicians. Reproducibility of these definitions, inter-observer, and intra-observer variability need to be properly studied. Also, our process was not fully automated, since the center or most medial aspect of each tumor was selected by the operator.

To the best of our knowledge, this is the largest study assessing multiple clear and specific definitions of tumor centrality for cT1N0M0 NSCLC and it is the only study to use dedicated software to facilitate this. Our data strongly supports the use of concentric lines and not vertical lines to divide the lung. We believe that our results along with the similar findings of Decaluwé and coworkers showing a low prevalence of N2 disease regardless of tumor location may help inform the current guidelines (13). These findings may challenge the recommendation for invasive mediastinal staging in patients with central cT1 tumors, particularly when surgery is the planned therapy. The radiographic group "C" from the ACCP guidelines that combines patients with cN1 disease with those with central tumors may need to be revised, since these may be two different kinds of patients with dissimilar risk of occult N2 disease (1). Nevertheless, tumor centrality should remain an indication for systematic invasive nodal staging (mediastinal and hilar) for patients with T1N0M0 tumors who will undergo a non-surgical local ablative treatment.

CONCLUSIONS

Our study found the overall prevalence of occult "mediastinal" disease to be relatively low regardless of tumor location in cT1N0M0 NSCLC. However, central location was associated with substantial risk of having occult nodal disease in any station (N1-2-3) which is of outmost importance for non-surgical candidates with early lung cancer. We identified two definitions of central tumor, and both entailed the use of concentric lines - and not vertical lines- to divide the lungs in thirds.

ACKNOWLEDGEMENTS:

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Figure 1. Processing of chest CT with dedicated image software.

Notice how the same right upper lobe nodule (cross-lines) can be assigned to the middle third by the "vertical" line pattern and to the outer third by the "concentric" line pattern.
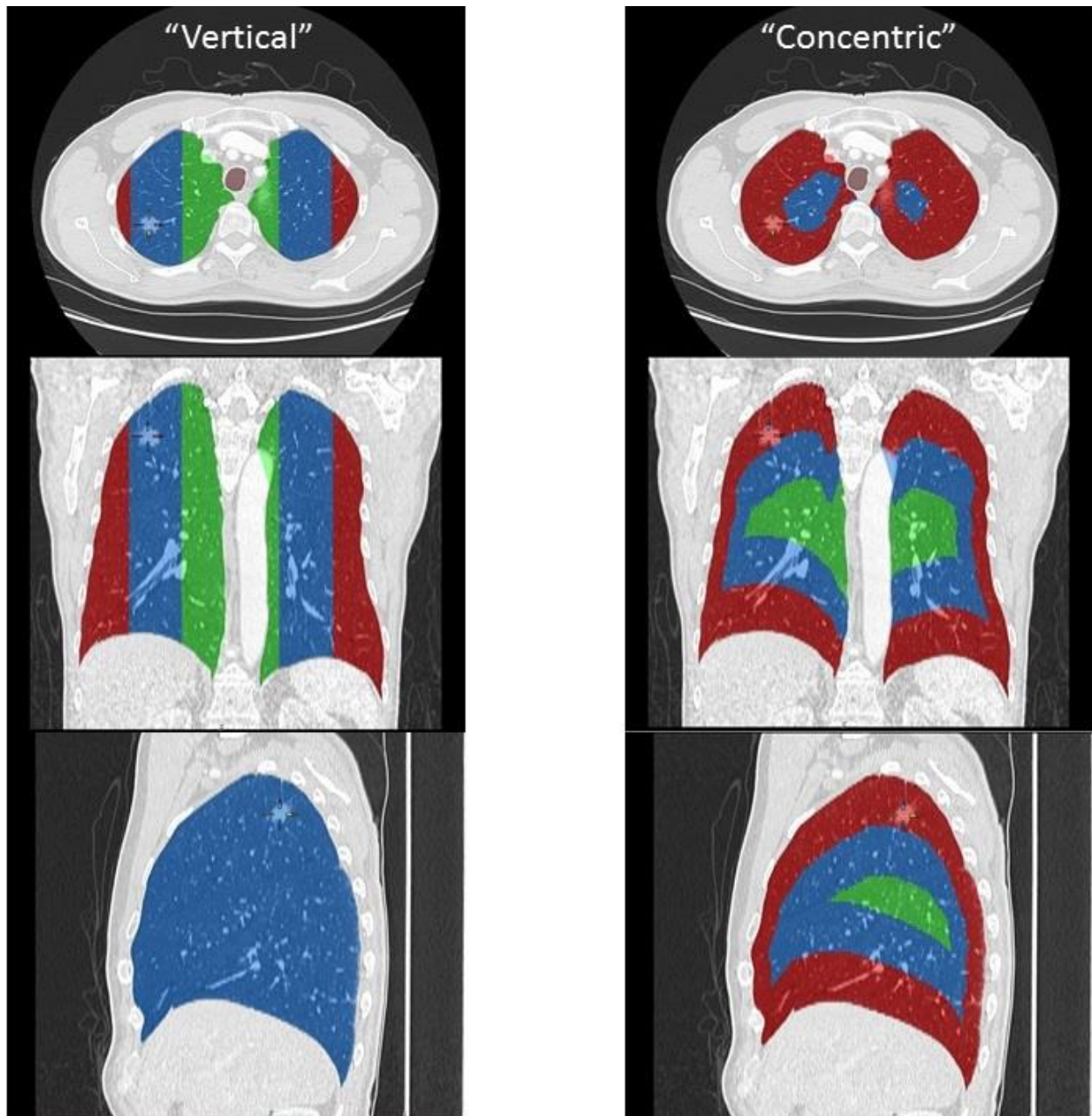
Table 1. Definitions of Central Tumors.

Definition	Line Pattern	Third	Tumor Aspect
1	Concentric	Inner 1/3	Medial
2	Concentric	Inner 2/3	Medial
3	Concentric	Inner 1/3	Center
4	Concentric	Inner 2/3	Center
5	Vertical	Inner 1/3	Medial
6	Vertical	Inner 2/3	Medial
7	Vertical	Inner 1/3	Center
8	Vertical	Inner 2/3	Center

Table 2. Baseline characteristics.

Age (years), mean ± SD	65 ± 9.2
Female gender, n (%)	374 (62)
Ethnicity, n (%)	
- Caucasian	506 (84)
- African-American	35 (6)
- Asian	37 (6)
- Hispanic	25 (4)
- Native American	2
Tumor size (cm), mean ± SD	1.94 ± 0.77
- cT1a	63 (10)
- cT1b	296 (49)
- cT1c	248 (41)
Tumor Location, n (%)	
- RUL	197 (32)
- RML	59 (10)
- RLL	104 (17)
- LUL	151 (25)
- LLL	96 (16)
Nodule Density on CT, n (%)	
- Solid	400 (66)
- Semisolid	148 (24)
- Ground-glass	59 (10)
EBUS-TBNA, n (%)	121 (20)
- N0	106 (17)
- N1	4
- N2	11(2)
Lung resection, n (%)	596 (98)

- Lobectomy	454 (75)
- Segmentectomy	83 (14)
- Wedge resection	76 (12)
- Bilobectomy	2
- Pneumonectomy	1
Histology, n (%)	
- Adenocarcinoma	441 (73)
- Squamous cell carcinoma	77 (13)
- Neuroendocrine (carcinoid)	76 (13)
- Large cell carcinoma	8 (1)
- Adeno-squamous	3
- Pleomorphic	1
- NSCLC, NOS	1
Histologic Degree of Differentiation, n (%)	
- Well differentiated	190 (31)
- Moderately differentiated	297 (49)
- Poorly differentiated	96 (16)
- Not available	24 (4)

Table 3. All Patients - Univariable Logistic Regression (pN0/pN1 vs. pN2/pN3)*

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	55	5 (9.09%)	1.22 (.46, 3.21)	.692	.51 (.46, .55)
2	Concentric Inner 2/3 Medial	316	31 (9.81%)	1.88 (1, 3.51)	.049	.58 (.5, .65)
3	Concentric Inner 1/3 Center	31	3 (9.68%)	1.3 (.38, 4.44)	.678	.51 (.47, .54)
4	Concentric Inner 2/3 Center	237	18 (7.59%)	.97 (.53, 1.79)	.92	.5 (.42, .57)
5	Vertical Inner 1/3 Medial	123	12 (9.76%)	1.39 (.7, 2.77)	.348	.53 (.46, .59)
6	Vertical Inner 2/3 Medial	528	43 (8.14%)	1.68 (.59, 4.83)	.332	.53 (.48, .57)
7	Vertical Inner 1/3 Center	84	7 (8.33%)	1.1 (.48, 2.54)	.824	.51 (.45, .56)
8	Vertical Inner 2/3 Center	466	36 (7.73%)	1 (.49, 2.01)	.993	.5 (.44, .56)
	Total	607	47 (7.73%)			

N=number of patients; n= number of patients with pN2/3

*Modeled on probability of pN2/pN3

Table 4. All Patients - Univariable Logistic Regression (pN0 vs. pN1/pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	55	15 (27.27%)	1.98 (1.05, 3.74)	.035	.53 (.5, .57)
2	Concentric Inner 2/3 Medial	316	67 (21.2%)	1.91 (1.23, 2.97)	.004	.58 (.53, .63)
3	Concentric Inner 1/3 Center	31	13 (41.94%)	3.91 (1.85, 8.26)	<0.001	.55 (.51, .58)
4	Concentric Inner 2/3 Center	237	48 (20.25%)	1.46 (.95, 2.24)	.083	.55 (.49, .6)
5	Vertical Inner 1/3 Medial	123	26 (21.14%)	1.42 (.86, 2.33)	.166	.53 (.48, .58)
6	Vertical Inner 2/3 Medial	528	94 (17.8%)	1.71 (.82, 3.54)	.149	.53 (.5, .56)
7	Vertical Inner 1/3 Center	84	18 (21.43%)	1.41 (.8, 2.49)	.239	.52 (.48, .56)
8	Vertical Inner 2/3 Center	466	84 (18.03%)	1.42 (.83, 2.44)	.198	.53 (.49, .57)
	Total	607	103 (16.94%)			

N=number of patients; n= number of patients with pN1/N2/N3.

*Modeled on probability of pN1/pN2/pN3

Table 5. Excluding patients without PET-CT. Univariate Logistic Regression (pN0/pN1 vs.

pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	40	4 (10%)	1.29 (.43, 3.83)	.648	.51 (.46, .56)
2	Concentric Inner 2/3 Medial	257	26 (10.12%)	1.83 (.91, 3.65)	.088	.57 (.49, .65)
3	Concentric Inner 1/3 Center	21	2 (9.52%)	1.2 (.27, 5.37)	.808	.5 (.47, .54)
4	Concentric Inner 2/3 Center	189	15 (7.94%)	.96 (.49, 1.89)	.912	.5 (.41, .58)
5	Vertical Inner 1/3 Medial	92	9 (9.78%)	1.3 (.59, 2.84)	.514	.52 (.45, .59)
6	Vertical Inner 2/3 Medial	419	37 (8.83%)	2.91 (.68, 12.37)	.149	.54 (.5, .58)
7	Vertical Inner 1/3 Center	65	5 (7.69%)	.94 (.35, 2.49)	.895	.5 (.44, .55)
8	Vertical Inner 2/3 Center	366	30 (8.2%)	1.05 (.48, 2.29)	.899	.5 (.43, .57)

N=number of patients; n= number of patients with pN2/3.

*Modeled on probability of pN2/pN3

Table 6. Excluding patients without PET-CT. Univariable Logistic Regression (pN0 vs.

pN1/pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	40	10 (25%)	1.65 (.77, 3.53)	.194	.52 (.48, .56)
2	Concentric Inner 2/3 Medial	257	55 (21.4%)	1.83 (1.12, 2.99)	.016	.57 (.52, .63)
3	Concentric Inner 1/3 Center	21	8 (38.1%)	3.11 (1.25, 7.76)	.015	.53 (.5, .56)
4	Concentric Inner 2/3 Center	189	39 (20.63%)	1.43 (.89, 2.29)	.142	.54 (.48, .6)
5	Vertical Inner 1/3 Medial	92	20 (21.74%)	1.41 (.8, 2.48)	.231	.53 (.48, .58)
6	Vertical Inner 2/3 Medial	419	77 (18.38%)	1.77 (.78, 4.03)	.175	.53 (.49, .56)
7	Vertical Inner 1/3 Center	65	15 (23.08%)	1.51 (.8, 2.84)	.202	.53 (.48, .57)
8	Vertical Inner 2/3 Center	366	67 (18.31%)	1.29 (.72, 2.31)	.386	.52 (.47, .57)

N=number of patients; n= number of patients with pN1/N2/N3.

*Modeled on probability of pN1/pN2/pN3

Table 7. Excluding carcinoids and GGOs - Univariable Logistic Regression (pN0 vs.

pN1/pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	39	13 (33.33%)	2.39 (1.18, 4.86)	.016	.54 (.5, .58)
2	Concentric Inner 2/3 Medial	236	56 (23.73%)	1.96 (1.22, 3.13)	.005	.58 (.53, .64)
3	Concentric Inner 1/3 Center	20	11 (55%)	5.96 (2.39, 14.85)	<0.001	.55 (.51, .58)
4	Concentric Inner 2/3 Center	170	38 (22.35%)	1.45 (.91, 2.32)	.119	.54 (.49, .6)
5	Vertical Inner 1/3 Medial	99	24 (24.24%)	1.55 (.91, 2.63)	.107	.54 (.49, .59)
6	Vertical Inner 2/3 Medial	420	82 (19.52%)	1.7 (.78, 3.7)	.183	.53 (.49, .56)
7	Vertical Inner 1/3 Center	67	16 (23.88%)	1.45 (.79, 2.69)	.233	.52 (.48, .57)
8	Vertical Inner 2/3 Center	368	72 (19.57%)	1.32 (.75, 2.33)	.33	.52 (.48, .57)
	Total	484	90 (18.6%)			

N=number of patients; n= number of patients with pN1/N2/N3.

*Modeled on probability of pN1/pN2/pN3

The software has the ability to equally divide each lung into thirds (inner, middle, outer) following 2 patterns: "vertical" and "concentric". The "vertical" pattern consists of straight lines that divide the lung in the sagittal plane, while the "concentric" pattern consists of lines that follow the contour of the lung (Figure 1 of main manuscript). The operator, however, needs to manually select the tumor. In our study, in order to study multiple definitions and to solve the problem of tumors that cross a boundary (a line dividing 2 thirds) raising the question of which third they belong to (most medial one or the third where the center of the tumor is located in), we had the operators chose both the center of the tumor and its most medial aspect.

-For the vertical sub-division we compute the bounding box of each lung (one separate bounding box each for the left and right lung) and then perform the division along the frontal axis into three zones of equal thickness.

-For the concentric sub-division we found the surface of the lungs that is in contact with the chest wall and the diaphragm (i.e., excluding the surfaces lining the mediastinum) and then perform region grow processes that are bound by a percentage of the total lung volume.

Figure e1: Manual selection of center and medial aspect of tumor
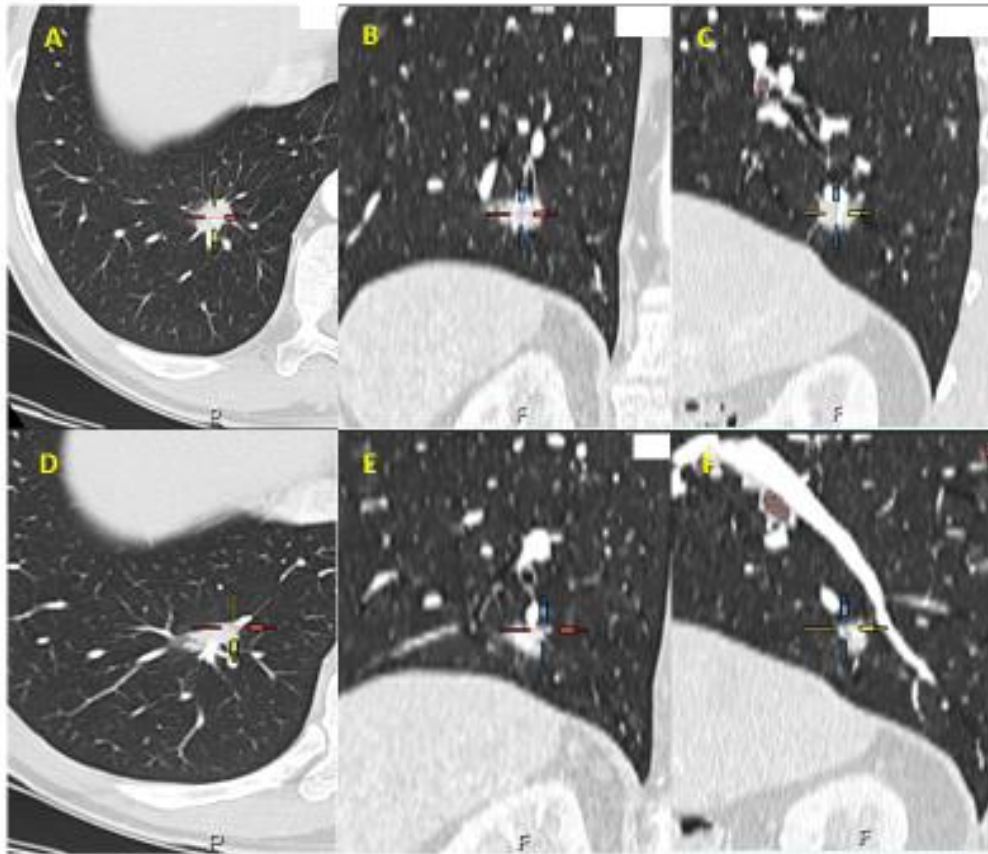
A, B, and C show selection of the center of the tumor simultaneously on axial, coronal, and sagittal axis, respectively. D, E, and F show selection of the most medial aspect of the same tumor (closest to hilum) in axial, coronal and sagittal views, respectively.

Table E1a. All patients. Multivariable Logistic Regression (pN0 vs. pN1/pN2/pN3)

Predictors	OR (95% CI)	P-value
Definition 2 -Concentric Inner 2/3 Medial	2.22 (1.2, 4.13)	**.012**
Tumor histology		
Adenocarcinoma, Ground-Glass	1.00 (.11, 9.55)	.998
Adenocarcinoma, NOT Ground-Glass	2.78 (1.18, 6.57)	**.020**
Neuroendocrine tumor	6.78 (1.65, 27.91)	**.008**
Tumor location (Upper lobe)	1.09 (.58, 2.07)	.790
Radiographic T (T1b/T1c)	2.95 (.62, 14.09)	.175
High FDG values (SUV>5)	1.05 (.97, 1.12)	.212
Tumor differentiation (moderate/poor)	9.22 (2.69, 31.59)	**<0.001**

Tumor histology (reference: neither neuroendocrine tumor nor ACA)
Tumor location (reference: middle/lower lobe)
Radiographic T (reference: T1a)
FDG values is a continuous measure
Tumor differentiation (reference: well)

Table E1b. All patients. Multivariable Logistic Regression (pN0 vs. pN1/pN2/pN3)

Predictors	OR (95% CI)	P-value
Definition 3 - Concentric Inner 1/3 Center	3.11 (1.02, 9.48)	**.047**
Tumor histology		
Adenocarcinoma, Ground-Glass	1.02 (.11, 9.62)	.989
Adenocarcinoma, NOT Ground-Glass	2.5 (1.06, 5.94)	**.037**
Neuroendocrine tumor	6.2 (1.45, 26.54)	**.014**
Tumor location (Upper lobe)	1.16 (.61, 2.2)	.658
Radiographic T (T1b/T1c)	3.67 (.74, 18.16)	.111
High FDG values (SUV>5)	1.05 (.98, 1.12)	.204
Tumor differentiation (moderate/poor)	8.6 (2.55, 29.03)	**.001**

Tumor histology (reference: neither neuroendocrine tumor nor ACA)
Tumor location (reference: middle/lower lobe)
Radiographic T (reference: T1a)
FDG values is a continuous measure
Tumor differentiation (reference: well)

Table E2a. Excluding patients without PET-CT. Multivariable Logistic Regression (pN0

vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 3 - Concentric Inner 1/3 Center	3.81 (1.29, 11.27)	.016
Tumor histology (Adenocarcinoma)	1.54 (.76, 3.11)	.229
Tumor location (Upper lobe)	1.03 (.55, 1.93)	.917
Radiographic T (T1b/T1c)	3.3 (.69, 15.78)	.135
High FDG values (SUV>5)	1.03 (.96, 1.1)	.414
Nodule type (Semisolid/Solid)	2.69 (.33, 21.65)	.353
Tumor differentiation (Moderate/poor)	5.54 (1.85, 16.64)	.002

SS= semisolid; SO= solid

Tumor histology (reference: others)
Tumor location (reference: middle/lower lobe)
Radiographic T (reference: T1a)
Nodule type (reference: GG)
FDG values is a continuous measure
Tumor differentiation (reference: well)
Same for below tables

Table E2b. Excluding patients without PET-CT. Multivariable Logistic Regression (pN0

vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 2 -Concentric Inner 2/3 Medial	2.29 (1.24, 4.22)	.008
Tumor histology (Adenocarcinoma)	1.67 (.83, 3.38)	.150
Tumor location (Upper lobe)	.97 (.52, 1.81)	.934
Radiographic T (T1b/T1c)	2.51 (.55, 11.53)	.237
High FDG values (SUV>5)	1.03 (.96, 1.11)	.384
Nodule type (Semisolid/Solid)	3.04 (.37, 24.95)	.300
Tumor differentiation (Moderate/poor)	5.49 (1.84, 16.43)	.002

Table E3a. Excluding patients with carcinoids and GGOs. Univariable Logistic

Regression (pN0/pN1 vs. pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	39	5 (12.82%)	1.53 (.57, 4.14)	.401	.52 (.47, .57)
2	Concentric Inner 2/3 Medial	236	28 (11.86%)	1.95 (1.03, 3.71)	.041	.58 (.51, .66)
3	Concentric Inner 1/3 Center	20	3 (15%)	1.82 (.51, 6.47)	.355	.51 (.48, .55)
4	Concentric Inner 2/3 Center	170	16 (9.41%)	1.06 (.56, 2.02)	.857	.51 (.43, .58)
5	Vertical Inner 1/3 Medial	99	12 (12.12%)	1.52 (.75, 3.08)	.242	.54 (.47, .61)
6	Vertical Inner 2/3 Medial	420	41 (9.76%)	2.2 (.66, 7.33)	.199	.54 (.49, .58)
7	Vertical Inner 1/3 Center	67	7 (10.45%)	1.2 (.51, 2.81)	.678	.51 (.45, .57)
8	Vertical Inner 2/3 Center	368	34 (9.24%)	1.08 (.52, 2.26)	.84	.51 (.44, .57)
	Total	484	44 (9.09%)			

N=number of patients; n= number of patients with pN2/3

Table E3b. Excluding patients with carcinoids and GGOs. Multivariable Logistic

Regression (pN0/PN1 vs. pN2/pN3) (N=299)

Predictors	OR (95% CI)	P-value
Definition 2 - Concentric Inner 2/3 Medial	1.83 (.73, 4.56)	.198
Tumor histology (Adenocarcinoma)	8.7 (1.11, 68.31)	.040
Tumor location (Upper lobe)	.48 (.2, 1.19)	.115
Higher FDG values (SUV>5)	1 (.89, 1.11)	.958
Tumor differentiation (moderate/poor)	7.13 (.89, 57.05)	.064

Table E4a. Excluding patients with carcinoids and GGOs. Multivariable Logistic

Regression (pN0 vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 3 - Concentric Inner 1/3 Center	4.9 (1.39, 17.32)	.014
Tumor histology (Adenocarcinoma)	2.53 (1.06, 6.06)	.037
Tumor location (Upper lobe)	.99 (.5, 1.96)	.987
Radiographic T (T1b/T1c)	2.82 (.56, 14.26)	.209
Higher FDG values	1.04 (.96, 1.12)	.314
Tumor differentiation (Moderate/poor)	17.22 (2.22, 133.6)	.006

Table E4b. Excluding patients with carcinoids and GGOs. Multivariable Logistic

Regression (pN0 vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 2 - Concentric Inner 2/3 Medial	2.2 (1.15, 4.2)	.017
Tumor histology (ACA)	2.8 (1.18, 6.63)	.019
Tumor location (Upper lobe)	.92 (.47, 1.8)	.800
Radiographic T (T1b/T1c)	2 (.43, 9.4)	.380
Higher FDG values	1.04 (.97, 1.12)	.264
Tumor differentiation (Moderate/poor)	16.09 (2.1, 123.03)	.007

Table E5. Excluding patients with carcinoid tumors, GGOs, and without a PET-CT.

Univariable Logistic Regression (pN0/pN1 vs. pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	32	4 (12.5%)	1.5 (.5, 4.55)	.473	.52 (.46, .57)
2	Concentric Inner 2/3 Medial	203	23 (11.33%)	1.81 (.89, 3.68)	.102	.57 (.49, .66)
3	Concentric Inner 1/3 Center	15	2 (13.33%)	1.59 (.34, 7.33)	.553	.51 (.47, .55)
4	Concentric Inner 2/3 Center	143	13 (9.09%)	1.02 (.5, 2.08)	.962	.5 (.42, .59)
5	Vertical Inner 1/3 Medial	77	9 (11.69%)	1.45 (.65, 3.23)	.361	.53 (.46, .61)
6	Vertical Inner 2/3 Medial	348	35 (10.06%)	5.7 (.76, 42.55)	.090	.56 (.52, .59)
7	Vertical Inner 1/3 Center	55	5 (9.09%)	1.01 (.38, 2.73)	.98	.5 (.44, .56)
8	Vertical Inner 2/3 Center	301	28 (9.3%)	1.17 (.51, 2.65)	.713	.51 (.44, .59)
	Total	400	36 (9%)			

N=number of patients; n= number of patients with pN2/3.

Table E6. Excluding patients with carcinoid tumors, GGOs, and without a PET-CT.

(pN0 vs. pN1/pN2/pN3)

Definitions	Tumor location	N	n (%)	OR (95% CI)	P-value	AUC (95% CI)
1	Concentric Inner 1/3 Medial	32	9 (28.13%)	1.79 (.79, 4.05)	.161	.52 (.49, .56)
2	Concentric Inner 2/3 Medial	203	47 (23.15%)	1.82 (1.09, 3.05)	.023	.57 (.51, .63)
3	Concentric Inner 1/3 Center	15	7 (46.67%)	4.08 (1.43, 11.63)	.009	.53 (.5, .57)
4	Concentric Inner 2/3 Center	143	32 (22.38%)	1.43 (.86, 2.39)	.167	.54 (.48, .6)
5	Vertical Inner 1/3 Medial	77	19 (24.68%)	1.56 (.86, 2.83)	.14	.54 (.48, .59)
6	Vertical Inner 2/3 Medial	348	69 (19.83%)	1.9 (.78, 4.62)	.159	.53 (.49, .57)
7	Vertical Inner 1/3 Center	55	14 (25.45%)	1.59 (.82, 3.1)	.173	.53 (.48, .58)
8	Vertical Inner 2/3 Center	301	59 (19.6%)	1.26 (.69, 2.32)	.448	.52 (.47, .57)
	Total	400	75 (18.75%)			

N=number of patients; n= number of patients with pN1/N2/N3.

Table E7a. Excluding patients with carcinoid tumors, GGOs, and without PET-CT.

Multivariable Logistic Regression (pN0 vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 3 - Concentric Inner 1/3 Center	4.9 (1.39, 17.32)	.014
Tumor histology (Adenocarcinoma)	2.53 (1.06, 6.06)	.037
Tumor location (Upper lobe)	.99 (.5, 1.96)	.987
Radiographic T (T1b/T1c)	2.82 (.56, 14.26)	.209
Higher FDG values	1.04 (.96, 1.12)	.314
Tumor differentiation (Moderate/poor)	17.22 (2.22, 133.6)	.006

Table E7b. Excluding patients with carcinoid tumors, GGOs, and without PET-CT.

Multivariable Logistic Regression (pN0 vs. pN1/N2/pN3)

Predictors	OR (95% CI)	P-value
Definition 2 - Concentric Inner 2/3 Medial	2.2 (1.15, 4.2)	.017
Tumor histology (ACA)	2.8 (1.18, 6.63)	.019
Tumor location (Upper lobe)	.92 (.47, 1.8)	.800
Radiographic T (T1b/T1c)	2 (.43, 9.4)	.380
Higher FDG values	1.04 (.97, 1.12)	.264
Tumor differentiation (Moderate/poor)	16.09 (2.1, 123.03)	.007