Online Supplement

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

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

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

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

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

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

[‖] Size of the tumour is measured in preoperative CT scan. [¶]P value for chi-square test is 0.011.
[+] For 10 patients who were confirmed to have N2 disease in EBUS-TBNA, the interval between PET-CT and EBUS-TBNA were used.
[#]Analysis was done in 851 patients after excluding 10 patients who were confirmed to have N2 disease in EBUS-TBNA and did not undergo MLND.

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

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

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

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

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

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

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

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

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

univariate analysis.

^ǀ Size of the tumour is measured in preoperative CT scan. ¶P value for chi-square test is 0.149.

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

[#]Analysis was done in 475 patients after excluding 10 patients who were confirmed to have N2 disease in EBUS-TBNA and did not undergo MLND.

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

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

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

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

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

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