Long-term survival differences for bronchiolo-alveolar carcinoma patients with ipsilateral intrapulmonary metastasis at diagnosis

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Background: It has been suggested that the current staging system does not accurately reflect survival outcomes for advanced bronchiolo-alveolar carcinoma (BAC) patients. 

Methods: We conducted a case-only analysis of US Surveillance, Epidemiology, and End Results (SEER) data (1998–2002). Overall survival (OS) and lung cancer-specific survival (LCSS) univariate analyses were conducted using the Kaplan–Meier method. Multivariate survival analyses were performed using Cox proportional hazards ratios.

Results: 2345 incident cases of BAC were analyzed, including 707 patients with stage IIIB or IV BAC. Patients with stage IIIB BAC due to multiple lesions in the same lobe (n = 93) had significantly improved median OS (46m) and LCSS (>58m) compared to other stage IIIB BAC patients (n = 111; OS = 9m, P < 0.0001; LCSS = 10m, P < 0.0001). Among stage IV BAC patients, those with intrapulmonary metastasis (n = 278) had significantly improved median OS (13m) and LCSS (15m) compared to those with distant metastasis (n = 225; OS = 7m, P < 0.0001; LCSS = 7m, P = 0.0001). These survival differences persisted after adjustment for age, gender, ethnicity, and surgical treatment status.

Conclusions: Among stage IIIB and IV BAC patients, those presenting with ipsilateral intrapulmonary metastasis have improved survival outcomes. Our results add further support for modification to the current staging system for BAC.

Key words: Bronchiolo-alveolar carcinoma, (BAC), epidemiology, staging, survival

introduction

Bronchiolo-alveolar carcinoma (BAC) is a subset of lung adenocarcinoma with characteristic clinical, epidemiologic, and histopathologic features [1–6]. The current staging system for advanced stage BAC has been noted to be problematic [7, 8]. In 1997, revisions in the International System for Staging Lung Cancer that were subsequently retained in the most recent 2002 edition designated the indicator for ‘separate tumors in the same lobe’ as T4, and ‘tumor nodules in different lobes’ as M1 [9, 10]. These designations were recorded in the ‘extent of disease’ category of SEER beginning in January 1998. The current staging system does not differentiate between stage IV BAC due to intrapulmonary spread or distant spread. In one small series of 14 surgically resected patients with multifocal stage IIIB and stage IV lung BAC, an excellent (i.e. 64%) five-year survival rate was reported [11]. The survival rates for multifocal BAC in that study was noted to be improved compared to historical standards, but direct comparisons to control groups were not performed, and the total number of BAC patients analyzed was small. Specifically, differences in survival for stage IIIB BAC due to separate tumors in the same lobe compared to survival for other stage IIIB tumors are unknown, as are the survival differences for stage IV BAC due to intrapulmonary spread compared to stage IV BAC due to distant metastasis. Thus we designed the present study to compare the survival rates for patients within these subsets of stage IIIB and stage IV BAC in a large population-based epidemiologic analysis.

methods
demographic and clinical data

Data were obtained on 85 306 incident cases of invasive lung cancer from the 13-registry US SEER public use file during the period 1998–2002 [12]. Tumor site and histology were coded according to criteria specified by the World Health Organization in International Classification of Diseases for Oncology [13]. All tumors were identified using primary site and histology codes for small cell carcinoma (8041–8045; n = 11 464), large cell carcinoma (8012, 8013, 8022, 8030, 8031; n = 4302), squamous cell carcinoma (8050–8052, 8070–8076; n = 15 626), adenocarcinoma (8140–8239, 8260–8550; n = 25 085), and BAC (8290–8294; n = 2633, representing 3.1% of all lung cancers) as previously described [6]. Non-small cell histologies that were not
identified with the above histologic codes and not coded as a metastatic lung lesion from a separate primary tumor were categorized as undifferentiated NSCLC (n = 26 176) – 85% of which were coded as 8010 (carcinoma NOS), 8046 (non-small cell carcinoma NOS), or 8000 (neoplasm NOS).

Subsequent analyses were restricted to BAC patients. Histologic confirmation was established in 2453 BAC cases (i.e. 92.5%). Because accurate diagnosis of BAC requires histologic examination of the entire lesion (for lesions <3cm), and cytology specimens are considered inadequate [8], only the histologically-confirmed BAC cases were included in our analysis. Among the excluded cases, cyologic confirmation was utilized in 151 BAC cases (5.7% of the total BAC population), and radiographic, clinical, or unknown source of diagnostic confirmation was used in 49 BAC cases (1.9% of the total BAC population). TNM data were available for 2345 out of the 2453 histologically-confirmed BAC cases (95.6%), thus subsequent analyses were restricted to these 2345 patients. For advanced stage BAC, TNM staging and extent of disease (EOD) were analyzed, using the SEER EOD code 65 denoting separate tumor nodule(s) in the same lobe, and code 77 denoting separate tumor nodule(s) in different lobes. Lymph node status was assessed using the SEER lymph node EOD coding variable specific for tumors of the lung and bronchus, which accounts for lymph node status as determined by radiography, mediastinoscopy, or pathology. Discrepancies in staging were noted for 84 patients classified as TNM stage IIIB, but with separate tumors in different lobes. These 84 patients were considered as TNM stage IV, according to the 1997 revised staging criteria, for all subsequent analyses. Demographic variables and survival rates were compared for advanced BAC patients across four categories: stage IIIB with a T4 descriptor indicating separate tumors in the same lobe and without documented N3 nodal involvement (i.e. T4NXM0 or T4N0-2M0), all other stage IIIB patients (referred to throughout the text as ‘other’ stage IIIB; includes other T4M0 BAC patients, and all N3 nodal stage patients without metastasis), stage IV due to M1 lesions in separate lobes, and stage IV due to distant metastasis. Within the category stage IV due to M1 lesions in separate lobes, patients were further categorized as having lesions in the same lung (i.e. ipsilateral lung), or contralateral lung. Lung cancer-specific survival analyses (i.e. the proportion of patients not suffering death from lung cancer) were performed on the various subsets of advanced stage BAC patients.

follow-up

Cause of death was recorded according to the International Classification of Diseases criteria in effect at the time of death [13]. 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 between patients with various categories (e.g. patients with BAC or non-BAC NSCLCs) were performed using Pearson chi-square statistic or Fisher’s exact test for nominal variables and Student 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 and Meier method, with comparisons made between 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 SEER database with no subject intervention. No identifiers were linked to subjects.

Therefore this study was approved by the University of California Irvine Institutional Review Board (IRB) under the category ‘exempt’ status (IRB #2004–3971).

results

BAC population characteristics

Identified among the 2345 incident cases of histologically-confirmed BAC were 1356 stage I BAC patients (57.8%), 139 (5.9%) stage II BAC patients, 143 (6.1%) stage IIIA BAC patients, 204 (8.7%) stage IIIB BAC patients, and 503 (21.5%) stage IV BAC patients. A majority of these BAC patients (60.4%) were female (n = 1416), and 929 were male (39.6%). The major ethnic group identified was Caucasians (n = 1697, or 72.4%), followed by Asians (n = 278, or 11.9 %), African–Americans (n = 193, or 8.2%), Hispanics (n = 163, or 7.0%), and Native Americans/Others (n = 14, or 0.6%). Specific histological typing as non-mucinous, mucinous, or mixed mucinous non-mucinous was available for only 6.5% of the BAC population (n = 152), and these designations were not recorded until the year 2001. Identified in the analysis were 82 mucinous, 66 non-mucinous, and four mixed mucinous non-mucinous BAC cases (two patients each with stage I and stage IV BAC). No significant differences in distribution by stage were detected for mucinous BAC cases versus non-mucinous BAC cases: 66% versus 70% stage I, 4% versus 5% stage II, 5% versus 5% stage IIIA, 7% versus 6% stage IIIB, and 18% vs. 15% stage IV (P = 0.98). Overall survival rates were similar for mucinous BAC patients (median OS NR; 75% one-year OS; 79% two-year OS) compared to non-mucinous BAC patients (median OS NR; 79% one-year OS) (P = 0.92).

Survival by stage at diagnosis for BAC is depicted in Figure 1. Median OS for stage I BAC was not reached (NR) at >59 months follow-up (95% CI NR-NR), compared to 42 months (95% CI 33–45) median OS for stage II BAC, 26 months median OS (95% CI 19–32) for stage IIIA BAC, 19 months (95% CI 14–26) for stage IIIB BAC, and 10 months (95% CI 8–11) for stage IV BAC (P < 0.0001). On multivariate analysis incorporating age, stage, ethnic origin, and gender into the model, advanced stage was the strongest predictor of poor survival when compared to stage I disease (HR for stage IV = 6.89, 95% CI 5.86–8.12, P < 0.0001; HR for stage IIIB = 3.92, 95% CI 3.15–4.87, P < 0.0001) (Table 1).

Female BAC patients had improved OS (56 months, 95% CI 51–NR) compared to males (33 months, 95% CI 28–39) (P < 0.0001). This survival improvement remained after adjustment for stage at diagnosis, ethnic origin, and age at diagnosis (HR for female gender = 0.69, 95% CI 0.60–0.78; P < 0.0001) (Table 1).

African–Americans (median OS = 19 months, 95% CI 13–33) had the poorest survival compared to Caucasians (median OS = 53 months, 95% CI 46-NR), Hispanics (median OS = 44 months, 95% CI 32-NR), Asians (median OS = 40 months, 95% CI 29-NR), and Native Americans/Others (median OS = NR at >58 months, 95% CI 7-NR) on univariate analysis (P < 0.0001). After adjustment for age, stage at diagnosis, and gender, this survival disadvantage for African–Americans compared to Caucasians persisted (HR=1.73, 95% CI 1.41–2.13, P < 0.0001) (Table 1).
adjusted analysis using Cox proportional hazards model.

<table>
<thead>
<tr>
<th>TNM stage at diagnosis</th>
<th>Hazard ratio (HR)</th>
<th>95% HR confidence limits</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>2.07</td>
<td>(1.56–2.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>2.99</td>
<td>(2.29–3.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>3.92</td>
<td>(3.15–4.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IV</td>
<td>6.89</td>
<td>(5.86–8.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.02</td>
<td>(1.01–1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.69</td>
<td>(0.60–0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African–American</td>
<td>1.73</td>
<td>(1.41–2.13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asian</td>
<td>1.01</td>
<td>(0.82–1.27)</td>
<td>0.94</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.09</td>
<td>(0.84–1.43)</td>
<td>0.51</td>
</tr>
<tr>
<td>Native American/Other</td>
<td>1.18</td>
<td>(0.49–2.84)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**advanced stage (IIIB, IV) BAC clinical characteristics**

Seven hundred and seven patients with advanced BAC (i.e. stage IIIB or IV) were identified out of the 2345 BAC cases. Included among these advanced BAC cases were 204 stage IIIB BAC cases of which 93 patients with separate tumors within the same lobe and without documented N3 nodal involvement, and 111 'other' stage IIIB BAC patients. 503 patients with stage IV BAC were identified, including 278 (55.3%) with intrapulmonary disease and 225 (44.7%) with distant metastasis. Among the 93 patients with stage IIIB due to separate tumors in the same lobe, 71 were T4N0M0, five were T4N1M0, 10 were T4N2M0, and seven were T4N3M0; no other descriptors of tumor extension (i.e. T stage) were included among these patients. For the 111 ‘other’ stage IIIB BAC patients, seven had T1-T3N3M0 disease, one had T4N3M0 where the T4 descriptor indicated multiple tumors in the same lobe, and one had TxN3M0 disease; 39 had a T4 lesion (including two cases of T4N3M0) due to involvement of the mediastinum, heart, major blood vessels, carina, trachea, esophagus, or vertebral body, and 63 had malignant pleural effusion. Thus only 11 N3 nodal stage patients were identified out of the 204 stage IIIB BAC cases (i.e. 5.4%). Out of the 707 stage IIIB and stage IV BAC patients analyzed, nine patients (1.3%) were identified with diffuse spread of tumor involving the entire lobe or lung (i.e. T4), including one patient that also had a malignant pleural effusion, nine patients with stage IV BAC due to intrapulmonary spread, and three patients with stage IV BAC due to distant metastasis. 21 mucinous BAC cases, 14 non-mucinous BAC cases, and two mixed mucinous non-mucinous BAC cases were identified out of these 707 stage IIIB and stage IV BAC patients. Patients with stage IV BAC due to distant metastasis (mean age of 64.3 years) were significantly younger than ‘other’ stage IIIB BAC patients (mean age of 70.4 years), and stage IV BAC patients due to intrapulmonary disease (mean age of 59.7 years) were significantly younger than ‘other’ stage IIIB BAC patients (mean age of 64.3 years). There were no differences in the proportion of females (P = 0.13), and borderline differences in the ethnic distribution (P = 0.054) among these four categories were noted (Table 2). Among all stage IIIB and stage IV BAC patients, the majority (n = 444, or 62.8%) were not treated surgically, five (0.7%) were treated with local excision, 85 (12.0%) were treated with wedge resection, segmentectomy, 140 (19.8%) were treated with lobectomy, and 32 (4.5%) were treated with pneumonectomy. A much higher proportion of stage IIIB BAC due to separate lesions in the same lobe received surgical treatment (91.4%) compared with other stage IIIB BAC cases (32.4%), stage IV BAC due to intrapulmonary spread (34.2%) or stage IV BAC due to distant metastasis (20.9%) (P < 0.0001; Table 2). Among 158 advanced BAC patients with N2 disease (i.e. 10 patients with stage IIIB due to separate lesions in the same lobe, 27 other stage IIIB patients, 56 with stage IV BAC due to intrapulmonary spread, and 65 with stage IV due to distant metastasis), only 40 (i.e. 25.3%) received surgical treatment. Among 35 advanced BAC patients with N3 disease (i.e. 11 ‘other’ stage IIIB patients, 12 with stage IV BAC due to intrapulmonary spread, and 12 with stage IV due to distant metastasis), only two (5.7%) received surgical treatment.

**overall survival in advanced stage (IIIB, IV) BAC**

Stage IIIB BAC patients due to separate lesions in the same lobe had significantly improved survival (median OS = 46 months, 95% CI 39–49) compared to ‘other’ stage IIIB BAC patients (median OS = 9 months, 95% CI 7–12; P < 0.0001) (Figure 2). This survival benefit remained after adjustment for gender, age at diagnosis, ethnicity, and surgical treatment status (HR for ‘other’ stage IIIB BAC patients compared to stage IIIB BAC due to single lesions in the same lobe = 3.20, 95% CI 2.05–4.98, P < 0.0001) (Table 3). On univariate analysis of survival by gender, no differences in survival were detected for stage IIIB BAC due to separate tumors in the same lobe (median OS for males = 46 months, 95% CI 28–NR versus median OS for females = NR at >58 months, 95% CI 42–NR; P = 0.29), or for ‘other’ stage IIIB BAC patients (median OS for males = 9 months,
95% CI 6–10 versus median OS for females = 9 months, 95% CI 7 to 13; \( P = 0.33 \). Within the category of ‘other’ stage IIIB BAC patients (\( n = 111 \)), 63 patients (57.3%) had malignant pleural effusion, and these patients with malignant pleural effusion had decreased overall survival (median OS = 7 months, 95% CI 7–9) compared to the remainder of ‘other’ stage IIIB BAC patients (median OS = 10 months, 95% CI 8–19) (\( P = 0.009 \)).

Stage IV BAC patients due to intrapulmonary metastasis had a significant improvement in survival (median OS = 13 months, 95% CI 10–15) compared to those with stage IV BAC due to distant spread (median OS = 7 months, 95% CI 6–8) (\( P < 0.0001 \) (Figure 3). This survival improvement is also reflected in the multivariate analysis, which includes adjustment for age, gender, ethnicity, and surgical treatment status (Table 3). On univariate analysis of survival by gender, no statistically significant survival differences were observed for patients with stage IV BAC due to intrapulmonary spread (median OS for males = 10 months, 95% CI 7–15 versus median OS for females = 7 months, 95% CI 6–8; \( P = 0.12 \)), or for patients with stage IV BAC due to distant metastasis (median OS for males = 7 months, 95% CI 6–8 versus median OS for females = 9 months, 95% CI 9–19; \( P = 0.35 \)).

Patients with stage IV BAC due to intrapulmonary metastasis (\( n = 278 \)) had either separate tumor nodules in different lobes of the ipsilateral lung (\( n = 80 \)), or separate tumor nodules in the contralateral lung (\( n = 198 \)). Median OS was significantly improved for patients with ipsilateral intrapulmonary stage IV BAC compared to those with contralateral intrapulmonary stage IV BAC (20 months, 95% CI 15–31, versus 10 months, 95% CI 8–13) (\( P < 0.0001 \) (Figure 4). Subset analysis revealed that stage IV BAC patients due to intrapulmonary metastasis (median OS = 13 months) had a statistically significant overall survival benefit compared to ‘other’ stage IIIB BAC patients (median OS = 9 months) (\( P = 0.011 \)).

**Table 2.** Comparisons for four categories of advanced stage BAC by clinicopathologic variables, 1998–2002 (\( n = 707 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage IIIB due to separate tumors in the same lobe (( n = 93 ))</th>
<th>‘Other’ stage IIIB (( n = 111 ))</th>
<th>Stage IV due to intrapulmonary spread (( n = 278 ))</th>
<th>Stage IV due to distant metastasis (( n = 225 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean ± standard error</td>
<td>67.2 ± 0.9</td>
<td>68.8 ± 1.1</td>
<td>67.5 ± 0.7</td>
<td>64.3 ± 0.8</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>57 (39.8)</td>
<td>42 (37.8)</td>
<td>109 (39.2)</td>
<td>109 (48.4)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>56 (60.2)</td>
<td>69 (62.2)</td>
<td>169 (60.8)</td>
<td>116 (51.6)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>Caucasian</td>
<td>78 (83.9)</td>
<td>76 (68.5)</td>
<td>180 (64.8)</td>
<td>139 (61.8)</td>
</tr>
<tr>
<td></td>
<td>African–American</td>
<td>5 (5.4)</td>
<td>14 (12.6)</td>
<td>29 (10.4)</td>
<td>31 (13.8)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>8 (8.6)</td>
<td>12 (10.8)</td>
<td>42 (15.1)</td>
<td>38 (16.9)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>2 (2.2)</td>
<td>7 (6.3)</td>
<td>24 (8.6)</td>
<td>16 (7.1)</td>
</tr>
<tr>
<td></td>
<td>Native American/Other</td>
<td>0 (0)</td>
<td>2 (1.8)</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Surgery performed</td>
<td>Any surgery</td>
<td>85 (91.4)</td>
<td>36 (32.4)</td>
<td>95 (34.2)</td>
<td>47 (20.9)</td>
</tr>
<tr>
<td></td>
<td>No surgery</td>
<td>8 (8.6)</td>
<td>75 (67.6)</td>
<td>183 (65.8)</td>
<td>178 (79.1)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Local resection</td>
<td>1 (1.1)</td>
<td>1 (0.9)</td>
<td>1 (0.4)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Wedge resection</td>
<td>12 (12.9)</td>
<td>10 (9.0)</td>
<td>44 (15.8)</td>
<td>19 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Lobectomy</td>
<td>67 (72.0)</td>
<td>18 (16.2)</td>
<td>33 (11.9)</td>
<td>22 (9.8)</td>
</tr>
<tr>
<td></td>
<td>Pneumonectomy</td>
<td>5 (5.4)</td>
<td>7 (6.3)</td>
<td>17 (6.1)</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

*\( P \)-value is given for stage IV due to distant metastasis compared to ‘other’ stage IIIB, and compared to stage IV due to intrapulmonary spread; all other comparisons by age are not significant.

**Figure 2.** Overall survival for stage IIIB BAC, 1998–2002 (\( n = 204 \)). Dashed line, stage IIIB BAC due to separate tumors in the same lobe (\( n = 93 \)), OS = 46m (95% CI 39–NR); Solid line, all other stage IIIB BAC tumors (\( n = 111 \)), OS = 9m (95% CI 7–10); \( P < 0.0001 \).

95% CI 6–10 versus median OS for females = 9 months, 95% CI 7 to 13; \( P = 0.33 \). Within the category of ‘other’ stage IIIB BAC patients (\( n = 111 \)), 63 patients (57.3%) had malignant pleural effusion, and these patients with malignant pleural effusion had decreased overall survival (median OS = 7 months, 95% CI 7–9) compared to the remainder of ‘other’ stage IIIB BAC patients (median OS = 10 months, 95% CI 9–19) (\( P = 0.009 \)).

Stage IV BAC patients due to intrapulmonary metastasis had a significant improvement in survival (median OS = 13 months, 95% CI 10–15) compared to those with stage IV BAC due to distant spread (median OS = 7 months, 95% CI 6–8) (\( P < 0.0001 \) (Figure 3). This survival improvement is also reflected in the multivariate analysis, which includes adjustment for cause of death and lung cancer specific survival in advanced stage (IIIB, IV) BAC

Overall, 477 deaths occurred among the 707 stage IIIB and stage IV BAC patients, and cause of death was available for each of these cases. Cause of death analysis revealed that lung cancer was responsible for 85.1% of the deaths suffered in this study. This included death due to lung cancer in 80.0% of stage IIIB patients.
due to multiple nodules in the same lobe, 81.6% of ‘other’ stage IIIB BAC patients, 85.6% of stage IV BAC patients with intrapulmonary disease, and 87.2% of stage IV BAC patients with distant metastasis (\(P = 0.55\)). The next most frequent cause of death was heart disease, which accounted for death in 19 patients (4%).

Lung cancer-specific survival was significantly improved for patients with stage IIIB BAC due to separate tumors in the same lobe (median OS = NR at >58 months follow-up, 95% CI 43-NR) compared to ‘other’ stage IIIB BAC patients (median OS = 10 months, 95% CI 9–14, \(P < 0.0001\)). Lung cancer-specific survival was significantly improved for stage IV BAC patients due to intrapulmonary metastasis (median OS = 15 months, 95% CI 13–18) compared to stage IV BAC patients due to distant metastasis (median OS = 7 months, 95% CI 7–10, \(P = 0.0001\)).

Surgical treatment in advanced stage (IIIB, IV) BAC

Patients who were able to receive surgery for their cancer had superior survival outcomes when compared to those who did not receive surgery on univariate analyses, across all categories of advanced BAC: median OS = NR at >58 months follow-up, 95% CI 42-NR) versus 13 months (95% CI 4–35) for stage IIIB BAC patients due to separate tumors in the same lobe (\(P < 0.0001\)); median OS = 14 months (95% CI 10–37) versus 7 months (95% CI 6–9) for ‘other’ stage IIIB patients (\(P < 0.0001\)); median OS = 19 months (95% CI 15–31) versus 10 months (95% CI 7–13) for stage IV BAC patients due to intrapulmonary spread (\(P < 0.0001\)); median OS = 16 months (95% CI 7–25) versus 6 months (95% CI 5–7) for stage IV BAC patients with distant disease (\(P = 0.0001\)). Surgical treatment was also found to be an independent predictor of survival on multivariate analysis (HR for patients who received surgery compared to those who did not have surgery = 0.44, 95% CI 0.35–0.55) (\(P < 0.0001\); Table 3).

Within the group of stage IV patients with BAC due to intrapulmonary metastasis, 54 out of 80 patients (67.5%) with ipsilateral metastasis received surgery (15 wedge resections/segmentectomies, 24 lobectomies, 15 pneumonectomies). Overall survival was significantly improved for these BAC patients with ipsilateral intrapulmonary metastasis who received surgery (median OS = 15 months, 95% CI 13–18) compared to those who did not receive surgery (median OS = 7 months, 95% CI 7–10, \(P = 0.0001\)). For the patients with contralateral intrapulmonary metastasis (\(n = 198\)), 41 patients (20.7%) received surgery (one local surgical procedure, 29 wedge resections/segmentectomies, nine lobectomies, two pneumonectomies) and their survival rate was significantly improved (\(median\ OS = 14\ months, 95\%\ CI 10–31\)) compared to those who did not have surgery (\(median\ OS = 9\ months, 95\%\ CI 7–11\)) (\(P = 0.026\)).

Subset analysis was performed to determine the contribution of the type of surgery performed on survival among these
advanced (stage IIIB and stage IV) BAC patients. An adjusted analysis was used to profile each of the major surgical treatment categories compared to no surgical treatment, including adjustment for age, stage, gender, and ethnicity. Statistically significant reductions in the risk of death compared to having no surgical treatment were observed for advanced BAC patients receiving a lobectomy (HR = 0.33, 95% CI 0.24–0.46; \( P < 0.0001 \)), pneumonectomy (HR = 0.48, 95% CI 0.29–0.78; \( P = 0.003 \)), or wedge resection/segmentectomy (HR = 0.60, 95% CI 0.44–0.81; \( P = 0.0007 \)); local surgical treatment was not associated with a statistically decreased risk of death compared to receiving no surgical treatment in this adjusted analysis of advanced BAC patients (HR = 0.40, 95% CI 0.13–1.26; \( P = 0.12 \)).

**discussion**

In this study, overall survival and lung cancer-specific survival for stage IIIB patients with BAC tumors in the same lobe (i.e. T4NMX0, T4N0-2M0) was significantly improved over ‘other’ stage IIIB BAC patients. Additionally, significant differences in overall survival and lung cancer-specific survival were detected for stage IV BAC patients, favoring those with intrapulmonary spread over those with distant metastasis.

Our findings correlate well with surgical series by Roberts et al. and Battafarano et al., suggesting a survival benefit for surgically-resected patients with stage IIIB disease due to separate tumors in the same lobe, and stage IV BAC due to intrapulmonary spread [11, 14]. Retrospective analysis by Ebright et al. on 100 surgically treated BAC patients (including 29 with multifocal disease) revealed excellent survival for patients with multifocal BAC [7]. In a separate study on BAC assessing surgical outcomes by Volpino et al., lymph node involvement and age were shown to be independent adverse prognostic factors, and the authors concluded that BAC patients with multiple nodules should not be denied surgery if they are under 60 years of age and have no lymph node involvement [15]. In another recent epidemiologic study from our group on BAC using a regional population-based cancer database, survival differences were noted for 138 advanced stage BAC patients, favoring those with T4M0 BAC due to separate tumors in the same lobe over stage IV BAC due to intrapulmonary metastasis over stage IV BAC due to distant metastasis [16]. However, the number of patients with stage IIIB BAC due to tumors within the same lobe in that study was small \( n = 12 \), and comparisons were not made for the different subsets of intrapulmonary stage IV BAC. The present study was sufficiently powered to address these issues, and supports the findings of previous surgical reports.

Across the four categories of advanced BAC patients, those receiving surgical treatment for their disease had improved survival. There were significant differences in the proportion of patients having received surgery among the four categories of advanced stage BAC. A large proportion (90.3%) of stage IIIB BAC patients with separate tumors in the same lobe received either wedge resection/segmentectomy, lobectomy or pneumonectomy, with a resultant improvement in survival. In the group of surgically resected stage IV BAC patients with ipsilateral intrapulmonary metastasis, an impressive median OS of 31 months was observed. Compared to those who were ineligible for surgery, surgical candidates likely reflect those with better Karnofsky performance status, better pulmonary reserve, and lower tumor burden. As noted in our study, few patients with N2 or N3 lymph node involvement received surgical treatment. Other factors unaccounted for in this study may explain differences between patients receiving surgery and those not receiving surgery, including access to subspecialty care, earlier diagnosis at time of relapse, patient acceptance of therapy, and compliance with therapy.

The earlier population-based analysis from our group revealed an overall survival benefit for BAC patients after release of the 1999 WHO Histological Classification of Tumors [16], at which time the pathologic definition of BAC was restricted to adenocarcinomas with a pure bronchiolo-alveolar growth pattern and lack of pleural, stromal, or vascular invasion [17]. WHO restricted the definition of BAC at that time because it had been shown that patients with solitary, noninvasive BAC tumors less than 2.0 cm could be cured [18]—and this definition was retained in the 2004 WHO classification [8]. Since the present study includes patients during 1998–2002 (i.e. prior to, and just after the 1999 WHO definition changes), we cannot confirm that each BAC case would be considered as BAC by the current definition. The spectrum of what is labeled BAC includes pure BAC, adenocarcinoma with BAC features, and adenocarcinoma with certain clinical presentations such as pneumonic, diffuse, and multifocal forms [3, 7, 8, 19, 20]. Each of these subtypes contain BAC components, and because there has not yet been uniform and widespread adoption of the WHO classifications, each of these subtypes are likely represented in our population-based analysis as ‘BAC’. As an epidemiologic study representing a diverse US population of BAC patients, independent histologic review was not possible, which results in heterogeneity of the diagnostic criteria for BAC. However, the accuracy of lung cancer histologic classification in SEER has been evaluated favorably compared to independent histologic review [21], because the large numbers involved are believed to result in regression towards the mean for histologic subtypes [22]. Despite proposed classifications [19], currently, no consensus has been reached as to the percent of invasive adenocarcinoma component sufficient to classify ‘minimally invasive BAC’ as a distinct prognostic entity [8]. The diffuse form of BAC has been noted to adversely affect prognosis [20, 23, 24], but we did not perform analysis on these patients due to small sample size (i.e. only nine patients with Tx, diffuse BAC were identified). Mucinous versus non-mucinous BAC histologies were noted to have similar distribution by stage at presentation, and also similar survival characteristics. However, few patients with these BAC histologic subtypes were identified (and none until the last 2 years of the 5-year period analyzed). Thus future epidemiologic studies on BAC will likely contain more information on these histologic subtypes, as the data become available in SEER.

The proportion of stage IV BAC patients with distant metastasis reported here (i.e. 44.7%) is higher than what is generally reported in the surgical literature, in part because these patients do not frequently undergo surgery. Specific extrathoracic sites of metastasis are not available in SEER, but others have shown that stage IV BAC patients have similar...
rates of bone and adrenal metastasis compared to stage IV non-BAC NSCLC patients, with fewer occurrences of brain or liver metastasis [3]. Lower proportions of extrathoracic metastasis among stage IV BAC patients (i.e. 24%) have been reported among patients enrolled in clinical trials [3], which may stem from selection bias occurring through exclusion of patients with ill-defined extrathoracic metastasis. The frequency of extrapulmonary stage IV BAC among non-selected patients (i.e. from population-based analyses) is not reported often in the literature. Major population-based analyses on BAC have focused on incidence and survival, with limited discussion on stage-related differences [2, 6]. In our previous population-based analysis of BAC, however, 59 out of 126 stage IV BAC patients (47%) had distant metastasis, compared to 67 (53%) with intrapulmonary stage IV BAC [16]—which correlates well with the proportions noted in the present study. African–American ethnicity was associated with poor survival in our subset of advanced stage BAC patients, even after adjustment for age, gender, stage at presentation, and surgical treatment status. Poor survival characteristics for African–American BAC patients were also noted by Hasan et al., in a report of 19 patients that were noted to have a 23 month mean survival rate for all stages [25]. However, only five of the patients had advanced stage BAC, and the two patients with stage IV disease had very poor mean OS (7 months). Thus the observed survival rates in the Hasan study are even lower than the 17 month median OS for African–American patients with advanced BAC observed in our study. Among African Americans, high lung cancer incidence rates combined with decreased lung cancer survival rates account for the observed high lung cancer mortality rates [26–28].

Certain limitations of this population-based analysis must be noted. Smoking status is not available in the SEER database, so we are not able to assess outcomes of BAC patients based on their smoking status. Most investigations of BAC and other NSCLC’s assessing smoking status note a modest survival benefit for NSCLC patients who were never smokers [16, 29–32]. Additionally, SEER data does not contain information on chemotherapy or biologic treatments, which is an important consideration in understanding outcomes for advanced BAC patients with the development of the oral EGFR tyrosine kinase inhibitors (i.e. gefitinib, erlotinib). Nonetheless, the vast majority of patients in our study were not likely to have received treatment with an EGFR tyrosine kinase inhibitor, as the US Food and Drug Administration did not approve the first of these agents (gefitinib) until 2003—a full year after the end of our study period [33]. In subsequent years, with additional follow-up duration (not yet available in SEER), widespread adoption of the revised WHO criteria, and novel treatment regimens, survival trends for advanced stage BAC will likely continue to improve. Incomplete nodal assessment remains a potential confounder in this study, particular for the seven patients with T4NXM0 BAC with a T4 lesion due to intralobar spread. These patients were analyzed together with the group of 93 stage IIIB BAC patients with a T4 lesion due to intralobar spread since the prevalence of N3 disease occurring among all stage IIIB BAC patients was very low (i.e. 5.4%). Excluding these seven T4NXM0 patients from the analysis did not affect the median overall survival for intralobar stage IIIB BAC patients, and thus a similar survival improvement for these patients compared to ‘other’ stage IIIB patients was observed (data not shown).

In conjunction with the available literature on survival in patients with advanced BAC, the results of this large population-based analysis encourage further revisions in the staging criteria for this unique NSCLC subtype. In particular, the large survival benefit observed for patients with stage IIIB BAC due to separate tumors in the same lobe (median OS = 46 months) compared to ‘other’ stage IIIB patients (median OS = 9 months), and the improved survival of patients with stage IV BAC due to intrapulmonary spread compared to ‘other’ stage IIIB BAC patients and stage IV BAC patients with distant metastasis reveal inconsistencies with the current staging system for BAC. Reclassification of the staging system would better stratify patients with advanced bronchiolo-alveolar carcinoma of the lung into clinically relevant prognostic groups.

references


