The IASLC Lung Cancer Staging Project

Proposals for the Inclusion of Broncho-Pulmonary Carcinoid Tumors in the Forthcoming (Seventh) Edition of the TNM Classification for Lung Cancer

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Objective: In the 2003 Supplement for tumor, node, metastasis (TNM) Staging classification it states that TNM staging "applies to all types of carcinoma including small cell carcinoma; however, it does not apply to carcinoids." Despite this caveat, most publications on typical and atypical carcinoids use the TNM staging system for nonsmall cell carcinoma and are able to demonstrate prognostic significance for the different stages. For this reason, as the next TNM Staging proposal is being considered, we sought to investigate the carcinoid cases submitted to the International Association for the Study of Lung Cancer (IASLC) database, as well as the National Cancer Institute Surveillance Epidemiology and End Results (SEER).

Materials and Methods: In the data collected for the IASLC Staging Project database over the time period 1990 to 2000, there were 513 broncho-pulmonary carcinoids. A total of 1619 broncho-pulmonary carcinoid cases diagnosed over the period 1990–2002 were analyzed from the SEER database, including 1437 surgical cases. Pathologic slides were not available for histologic review.

Results: Most of tumors in both the IASLC and SEER databases were Stage I (82% and 78%, respectively), as defined by the IASLC proposals for the 7th edition of TNM staging system. T status was a statistically significant predictor of survival for both the SEER data ($p < 0.0001$) and the IASLC database ($p = 0.0156$), though for different reasons. N status showed significant survival correlations in both data sets ($p < 0.0001$). The effect of M status was significant ($p < 0.0001$) within the SEER data and not studied in the IASLC cases, which were almost exclusively M0. We found that all three T, N, and M categories as defined for non-small cell lung cancer are generally useful for staging of pulmonary carcinoid tumors. Significant differences in survival for overall stages I versus II versus III/IV were identified in both data sets. Patients with multiple same lobe nodules had a 100% 5-year survival, which may be a reason to reevaluate their status in the IIB category in future analyses.

Conclusions: In summary, the IASLC proposals for the 7th edition of TNM are helpful in predicting prognosis for broncho-pulmonary carcinoid tumors. It is the recommendation of the IASLC Staging project that TNM be applied to broncho-pulmonary carcinoid tumors. A prospective collection of data through an International Registry of Pulmonary Neuroendocrine Tumors planned by the IASLC will allow for further detailed analysis of staging data for broncho-pulmonary carcinoids.

Key Words: Carcinoid, Typical carcinoid, Atypical carcinoid, Stage, Lung, TNM, UICC, AJCC, Survival.

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The International Association for the Study of Lung Cancer (IASLC) has sponsored a project since 1998 to formulate proposals for revision of the tumor, node, metastasis (TNM) staging system.[1] A database of 100,869 lung cancer cases was collected for this project. Data were accepted from all parts of the globe, for all modalities of care, including best supportive care, enrolled between 1990 and 2000.

Based on a statistical analysis of these cases, a series of papers have recently been published with proposals for modifications in the T, N, and M categories as well as the resultant stage groupings.[2–6] These papers contain a series of proposals for modifications to the current 6th Edition of the TNM Classification of Malignant Tumors. Throughout this paper,

we refer to these new proposals as "proposed IASLC" stage and have classified cases according to this proposed system, unless otherwise noted. Although carcinoid tumors were not specifically requested, data on over 500 pulmonary carcinoid tumors were submitted to Cancer Research And Biostatistics for analysis. This led us to consider how these cases could be analyzed in the context of the IASLC Lung Cancer Staging Project.

In the 3rd Edition of their TNM Supplement: A Commentary on Uniform Use, published in 2003, the International Union Against Cancer (UICC) state that TNM staging "applies to all types of carcinoma including small cell carcinoma; however it does not apply to carcinoids."[7] Despite this caveat, most publications on typical and atypical carcinoids use the TNM staging system for nonsmall cell carcinoma and are able to demonstrate prognostic significance for the different stages.[8–16] For this reason, as the next TNM Staging proposal is being considered, we sought to investigate the National Cancer Institute Surveillance Epidemiology and End Results (SEER) registry, as well as the cases submitted to the IASLC database,[1]to determine whether the current and the proposed TNM staging systems are suitable for predicting outcome in broncho-pulmonary carcinoids.

METHODS

IASLC Proposals for the 7th Edition of the UICC and AJCC TNM Staging Classification for Lung Cancer

The derivation model for the proposed IASLC Staging system used in this manuscript has been reported in a series of prior publications and is being considered for the upcoming 7th edition of the UICC and AJCC staging system.[2–6]

SEER Database

Over the period 1990–2002, the SEER database had 1619 total cases with complete TNM staging and carcinoid (ICDO-3 codes 8240 and 8249/3) as the first neoplasm. This included 947 (58%) SEER cases between 1990 and 1997 and 672 during 1998 and through 2002. The 1437 surgically managed cases from this cohort were chosen as a validation group for findings based on the IASLC data. The distribution of these cases according to the proposed IASLC pathologic stage groupings is summarized in Table 1.

Histologic distinction between typical versus atypical carcinoid was not generally made in the SEER data for this time period; however, cause of death was documented. Clinical stage was not reported due to lack of information regarding typical versus atypical carcinoid and concerns that the data might be contaminated by cases of large cell neuroendocrine carcinoma or small cell carcinoma.

IASLC Database

In the data collected for the IASLC Staging Project database over the time period between 1990 and 2000, there were 513 carcinoids. The contributors for the cases, summarized in Table 2, were predominantly surgical centers. Sufficient pathologic TNM data were available for 392 surgically managed carcinoid cases. The distribution of these cases according to pathologic stage groupings is summarized in Table 3. Clinical stage was not evaluated because of the smaller numbers of cases with clinical stage data. Information specifying typical versus atypical carcinoid was only available in half of the cases. Data on cause of death were not available in the IASLC database.

TABLE 1. IASLC Proposed Staging for Seer Carcinoid Database by Overall Stage, Tm-Descriptor and N; Surgically Managed Cases Only

		N-Category				
Total	**Total**	**N0**	**N1**	**N2**	**N3**	**NX**
	1437	1243	124	56	4	10
IA Total stage 1A	814	814				
T1a T1a: ≤2 cm	566	566				
T1b T1b: >2–3 m	248	248				
IB Total stage 1B	314	314				
T2a T2a: ≤5 cm	314	314				
IIA Total stage IIA	126	31	95			
T1a T1a: ≤2 m	27		27			
T1b T1b: >2–3 cm	23		23			
T2a T2a: ≤5 cm	45		45			
T2b T2b: >5–7 cm	31	31				
IIB Total stage IIB	42	39	3			
T2b T2b: >5–7 cm	3		3			
T3 T3: >7 cm	7	7				
T3 by invasion	19	19				
T3 by same-lobe nodules	13	13				
IIIA Total stage IIIA	84	15	23	46		
T1a T1a: ≤2 cm	7			7		
T1b T1b: >2–3 cm	10			10		
T2a T2a: ≤5 cm	19			19		
T2b T2b: >5–7 cm	6			6		
T3 T3: >7 cm	2		2	0		
T3 by invasion	10		9	1		
T3 by same-lobe nodules	5		2	3		
T4 T4 by same-side nodules	9	7	2			
T4 by extension	16	8	8			
IIIB Total stage IIIB	8			4	4	
T1b T1b: >2 m	2				2	
T4 T4 by same-side nodules	2			1	1	
T4 by extension	4			3	1	
IV Total stage IV	49	30	3	6	0	10
M1a Contralateral nodules	9	4	0	2	0	3
Malignant pleural effusion	18	9	2	1	0	6
M1b Distant metastasis	22	17	1	3	0	1

IASLC, International Association for the Study of Lung Cancer.

Tumor Size

Tumor size histograms were generated to compare the distributions of tumor size for carcinoid N0 cases versus nonsmall cell lung cancer (NSCLC) N0 cases, taking into account IASLC T-category. More complete analyses of the NSCLC cases from these databases are published elsewhere.[2,5] Tumorlets, i.e., neuroendocrine proliferations measuring less than 0.5 cm, were by definition excluded from analyses of carcinoid cases.

TABLE 2. IASLC Staging Project Carcinoid Database, Types of Stage Data Available

Submitting Group	Clinical TNM	Pathologic TNM	Clinical and Path TNM	Insufficient for Proposed System
Clinical centre of Serbia	0	1	2	0
Guangdong provincial people's hospital	0	4	0	2
Faculty hospital Plzen	0	0	6	0
Flemish lung cancer registry-VRGT	6	5	4	22
Grenoble university hospital-isere cancer registry	6	0	0	21
Intergroupe Francophone de Cancerologie Thoracique (IFCT)	0	0	0	1
Japanese joint committee of lung cancer registry	2	15	54	2
John Hopkins University	4	6	29	3
Leuven lung cancer group	4	1	2	7
MD Anderson Cancer Center-Thoracic and Cardiovascular Surgery (MDACC-TCVS)	1	5	3	8
Memorial Sloan-Kettering Cancer Center	0	9	27	1
Cancer registry of Norway	0	108	0	2
Prince Charles hospital, Brisbane	0	6	8	1
Queensland Radium Institute	10	0	0	8
St Vincent's Hospital, Victoria	1	0	1	0
University of Sydney	1	80	0	3
Taiwan lung cancer society	0	0	3	2
Institute of lung diseases, Warsaw	0	0	13	0
Western Hospital, Melbourne	1	0	0	2
Total	36	240	152	85
Sufficient path TNM		392		

IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, metastasis; IFCT, Intergroupe Francophone de Cancerologie Thoracique.

Survival Analysis

Survival was measured from the date of diagnosis for the SEER data, and from the date of surgery for the IASLC data. Survival was estimated using the Cox regression method. Prognostic groups were assessed by Cox regression analysis, using the SAS system for Windows version 9.0 PHREG method. Significance values from pairwise comparisons reflect the Wald test; those from joint model effects (e.g., comparing the full model to the null model) reflect the likelihood ratio test. Significance values were not adjusted for multiple comparisons. Survival curves were compared by T and N status in M0 patients and by M status according to the proposed IASLC Staging system. Survival was also analyzed by tumor size.

Survival differences among the overall proposed stage groupings were modeled by Cox regression, with adjustment for gender (male versus female) and age (greater than 60 years versus 60 or younger). The percent variation explained by this model was approximated using the R^2 statistic.[17]

Because of the indolent clinical course of many carcinoid tumors, and the available information about cause of death in the SEER database, we made further analyses of cancer specific survival. Here, survival was characterized in terms of cumulative incidence of death by the carcinoid tumor, so as to allow adjustment for the competing risk of death due to other or unknown causes.

RESULTS

SEER Database

Clinical Features

In the SEER dataset, there were 1619 total cases with 1063 females (66%) and 556 males (34%). There were 1437 surgical cases, the focus of this analysis, with 949 females (66%) and 488 males (34%). The median and mean age for the surgically managed subset was 59 and 55 years (range, 12–91 years). Sixty percent were followed 5 years or until death; and 26% were followed 10 years or until death.

Tumor Size

In the SEER surgical cases, the median and mean size for tumors regardless of nodal status was 2 and 2.4 cm, (range, 0.5–16.5 cm). Among the 1194 N0 cases, the peak range for tumor size was >1.0 to 1.5 cm (Figure 1*A*). There were relatively few carcinoid tumors larger than 3.0 cm compared with NSCLC (Figure 1*B*).

pT, N, and M Status

The overall stages for the surgically managed SEER carcinoid cases by TM descriptor and N are summarized in Table 1. The SEER database documents only "best" stage–generally, a pathologic stage if tissue was obtained, otherwise clinical–but for these surgically managed cases, findings were assumed to be based on the resection attempt. Stage I

TABLE 3. IASLC Proposed Staging or IASLC Carcinoid Database, Pathologic Stage by pTM-Descriptor and pN

		pN-Category		
Total	**Total**	**N0**	**N1**	**N2**
	392	350	29	13
IA Total stage 1A	267	267		
T1a T1a: ≤2 cm	154	154		
T1b T1b: >2–3cm	72	72		
T1x T1x, no size	41	41		
IB Total stage 1B	56	56		
T2a T2a: ≤5 cm	56	56		
IIA Total stage IIA	37	10	27	
T1a T1a: ≤2 cm	8		8	
T1b T1b: >2–3 cm	8		8	
T1x T1x, no size	1		1	
T2a T2a: ≤5 cm	10		10	
T2b T2b: >5–7 cm	10	10		
IIB Total stage IIB	18	17	1	
T2b T2b: >5–7 cm	1		1	
T3 T3: >7 cm	1	1		
T3 by invasion	9	9		
T3 by same-lobe nodules	7	7		
IIIA Total stage IIIA	13	0	1	12
T1a T1a: ≤2 cm	2		2	
T1b T1b: >2–3 cm	1			1
T2a T2a: ≤5 cm	5			5
T2b T2b: >5–7 cm	1			1
T3 T3: >7 cm	1		1	0
T3 by invasion	3		0	3
IV Total stage IV	1	0	0	1
M1b Distant metastasis	1	0	0	1

IASLC, International Association for the Study of Lung Cancer.

tumors represented 1128 of the 1437 tumors (78%); the majority of tumors were stage IA: 57% with 39% in T1a and 17% in T1b. Stage II tumors comprised 168 (12%) of the tumors with 9% in Stage IIA and 3% in Stage IIB. The majority of the Stage IIA cases were T2a and T2b. Most of the IIB tumors were T3 for reasons other than tumor size. Stage III tumors represented 92 (6%) of all cases with 6% in IIIA and <1% in IIIB. The largest group in stage IIIA was T2a (1%). Stage IV represented 3% of all tumors.

Survival Analysis

For surgical cases in the SEER database, increasing T, N, and M status generally showed correlations with reductions in survival (Figures 2*A–C*). Survival for T3 was significantly different from T1 to T2 ($p < 0.0001$); however, there was little difference in survival between T1 and T2 in this dataset. For T status, with any N category, T1a/T1b had the same 5-year estimated survival at 93/92% and T2a/T2b had the same survival at 90% (Figure 2*A*). T3 with size greater than 7 cm had a slightly worse survival at 65% compared with 79% assigned to T3 because of same lobe nodules and 74% assigned to T3 because of other descriptors (Figure 2*A*). There were significant differences ($p < 0.0001$) in survival by N status in M0 cases, with 5-year survival estimates reduced from 92% for N0 to 81% for N1, 74% for N2 and 0% for N3 (Figure 2*B*). Survival for M0 cases was significantly different from M1 ($p < 0.0001$), with 5-year survival of 57% for M1 compared with 91% for M0 cases (Figure 2*C*). In surgically treated M1 cases (data not shown), there were no deaths in 7 cases with contralateral nodules nor in the 11 T4 cases with same-side nodules and only 2 deaths in the 18 T3 cases with same-lobe nodules (79% 5-year survival).

When applying the IASLC TNM proposal for the 7th Edition to pathologic stage cases, Stage 1A/1B contained 814/314 cases, respectively, and 5-year survival was similar at 91 to 93% (Figure 3*A*). The numbers of cases were much smaller for IIA/IIB with 126/42 cases for proposed IASLC, respectively. The 5-year estimated survival for IIA/IIB cases in the proposed IASLC staging system was similar (85/86%). For Stage IIIA/B and IV, there were 84/8 and 49 cases, respectively, using the proposed IASLC staging system. Survival for IIIB (47%) was worse than both IIIA (78%) and stage IV (57%). For the combined stage groups survival for Stage 1 was 93%, for Stage II it was 85%, for Stage III it was 75% and for Stage IV it was 57% (Figure 3*B*).

Table 4 summarizes the results of Cox proportional hazards regression applied to the SEER data, modeling survival differences between the main overall stage groups (I versus II versus III versus IV) with adjustment for age and sex. In this model, stage II was significantly different from stage I (hazard ratio = 1.98, $p = 0.0012$), and stage III was significantly different from stage II (hazard ratio = 2.25, $p = 0.0028$), but stage IV and III were not significantly different (hazard ratio = 1.19, $p = 0.5656$). Older age greater than 60 years compared with 60 years or less (hazard ratio = 3.75, $p < 0.0001$) and male sex (hazard ratio = 1.40, $p = 0.0291$) significantly correlated with worse survival.

Cancer Specific Survival, SEER Database

There were 195 deaths in the 1437 surgically managed SEER patients (13.6%), but only 56 of these deaths were specifically attributed to the primary lung tumor. In our analysis of the cumulative incidence of death due to carcinoid with adjustment for competing risk of death due to other or unknown causes, the 5-year estimates for all stages for the IASLC proposal showed substantially less mortality (Figure 4) compared with Kaplan Meier survival analysis using death for any cause (Figures 3*A*, *B*). In general, these curves showed increased tumor-related deaths with increasing stage. Nevertheless, in the IASLC proposed system, there were fewer deaths in the IIB (1 total/3% at 5 years) than the IIA patients (11 total/7% at 5 years) (Figure 4). In addition, we were not able to demonstrate significant differences according to tumor size for T1N0 at 2 cm or for T2N0 at 4 or 5 cm cutoffs (data not shown).

There were insufficient data for typical versus atypical carcinoids to make any conclusion regarding stage and survival.

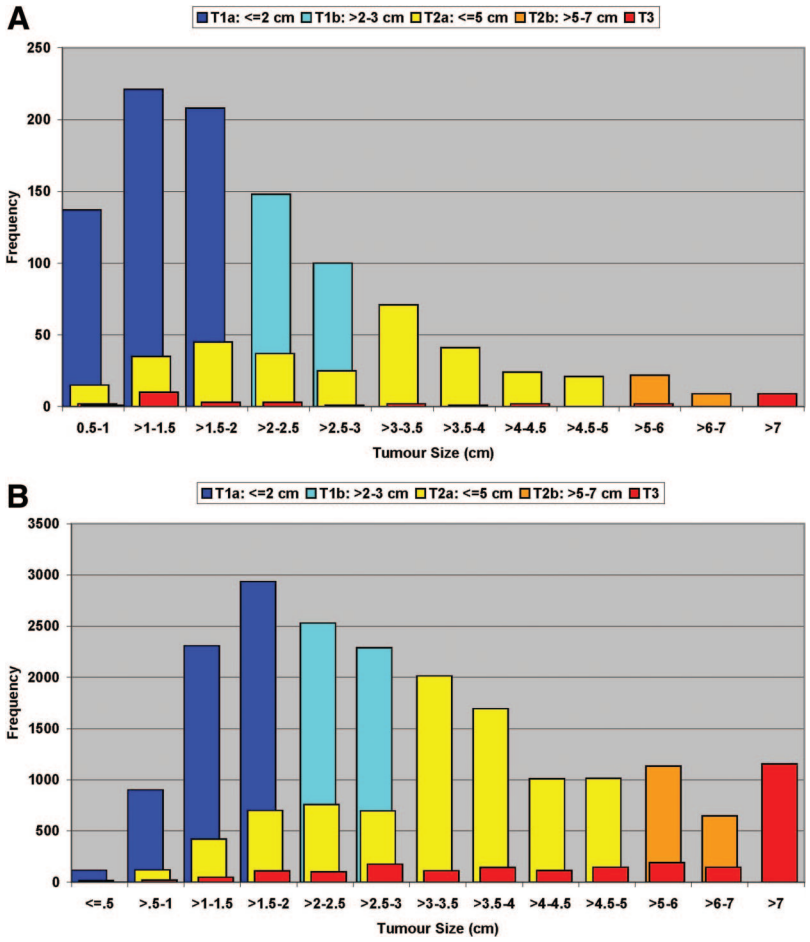

FIGURE 1. Histograms of tumor size, SEER surgically treated cases diagnosed 1990–2002. *A*, Carcinoid (n = 1194); tumor size by proposed IASLC T-category, N0 cases only. *B*, Non-small Cell Lung Carcinoma (NSCLC) database (n = 23,780); tumor size by proposed IASLC T-category, N0 cases only.

IASLC Database

Clinical Features

There were a total of 513 carcinoids in the IASLC database. The median and mean age for all tumors was 58 and 54 years (range, 13–88 years). There were 269 females (55%), 216 males (45%), and 28 with no gender data.

For the IASLC surgical database, 75% were followed 5 years or until death; and 29%, were followed 10 years or until death.

Tumor Size

In the IASLC database the pathologically measured tumor size, regardless of nodal status, was a median and mean of 2.0 and 2.3 cm (range, 0.5–8.5 cm). In the IASLC database, the peak range for T1a carcinoid tumors was >1.5 to 2.0 cm. There were relatively few tumors larger than 3.0 cm compared with NSCLC (data not shown).

pT, N, and M Status

The pathologic stage, by pTM descriptor and pN for the IASLC carcinoid database is summarized in Table 3. Stage I tumors represented 323 of the 392 tumors (82%); the majority of tumors were stage IA: 68% with 39% in T1a, 18% in T1b, and unknown tumor size in 10%. Stage II tumors comprised 55 (14%) of the tumors with 9% in Stage IIA and 5% in Stage IIB. Most of the IIB tumors were T3 for reasons other than tumor size; 17 were N0 and only one was N1 including 7 cases that were T3 by multiple nodules and showed 100% 5-year survival. Stage III tumors represented 13 (3%) of all cases, all of them in IIIA. There was only one Stage IV case (<1%) by distant metastases.

Survival Analysis

Survival by T and N status generally showed reductions in survival with increasing category. Pairs of adjacent pT subcategories were not formally compared due to the small numbers of cases, however, the overall effect of pT status on survival was significant (p = 0.0156) There were no deaths in the seven cases designated T3 by reason of same-lobe additional nodules.

The effect of pN status on survival was significant ($p < 0.0001$); there was a reduction in survival from pN0 cases to pN1 and pN2 cases that was more apparent at 10 years (84%, 54%, and 0%) than at 5 years (92%, 68%, and 64%), respectively. Overall, there was a significant difference in survival for the majority pN0 versus pN1 (p = 0.0006), but not between the less populated groups of pN2 versus pN1.

Analyzing the data according to the proposed IASLC pathologic stage, Stage 1A/1B contained 267/56 cases respectively and 5-year survival was similar at 93 to 94%

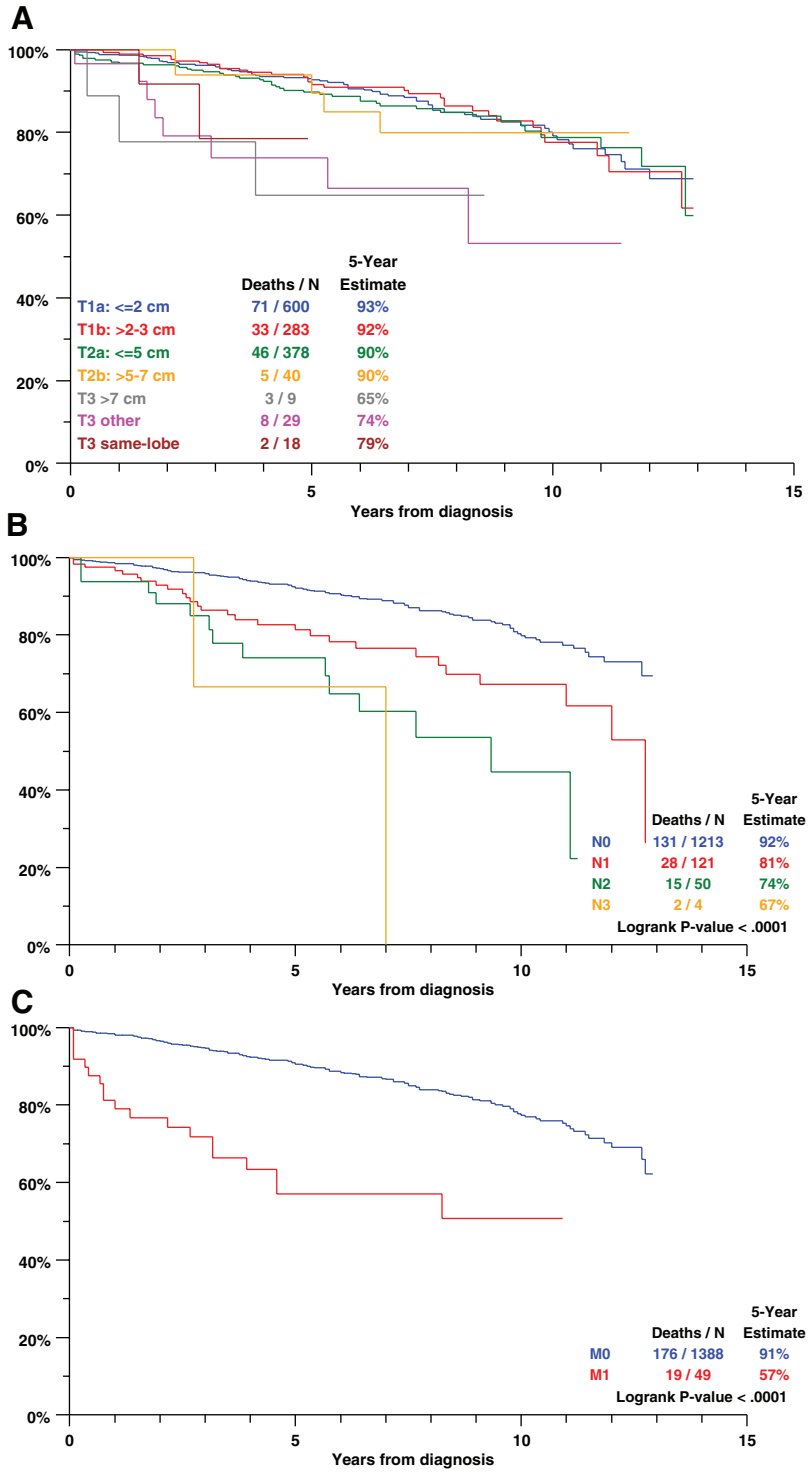

FIGURE 2. SEER surgically treated carcinoid cases diagnosed 1900–2002, death by any cause. *A*, T1–T3 by size and proposed IASLC T-category, any N. *B*, Survival by N-category in M0 cases. *C*, survival by IASLC proposed M-category.

(data not shown). Five-year survival for IIA/IIB was 74%/83%, but there were only 37/18 cases respectively. Five-year survival for IIIA was 67%, and there were no IIIB cases. With only one Stage IV case, survival was not assessed.

Table 5 summarizes the results of Cox proportional hazards regression applied to the IASLC data, modeling survival differences between the main overall pathologic stage groups represented in the data, with adjustment for age and sex. In this model, stage II was significantly different from stage I (hazard ratio = 2.94, $p = 0.0005$), and stage III (exclusively IIIA) was significantly different from stage II (hazard ratio = 5.15, $p < 0.0001$). Older age greater than 60 years compared with 60 years or less (hazard ratio = 8.85, $p <$

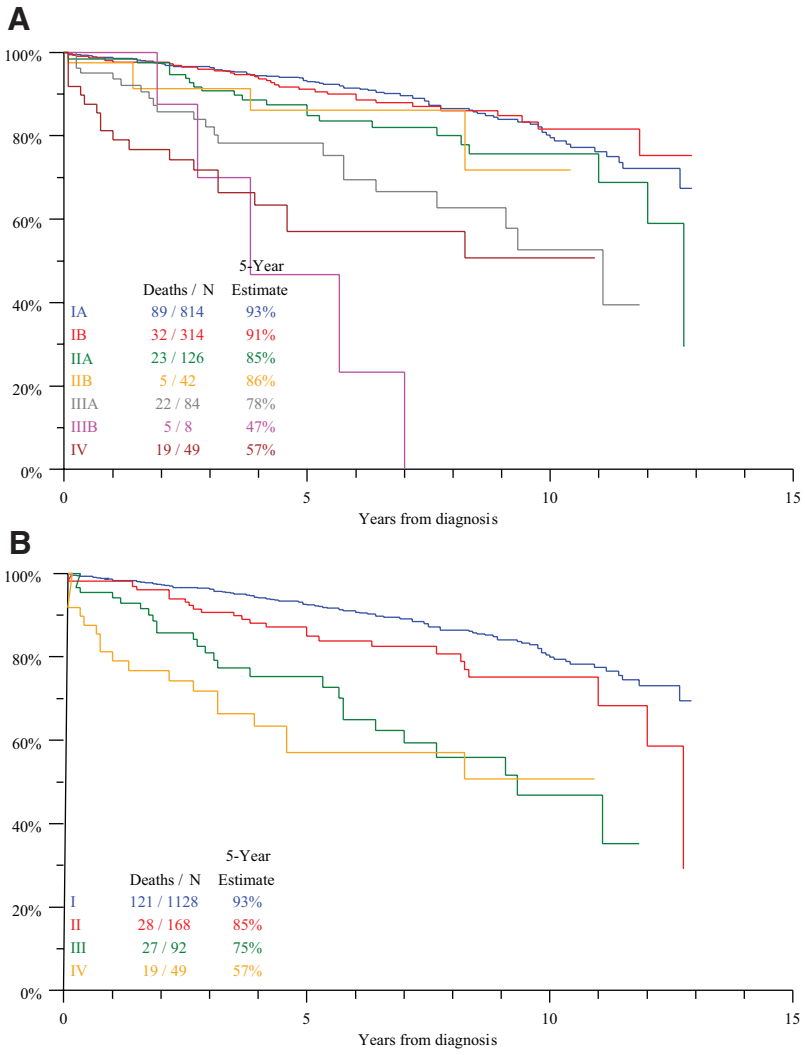

FIGURE 3. SEER Surgically treated carcinoid cases diagnosed 1900–2002, death by any cause. *A*, IASLC proposed stage, all stage groupings. *B*, IASLC proposed stage, combined stage groupings.

TABLE 4. Survival Comparisons Between Proposed Stages (I vs. II vs. III vs. IV) Within Seer Database, Surgically Managed Cases

Comparison	Hazard Ratio	*p*
II vs. I	1.98	0.0012
III vs. II	2.25	0.0028
IV vs. III	1.19	0.5656
Age >60 vs. ≤60	3.75	<0.0001
Male vs. female	1.40	0.0291
R^2 = 41.3		

Cox regression model adjusted for age and sex.
n = 1437 (195 events).

0.0001) significantly correlated with worse survival but male sex did not and the effect of being male bordered on significance (hazard ratio = 1.69, $p = 0.0557$).

For the T1N0 carcinoids, there was significantly worse survival ($p = 0.0077$) for those with tumors >2 to 3 cm (88%) compared with ≤2 cm (94%).

There were insufficient data for typical versus atypical carcinoids to make any conclusion regarding stage and survival.

DISCUSSION

We found that all T, N, and M categories as defined by the IASLC proposal for the 7th Edition of the NSCLC TNM staging system are generally useful for staging of broncho-pulmonary carcinoid tumors. While the subcategories of the stage groupings for (IA versus IB and IIA versus IIB) do not show significant differences in survival across the board in our analysis, the combined stage categories (I versus II versus III/IV) do show significant differences. Our findings indicate there are two major issues that need further study in staging of broncho-pulmonary carcinoids: (1) carcinoids presenting with multiple nodules and (2) whether the new larger proposed size cutoffs of 5 and 7 cm are meaningful in carcinoids.

In the SEER data base, patients with multiple nodules had an excellent survival with no deaths in the 17 patients with M1a contralateral nodules or T4 same side nodules (but separate lobe to that of the primary tumor) and only 2 deaths

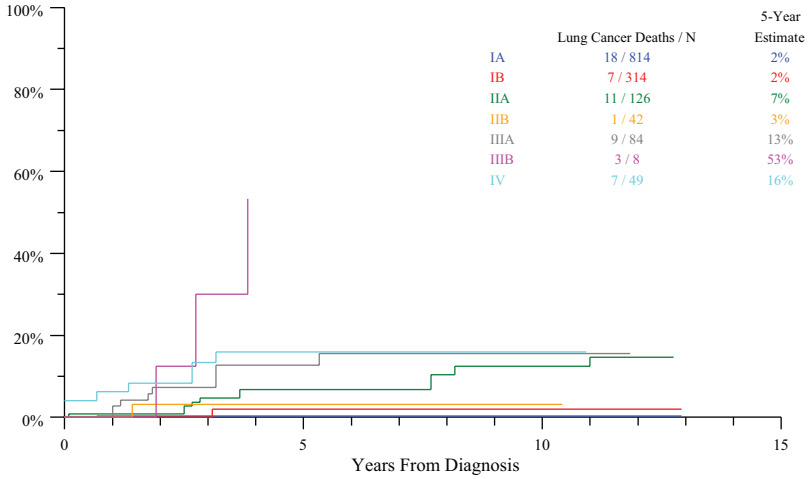

FIGURE 4. SEER surgically treated carcinoid cases diagnosed 1900–2002, cancer specific cause of death, cumulative incidence of lung cancer death, all stage groupings.

TABLE 5. Survival Comparisons Between Proposed Pathological Stages (I vs. II vs. III) Within IASLC Carcinoid Database

Comparison	Hazard Ratio	*p*
II vs. I	2.94	0.0005
III vs. II	5.15	<0.0001
Age >60 vs. ≤60	8.85	<0.0001
Male vs. female	1.69	0.0557
R^2 = 52.0		

Cox Regression model adjusted for age and sex.
n = 372 (56 events), excluding cases with unknown age or sex.
IASLC, International Association for the Study of Lung Cancer.

in 18 T3 patients with same lobe nodules. In the IASLC database, the 7 cases with multiple same lobe nodules were in the IIB category and they had a 100% 5-year survival. Patients with multiple pulmonary carcinoids are likely to have the recently recognized underlying preinvasive lesion of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.[18–21] Most of these patients are women, nonsmokers and approximately half present with one or more pulmonary nodules that are usually discovered as an incidental finding, while the remaining patients present with findings of interstitial lung disease with features of small airways disease. The prognosis for these patients is usually excellent,[19] which is one potential explanation for why the patients with multiple pulmonary nodules of carcinoid tumors in both the IASLC and SEER database had such a favorable outcome. Because of its extremely favorable survival in both the SEER and IASLC datasets, it is possible that the multiple nodule subset of pulmonary carcinoids should be staged differently from NSCLC. However, addressing this would require more detailed data describing T factor status in a larger number of cases.

A major difference between carcinoids and NSCLC that impacts on staging is that carcinoids are smaller. About half the carcinoid tumors we studies were 2 cm or smaller, whereas, the majority of NSCLC were larger than 2 cm. For this reason, the additional tumor size splits in the proposed IASLC staging system at 5 and 7 cm were difficult to assess. Analysis of the IASLC database demonstrated significant reductions in survival for pT1N0 carcinoids according to size at 1 and 2 cm cutoffs. In the SEER database, we attempted to perform a running log-rank test to determine the optimal size cut offs for predicting prognosis similar to the approach by Rami-Porta et al.[5] However, the variation in individual size measurements among SEER pT1N0 cases was greater than our threshold for a meaningful split point, so we did not use the running log rank analysis in this study.

Although the distinction between typical and atypical carcinoid is a very important issue in the study of pulmonary carcinoids, these data were unavailable in both the SEER and the IASLC datasets for several reasons. First, the diagnostic criteria evolved over the time period of data collection for this study, with new criteria being adopted by the World Health Organization in 1999.[22] To achieve accurate data regarding the classification of typical versus atypical carcinoid histologic review of all pathology slides would have been required; however, for practical reasons this was not possible. The SEER registry has not recorded data on typical versus atypical carcinoid over the study period. Because we could not perform pathology review for either the SEER or the IASLC datasets analyzed in this study, we chose to analyze all carcinoids together, realizing from the outset the limitations of this approach. A potential source of bias in our data with nodal and metastasis categories is the inextricable link to cell type, where atypical carcinoid tumors carry a worse prognosis. However, since some useful observations regarding overall use of TNM in carcinoids resulted from these data, we sought to report them in this manuscript.

Most of the survival analyses in this study are based on overall survival that includes death from any cause, even if not related to the carcinoid tumor. Because of the relatively favorable survival of patients with carcinoid tumors compared with NSCLC, particularly for typical carcinoid, the overall survival data presented in this paper probably exaggerate the mortality due to carcinoids. Unfortunately, cancer specific cause of death was not recorded in the IASLC database and only was available in a small subset of the SEER database. To address this issue using cancer specific cause of death, we performed a survival analysis by all stage groupings using cumulative incidence of death due to carcinoid tumor; as expected, we found substantially reduced mortality compared with the overall survival curves. To evaluate critically TNM for staging of broncho-pulmonary

carcinoids future collection of staging data should require cancer specific survival in addition to overall survival.

There are several limitations to this study that present challenges to establishing TNM as applicable to pulmonary carcinoids. Firstly, carcinoids only comprise 1 to 2% of all resected lung malignancies so there are relatively few cases. For this reason, it is difficult for single institutions to have sufficient cases to publish definitive studies. Some of the largest studies to date are from international registries[9,23] or institutions with large referral case material.[15,16] Secondly, as survival is very favorable compared with NSCLC, it is difficult to accumulate sufficient events such as recurrence or death to perform a rigorous statistical analysis for prognostic factors. Another major problem is that carcinoid tumors have historically been regarded as "benign" tumors so some cancer registries including the SEER registry have not always captured data for these patients. While patients with typical carcinoids have an excellent survival even if they present with lymph node metastases,[24] all carcinoids are malignant tumors with the potential to metastasize and result in fatal outcome.[15] Finally, because the UICC/AJCC TNM staging system has not been formally recommended for staging of carcinoid tumors, a concerted effort has not been made to collect detailed TNM factor status in these patients. In many of the cases analyzed in this study, detailed T factor status was not available, and all T factors were not captured for the entire time period of the study. For example, SEER uses a single variable to code extent of disease. The farthest extension is coded, rather than all aspects of tumor extension. Also, the "additional nodules, same lobe" code was added in 1997, so we were not able to identify these cases if diagnosed prior to 1997. It would be worth gathering specific data to determine if T factors such as tumor location in the main bronchus less than 2 cm from the carina and pleural invasion in addition to tumor size are important in staging of pulmonary carcinoids.

In summary, TNM provides an excellent way to record the anatomic extent of disease for broncho-pulmonary carcinoid tumors in a prognostically meaningful way. We hope that, with recommendation by the UICC and AJCC to use TNM for staging of broncho-pulmonary carcinoids, future investigators will gather greater detail on TNM factors to allow for a more thorough evaluation of staging for these tumors. Two areas that need attention are the multicentric carcinoid tumors arising in the setting of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and collection of larger number of cases to see if the proposed size cutoffs are as applicable to carcinoids as to NSCLC. Another important issue is to obtain disease specific survival data for both typical and atypical carcinoids. Because of the favorable survival in most carcinoid patients, death of unknown cause should not be assumed to be tumor related and every effort should be made to determine if the patient died because of their pulmonary carcinoid tumor. The IASLC proposes to include neuroendocrine tumors in the prospective database planned for the next phase of the Lung Cancer Staging Project. In this project, detailed T, N, and M factor data in addition to cancer specific cause of death will be collected. We expect that collection of these pivotal data will allow for better determination of the optimal staging system for broncho-pulmonary carcinoids.

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APPENDIX

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