

## Modification of Pathologic T Classification for Non-small Cell Lung Cancer With Visceral Pleural Invasion

Data From 1,055 Cases of Cancers  $\leq 3$  cm

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### 【要旨】

**Background:** p1 または p2 による臓側胸膜浸潤(VPI)は、非小細胞肺癌(NSCLC)  $\leq 3$ cm で T 分類を T1 から T2 に増加させる。補助療法に関して VPI に基づく修正 T 分類を提案する。

**Research question:** NSCLC が 3cm 以下の場合、p1 陽性症例を T1 から T2 にアップステージすることは合理的か。

**Study design and methods:** 後ろ向き研究で、2001年1月から2014年12月までの間で Sun Yat-sen University Cancer Center で外科的に切除された計 1055 人の NSCLC 症例を対象とした。腫瘍切片は弾性線維の評価のため HE 染色とビクトリアブルー弾性染色で再染色された。無病生存率(DFS)と全生存期間(OS)は Kaplan-Meier 法によって計算された。サブグループ解析として Cox 比例ハザードモデルを用いて、生存に対する VPI の影響をさらに検討した。

**Results:** VPI は 824 人の患者で p0、133 人の患者で p1、98 人の患者で p2 と診断された。p0、p1、および p2 の患者の 5 年 DFS はそれぞれ 62.6%、60.2%、および 28.8% ( $p < .01$ ) だった。一方で 5 年 OS はそれぞれ 78.6%、74.4%、および 50.0% だった ( $p < .01$ )。予測されたように、p2 の患者の DFS と OS は p0 ( $p < .01$ ) と p1 ( $p < .01$ ) の患者よりもはるかに予後不良であり、p0 と p1 の患者の DFS と OS はどちらも同等だった (DFS:  $p = .198$ ; OS:  $p = .150$ )。リンパ節転移陰性の症例において、p0 と p1 の患者の DFS と OS は同等だった (DFS:  $p = .468$ ; OS:  $p = .388$ ) が、p2 の患者は p0 ( $p < .01$ ) および p1 ( $p < .01$ ) の患者よりも DFS と OS ははるかに悪かった。多変量解析では p2 はリンパ節転移陽性と細胞分化の低下とともに、独立した予後不良因子であることが示唆された。

**Interpretation:** 3cm 以下の NSCLC では、p1 の腫瘍は T2 ではなく T1 として定義されたままである必要がある。p1 の症例ではリンパ節転移陰性かつ 3cm 以下の NSCLC の場合の補助化学療法による過剰治療を回避できる可能性がある。

### 【Take home message】

- ✓ 腫瘍サイズが 3cm 以下の NSCLC では、p12 症例は T1→T2 にアップステージすることが適切だが、p11 の症例は T1 のままである必要がある。
- ✓ 腫瘍サイズ 3cm 以下の N0PL1NSCLC 患者での術後補助化学療法による過剰治療は避けるべきである。

**Table 1 Distribution of Clinicopathologic Characteristics (N = 1,055)**

Characteristics	PL0 (n = 824)	PL1 (n = 133)	PL2 (n = 98)	P Value
Sex				
Male	479 (58.1)	74 (55.6)	48 (49.0)	.212
Female	345 (41.9)	59 (44.4)	50 (51.0)	...
Age, y				
Mean ± SD	59.2 ± 10.1	59.7 ± 9.8	60.4 ± 9.6	.585 <sup>a</sup>
Median (range)	60.0 (19-81)	60.0 (39-81)	61.0 (39-83)	...
≤ 60	429 (52.1)	69 (51.9)	45 (45.9)	.513
> 60	395 (47.9)	64 (48.1)	53 (54.1)	...
Histology				
Adenocarcinoma	702 (85.2)	118 (88.7)	88 (89.8)	.295 <sup>b</sup>
Squamous cell carcinoma	101 (12.3)	14 (10.5)	6 (6.1)	...
Other	21 (2.5)	1 (0.8)	4 (4.1)	...
Anatomic type				
Central	43 (5.2)	6 (4.5)	4 (4.1)	.852
Peripheral	781 (94.8)	127 (95.5)	94 (95.9)	...
Cell differentiation <sup>c</sup>				

Characteristics	PL0 (n = 824)	PL1 (n = 133)	PL2 (n = 98)	P Value
Well	66 (8.0)	6 (4.5)	4 (4.1)	.130
Moderate	414 (50.2)	58 (43.6)	42 (42.9)	...
Poor	285 (34.6)	62 (46.6)	47 (48.0)	...
NA	59 (7.2)	7 (5.3)	5 (5.1)	...
Smoking history				
Never	454 (55.1)	81 (60.9)	64 (65.3)	.076
Current	278 (33.7)	39 (29.3)	31 (31.6)	...
Former	92 (11.2)	13 (9.8)	3 (3.1)	...
Surgical resection				
Lobectomy	756 (91.8)	122 (91.7)	85 (86.7)	.089
Bilobectomy	34 (4.1)	8 (6.0)	3 (3.1)	...
Pneumonectomy	19 (2.3)	1 (0.8)	6 (6.1)	...
Sublobar resection	15 (1.8)	2 (1.5)	4 (4.1)	...
Tumor location				
Right side of the lung	489 (59.3)	84 (63.2)	53 (54.1)	.382
Left side of the lung	335 (40.7)	49 (36.8)	45 (45.9)	...
Tumor size, cm				
Mean ± SD	2.2 ± 0.7	2.4 ± 0.6	2.4 ± 0.6	<.01 <sup>a</sup>

Characteristics	PL0 (n = 824)	PL1 (n = 133)	PL2 (n = 98)	P Value
Median (range)	2.0 (0.3-3.0)	2.5 (0.8-3.0)	2.5 (1.0-3.0)	...
0-2	434 (52.7)	51 (38.3)	41 (41.8)	< .01 <sup>d</sup>
2-3	390 (47.3)	82 (61.7)	57 (58.2)	...
Pathologic N category <sup>g</sup>				
N0	580 (70.4)	73 (54.9)	49 (50.0)	< .01 <sup>f</sup>
N1	92 (11.2)	24 (18.0)	15 (15.3)	...
N2	152 (18.4)	36 (27.1)	34 (34.7)	...
Pathologic stage <sup>e</sup>				
I	568 (68.9)	70 (52.6)	47 (48.0)	< .01 <sup>g</sup>
II	96 (11.7)	26 (19.6)	17 (17.3)	...
III	160 (19.4)	37 (27.8)	34 (34.7)	...
Adjuvant therapy				
No	521 (63.2)	76 (57.1)	46 (46.9)	< .01 <sup>h</sup>

**Table 2 Assessment of VPI Status Using H&E Only vs Using Both H&E and ES by Pathologist A and B (N = 1,055)**

VPI	Pathologist A (H&E Only)	Pathologist A (H&E + ES)	Pathologist B (H&E Only)	Pathologist B (H&E + ES)	Final Diagnosis <sup>a</sup>
PL0	552 (52.3)	803 (76.1)	635 (60.2)	849 (80.5)	824 (78.1)
PL1	130 (12.3)	165 (15.6)	107 (10.1)	119 (11.3)	133 (12.6)
PL2	82 (7.8)	87 (8.2)	80 (7.6)	87 (8.2)	98 (9.3)
Indeterminate	291 (27.6)	0 (0.0)	233 (22.1)	0 (0.0)	0 (0.0)

Values are No. (%). ES = elastic stain; H&E = hematoxylin and eosin stain; VPI = visceral pleural invasion.  
<sup>a</sup> When the diagnoses were inconsistent, a third pathologist was invited to join the diagnosis team to discuss for a final diagnosis.

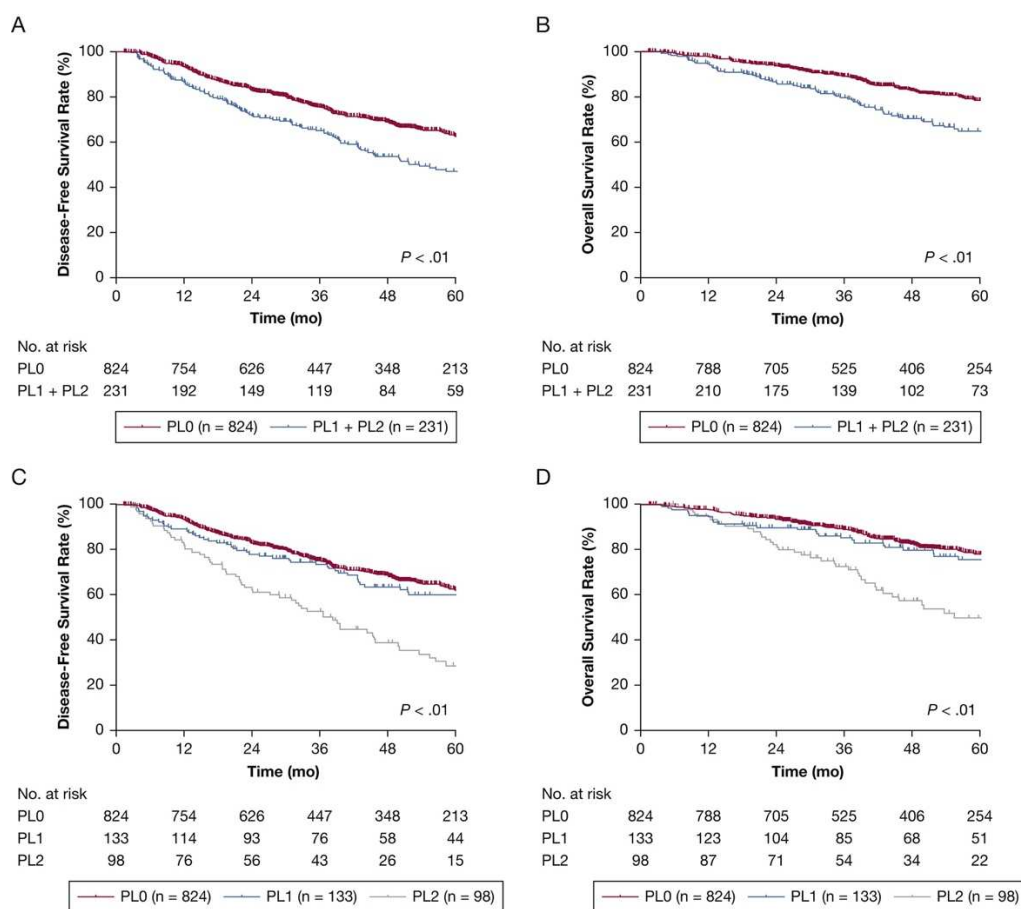


Figure 1A-D, Disease-free survival and overall survival curves for the entire cohort. A, Disease-free survival curves for two categories of patients according to the extent of visceral pleural invasion (VPI) (PL0 and PL1 + PL2) in the 1,055 patients. Among these two categories, PL0 vs PL1 + PL2,  $P < .01$ . B, Overall survival curves for two categories of patients according to the extent of VPI (PL0 and PL1 + PL2) in the 1,055 patients. Among these two categories, PL0 vs PL1 + PL2,  $P < .01$ . C, Disease-free survival curves for three categories of patients according to the extent of VPI (PL0, PL1, and PL2) in the 1,055 patients. Among the three categories,  $P < .01$ ; PL0 vs PL1,  $P = .198$ ; PL0 vs PL2,  $P < .01$ ; PL1 vs PL2,  $P < .01$ . D, Overall survival curves for three categories of patients according to the extent of VPI (PL0, PL1, and PL2) in the 1,055 patients. Among the three categories,  $P < .01$ ; PL0 vs PL1,  $P = .150$ ; PL0 vs PL2,  $P < .01$ ; PL1 vs PL2,  $P < .01$ .

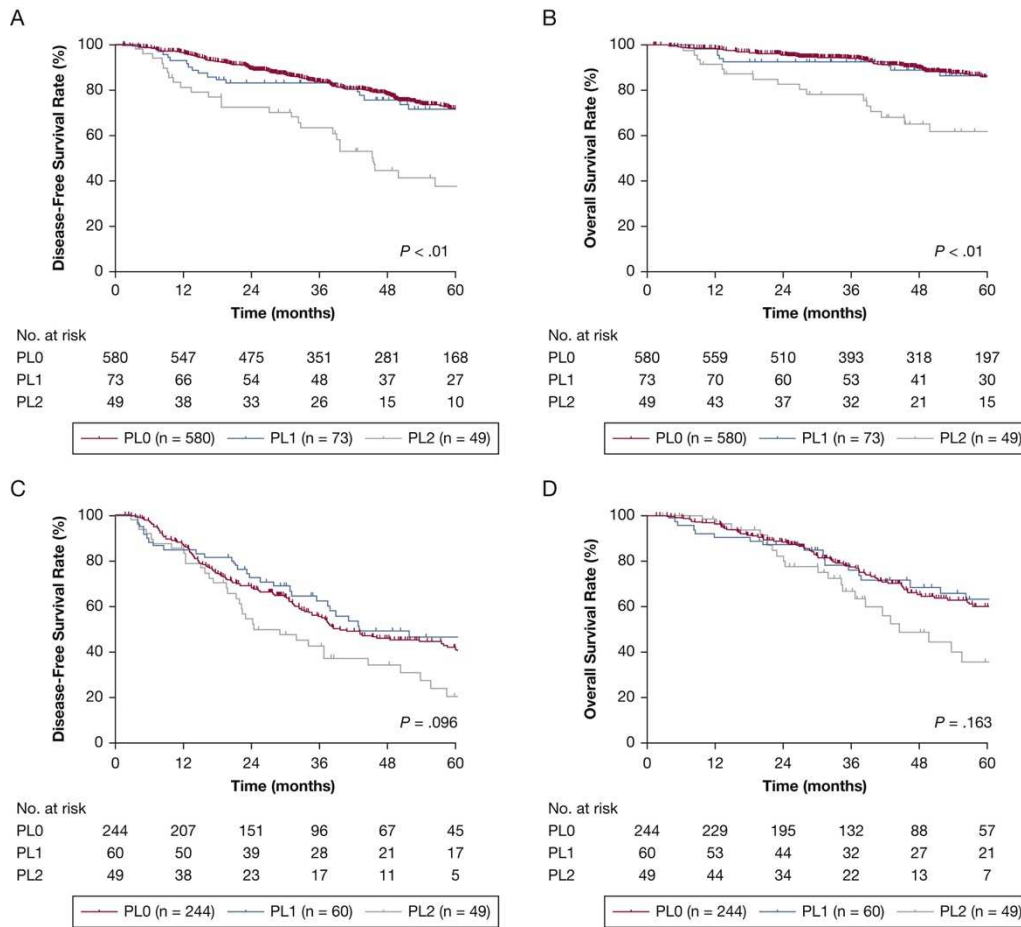


Figure 2A-D, Disease-free survival and overall survival curves for the node-negative and node-positive subgroups. A, Disease-free survival curves for three categories of patients according to the extent of visceral pleural invasion (VPI) (PL0, PL1, and PL2) in the node-negative subgroup (n = 702). Among the three categories,  $P < .01$ ; PL0 vs PL1,  $P = .468$ ; PL0 vs PL2,  $P < .01$ ; PL1 vs PL2,  $P < .01$ . B, Overall survival curves for three categories of patients according to the extent of VPI (PL0, PL1, and PL2) in the node-negative subgroup (n = 702). Among the three categories,  $P < .01$ ; PL0 vs PL1,  $P = .388$ ; PL0 vs PL2,  $P < .01$ ; PL1 vs PL2,  $P < .01$ . C, Disease-free survival curves for three categories of patients according to the extent of VPI (PL0, PL1, and PL2) in the node-positive subgroup (n = 353). Among the three categories,  $P = .096$ ; PL0 vs PL1,  $P = .532$ ; PL0 vs PL2,  $P = .060$ ; PL1 vs PL2,  $P = .038$ . D, Overall survival curves for three categories of patients according to the extent of VPI (PL0, PL1, and PL2) in the node-positive subgroup (n = 353). Among the three categories,  $P = .163$ ; PL0 vs PL1,  $P = .701$ ; PL0 vs PL2,  $P = .083$ ; PL1 vs PL2,  $P = .094$ .

**Table 3 Prognostic Factors for DFS and OS by Multivariate Cox Regression Analysis in the Entire Cohort (n = 984)<sup>a</sup>**

Variable	DFS			OS		
	HR	95% CI for HR	P Value	HR	95% CI for HR	P Value
Anatomic type			.561			.443
Central	1			1		
Peripheral	1.160	0.704-1.910		1.277	0.683-2.389	
Histology type			.067			.951
Adenocarcinoma	1			1		
Squamous	0.710	0.498-1.010	.057	0.981	0.651-1.477	.925
Other	1.527	0.740-3.149	.252	1.145	0.459-2.854	.771
Cell differentiation <sup>b</sup>			.253			.065
Well	1			1		
Moderate	1.019	0.633-1.638	.939	0.847	0.456-1.575	.600
Poor	1.229	0.753-2.007	.409	1.201	0.637-2.261	.572
Tumor size, cm			.265			.490

Variable	DFS			OS		
	HR	95% CI for HR	P Value	HR	95% CI for HR	P Value
0-2	1			1		
2-3	1.132	0.910-1.408		1.106	0.831-1.470	
VPI			<.01			<.01
PL0	1			1		
PL1	1.072	0.795-1.448	.648	1.123	0.761-1.659	.559
PL2	1.692	1.251-2.289	<.01	2.169	1.494-3.149	<.01
Pathologic N category <sup>c</sup>			<.01			<.01
N0	1			1		
N1	1.976	1.453-2.688	<.01	2.765	1.870-4.089	<.01
N2	2.412	1.855-3.136	<.01	3.118	2.203-4.413	<.01
Smoking history			<.01			<.01
Never	1			1		
Current	1.616	1.286-2.031	<.01	1.730	1.281-2.335	<.01
Former	1.386	0.956-2.009	.085	1.583	0.985-2.545	.058

Variable	DFS			OS		
	HR	95% CI for HR	P Value	HR	95% CI for HR	P Value
Adjuvant therapy			.030			.378
No	1			1		
Yes	1.287	1.025-1.616		0.874	0.648-1.179	

DFS = disease-free survival; HR = hazard ratio; OS = overall survival; VPI = visceral pleural invasion.

<sup>a</sup> Seventy-one cases unavailable for cell differentiation were excluded.

<sup>b</sup> According to the *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*.<sup>30</sup>

<sup>c</sup> According to the eighth edition lung cancer stage classification.<sup>12</sup>

**Table 4 Prognostic Factors for DFS and OS by Multivariate Cox Regression Analysis in N0 Cases (n = 644)<sup>a</sup>**

Variable	DFS			OS		
	HR	95% CI for HR	P Value	HR	95% CI for HR	P Value
Anatomic type			.255			.159
Central	1			1		
Peripheral	1.803	0.654-4.970		2.833	0.665-12.068	
Histology type			.618			.672
Adenocarcinoma	1			1		
Squamous	0.765	0.447-1.308	.327	1.199	0.639-2.247	.572
Other	0.981	0.302-3.193	.975	1.611	0.467-5.561	.450
Cell differentiation <sup>b</sup>			.019			< .01
Well	1			1		
Moderate	0.874	0.520-1.470	.612	0.660	0.318-1.370	.265
Poor	1.401	0.813-2.415	.225	1.516	0.728-3.157	.266
Tumor size, cm			.089			.048

Variable	DFS			OS		
	HR	95% CI for HR	P Value	HR	95% CI for HR	P Value
0-2	1			1		
2-3	1.303	0.961-1.766		1.526	1.003-2.321	
VPI			< .01			< .01
PL0	1			1		
PL1	1.115	0.699-1.778	.647	1.268	0.669-2.404	.466
PL2	2.320	1.472-3.657	< .01	3.856	2.200-6.758	< .01
Smoking history			.053			.078
Never	1			1		
Current	1.458	1.038-2.048	.030	1.525	0.946-2.459	.063
Former	1.544	0.947-2.518	.082	1.960	1.020-3.766	.043
Adjuvant therapy			.021			.920
No	1			1		
Yes	1.450	1.058-1.968		1.024	0.648-1.617	

DFS = disease-free survival; HR = hazard ratio; OS = overall survival; VPI = visceral pleural invasion.

<sup>a</sup> Fifty-eight cases unavailable for cell differentiation were excluded.

<sup>b</sup> According to the WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart.<sup>30</sup>