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Article

Which descriptor should spread through air spaces (STAS) be incorporated into? T descriptor versus residual tumor classification. Mi Y, Chen D, Chen Z, et al. J Pathol Clin Res. 2025 Jul;11(4):e70039.

Spread through air spaces （STAS）はその存在が予後予測因子のみならず区域切除、部分切除後の局所再発因子として報告されているが、STAS を T 因子に組み込むべきか、それとも 不完全切除［R(un)］に組み込むべきかは一定の見解が得られていない。筆者らは病理学的 Stage I 肺腺癌 807 例の多施設コホートを用いて、STAS を T 因子または R(un) に組み込む妥当性を、無再発生存（RFS）および全生存（OS）に基づき検討、決定曲線解析（DCA）では、新しい T（nT）カテゴリーおよび新しい残存腫瘍分類（nR）を現行分類と比較し、その優位性を検討した。Table 1 は primary コホート、vadidation コホートにおける STAS と臨床病理学的背景との関連を示している（腫瘍サイズ大（p<0.001)、T ステージ高（p<0.001)、高グレード（p<0.001）、LVI, VPI と相関)。Figure 1:ログランク検定では、pT1/STAS 陽性肺腺癌は R 状態に関わらず、pT2a と類似した RFS・OS を示した。Figure 2： STAS を R0→R(un) のアップグレード指標とみなすと、pT1–2a/STAS 陽性で R0 区域切除を受けた患者は、R(un) 区域切除を受けた pT1–2a と生存が同等であった。よって Figure 3 のように提案するとのべている。STAS 陽性 T1→T2a（nT2a）または STAS 陽性区域切除 →nR(un)。Cox 解析でも T 因子への組み込みが有意であった（Table 2, 3)。検証コホートでも同様の傾向が認められた。特に T 因子への組み込み (nT) は、術式別のサブグループ解析でも RFS/OS を良好に層別化した。一方、pT2a では nR0 と nR(un) の分離は不十分であった。決定曲線解析でも、nT が現行の T より優れた予測能を示した（Figure 4）。結論：STAS は今後の TNM において、pT1 を pT2a にアップグレードする指標として組み込むことが推奨される。

Table 1. Clinicopathological characteristics of the included patient cohorts stratified by STAS status

Variables	Primary cohort			Validation cohort		
	STAS-positive ($n = 312$)	STAS-negative ($n = 495$)	p	STAS-positive ($n = 198$)	STAS-negative ($n = 342$)	p
Age, *n* (%)			0.135			0.868
≤65 years	144 (46.2)	202 (40.8)		101 (51.0)	177 (51.8)	
>65 years	168 (53.8)	293 (59.2)		97 (49.0)	165 (48.2)	
Sex, *n* (%)			0.149			0.431
Male	166 (53.2)	289 (58.4)		85 (42.9)	135 (39.5)	
Female	146 (46.8)	206 (41.6)		113 (57.1)	207 (60.5)	
Smoking history, *n* (%)			0.274			0.240
Never	221 (70.8)	368 (74.3)		157 (79.3)	285 (83.3)	
Ever	91 (29.2)	127 (25.7)		41 (20.7)	57 (16.7)	
Tumor location, *n* (%)			0.151			0.424
Upper lobe	168 (53.8)	292 (59.0)		117 (59.1)	190 (55.6)	
Middle/lower lobe	144 (46.2)	203 (41.0)		81 (40.9)	152 (44.4)	
Surgical procedure, *n* (%)			0.584			0.466
Lobectomy	165 (52.9)	252 (50.9)		110 (55.6)	201 (58.8)	
Segmentectomy	147 (47.1)	243 (49.1)		88 (44.4)	141 (41.2)	
Tumor size, *n* (%)			<0.001			< 0.001
≤2 cm	87 (27.9)	381 (77.0)		73 (36.9)	230 (67.3)	
>2 cm	225 (72.1)	114 (23.0)		125 (63.1)	112 (32.7)	
Pathologic T stage, *n* (%)			<0.001			< 0.001
T1a	23 (7.4)	77 (15.5)		10 (5.1)	36 (10.5)	
T1b	30 (9.6)	179 (36.2)		46 (23.2)	121 (35.4)	
T1c	125 (40.1)	50 (10.1)		53 (26.8)	36 (10.5)	
T2a	134 (42.9)	189 (38.2)		89 (44.9)	149 (43.6)	
Tumor grade, *n* (%)*			<0.001			0.010
Grade 1	5 (1.6)	47 (9.5)		10 (5.1)	33 (9.6)	
Grade 2	87 (27.9)	400 (80.8)		138 (69.7)	254 (74.3)	
Grade 3	220 (70.5)	48 (9.7)		50 (25.2)	55 (16.1)	
No. of harvested lymph nodes, *n* (%)			0.658			0.308
≤8	157 (50.3)	257 (51.9)		108 (54.5)	171 (50.0)	
>8	155 (49.7)	238 (48.1)		90 (45.5)	171 (50.0)	
Lymphovascular invasion, *n* (%)			0.021			0.029
Present	47 (15.1)	48 (9.7)		11 (5.6)	7 (2.0)	
Absent	265 (84.9)	447 (90.3)		187 (94.4)	335 (98.0)	
Visceral pleural invasion, *n* (%)			0.178			0.755
Present	134 (42.9)	189 (38.2)		89 (44.9)	149 (43.6)	
Absent	178 (57.1)	306 (61.8)		109 (55.1)	193 (56.4)	
R classification, *n* (%)†			<0.001			0.113
R0	176 (56.4)	343 (69.3)		121 (61.1)	232 (67.8)	
R(un)	136 (43.6)	152 (30.7)		77 (38.9)	110 (32.2)	
Adjuvant chemotherapy, *n* (%)			0.040			0.025
No	220 (70.5)	381 (77.0)		124 (62.6)	246 (71.9)	
Yes	92 (29.5)	114 (23.0)		74 (37.4)	96 (28.1)	

Figure 1

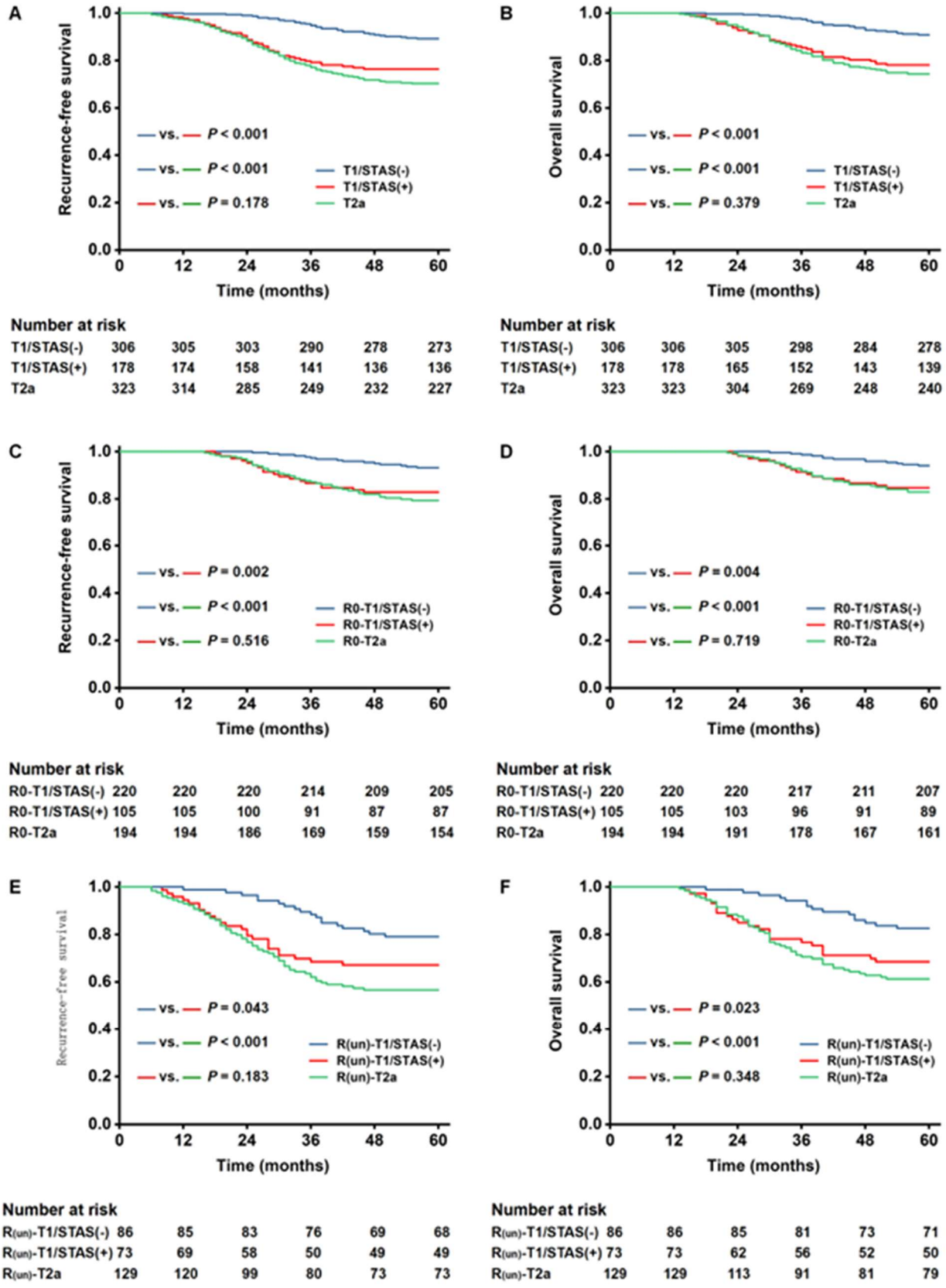
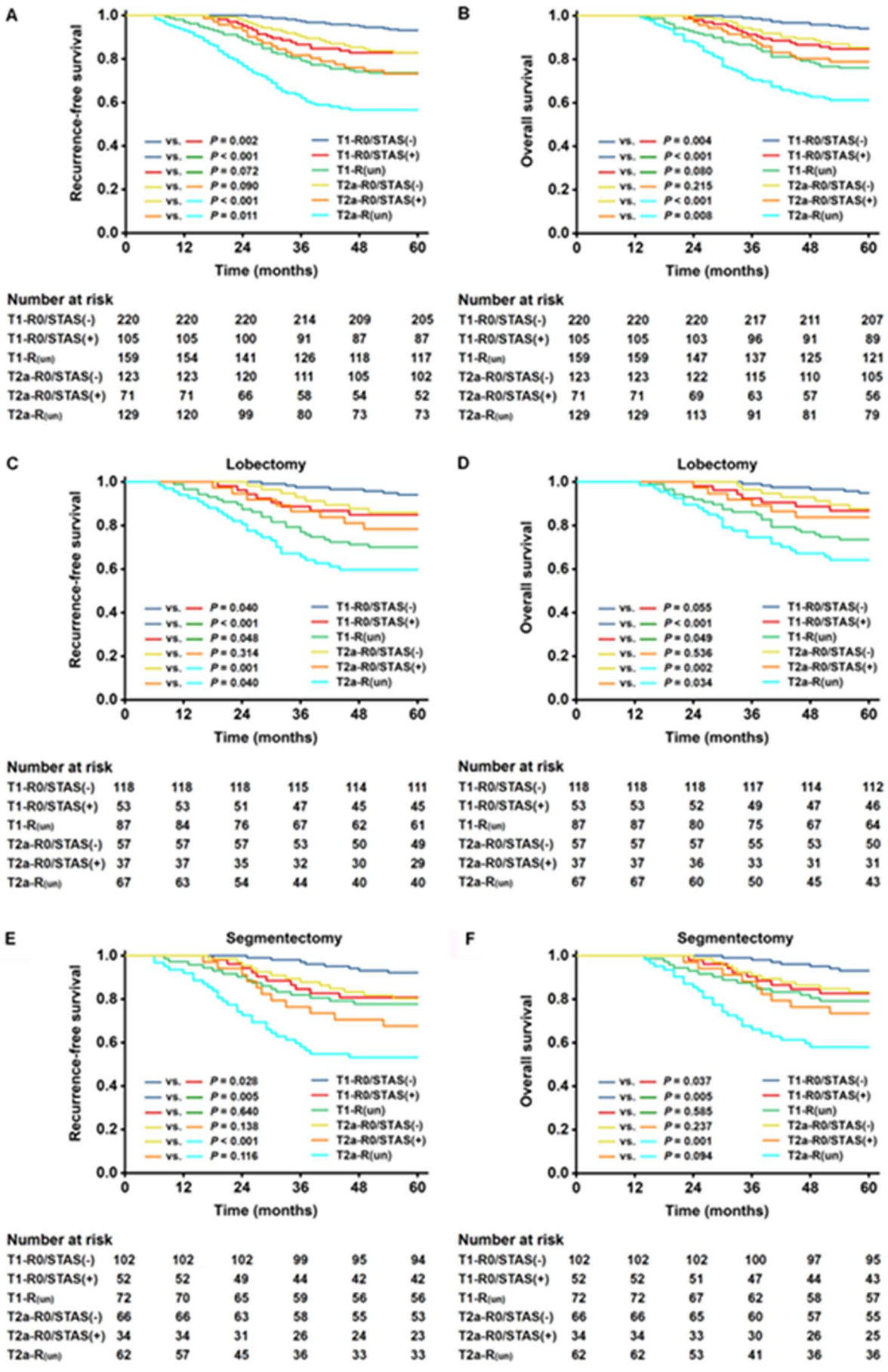

A
Recurrence-free survival
vs. P < 0.001
vs. P < 0.001
vs. P = 0.178
T1/STAS(-)
T1/STAS(+)
T2a
Time (months)
Number at risk
T1/STAS(-) 306 305 303 290 278 273
T1/STAS(+) 178 174 158 141 136 136
T2a 323 314 285 249 232 227
B
Overall survival
vs. P < 0.001
vs. P < 0.001
vs. P = 0.379
T1/STAS(-)
T1/STAS(+)
T2a
Time (months)
Number at risk
T1/STAS(-) 306 306 305 298 284 278
T1/STAS(+) 178 178 165 152 143 139
T2a 323 323 304 269 248 240
C
Recurrence-free survival
vs. P = 0.002
vs. P < 0.001
vs. P = 0.516
R0-T1/STAS(-)
R0-T1/STAS(+)
R0-T2a
Time (months)
Number at risk
R0-T1/STAS(-) 220 220 220 214 209 205
R0-T1/STAS(+) 105 105 100 91 87 87
R0-T2a 194 194 186 169 159 154
D
Overall survival
vs. P = 0.004
vs. P < 0.001
vs. P = 0.719
R0-T1/STAS(-)
R0-T1/STAS(+)
R0-T2a
Time (months)
Number at risk
R0-T1/STAS(-) 220 220 220 217 211 207
R0-T1/STAS(+) 105 105 103 96 91 89
R0-T2a 194 194 191 178 167 161
E
Recurrence-free survival
vs. P = 0.043
vs. P < 0.001
vs. P = 0.183
R(un)-T1/STAS(-)
R(un)-T1/STAS(+)
R(un)-T2a
Time (months)
Number at risk
R(un)-T1/STAS(-) 86 85 83 76 69 68
R(un)-T1/STAS(+) 73 69 58 50 49 49
R(un)-T2a 129 120 99 80 73 73
F
Overall survival
vs. P = 0.023
vs. P < 0.001
vs. P = 0.348
R(un)-T1/STAS(-)
R(un)-T1/STAS(+)
R(un)-T2a
Time (months)
Number at risk
R(un)-T1/STAS(-) 86 86 85 81 73 71
R(un)-T1/STAS(+) 73 73 62 56 52 50
R(un)-T2a 129 129 113 91 81 79

Figure 2


A
Recurrence-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.002
vs. P < 0.001
vs. P = 0.072
vs. P = 0.090
vs. P < 0.001
vs. P = 0.011
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 220 220 220 214 209 205
T1-R0/STAS(+) 105 105 100 91 87 87
T1-R(un) 159 154 141 126 118 117
T2a-R0/STAS(-) 123 123 120 111 105 102
T2a-R0/STAS(+) 71 71 66 58 54 52
T2a-R(un) 129 120 99 80 73 73
B
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.004
vs. P < 0.001
vs. P = 0.080
vs. P = 0.215
vs. P < 0.001
vs. P = 0.008
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 220 220 220 217 211 207
T1-R0/STAS(+) 105 105 103 96 91 89
T1-R(un) 159 159 147 137 125 121
T2a-R0/STAS(-) 123 123 122 115 110 105
T2a-R0/STAS(+) 71 71 69 63 57 56
T2a-R(un) 129 129 113 91 81 79
C
Lobectomy
Recurrence-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.040
vs. P < 0.001
vs. P = 0.048
vs. P = 0.314
vs. P = 0.001
vs. P = 0.040
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 118 118 118 115 114 111
T1-R0/STAS(+) 53 53 51 47 45 45
T1-R(un) 87 84 76 67 62 61
T2a-R0/STAS(-) 57 57 57 53 50 49
T2a-R0/STAS(+) 37 37 35 32 30 29
T2a-R(un) 67 63 54 44 40 40
D
Lobectomy
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.055
vs. P < 0.001
vs. P = 0.049
vs. P = 0.536
vs. P = 0.002
vs. P = 0.034
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 118 118 118 117 114 112
T1-R0/STAS(+) 53 53 52 49 47 46
T1-R(un) 87 87 80 75 67 64
T2a-R0/STAS(-) 57 57 57 55 53 50
T2a-R0/STAS(+) 37 37 36 33 31 31
T2a-R(un) 67 67 60 50 45 43
E
Segmentectomy
Recurrence-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.028
vs. P = 0.005
vs. P = 0.640
vs. P = 0.138
vs. P < 0.001
vs. P = 0.116
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 102 102 102 99 95 94
T1-R0/STAS(+) 52 52 49 44 42 42
T1-R(un) 72 70 65 59 56 56
T2a-R0/STAS(-) 66 66 63 58 55 53
T2a-R0/STAS(+) 34 34 31 26 24 23
T2a-R(un) 62 57 45 36 33 33
F
Segmentectomy
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0 12 24 36 48 60
Time (months)
vs. P = 0.037
vs. P = 0.005
vs. P = 0.585
vs. P = 0.237
vs. P = 0.001
vs. P = 0.094
T1-R0/STAS(-)
T1-R0/STAS(+)
T1-R(un)
T2a-R0/STAS(-)
T2a-R0/STAS(+)
T2a-R(un)
Number at risk
T1-R0/STAS(-) 102 102 102 100 97 95
T1-R0/STAS(+) 52 52 51 47 44 43
T1-R(un) 72 72 67 62 58 57
T2a-R0/STAS(-) 66 66 65 60 57 55
T2a-R0/STAS(+) 34 34 33 30 26 25
T2a-R(un) 62 62 53 41 36 36

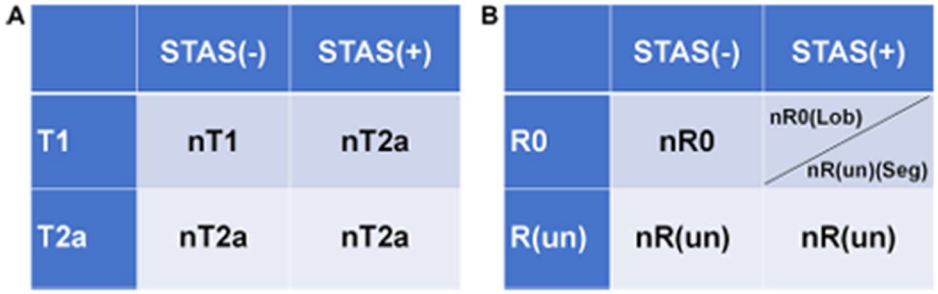


Figure 3. Illustration of STAS as an indicator for upgrading T1 disease to T2a or upgrading R0 segmentectomy to the R(un) category.

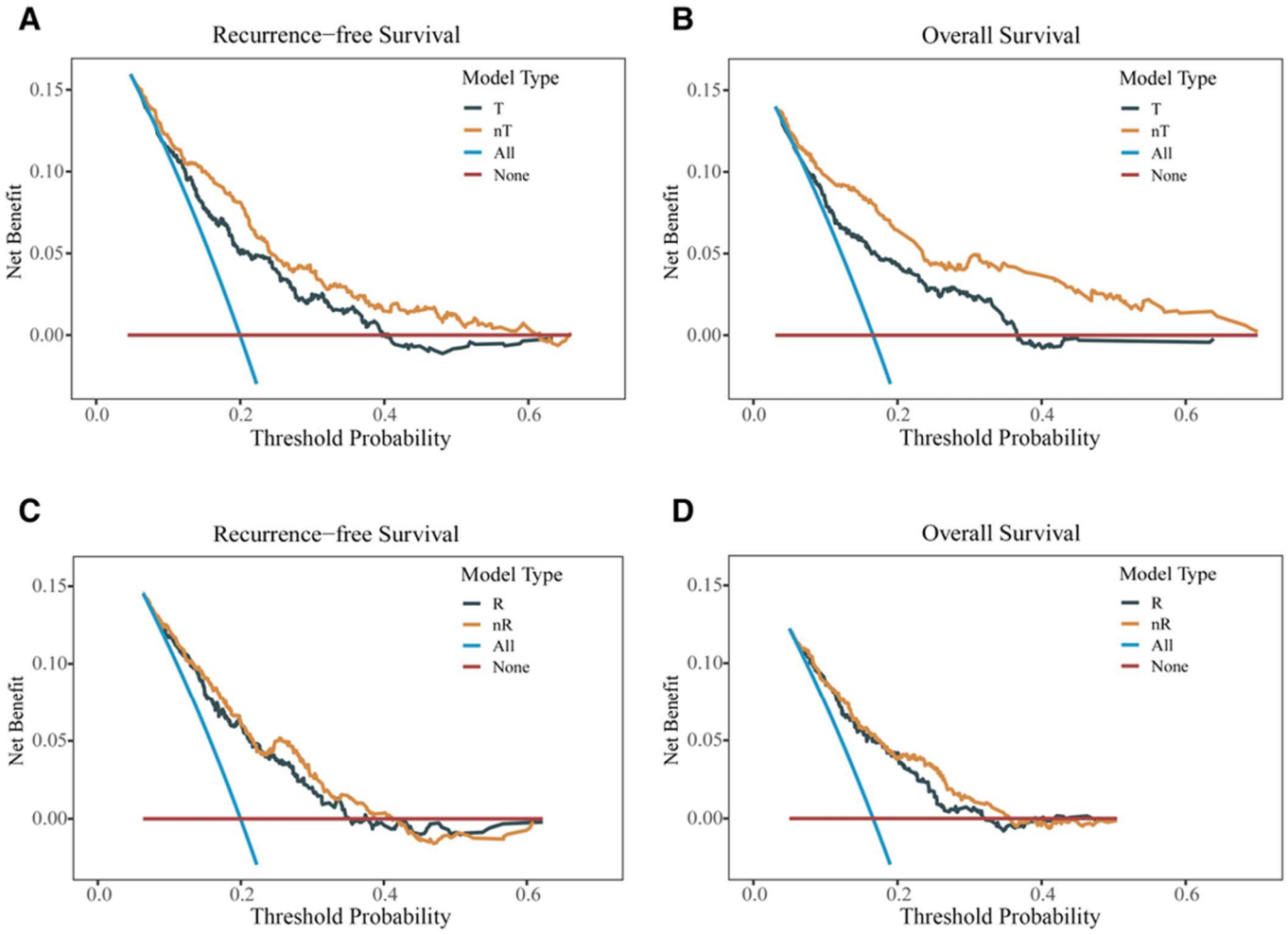
Table 2. Multivariate Cox regression analysis of prognosis for current T classification and proposed T classification in the primary cohort

	Current T classification				Proposed T classification			
	Recurrence-free survival		Overall survival		Recurrence-free survival		Overall survival	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (>65 versus ≤65 years)	0.93 (0.65–1.33)	0.683	0.97 (0.65–1.43)	0.865	0.94 (0.66–1.35)	0.750	0.99 (0.67–1.46)	0.942
Sex (female versus male)	1.03 (0.75–1.40)	0.877	1.01 (0.73–1.41)	0.941	0.98 (0.72–1.34)	0.894	0.98 (0.70–1.36)	0.905
Smoking history (ever versus never)	0.81 (0.54–1.21)	0.302	0.86 (0.56–1.33)	0.505	0.87 (0.58–1.31)	0.503	0.93 (0.60–1.43)	0.739
Tumor location (middle/lower lobe versus upper)	0.97 (0.71–1.33)	0.853	1.08 (0.78–1.51)	0.631	0.99 (0.73–1.36)	0.980	1.12 (0.81–1.56)	0.486
Surgical procedure (segmentectomy versus lobectomy)	1.16 (0.85–1.59)	0.357	1.13 (0.81–1.59)	0.472	1.14 (0.83–1.56)	0.430	1.10 (0.79–1.54)	0.581
STAS (present versus absent)	1.64 (1.08–2.48)	0.020	1.63 (1.05–2.53)	0.030				
Current T classification (T2a versus T1)	1.94 (1.29–2.90)	0.001	1.84 (1.21–2.80)	0.005				
Proposed T classification (T2a versus T1)					2.54 (1.64–3.93)	<0.001	2.42 (1.51–3.87)	<0.001
Tumor grade (3 versus 2 or 1)	1.64 (1.07–2.50)	0.023	1.77 (1.13–2.76)	0.013	1.76 (1.26–2.45)	0.001	1.99 (1.40–2.85)	<0.001
No. of HLNs (>8 versus ≤8)	0.92 (0.67–1.27)	0.616	0.91 (0.65–1.28)	0.581	0.89 (0.65–1.22)	0.466	0.89 (0.64–1.25)	0.515
LVI (present versus absent)	1.46 (0.98–2.17)	0.063	1.19 (0.75–1.88)	0.457	1.37 (0.92–2.04)	0.118	1.14 (0.74–1.65)	0.501
R classification [R(un) versus R0]	1.40 (1.02–1.93)	0.038	1.40 (0.99–1.97)	0.051	1.38 (1.01–1.90)	0.045	1.43 (1.02–2.01)	0.037
ACT (yes versus no)	0.82 (0.53–1.26)	0.358	0.84 (0.54–1.31)	0.438	0.81 (0.56–1.15)	0.238	0.84 (0.58–1.23)	0.378

Table 3. Multivariate Cox regression analysis of prognosis for current R classification and proposed R classification in the primary cohort

	Current R classification				Proposed R classification			
	Recurrence-free survival		Overall survival		Recurrence-free survival		Overall survival	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (>65 versus ≤65 years)	0.93 (0.65–1.33)	0.683	0.97 (0.65–1.43)	0.865	0.90 (0.63–1.28)	0.548	0.93 (0.63–1.37)	0.706
Sex (female versus male)	1.03 (0.75–1.40)	0.877	1.01 (0.73–1.41)	0.941	1.01 (0.74–1.37)	0.963	1.00 (0.72–1.40)	0.980
Smoking history (ever versus never)	0.81 (0.54–1.21)	0.302	0.86 (0.56–1.33)	0.505	0.81 (0.54–1.22)	0.315	0.88 (0.57–1.35)	0.551
Tumor location (middle/lower lobe versus upper)	0.97 (0.71–1.33)	0.853	1.08 (0.78–1.51)	0.631	0.99 (0.73–1.35)	0.943	1.12 (0.80–1.55)	0.517
Surgical procedure (segmentectomy versus lobectomy)	1.16 (0.85–1.59)	0.357	1.13 (0.81–1.59)	0.472	1.14 (0.84–1.56)	0.408	1.16 (0.82–1.64)	0.416
Pathologic T stage (T2a versus T1)	1.94 (1.29–2.90)	0.001	1.84 (1.21–2.80)	0.005	1.83 (1.26–2.67)	0.002	1.78 (1.20–2.66)	0.005
Tumor grade (3 versus 2 or 1)	1.64 (1.07–2.50)	0.023	1.77 (1.13–2.76)	0.013	1.48 (1.07–2.05)	0.017	1.47 (1.04–2.07)	0.029
No. of HLNs (>8 versus ≤8)	0.92 (0.67–1.27)	0.616	0.91 (0.65–1.28)	0.581	0.90 (0.66–1.23)	0.503	0.88 (0.63–1.24)	0.474
LVI (present versus absent)	1.46 (0.98–2.17)	0.063	1.19 (0.75–1.88)	0.457	1.42 (0.95–2.11)	0.088	1.31 (0.84–2.05)	0.231
STAS (present versus absent)	1.64 (1.08–2.48)	0.020	1.63 (1.05–2.53)	0.030				
Current R classification [R(un) versus R0]	1.40 (1.02–1.93)	0.038	1.40 (0.99–1.97)	0.051				
Proposed R classification [R(un) versus R0]					1.50 (1.07–2.08)	0.017	1.46 (1.03–2.08)	0.034
ACT (yes versus no)	0.82 (0.53–1.26)	0.358	0.84 (0.54–1.31)	0.438	0.78 (0.52–1.17)	0.224	0.73 (0.47–1.13)	0.159

Figure 4


A
Recurrence−free Survival
Model Type
T
nT
All
None
Net Benefit
0.15
0.10
0.05
0.00
0.0
0.2
0.4
0.6
Threshold Probability
B
Overall Survival
Model Type
T
nT
All
None
Net Benefit
Threshold Probability
C
Recurrence−free Survival
Model Type
R
nR
All
None
Net Benefit
Threshold Probability
D
Overall Survival
Model Type
R
nR
All
None
Net Benefit
Threshold Probability