Peer Review File

Article Information: http://dx.doi.org/10.21037/atm-20-5910

Review Comments

Comment 1: *First, I want to tell the ambiguity of the terminology used in the article. The terminology used in this paper 'grade' is somewhat confusing.*
As IASLC used the term "types" in their published book ("Four major types of neuroendocrine tumors of the lung are recognized: typical and atypical carcinoids, considered low- and intermediate-grade tumors, respectively; and LCNEC and SCLC, considered high-grade malignancies., page 155, IASLC Throacic Oncology). Also other published paper used "histotype" rather than "grade" indicating the typical, atypical carcinoid and other subtype of neuroendocrine tumor of the lung (for example, Righi et al. J Thorac Dis 2017 Nov; 9(Suppl 15): S1442–S1447.)

The 'grade' means degree of differentiation. Typical carcinoid and atypical carcinoid are low-intermediate grade, while there are high grade poorly differentiated large cell neuroendocrine tumor in the other end. In the lung neuroendocrine tumors, there has benn no specific grading system widely recognized and used, because grading is actually part of histologic definition. For this reason, I think it is more reasonable to use the term 'histology' instead of 'grade' for this article.

Reply 1: Thank you for your advice. We have changed “grade” into “histotype” in the paper and made relevant changes.

Changes in the text:
(Page 3, Line 44)
multivariate Cox analysis showed that tumor histotype and nodal status were independently associated with survival, rather than T stage. Therefore, by incorporating histotype of NETL (G1,low-grade typical pulmonary….
(Page 6, Line 94)
Tumor histotype and differentiation are crucial determinants of the clinical behavior of NETL
(Page 6, Line 103)
However, a recent study pointed out that staging systems for NETL should include histotype (6).
(Page 9, Line 201)
For histotype, G2 (HR [95%CI]: 2.42 [1.81-3.23]) and G3 (HR [95%CI]: 5.89 [4.83-7.19]) were significantly associated with reduced survival compared with G1. Consistently, histotype and N-stage were more significantly associated with survival in the RF model (importance: 0.102, 0.005, Table 2). By subgroup analysis of N stage, histotype of tumor could better discriminate patients’ survival in each subgroup of N stage, compared to T stage (Table 3). Subgroup analysis of histotype showed that TNM stage wasn’t suit for discriminating patients’ survival in different histotypes…
(Page 9, Line 201)
The survival tree was then built by regrouping tumor histotype and the nodal stage (Figure 1).
(Page 11, Line 378)
Histotype of NETL had a better survival predictive ability than T stage. Therefore, we created a new pathological staging system based on histotype and nodal status of the NETL…
(Page 12, Line 394)

Tumor histotype and differentiation are crucial determinants of the clinical behavior of NETL. Similar to the study by Skuladottir et al. (13), we found that the histotype of NETL was a significant prognostic factor for NETL.
(Page 12, Line 407)
Although Jackson et al.(6) explored staging system for NETL included histotype, N- and T-stage
(Page 12, Line 411)
Moreover, histotype showed a good survival discrimination in non-surgical patients while T-stage did not
(Page 13, Line 420)
Given the practicality of the staging system, it's reasonable to replace T stage with the histotype of NETL
(Page 13, Line 430)
Together, replacing T with histotype could help redefine prognostication and would have great potential for advising postoperative treatment for patients with these tumors
(Page 14, Line 449)
Our study found tumor histotype and nodal status were independently associated with survival for these patients, rather than T stage, therefore, we established the new pathological staging system for postoperative patients by recombining the histotype of NETL…
(Page 18, Line 538)
Figure 1. New staging system is proposed by survival tree. (a) Survival tree based on the best stage for 3224 M0 resected cases in the training group. Histotype and N…
(Page 18, Line 559)
Figure S5. (a) Overall survival by histotype in patients with the stage IIIC and IV

Table with track.doc_ **Table 1**

Variables	Training group (n=3204)	Validation group (n=3204)	p-value	SEER cohort (n=6408)	Shanghai cohort (n=132)	p-value
…	…	…	…	…	…	…
Histotype, n(%)			0.99			<0.001
G1	2361(73.7)	2358(73.6)		4719(73.6)	61(46.2)	
…	…	…	…	…	…	…

Table with track_ **Table 2**

	Univariate analysis		Multivariate analysis		Random forest model	
Variables	HR(95%CI)	p-value	HR(95%CI)	p-value	Importance	Relative importance
…	…	…	…	…	…	…

Histotype（G1 as reference）					0.102	1.000
G2	2.96(2.24,3.92)	<0.001	2.42(1.81,3.23)	<0.001		
…	…	…	…	…	…	…

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Comment 2: *How did you convert 7th stage to 8th stage? I suppose mostly the conversion was based on tumor size, but for some cases of the SEER data, restaging is somewhat difficult. For example, The tumor invading diaphragm is T3 based on 7th TNM, that is the very value in the SEER database. However, actually that case is T4 according to the 8th TNM. This should happen, and that would make the analysis incorrect. How did you handle it? Also, the SEER database recommends 'do not change the staging' for fear of possible error. How can you explain it?*

Reply 2: Thank you for your question. Since the eighth edition of the TNM classification was enacted on January 1, 2017, this revision enhances our capacity for prognostication and will have an important impact in the management of patients with lung cancer and in future research (1). Moreover, this version has been widely used by clinicians recently. Therefore, 8^{th} stage is more convincing than 7^{th} stage as a control object. On the other hand, we convert 7th stage to 8th stage by restaging these patients through tumor size (CS Tumor Size) and tumor extension (CS Extension). But we ignored the code “600” of CS Extension included direct extension to: chest (thoracic) wall, diaphragm, pancoast tumor (superior sulcus syndrome), parietal pleura, we can’t differentiate the stages of these patients as your advice, so we exclude these patients (40 patients) and we pointed out this limitation in the limitation part. Thanks for your advice again. Accordingly, all results have been slightly changed. And main revised Tables and Figures were showed below.

Reference:

1. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Mar;67(2):138-155. doi: 10.3322/caac.21390. Epub 2017 Jan 31. PMID: 28140453.

Changes in the text:

(Page 7, Line 125)

And patients whose tumor can’t be confirmed whether invading diaphragm were excluded.

(Page 13, Line 433)

Second, detailed data about invasion of diaphragm, positive margin, mitotic rate and Ki-67 weren’t recorded in SEER database

Table with track.doc_ **Table 1.** Characteristics of the patients

Variables	Training group (n=3204)	Validation group (n=3204)	p-value	SEER cohort (n=6408)	Shanghai cohort (n=132)	p-value
Age (mean±SD)	60.3±14.1	60.6±14.0	0.48	60.5±14.1	59.8±9.7	0.58
Race, n(%)			0.59			- †
White	2886(90.1)	2869(89.5)		5755(89.8)	-	
Black	198(6.2)	218(6.8)		416(6.5)	-	
Others	120(3.7)	117(3.7)		237(3.7)	-	
Male, n(%)	1070(33.4)	1146(35.8)	0.05	2216(34.6)	82(46.5)	<0.001
Histotype, n(%)			0.99			<0.001
G1	2361(73.7)	2358(73.6)		4719(73.6)	61(46.2)	
G2	260(8.1)	259(8.1)		519(8.1)	6(4.5)	
G3	583(18.2)	587(18.3)		1170(18.3)	65(49.2)	
8th edition Stage, n(%)			0.77			<0.001

IA1	351(11.0)	355(11.1)		706(11.0)	20(15.2)
IA2	1085(33.9)	1119(34.9)		2204(34.4)	16(12.1)
IA3	584(18.2)	583(18.2)		1167(18.2)	12(9.1)
IB	473(14.8)	427(13.3)		900(14.0)	35(26.5)
IIA	107(3.3)	120(3.7)		227(3.5)	5(3.8)
IIB	322(10.0)	324(10.1)		646(10.1)	16(12.1)
IIIA	254(7.9)	244(7.6)		498(7.8)	26(19.7)
IIIB	28(0.9)	32(1.0)		60(0.9)	2(1.5)
8th edition T Stage, n(%)			0.28		<0.001
T1a	376(11.7)	383(12.0)		759(11.8)	21(15.9)
T1b	1184(37.0)	1223(38.2)		2407(37.6)	20(15.2)
T1c	663(20.7)	689(21.5)		1352(21.1)	16(12.1)
T2a	597(18.6)	549(17.1)		1146(17.9)	45(34.1)
T2b	148(4.6)	162(5.1)		310(4.8)	13(9.8)
T3	135(4.2)	118(3.7)		253(3.9)	9(6.8)

T4	101(3.2)	80(2.5)		181(2.8)	8(6.1)	
8th edition N stage, n(%)			0.36			<0.001
N0	2772(86.5)	2732(85.3)		5504(85.9)	103(78.0)	
N1	262(8.2)	285(8.9)		547(8.5)	9(6.8)	
N2	170(5.3)	187(5.8)		357(5.6)	20(15.2)	
Surgery, n(%)			0.59			0.104
sub-lobectomy	871(27.2)	857(26.7)		1728(27.0)	25(18.9)	
lobectomy	2207(68.9)	2201(68.7)		4408(68.8)	99(75.0)	
pneumonectomy	114(3.6)	129(4.0)		243(3.8)	8(6.1)	
unknow	12(0.4)	17(0.5)		29(0.5)	0(0.0)	
Number of regional lymph nodes removed, n(%)			0.73			-
none	547(17.1)	578(18.0)		1125(17.6)	-	
1-3	616(19.2)	603(18.8)		1219(19.0)	-	

>3	1917(59.8)	1893(59.1)		3810(59.5)	-	
unknow	124(3.9)	130(4.1)		254(4.0)	-	
Radiotherapy, n(%)			0.81			0.797
no	3075(96.0)	3077(96.0)		6152(96.7)	124(93.9)	
neoadjuvant	16(0.5)	19(0.6)		35(0.5)	0(0.0)	
adjuvant	108(3.4)	106(3.3)		214(3.3)	8(6.1)	
neo- and adjuvant	2(0.1)	1(0.0)		3(0.0)	0(0.0)	
unknow	3(0.1)	1(0.0)		4(0.1)	0(0.0)	
Adjuvant chemotherapy, n(%)			0.20			<0.001
No	2943(91.9)	2914(90.9)		5857(91.4)	86(65.2)	
yes	261(8.1)	290(9.1)		551(8.6)	46(34.8)	

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas; SD, standard deviation; †, none.

Table with track.doc_ **Table 2.** Univariate, multivariate Cox regression analysis and random forest model on factors influencing survival in the training group.

	Univariate analysis		Multivariate analysis		Random forest model	
Variables	HR(95%CI)	p-value	HR(95%CI)	p-value	Importance	Relative importance
Age	1.06(1.05,1.07)	<0.001	1.05(1.05,1.06)	<0.001	0.044	0.430
Race (White as reference)					-0.0001	-0.011
Black	1.49(1.12,1.98)	<0.01	1.33(1.00,1.79)	0.05		
Others	0.77(0.49,1.29)	0.30	0.57(0.34,0.95)	0.03		
Gender (female as reference)					-0.005	-0.047
male	1.77(1.51,2.07)	<0.001	1.32(1.12,1.56)	<0.01		
T（T1a as reference）					-0.006	-0.056
T1b	0.95(0.71,1.27)	0.74	0.89(0.67,1.20)	0.45		
T1c	1.02(0.75,1.39)	0.90	0.86(0.63,1.19)	0.36		
T2a	1.21(0.89,1.65)	0.21	1.12(0.81,1.54)	0.51		
T2b	1.74(1.17,2.59)	<0.01	1.03(0.68,1.57)	0.88		

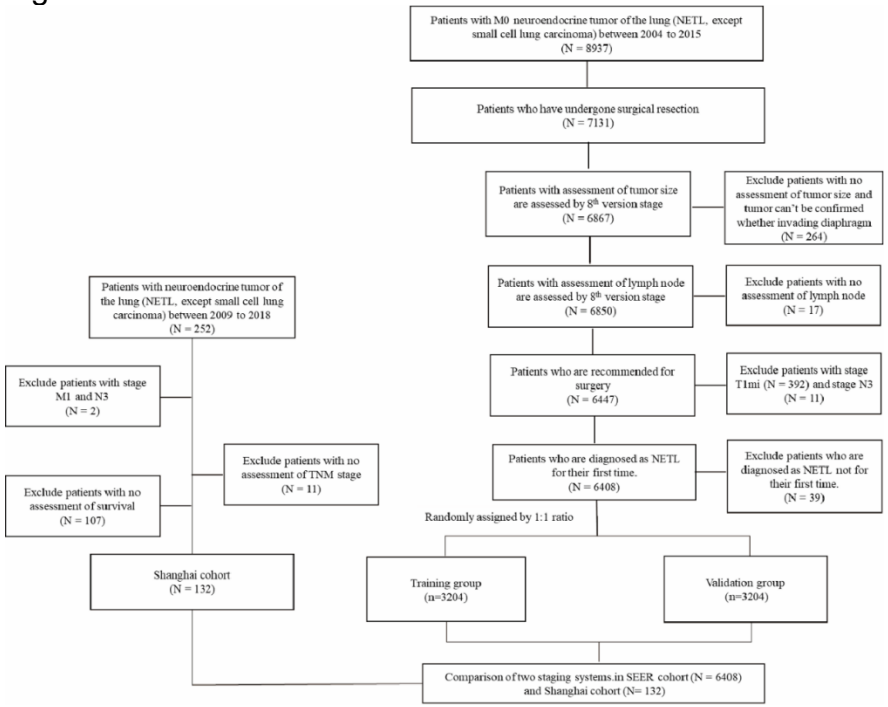
T3	2.07(1.39,3.08)	<0.001	1.10(0.71,1.70)	0.68		
T4	2.81(1.86,4.25)	<0.001	1.47(0.95,2.28)	0.09		
N（N0 as reference）					0.005	0.046
N1	2.12(1.67,2.69)	<0.001	2.10(1.62,2.73)	<0.001		
N2	3.11(2.43,3.99)	<0.001	2.75(2.05,3.69)	<0.001		
Histotype（G1 as reference）					0.102	1.000
G2	2.96(2.24,3.92)	<0.001	2.42(1.81,3.23)	<0.001		
G3	7.61(6.42,9.02)	<0.001	5.89(4.83,7.19)	<0.001		
8th edition stage (IA1 as reference）					-0.008	-0.082
IA2	1.10(0.81,1.50)	0.53	-	- †		
IA3	0.96(0.74,1.25)	0.78	-	-		
IB	1.20(0.93,1.56)	0.17	-	-		
IIA	1.33(0.84,2.09)	0.22	-	-		
IIB	2.14(1.65,2.78)	<0.001	-	-		
IIIA	3.18(2.48,4.09)	<0.001	-	-		

IIIB	4.26(2.42,7.50)	<0.001	-	-		
Surgery（sub-lobectomy as reference）					-	-
lobectomy	0.85(0.71,1.02)	0.07	0.87(0.69,1.10)	0.24		
pneumonectomy	1.63(1.14,2.33)	<0.01	1.53(1.00,2.34)	0.05		
unknow	0.25(0.04,1.80)	0.17	0.60(0.08,4.33)	0.61		
Number of regional lymph nodes removed (none as reference)					-	-
1-3	1.00(0.77,1.28)	0.97	0.94(0.71,1.25)	0.66		
>3	0.91(0.74,1.13)	0.39	0.69(0.52,0.91)	0.01		
unknow	0.99(0.66,1.49)	0.95	0.59(0.38,0.91)	0.02		
Radiotherapy (no as reference)						
neoadjuvant	0.00(0.00, 1.532E+052)	0.89				
adjuvant	0.92(0.56,1.52)	0.75				
neo- and adjuvant	8.62(1.21,61.37)	0.03				

unknow	0.00(0.00, 1.644E+185)	0.97			
Adjuvant chemotherapy (no as reference)				-0.0001	-0.001
yes	3.14(2.55,3.85)	<0.001	0.62(0.47,0.81)	<0.001	

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas. †, none.

Figure S1



Comment 3: *Why did you set IA2 as reference in the Cox anaylsis?*

Reply 3: Thank you for your question. Considering patients with stage IA2 occupies the most part, these patients were more suitable for the Cox analysis as reference statistically, but it is undeniable that it is really misleading for readers, therefore, we have revised this part and set stage IA1 as reference.

Changes in the text:
(Page 9, Line 199)
hazard ratios of survival in TNM stage IA2 to IIA were similar, ranging from 0.96 to 1.33 (IA1 as reference, Table 2)

Table with track.doc_ **Table 2**

Variables	Univariate analysis		Multivariate analysis		
	HR(95%CI)	p-value	HR(95%CI)	p-value	
…	…	…	…	…	
8th edition stage (IA1 as reference)					
IA2	1.10(0.81,1.50)	0.53	-	- †	
IA3	0.96(0.74,1.25)	0.78	-	-	
IB	1.20(0.93,1.56)	0.17			-
IIA	1.33(0.84,2.09)	0.22	-	-	
IIB	2.14(1.65,2.78)	<0.001		-	-
IIIA	3.18(2.48,4.09)	<0.001	-	-	
IIIB	4.26(2.42,7.50)	<0.001	-	-	
…	…	…	…	….	

Comment 4: *The radiotherapy variable in the SEER database has many values : neoadjuvant, adjuvant, unknown sequence, etc. Your analysis only included 'adjuvant radiotherapy'. Did you set all the other type of radiation as 'no'? Same question applies to the 'chemotherapy' variable.*

Reply 4: Thank you for your advice. We have supplemented this part of the data about radiotherapy. However, the 'chemotherapy' variable doesn't include these detailed data in the SEER database and this limitation has been mentioned in the limitation.

Changes in the text:

(Page 13 Line 438)
Last, even though the new staging system had been verified in Shanghai cohort, the lack of data (especially for G2 patients, adjuvant chemotherapy and hormonal or targeted therapy)

Table with track.doc_ **Table 1**

Variables	Training group (n=3204)	Validation group (n=3204)	p-value	SEER cohort (n=6408)	Shanghai cohort (n=132)	p-value
…	…	…	…	…	…	…
Radiotherapy, n(%)			0.81			0.797
no	3075(96.0)	3077(96.0)		6152(96.7)	124(93.9)	
neoadjuvant	16(0.5)	19(0.6)		35(0.5)	0(0.0)	
adjuvant	108(3.4)	106(3.3)		214(3.3)	8(6.1)	
neo- and adjuvant	2(0.1)	1(0.0)		3(0.0)	0(0.0)	
unknow	3(0.1)	1(0.0)		4(0.1)	0(0.0)	
…	…	…	…	…	…	…

Table with track.doc_ **Table 2**

	Univariate analysis	Multivariate analysis	Random forest model

Variables	HR(95%CI)	p-value	HR(95%CI)	p-value	Importance	Relative importance
…	…	…	…	…	…	…
Radiotherapy (no as reference)						
neoadjuvant	0.00(0.00, 1.532E+052)	0.89				
adjuvant	0.92(0.56,1.52)	0.75				
neo- and adjuvant	8.62(1.21,61.37)	0.03				
unknow	0.00(0.00, 1.644E+185)	0.97				
…	…	…	…	…	…	…

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas. †, none.

Comment 5: What is the exact endpoint of survival you used? I mean, cancer-specific survival or overall survival? SEER provides two types of survival data.

Reply 5: Thank you for your question. Because our study used data from the two databases for mutual verification, we only have overall survival data for patients in the Shanghai cohort. Considering the consistency and completeness of the entire study, we adopted overall survival as the exact endpoint of survival and we have pointed out this in the methods part. Moreover, we have done the cox analysis by cancer-specific survival, and T stage still show little survival prediction ability in the cox model and random forest model. Also, considering the consistency and completeness of the entire study, we don't insert this table into the manuscript and show the table below.

Changes in the text:
(Page 7, Line 129)
Overall survival was used as endpoint of survival.

Table. Univariate, multivariate Cox regression analysis and random forest model on factors influencing survival in the training group by cancer-specific survival.

	Univariate analysis		Multivariate analysis		Random forest model	
Variables	HR(95%CI)	p-value	HR(95%CI)	p-value	Importance	Relative importance
Age	1.05(1.04,1.06)	<0.001	1.03(1.02,1.05)	<0.001	0.015	0.100
Race (White as reference)					-0.0001	-0.011
Black	1.91(1.27,2.88)	<0.01	1.47(0.97,2.22)	0.07		
Others	0.867(0.41,1.83)	0.70	0.52(0.24,1.13)	0.10		
Gender (female as reference)					-0.000	-0.004
male	1.98(1.54,2.54)	<0.001	1.16(0.89,1.51)	0.28		
T（T1a as reference）					0.001	0.006
T1b	1.53(0.82,2.85)	0.18	1.30(0.67,1.20)	0.41		
T1c	2.20 (1.17,4.13)	0.02	1.62(0.85,3.09)	0.14		
T2a	2.87(1.54,5.36)	<0.01	1.91(1.00,3.66)	0.05		
T2b	5.29(2.65,10.58)	<0.001	2.31(1.12,4.75)	0.02		

T3	4.73(2.28,9.82)	<0.001	1.72(0.79,3.74)	0.68		
T4	9.35(4.67,18.70)	<0.001	3.22(1.55,6.72)	<0.01		
N（N0 as reference）					0.011	0.070
N1	3.24(2.31,4.56)	<0.001	2.57(1.77,3.73)	<0.001		
N2	5.22(3.72,7.31)	<0.001	3.63(2.40,5.48)	<0.001		
Histotype（G1 as reference）					0.152	1.000
G2	6.12(3.95,9.48)	<0.001	4.20(2.67,6.61)	<0.001		
G3	15.81(11.65,21.46)	<0.001	11.76(8.30,16.68)	<0.001		
8th edition stage (IA1 as reference）					-	-
IA2	1.28(0.66,2.48)	0.46	-	- †		
IA3	1.57(0.79,3.12)	0.20	-	-		
IB	2.23(1.13,4.39)	0.17	-	-		
IIA	2.94(1.25,6.93)	0.22	-	-		
IIB	4.99(2.58,9.65)	<0.001	-	-		
IIIA	8.62(4.53,16.40)	<0.001	-	-		

IIIB	10.08(3.91,26.03)	<0.001	-	-		
Surgery（sub-lobectomy as reference）					0.006	0.037
lobectomy	1.04(0.77,1.40)	0.80	0.73(0.49,1.07)	0.11		
pneumonectomy	2.97(1.82,4.85)	<0.001	1.46(0.80,2.67)	0.22		
unknow	0.00(0.00, 8.000E+108)	0.94	0.00(0.00, 3.391E+132)	0.95		
Number of regional lymph nodes removed (none as reference)					-	-
1-3	1.11(0.71,1.75)	0.64	0.97(0.58,1.61)	0.90		
>3	1.42(0.98,2.07)	0.07	0.87(0.54,1.42)	0.58		
unknow	1.55(0.81,2.94)	0.18	0.73(0.37,1.44)	0.36		
Radiotherapy (no as reference)						
neoadjuvant	0.00(0.00, 3.250E+124)	0.95				
adjuvant	1.16(0.58,2.35)	0.68				
neo- and adjuvant	0.00(0.00, -)	0.99				

unknow	0.00(0.00, -)	0.98					
Adjuvant chemotherapy (no as reference)						-0.007	-0.047
yes	5.05(3.80,6.71)	<0.001	0.60(0.42,0.87)	<0.01			

G1, low-grade typical pulmonary carcinoids; G2 intermediate-grade atypical pulmonary carcinoids; G3, high-grade large cell neuroendocrine carcinomas. †, none.

Comment 6: *6. For designing new staging system. tumor size has been important prognostic factor. Probably the size criteria would be different for the neuroendocrine tumors. I think just erasing the tumor size from the staging sytem is rather aggressive, and it has to be prudent (see:J Thorac Cardiovasc Surg 2018;155:405-13). Why don't you incorporating tumor size with the histology together? Probably the size cut would be different from NSCLC staging.*

Reply 6: Thanks for your constructive suggestions. Although Maria Cattoni et al. (1) explored that T stage was an independent factor of survival for NETL, the number of patients that involved in that study was too small, especially for pT4 (only 10 patients), which may cause considerable data bias. Moreover, T2 and T3 stage didn't show significant HR (1.49 [0.76-2.93], 1.50 [0.64-3.74] for T2 and T3, T1 as reference). And a research (2) about evaluation of the prognostic significance of TNM staging Guidelines in lung carcinoid tumors based on the SEER database revealed that no significant differences in survival were found for any T status compared with for the T1a group in the Atypical carcinoids subgroup and there were overlaps between adjacent categories for typical carcinoids subgroup. Further, in the discussion, we also point out "Jackson et al.(6) explored staging system for NETL included histotype, N- and T-stage, there was no significant improvement for ability of prognostic discrimination compared to our new stage (NRI [95%CI], 0.03 [<-0.01, 0.38]; IDI [95%CI], -0.6% [-1.7%, 0.7%], Supplementary Table S2)." Based on the published papers and our data, it supports our results that T stage didn't have good prognostic discrimination for NETL. Instead of adding T staging to the system to complicate the staging system, it is better to delete this variable and add more valuable variables related to survival to optimize staging system (such as histotype mentioned in this article, and positive margin, mitotic rate and Ki-67 mentioned in limitation part).

Limitation part: (Page 13, Line 433)
"Second, detailed data about invasion of diaphragm, positive margin, mitotic rate and Ki-67 weren't recorded in SEER database, all of which were reportedly associated with survival."

Reference:
1. M. Cattoni, E. Vallieres, L.M. Brown, A.A. Sarkeshik, S. Margaritora, A. Siciliani, P.L. Filosso, F. Guerrera, A. Imperatori, N. Rotolo, F. Farjah, G. Wandell, K. Costas, C. Mann, M. Hubka, S. Kaplan, A.S. Farivar, R.W. Aye, B.E. Louie, Improvement in TNM staging of pulmonary neuroendocrine tumors requires histology and regrouping of tumor size, J Thorac Cardiovasc Surg 155(1) (2018) 405-413.
2. Yoon JY, Sigel K, Martin J et al. Evaluation of the prognostic significance of tnm staging guidelines in lung carcinoid tumors. J Thorac Oncol 2019;14(2):184-192.
6. Jackson AS, Rosenthal A, Cattoni M et al. Staging system for neuroendocrine tumors of the lung needs to incorporate histologic grade. Ann Thorac Surg 2020;109(4):1009-1018.