"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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VIDA Lung Zones Software (VIDA Diagnostics, Iowa, USA)

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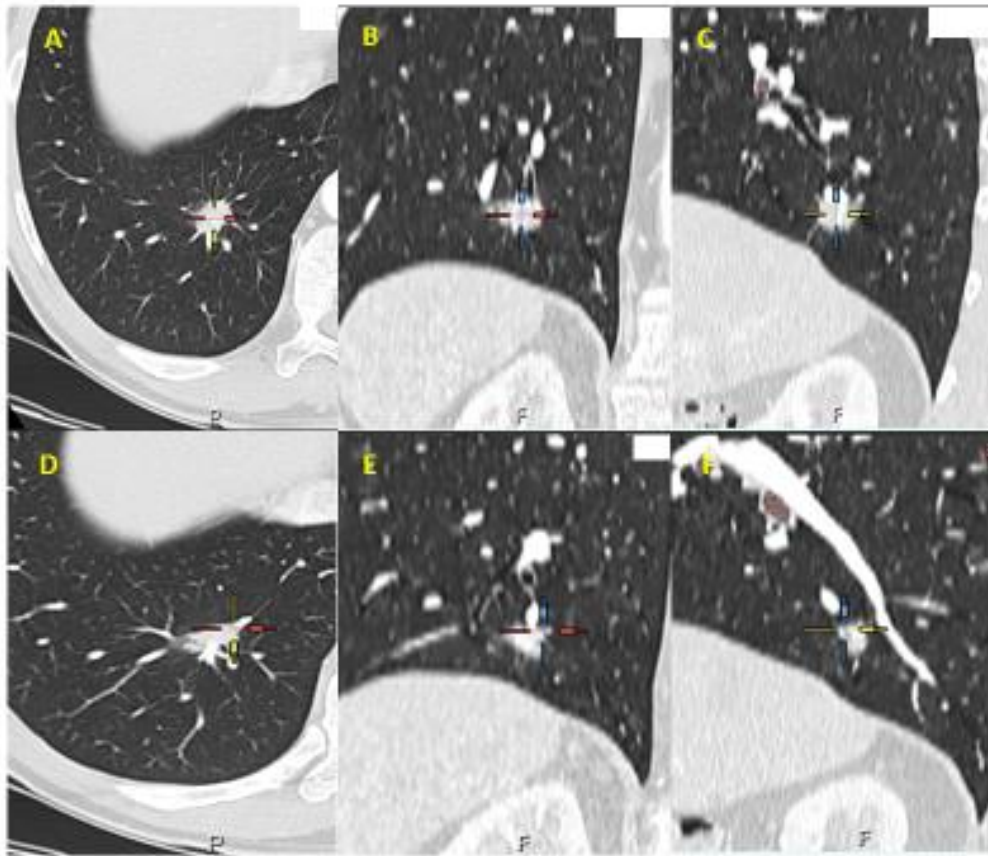
A, B, and C show selection of the center of the tumor simultaneously on axial, coronal, and sagittal axis, respectively. D, E, and F show selection of the most medial aspect of the same tumor (closest to hilum) in axial, coronal and sagittal views, respectively.

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 E4a. 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