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Bronchopulmonary Carcinoid Tumors: Long-Term Outcomes After Resection

Christopher Cao, BSc (Med) MBBS, Tristan D. Yan, BSc (Med) MBBS, PhD, Catherine Kennedy, RMRA, Nick Hendel, MBBS, FRACS, Paul G. Bannon, MBBS, PhD, and Brian C. McCaughan, MBBS, FRACS

The University of Sydney, Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, and The Baird Institute for Applied Heart and Lung Surgical Research, Sydney, Australia

Background. Bronchopulmonary carcinoid tumors are considered as a relatively uncommon and less malignant group of lung cancers. However, patients with histologically atypical disease are known to have a worse prognosis. The present study aims to evaluate the long-term outcomes after resection of bronchopulmonary carcinoid tumors according to the new tumor, nodes, metastasis (TNM) staging system.

Methods. Patients with histologically proven bronchopulmonary carcinoid tumors who underwent surgery in our thoracic unit over the last 25 years were identified from a prospectively collected database.

Results. One hundred and eighty-six patients were identified from our electronic database. Of these, 164 were known to have typical disease, while 22 had atypical disease. Median overall survival was 20.0 years. The mean follow-up was 8.0 years (median 7.0 years). Univariate analysis found age over 60, atypical disease, TNM staging, N status, and M status to have a statistically significant influence on overall survival. Multivariate analysis found age over 60 and atypical histopathology to have a detrimental impact on overall survival. Patients in the atypical subgroup were found to be significantly older, and presented with higher stage disease.

Conclusions. It is clear from the current study and previous reports that patients with atypical histopathology have different baseline characteristics, disease behavior, and prognosis compared with patients with typical disease. The proposed TNM staging system appears to be applicable to patients in our surgical experience, and may offer more accurate prognostic information and assist in the management plans for individuals.

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Carcinoids are an uncommon and heterogeneous group of tumors belonging to the neuroendocrine tumor spectrum. Typical and atypical forms of bronchopulmonary carcinoid tumors were initially described by Engelbreth-Holm in 1944 [1]. Since then, a myriad of histologic and electron microscopic techniques, immuno-histochemical stains, biochemical tests, and cytogenetic studies have contributed to the evolution of carcinoid tumor classification [2, 3]. In the latest World Health Organization classification published in 2004, bronchopulmonary neuroendocrine tumors were divided into low-grade typical carcinoid tumors, intermediate-grade atypical carcinoid tumors, and high-grade large cell neuroendocrine carcinomas and small-cell lung carcinomas [4].

The forthcoming 7th edition of the tumor, nodes, metastasis (TNM) staging system was primarily based on a global database created by the IASLC (International Association for the Study of Lung Cancer), which included 100,869 lung cancer patients from 1990 to 2000. Travis and colleagues [5] extracted 513 patients from this database and 1,437 surgically treated patients from the National Cancer Institute SEER (Surveillance Epidemiology and End Results) database around the same period to assess the applicability of the new staging system for patients with bronchopulmonary carcinoid tumors. After a thorough analysis of these two large multiinstitutional databases, the authors concluded that the proposed 7th edition of TNM classification will be a more useful prognostic tool than its predecessor.

The aim of the current study was to analyze our surgical group’s experience in treating patients with bronchopulmonary carcinoid tumors. The primary outcome was overall survival. In addition, we assessed a number of potential prognostic factors and reclassified our patients according to the newly proposed TNM classification system. Demographic and clinicopathologic data were also analyzed separately for typical and atypical histologic subgroups to assess any differences in patient characteristics and disease behavior.
Material and Methods

All patients with histologically proven bronchopulmonary carcinoid tumors treated by surgical resection by the thoracic surgical team led by the same surgeon (B.C.M.) were identified from our database. Patient characteristics, treatment details and clinicopathologic data were collected through an electronic database. For patients operated from earlier dates, clinical files were manually searched for any missing data. Patients with undefined histologic subtype were excluded from statistical analysis. The study was approved by the Institutional Human Research Ethics Committee.

Preoperative workup included a review of clinical history, physical examination, serum hematology and biochemistry, pulmonary function tests, chest X-ray, and computed tomography of the chest. A number of patients underwent preoperative positron emission tomography scans to identify potential extrathoracic spread after this technology became available in one of our treatment centers in 2000. Selected patients with radiographic or clinical suspicion of nodal involvement underwent mediastinoscopy prior to surgical resection. Patients were eligible for surgery if they had adequate pulmonary, cardiac, renal and liver function. A variety of surgical procedures was employed. These included pneumonectomy, bilobectomy, lobectomy, segmentectomy, wedge resection, sleeve resection, or a combination of the above. The type of surgery performed was dependent on preoperative investigations as well as intraoperative findings. All patients provided written informed consent prior to surgery.

Statistical Analysis

For univariate analysis, the $\chi^2$ or Fisher exact test was used for categoric variables. The Mann-Whitney U test was used for the comparison of differences in the means of continuous variables. Overall survival analysis was performed using the Kaplan-Meier method and compared using the log-rank test. Survival was calculated from the date of the surgery to the last date of follow-up or death. The parameters evaluated included age, gender, histology subtype, T status, N status, M status, 7th edition of TNM staging, laterality, type of surgery, and resection margin. A significant difference was predetermined to be a $p$ value less than 0.05. For multivariate analysis, a Cox regression model was used with a forward stepwise selection of covariates. These analyses were performed using SPSS version 11.5 for Windows (SPSS GmbH, Munich, Germany).

Results

One hundred and eighty-six patients who underwent surgical intervention for bronchopulmonary carcinoid tumors from September 1984 to February 2010 were identified through our electronic database. The mean follow-up was 8.0 years from the date of surgery (median 7.0 years). There were 68 female patients. Disease was located on the left side in 68 patients. According to the proposed 7th edition of the TNM staging system, there were 121 patients with T1, 50 with T2, 12 with T3, and 3 patients with T4 disease. One hundred and fifty-four patients were found to have N0 disease, 22 patients had N1 disease, and 10 patients had N2 disease. Two patients were classified as M1 at the time of operation. Accordingly, overall stage was classified as stage I in 121 patients, stage II in 48 patients, stage III in 15 patients, and stage IV in 2 patients.

Of the 186 patients, 30 underwent pneumonectomy, 32 underwent bilobectomy, 111 underwent lobectomy, 9 underwent sleeve resection, 4 underwent segmentectomy, and 12 had wedge resection. Twelve patients underwent two separate surgical procedures during the same operation. These included lobectomy and sleeve resection in 6 patients, lobectomy and wedge resection in 4 patients, segmentectomy and wedge resection in 1 patient, and bilobectomy and sleeve resection in 1 patient. Residual disease was found to be present in eight patients after pathologic examination of the resected specimens.

The median overall survival was 20.0 years (range, 0 to 25.7 years), with 5-year, 10-year, and 15-year survival rates of 93.7%, 81.7%, and 71.4%, respectively, as shown in Figure 1. At the time of the latest follow-up, 154 patients from our series remained alive. No patients were lost to follow-up.

Five potential prognostic factors were found to have a statistically significant effect on overall survival during univariate analysis. These included age above 60 ($p < 0.0001$), atypical histology ($p < 0.0001$), N staging ($p = 0.0004$), presence of metastatic disease at the time of surgery ($p < 0.0001$), and the TNM stage according to the proposed 7th edition of the AJCC/UICC staging system ($p < 0.0001$). Gender ($p = 0.4510$), laterality of disease ($p = 0.3232$), T staging ($p = 0.04480$), presence of residual disease ($p = 0.3668$), and type of surgical procedure performed ($p = 0.9220$) were not significant for overall survival. Of the 186 patients, 164 were found to have
Atypical histologic subtype, as seen in Table 1. These included age over 60 at the time of surgery and the remained to have a significant effect on overall survival. On multivariate analysis, two clinicopathologic factors only significant prognostic factors on multivariate analysis.

The current case-series represents one of the largest studies on bronchopulmonary carcinoid tumors in recent times, being the first to evaluate the upcoming 7th edition of the TNM staging system. A review of the literature focusing on individual studies involving more than 100 patients indicates that our long-term survival is comparable with past reports, as shown in Table 2. Recently, Rea and colleagues included 252 patients in their multiinstitutional retrospective study, reporting a favorable 5-year, 10-year, and 15-year survival of 90%, 83%, and 77%, respectively [16]. However, patients in this cohort appeared to be younger, with a median age of 45, and there was limited data on T and M staging. Lim and colleagues [15] collated data from 177 patients with pulmonary neuroendocrine tumors, of whom 104 had typical or atypical carcinoid tumors. Apart from reporting similar 5-year and 10-year survival rates to the current study, the authors also found age and cell type to be the only significant prognostic factors on multivariate analysis.

Assessment of potential prognostic factors from our data found histologic type, age above 60, nodal stage, presence of metastatic disease, and TNM stage using the 7th edition of the AJCC/UICC staging system to be significant factors on overall survival. Multivariate analysis found age over 60 and the atypical histologic subtype to be independent risk factors for overall survival. However, it should be acknowledged that these factors cannot be assessed completely independent of each other, as patients with atypical disease were also found to be significantly older. The most consistent finding for prognostic factors from the current literature is the significant difference in long-term survival between typical and atypical histologic subtypes [6–16]. Other common prognostic factors found to be significant on multivariate analysis in the literature include pathologic staging, nodal status, and gender.

An improvement in the prognostication process may enable more accurate management decisions to be made with a significantly worse prognosis, and generally present at a higher stage with or without metastatic disease [6–16]. In many regards, the considerable differences in patient characteristics, disease patterns, and prognosis between typical and atypical carcinoid tumors is comparable with differences between small cell lung cancers and non-small cell lung cancers. In fact, it has been long proposed that these two subgroups be considered as two separate disease entities [17].

Traditionally, bronchopulmonary carcinoid tumors have been considered as a relatively benign disease with a more favorable outcome compared with most other lung cancers. However, the atypical subtype is associated

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.524</td>
<td>1.517–8.186</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>Atypical</td>
<td>13.461</td>
<td>4.734–38.274</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio.

Comment

The results of the current study suggest that bronchopulmonary carcinoid tumors as a group are associated with favorable long-term survival outcomes after surgical resection. However, typical and atypical subgroups have different patient characteristics, disease behavior, and long-term prognosis, and hence should be considered separately as distinct disease entities. The recently proposed 7th edition of the AJCC/UICC (American Joint Cancer Committee/Union Internationale Contre le Cancer) TNM staging system appears to be applicable to surgical patients with bronchopulmonary carcinoid tumors.

Traditionally, bronchopulmonary carcinoid tumors have been considered as a relatively benign disease with a more favorable outcome compared with most other lung cancers. However, the atypical subtype is associated

Histologically typical disease and 22 had atypical disease. The median overall survival of the atypical histologic group was found to be significantly less than the typical group, as shown in Figure 2 (5.1 vs 20.2 years, \( p < 0.0001 \)). On multivariate analysis, two clinicopathologic factors remained to have a significant effect on overall survival. These included age over 60 at the time of surgery and the atypical histologic subtype, as seen in Table 1.

Comparing atypical and typical histologic groups, patients with atypical disease were more likely to be older, with a mean age of 64 compared with 53 (\( p = 0.001 \)). There was a higher proportion of females in the atypical group (73% vs 63%), but this did not reach statistical significance. In addition, patients with atypical disease presented with more advanced disease, with \( \chi^2 \) tests indicating a significant association with nodal involvement (\( p < 0.001 \)), metastatic disease (\( p < 0.001 \)), and higher TNM staging (\( p < 0.001 \)).
Table 2. Review of Literature on Survival Outcomes and Prognostic Factors After Surgical Management for Patients With Bronchopulmonary Carcinoid Tumors

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Mean Age</th>
<th>TC</th>
<th>AT</th>
<th>Significant Prognostic Factors</th>
<th>Nonsignificant Prognostic Factors</th>
<th>5-Year</th>
<th>10-Year</th>
<th>15-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okike [6]</td>
<td>1976</td>
<td>203</td>
<td>48</td>
<td>203</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>94%</td>
<td>87%</td>
<td>N/A</td>
</tr>
<tr>
<td>Wilkins [7]</td>
<td>1984</td>
<td>111</td>
<td>N/A</td>
<td>100</td>
<td>11</td>
<td>N/A</td>
<td>N/A</td>
<td>92%</td>
<td>77%</td>
<td>N/A</td>
</tr>
<tr>
<td>McCaughan [8]</td>
<td>1985</td>
<td>124</td>
<td>55</td>
<td>81</td>
<td>19</td>
<td>Histology type, size &gt;3 cm, nodal status</td>
<td>Disease location</td>
<td>78%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Harpole [9]</td>
<td>1992</td>
<td>126</td>
<td>53</td>
<td>66</td>
<td>34</td>
<td>Histology type, pathologic stage, symptoms, gender, serum serotonin, urine HIAA/serotonin, primary location, size &gt;2 cm, hilar lymph nodes</td>
<td>Age, smoking history, environmental exposure, family history of lung tumors, hemoptysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ducrocq [10]</td>
<td>1998</td>
<td>139</td>
<td>47</td>
<td>139</td>
<td>0</td>
<td>None</td>
<td>Gender, T status, tumor location, type of resection</td>
<td>92.4</td>
<td>88.3</td>
<td>76.4</td>
</tr>
<tr>
<td>Beasley [11]</td>
<td>2000</td>
<td>106</td>
<td>54</td>
<td>0</td>
<td>102</td>
<td>Size &gt; 3.5 cm, pathologic stage, presence of rosettes, mitotic rate, gender</td>
<td>None</td>
<td>61%</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Fink [12]</td>
<td>2001</td>
<td>142</td>
<td>52</td>
<td>128</td>
<td>14</td>
<td>Histology type (10-year survival)</td>
<td>None</td>
<td>87%</td>
<td>79%</td>
<td>N/A</td>
</tr>
<tr>
<td>Skuladottir [13]</td>
<td>2002</td>
<td>112</td>
<td>N/A</td>
<td>43</td>
<td>69</td>
<td>N/A</td>
<td>N/A</td>
<td>87%/44%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Filosso [14]</td>
<td>2002</td>
<td>126</td>
<td>47</td>
<td>82</td>
<td>44</td>
<td>Histology type, nodal status, pathologic stage</td>
<td>None</td>
<td>89%</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td>Lim [15]</td>
<td>2005</td>
<td>104</td>
<td>54</td>
<td>89</td>
<td>15</td>
<td>Histology type, age, nodal stage</td>
<td>T status, N status,</td>
<td>86%</td>
<td>81%</td>
<td>N/A</td>
</tr>
<tr>
<td>Rea [16]</td>
<td>2007</td>
<td>252</td>
<td>45</td>
<td>174</td>
<td>78</td>
<td>Histology type, age, N0 status, gender, type of surgery, localization</td>
<td>Time of surgery</td>
<td>90%</td>
<td>83%</td>
<td>77%</td>
</tr>
<tr>
<td>Current study</td>
<td>2010</td>
<td>186</td>
<td>54</td>
<td>164</td>
<td>22</td>
<td>Histology type, age, pathologic stage, nodal stage, metastatic disease</td>
<td>Gender, T status, tumor location, type of resection, residual disease</td>
<td>94%</td>
<td>82%</td>
<td>71%</td>
</tr>
</tbody>
</table>

a Patients lost to follow up and death within 5 years excluded from survival analysis.  b data relates to disease-free survival.  c Median.  d Significant on multivariate analysis.  e Rates refer to TC/AT.

AT = atypical carcinoid; HIAA = hydroxyindoleacetic acid; N/A = not applicable; TC = typical carcinoid.
for individual patients. A joint effort by the International Staging Committee utilizing combined data from the SEER and IASLC databases recently demonstrated the applicability of the proposed 7th edition of the TNM staging system for bronchopulmonary carcinoid tumors [5]. Unfortunately, histologic distinction between typical carcinoid and atypical carcinoid was generally absent from the SEER database and was present in only half of the cases from the IASLC database. Results from the current study found a significant effect of using the updated TNM staging system on predicting overall survival in univariate analysis. However, further prospective collection of data from the International Registry of Pulmonary Neuroendocrine Tumors is likely to provide additional insight into the applicability of the new TNM staging system, possibly with separate analysis of typical and atypical subgroups.

References