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Validation of the Proposed International Association for the Study of Lung Cancer Non-small Cell Lung Cancer Staging System Revisions for Advanced Bronchioloalveolar Carcinoma Using Data from the California Cancer Registry

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Background: Recently, the International Association for the Study of Lung Cancer (IASLC) has proposed significant modifications to the existing TNM and stage grouping classifications affecting the T4 and M descriptors. We set out to validate this staging system for bronchioloalveolar carcinoma (BAC) cases using data from the California Cancer Registry (CCR).

Methods: We identified 1909 patients from the CCR between 1999 and 2003 with histologically confirmed BAC and complete TNM staging and reclassified them according to the IASLC proposed staging revisions. There were 657 patients with stage IIIB and IV disease who formed the primary analysis of the changes to T4 and M descriptors. Surveillance Epidemiology and End Results (SEER) extent of disease codes (EOD) were used to identify various T4 and M descriptors. The primary outcome measured was overall survival (OS) for stage-specific comparisons of the existing to the proposed staging systems, using the Kaplan-Meier method. Multivariate survival analyses were performed using Cox proportional hazards ratios.

Results: Using the proposed criteria, 162 (25%) of the 657 patients with advanced BAC were reclassified: 73 patients with multiple lesions in the same lobe as T3 (stage II T3N0M0 [$n = 53$], stage IIIA T3N1-2M0 [$n = 18$], stage IIIB T3N3M0 [$n = 1$] or T3NXM0 [$n = 1$]); 89 patients with ipsilateral intrapulmonary metastasis were reclassified as T4 (stage IIIA T4N0-N1M0 [$n = 54$], stage IIIB T4N2-3M0 [$n = 23$] or T4NXM0 [$n = 12$]). Univariate and multivariate survival analysis of this validation set revealed an improved fit for the proposed IASLC staging system compared with the existing staging system.

Conclusions: The proposed IASLC staging system modifications accurately reflect survival characteristics for BAC and represent an improvement compared with the existing staging system.

Key Words: AJCC staging system, BAC, Bronchioloalveolar carcinoma, Lung cancer staging, NSCLC, Survival.

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The current sixth edition of the Union Internationale Contre le Cancer (UICC6) staging system for advanced-stage non-small cell lung cancer (NSCLC) has been noted to be problematic, particularly for BAC.[1–3] Revisions in the 1997 International System for Staging lung cancer that were retained in the recent 2002 edition[4–8] designated the indicator for "separate tumors in the same lobe" as T4, and "tumor nodules in different lobes" as M1. These T and M designations were catalogued in the "extent of disease" variable of the United States Surveillance, Epidemiology, and End Results (SEER) public use file beginning in January 1998. The current UICC6 NSCLC staging system does not differentiate between stage IIIB disease resulting from a satellite T4 lesion and other stage IIIB lesions, or stage IV disease resulting from intrapulmonary metastasis versus distant metastasis.

However, emerging data suggest that these clinical categories of intrapulmonary disease (i.e., satellite T4 and intrapulmonary M1) are unique and exhibit favorable survival characteristics. In one small series of patients with surgically resected multifocal stage IIIB and stage IV bronchioloalveo-

lar carcinoma (BAC) and other NSCLC, excellent (i.e., >60%) 5-year survival rates were reported.[9] Others have shown a trend toward survival benefit for patients with surgically resected lymph node-negative NSCLC with stage IIIB disease resulting from separate tumors in the same lobe, and stage IV BAC resulting from intrapulmonary spread.[10] Initially, in a smaller population-based study of patients with BAC (n = 626)[11] and subsequently in a large U.S. SEER study on BAC (n = 2345),[12] we demonstrated improved survival for patients with BAC with stage IIIB disease resulting from multiple lesions in the same lobe (i.e., satellite T4) compared with patients with other stage IIIB disease and for patients with multicentric BAC compared with those with distant metastasis.

New revisions to the TNM descriptors of the UICC lung cancer staging system have been proposed by the International Association for the Study of Lung Cancer (IASLC).[13–15] Major revisions include down-staging T4 resulting from additional nodules in the same lobe to T3 and up-staging pleural dissemination and pericardial effusion from T4 to M1a.[13] The nodal staging system would remain unaffected,[14] and the M descriptor would be subdivided: "contralateral intrapulmonary nodules," "malignant pleural dissemination," and "malignant pericardial effusion" as M1a, and distant metastasis as M1b.[15] The stage groupings have been revised accordingly, with the notable change that T4N0-1M0 would now be considered as stage IIIA instead of stage IIIB.[16] All data have been validated internally, then externally using SEER data.[17] The prognostic utility of the proposed IASLC staging revisions for each of the major NSCLC histologies has not been reported.

To test whether the proposed IASLC staging revisions adequately predict survival for advanced BAC, which is unique among the major NSCLC histologies, we designed a validation study using data from the large population-based California Cancer Registry (CCR).

MATERIALS AND METHODS

Demographic and Clinical Data

A case-only analysis was conducted on 1909 incident patients with BAC from the CCR diagnosed between 1999 and 2003 with TNM staging data and complete follow-up data available. We limited the analysis to patients diagnosed after 1999, which is the year the World Health Organization revised classification of lung tumors, when the pathological definition of BAC was restricted to tumors lacking evidence of stromal, vascular, or pleural invasion.[18] Data were abstracted from medical and laboratory records by trained tumor registrars according to CRC.[19]

Tumor site and histology were abstracted as previously described.[12] Cytology specimens have been shown to be less accurate in NSCLC diagnoses than histology specimens.[20] Thus, in an attempt to limit some of the variability in histologic classification, only cases of histologically confirmed BAC were analyzed. Demographic and tumor data were abstracted using SEER codes. The measurement of socioeconomic status (SES) used in this analysis was a composite measure using CCR and census data as previously

described.[21,22] Radiation therapy and surgical techniques, including local treatment, wedge/segmentectomy, lobectomy, and pneumonectomy, were abstracted using SEER codes. Chemotherapy administered during the first course of therapy was ascertained using CCR codes.

For each patient in CCR, the Extent of Disease (EOD) coding variable was analyzed to allow recoding into appropriate UICC staging groups, and comparison of the existing versus the proposed revised staging system. This staging classification was therefore based on the best stage classification to include available clinical and/or pathologic staging information. EOD 65, which codes for "separate tumor nodule(s) in the same lobe;" EOD 72, which codes for "malignant pleural effusions;" EOD 77, which codes "separate tumor nodule(s) in separate lobe;" EOD 78, which codes for "separate tumor nodule(s) in contralateral lung;" and EOD 79, which codes for "(malignant) pericardial effusion," were used to identify the various T and M descriptors that were reclassified by IASLC.

Restaging Patients According to the IASLC Revisions for T4 and M Descriptors

Based on proposed IASLC revisions and stage grouping, the T4 descriptor for additional tumor nodules in the same lobe was down-staged to T3. We restaged these patients (T3N0M0) as stage IIB, patients with T3N1-2M0 were restaged as IIIA, and patients with T3N3M0 remained staged IIIB. The T4 descriptor for pleural dissemination (malignant pleural effusion/pleural nodules) was up-staged as M1a, as were patients with pericardial effusion, and we restaged these patients as stage IVA. The M descriptor for ipsilateral intrapulmonary nodules was down-staged to T4. These patients were staged further according to the nodal status. We down-staged all patients with T4N0-1M0 to IIIA as proposed.[16] Patients with contralateral intrapulmonary nodules were staged as M1a and grouped as stage IV. We also reclassified all patients with early-stage disease according to their tumor size and their stage grouping according to the proposed IASLC changes.

The primary outcome measured was stage-specific overall survival (OS) for the existing UICC6 staging system and for the revised IASLC staging system. Lung cancer-specific survival analyses (i.e., the proportion of patients that did not die from lung cancer) were performed on the entire cohort of patients with BAC using the existing UICC6 and proposed IASLC staging systems.

Follow-Up

Cause of death was recorded according to the International Classification of Diseases criteria at the time of death.[23] The last date of follow-up was either the date of death or the last date the patient was contacted.

Statistical Analyses

Comparisons of demographic, clinical, and pathologic variables were made for patients with BAC, using Pearson's χ^2 or Fisher's exact test for nominal variables and Student's t test for continuous variables. Analysis of variance (ANOVA) with Tukey's post hoc test was used for multiple

comparisons of continuous variables. Univariate survival rate analyses were estimated using the Kaplan-Meier method, with comparisons made among groups by the log rank test. Cox proportional hazards modeling using time since diagnosis were performed. Each variable in the model was coded using dummy variables. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed *p* value less than 0.05.

Ethical Considerations

This research study involved analysis of existing data from the CCR database with no identifiers linked to subjects or subject intervention. Therefore, this study was approved by the University of California Irvine institutional review board under the category exempt status (IRB 2004-3971).

RESULTS

Case Ascertainment and BAC Demographics

We identified 2010 incident cases of BAC among 43,655 patients with NSCLC (4.6%) from 1999 to 2003 in CCR. Of the patients with BAC, 101 were diagnosed based on cytology specimens alone; thus, 1909 incident cases of histologically confirmed BAC were available for analysis.

TABLE 1. Clinicopathologic Features of Patients With BAC With UICC6 T4 and M Descriptors that Undergo Revisions as Proposed by IASLC[a]

	UICC6 Stage IIIB				UICC6 Stage IV		
	T4 "Additional Nodules" (%)	T4 "Pleural Dissemination" (%)	T4 "Pericardial Effusion" (%)	T4 "Invasion" (%)	M "Ipsilateral Pulmonary Nodules" (%)	M "Contralateal Pulmonary Nodules" (%)	M "Distant" (%)
N	73	70	6	24	89	194	201
Age at diagnosis (yr)	68 ± 9	72 ± 9.9	66.8 ± 11.4	71.8 ±13.1	66.7 ± 11.7	68.9 ± 11.9	65.3 ± 10.9
Gender							
Male	24 (33)	26 (37)	3 (50)	8 (33)	35 (39)	78 (40)	86 (43)
Female	49 (67)	44 (63)	3 (50)	16 (67)	54 (61)	116 (60)	115 (57)
Race							
Caucasian	62 (85)	50 (71)	4 (67)	16 (67)	66 (74)	117 (60)	118 (59)
African American	3 (4)	6 (9)	0	3 (103)	4 (4)	19 (10)	23 (11)
Hispanic	5 (7)	4 (6)	0	3 (13)	13 (15)	24 (12)	19 (9)
Chinese	1 (1)	2 (3)	1 (17)	1 (4)	4 (4)	15 (8)	9 (4)
Non-Chinese Asian	2 (3)	8 (11)	1 (17)	1 (4)	1 (1)	18 (9)	31 (15)
Other	0 (0)	0	0	0	1 (1)	1 (0.5)	1 (0.5)
SES							
Quintile 1 (SES1-lowest)	7 (10)	17 (24)	2 (13)	3 (13)	8 (9)	24 (12)	36 (18)
Quintile 2 (SES2)	10 (14)	11 (16)	2 (33)	6 (25)	14 (16)	39 (20)	38 (19)
Quintile 3 (SES3)	19 (26)	12 (17)	0	5 (21)	16 (18)	40 (21)	52 (26)
Quintile 4 (SES4)	14 (19)	15 (21)	1 (17)	7 (29)	23 (26)	41 (21)	35 (17)
Quintile 5 (SES5-highest)	23 (32)	15 (21)	1 (17)	3 (13)	28 (32)	50 (26)	40 (20)
Histologic grade							
1	23 (37)	19 (27)	2 (33)	5 (21)	27 (30)	43 (22)	39 (19)
2	27 (44)	23 (33)	0	6 (25)	20 (22)	34 (18)	35 (18)
3	10 (16)	9 (13)	0	5 (21)	13 (15)	9 (5)	18 (9)
4	2 (3)	0	0	0	0	1 (0.5)	1 (0.5)
Unknown	0	19 (27)	4 (67)	8 (33)	29 (33)	107 (55)	108 (54)
Surgery							
Yes	67 (92)	19 (27)	0	11 (46)	58 (65)	51 (26)	35 (17)
No	6 (8)	51 (73)	6 (100)	13 (54)	31 (35)	143 (72)	166 (83)
Radiation							
Yes	13 (18)	17 (24)	0	11 (46)	6 (7)	16 (8)	87 (43)
No	60 (82)	53 (76)	6 (100)	13 (54)	83 (93)	178 (92)	114 (57)
Chemotherapy							
Yes	12 (16)	20 (29)	2 (33)	8 (33)	22 (24)	90 (46)	86 (43)
No	61 (84)	44 (63)	4 (67)	16 (67)	57 (64)	99 (51)	104 (52)
Unknown	0	6 (9)	0	0	10 (11)	5 (3)	11 (5)

SES, socioeconomic status. [a] CCR data 1999–2003 (*n* = 657).

The mean age was 68.2 ± 10.5 years; 1183 women (62%) and 726 men (38%) were identified in the analysis. Ethnicity was recorded as follows: Caucasian (70%), African American (7%), Hispanic (10%), Chinese (4%), non-Chinese Asian (8.5%). Stage distribution using the existing UICC6 criteria was as follows: stage I ($n = 1054$, 55%), stage II ($n = 97$, 5%), stage IIIA ($n = 101$, 5%), stage IIIB ($n = 173$, 9%), and stage IV ($n = 484$, 25%). The distribution of tumor grade for these patients was 45% grade 1, 42% grade 2, 13% grade 3, and 1% grade 4. Overall, 74% of these patients received surgery, 12.5% received radiation therapy, and 18% received treatment with chemotherapy. SES quintile ranged (from lowest to highest) as follows: SES-1 (11%), SES-2 (17%), SES-3 (20%), SES-4 (23%), and SES-5 (28%).

Advanced Stage (IIIB, IV) BAC Clinical Characteristics

Clinical comparisons for the seven major categories of advanced-stage BAC that undergo revisions as proposed by IASLC are presented in Table 1. Patients with T4 lesions resulting from additional nodules were more likely to be of Caucasian ethnicity compared with the other major advanced-stage patient subgroups. A high proportion of these patients with BAC resulting from T4 lesions with additional nodules received surgery (92%), compared with patients with T4 lesions resulting from direct invasion (46%), pleural dissemination (27%), pericardial effusion (no cases), patients with ipsilateral intrapulmonary M1 (65%), patients with contralateral intrapulmonary M1 (26%), or patients with M1 resulting from distant metastasis (17%). Survival by stage at diagnosis for the seven categories of advanced BAC using the existing UICC6 staging system is depicted in Figure 1.

Proposed IASLC Staging Modifications

Using the proposed criteria, 162 of the 657 patients with advanced BAC (25%) were reclassified as follows: 73 patients with multiple lesions in the same lobe were reclassified from a T4 descriptor (stage IIIB) to a T3 descriptor (53 with stage II, T3N0M0, 18 as stage IIIA,T3N1-2M0, one as stage IIIB = T3N3M0, and one as T3NXM0). There were 89 patients with ipsilateral intrapulmonary metastasis reclassified as T4 (stage IIIA T4N0-N1M0 [$n = 54$], stage IIIB T4N2-3M0 [$n = 23$], or T4NXM0 [$n = 12$]). Additionally, the proposed IASLC size-based definitions for the T descrip-
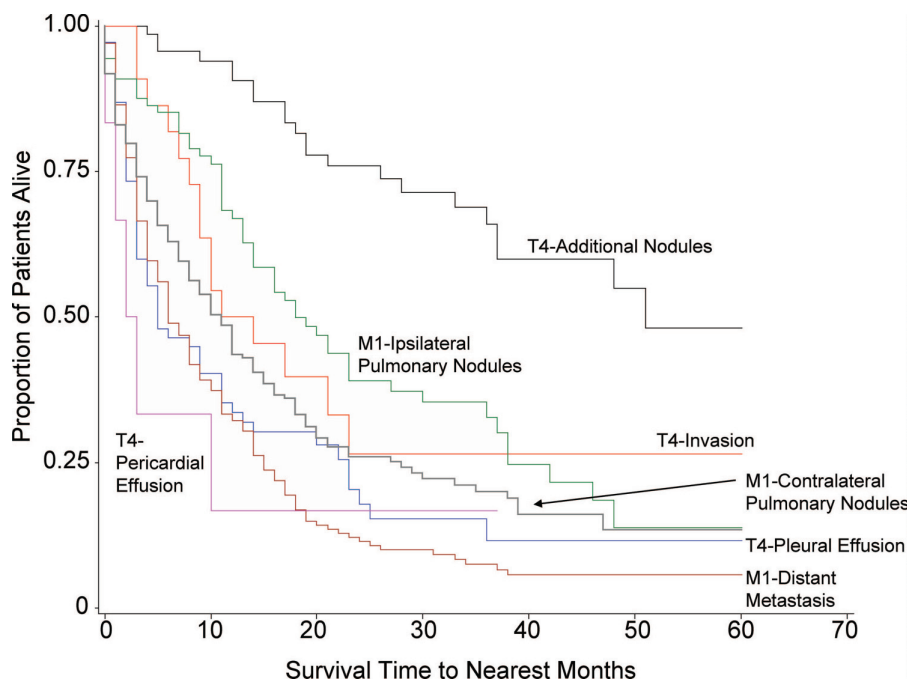

FIGURE 1. Overall survival analysis of advanced-stage bronchioloalveolar carcinoma (BAC) ($n = 657$) reveals inconsistencies with the existing UICC6 staging system. CCR data, 1999–2003.

TABLE 2. Distribution of Patients With BAC by Stage at Presentation[a]

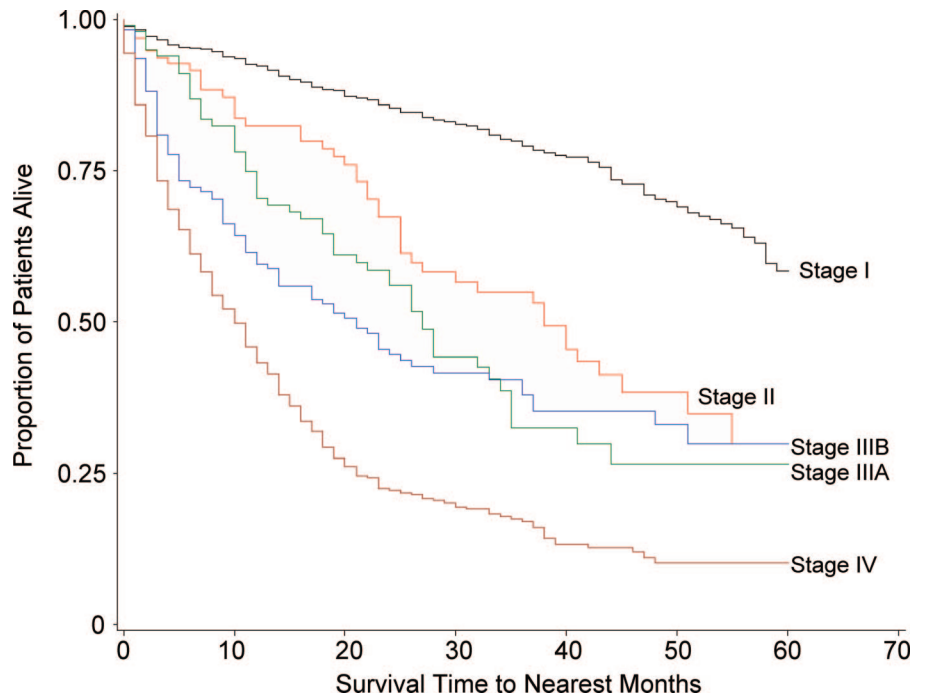|	IASLC Stage I ($n = 627$)	IASLC Stage II ($n = 572$)	IASLC Stage IIIA ($n = 182$)	IASLC Stage IIIB ($n = 57$)	IASLC Stage IV ($n = 471$)
UICC6 stage I ($n = 1054$)	627	427	0	0	0
UICC6 stage II ($n = 97$)	0	92	5	0	0
UICC6 stage IIIA ($n = 101$)	0	0	101	0	0
UICC6 stage IIIB ($n = 173$)	0	53	22	22	76
UICC6 stage IV ($n = 484$)	0	0	54	35	395

[a]CCR data 1999–2003 ($n = 1909$).

FIGURE 2. Five-year overall survival curves for patients with stage I–IV bronchioloalveolar carcinoma (*n* = 1909) using the existing UICC6 staging system. CCR data 1999–2003.
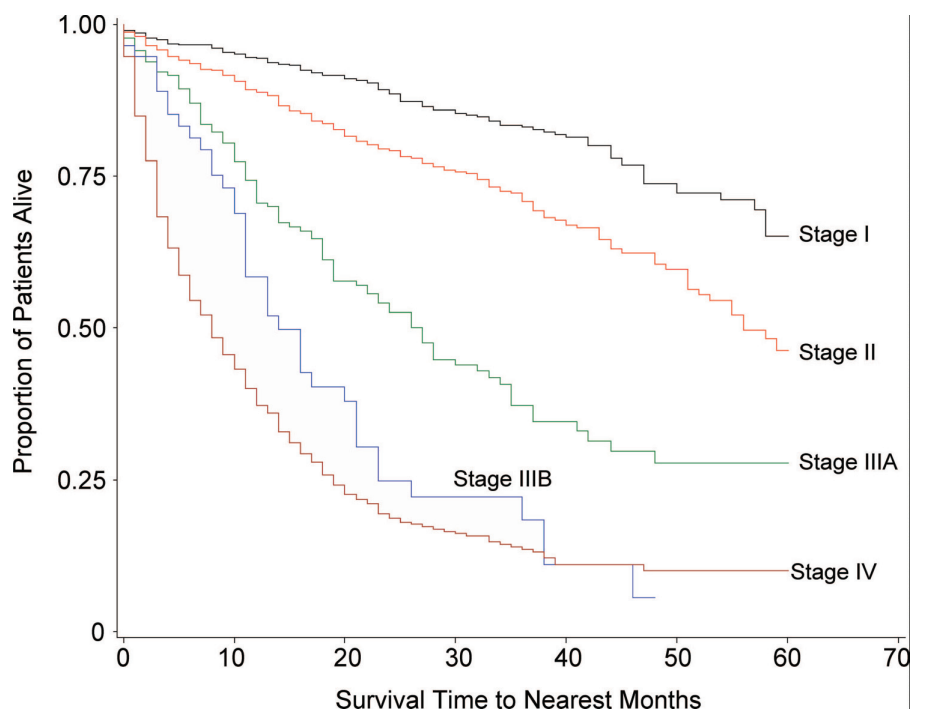

FIGURE 3. Five-year overall survival curves for patients with stage I–IV bronchioloalveolar carcinoma (*n* = 1909) using the proposed IASLC staging modifications. CCR data, 1999–2003.

tor[13] were incorporated, which affected UICC6 stage I and II patients. Using these modifications, the IASLC stage distribution for the entire BAC cohort was as follows: stage I (*n* = 627, 33%), stage II (*n* = 572, 30%), stage IIIA (*n* = 182, 10%), stage IIIB (*n* = 57, 3%) stage IV (*n* = 471, 25%). The distribution of patients with BAC by stage at presentation using the existing UICC6 and proposed IASLC staging systems is presented in Table 2 for comparison.

Univariate and Multivariate Survival Comparisons for the Existing UICC6 Versus Proposed IASLC Staging System

The univariate survival curves for the existing UICC6 staging system and the proposed IASLC staging system are presented in Figures 2 and 3, respectively. Analysis of these curves reveals an improved fit for the proposed IASLC

TABLE 3. Multivariate Overall Survival and Lung Cancer-specific Survival Analysis[a,b]

	Overall Survival (*n* = 1909, Deaths = 777)		Lung Cancer-specific Survival (*n* = 1909, Lung Cancer Deaths = 567)	
	UICC6	IASLC	UICC6	IASLC
Stage I	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Stage II	2.48 (1.78–3.44)	1.69 (1.32–2.16)	3.19 (2.15–4.73)	2.12 (1.52–2.96)
Stage IIIA	2.47 (1.78–3.43)	3.42 (2.54–4.61)	3.34 (2.28–4.88)	4.81 (3.29–7.03)
Stage IIIB	2.82 (2.17–3.67)	4.61 (3.08–6.89)	3.84 (2.80–5.27)	6.04 (3.68–9.92)
Stage IV	4.07 (3.23–5.14)	6.21 (4.69–8.21)	5.40 (4.07–7.16)	9.59 (6.71–13.71)

[a]Cox proportional hazards model (95% confidence interval). CCR data 1999–2003.
[b]Models include adjustment for age, gender, race, socioeconomic status, tumor grade, treatment with surgery, radiation therapy, and chemotherapy.

staging system compared with UICC6. In the UICC6 staging system, overall survival for stage II, IIIA, IIIB is poorly delineated (1-year, 5-year, and median OS are as follows: stage I (92%, 58%, not reached [NR]), stage II (82%, 30%, 38 months), stage IIIA (70%, 26%, 27 months), stage IIIB (59%, 30%, 21 months), and stage IV (43%, 10%, 10 months) (Figure 2). After modifying the T4 and M1 descriptors as described in the IASLC revisions, clear survival improvements were noted for patients with BAC with each incremental decrease in stage (1-year, 5-year, and median OS are as follows: stage I (94%, 65%, NR), stage II (89%, 46%, 56 months), stage IIIA (71%, 28%, 27 months), stage IIIB (58%, 6%, 14 months), and stage IV (37%, 10%, 8 months) (Figure 3). Multivariate overall survival analysis was performed for each staging system, adjusting for age, gender, race, socioeconomic status, tumor grade, surgery, radiation therapy, and chemotherapy (Table 3). For the UICC6 staging system, the adjusted survival for stage II (hazard ratio [HR] 2.48, 95% confidence interval [CI] 1.78–3.44), IIIA (HR 2.47, 95% CI 1.78–3.43), and IIIB (HR 2.82, 95% CI 2.17–3.67) are equivocal compared with stage I BAC (HR 1.00, referent). However, using the proposed IASLC staging criteria, incrementally higher HRs were noted with increased stage.

Cause of Death and Lung Cancer-Specific Survival

Cause of death analysis revealed that there were 777 deaths among the 1909 patients with BAC in CCR. There were 567 patients who died as a result of lung cancer (73% of all deaths). Unknown cause of death was reported for 93 patients (12%), infection caused death in 70 patients (9%), heart disease resulted in death for 43 patients (5%), and COPD was the cause of death for 10 patients (1%). Adjusted analysis of lung cancer-specific survival (LCSS) analysis was performed to quantify stage-specific risk of death from lung cancer for the existing UICC6 and proposed IASLC staging systems (Table 3). Similar to the observed adjusted OS analyses, these LCSS analyses demonstrate improved prognostic data from the proposed IASLC versus the existing UICC6 staging system (Table 3).

DISCUSSION

Using prospectively defined IASLC modifications to the existing UICC6 TNM staging system for advanced BAC, in this population-based validation study, we demonstrated that the current UICC6 staging system is greatly improved with simple changes to the T4 and M1 descriptors. Specifically, by down-staging the T4 descriptor for satellite T4 nodules to a T3, down-staging the M1 descriptor for ipsilateral intrapulmonary metastasis to a T4, up-staging the T4 descriptor for pericardial and pleural effusion to an M1 descriptor, and changing the stage grouping to reclassify T4N0-1M0 as stage IIIA, the unadjusted and adjusted survival outcomes for advanced BAC are accurately delineated. After incorporating the T descriptor size-based criteria to the cohort, these changes affected 31% of the BAC population, and they provide much more accurate prognostic information compared with the existing staging criteria.

Down-staging the 53 patients with BAC with multiple nodules in the same lobe from T4N0M0 (UICC6 stage IIIB) to T3N0M0 (IASLC stage II) resulted in dramatically improved survival estimates (median OS 21 months for UICC6 stage IIIB vs. 56 months for IASLC stage II). As we noted in our prior analysis,[12] a large proportion (92%) of patients with stage IIIB BAC in this study with satellite T4 nodules underwent wedge resection/segmentectomy, lobectomy, or pneumonectomy, with a resultant improvement in survival. This indicates that thoracic surgeons in the community already treat most of these patients with curative intent. The shift toward more patients with stage II BAC in the proposed IASLC staging system stems from up-staging patients with T1 and T2 disease based on the tumor size descriptor and (to a much lesser degree) from down-staging patients with T4 resulting from additional nodules. These changes will likely result in more patients being considered for adjuvant chemotherapy. Furthermore, tumors in separate lobes of the same lung are currently staged as M1 in the current UICC6 staging system; however, the tumor can be completely resected with a bi-lobectomy or pneumonectomy. Thus, the IASLC proposals to down-stage T4 intrapulmonary nodules to T3, and M1 resulting from ipsilateral intrapulmonary metastasis to T4, are

clinically relevant for BAC and supported by our validation study. It must be acknowledged that patients with advanced-stage BAC who received surgery likely reflect those with better Karnofsky performance status and fewer comorbidities compared with those who were ineligible for surgery. Based on these data, we cannot advocate routine surgery for subsets of patients with advanced BAC. Rather, such recommendations are better evaluated in the surgical literature on smaller numbers of patients.[4–8]

We focused on the IASLC revisions for advanced BAC, but IASLC and others have addressed discrepancies for early-stage NSCLC, i.e., the T1 and T2 tumor size descriptors and the T2 visceral pleural invasion descriptor.[13,24–30] A limitation of this study is that CCR data contain limited information on chemotherapy and biologic treatments, and it is not possible to obtain information on method used for nodal staging (i.e. mediastinoscopy, computed tomography, positron emission tomography). Tobacco smoking has been shown to be at least a modest predictor of poor survival in NSCLC,[11,31–34] but CCR data do not readily contain information on smoking status. Similar to other population-based analyses, there was no centralized repeat review of pathologic specimens, which results in heterogeneity of reporting practices. However, the accuracy of NSCLC histologic reporting in population-based analyses has been evaluated favorably compared with independent histologic review.[35] The prospective analytic technique used in this validation study, involving large numbers of patients with BAC from a high-quality geographically contiguous regional cancer registry, is a great strength of this study. Our analytic plan was strengthened by restricting analyses to histologically confirmed BAC diagnoses and to patients diagnosed after release of the World Health Organization revised classification of lung tumors, a definition change that has resulted in improved survival outcomes for this unique tumor subtype.[11]

Using a large, population-based validation study on a separate patient database, we have demonstrated the appropriateness of the IASLC proposals classifying "separate tumor nodules in the same lobe" as T3 rather than T4 and "separate tumors in a separate ipsilateral lobe" as T4 instead of M1 for BAC. The proposed IASLC staging changes provide improved differentiation of what is currently labeled as advanced-stage (stage IIIB, IV) BAC into clinically relevant subgroups.

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