The Surgical Spectrum of Pulmonary Neuroendocrine Neoplasms*

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Objectives: The purpose of this study is to review our experience with the spectrum of neuroendocrine neoplasms of the lung with emphasis on the histopathologic classification and surgical therapy of each class of neoplasm.

Design: This retrospective review covers the entire spectrum of neuroendocrine neoplasms of the lung over an 11-year period (January 1985 to December 1995) in a university hospital setting. Only patients who underwent surgical resection were included in this review.

Patients: During this period, a total of 77 patients underwent lung resection for the following neuroendocrine neoplasms: typical carcinoid (TC), 50 patients; atypical carcinoid (AC), 5 patients; large cell neuroendocrine carcinoma (LCNEC), 9 patients; mixed large-small cell neuroendocrine carcinoma (LSNEC), 4 patients; or small cell neuroendocrine carcinoma (SCC), 9 patients. There were 37 men (48.1%) and 40 women (51.9%) among the patients, with a mean age of 57.9 years (range, 14 to 87 years).

Interventions: Primary surgical resection consisted of the following procedures: 52 lobectomies (67.5%); 10 pneumonectomies (13%); 13 limited resections (16.9%); 1 left main bronchus sleeve resection; and 1 carinal resection. Six patients had the following concomitant procedures: pericardiectomy, 2 patients; mediastinoscopy, 1 patient; chest wall resection, 1 patient; stapling blebs, 1 patient; and transdiaphragmatic liver biopsy, 1 patient. Four patients underwent bilobectomies, and two patients underwent multiple wedge resections.

Results: The hospital mortality rate was 2.6% (2 of 77 patients), and both patients died of pulmonary failure. Follow-up was obtained in 62 of 77 patients (80.9%) for an average of 38.1 months (range, 2 to 132 months). There were a total of 13 deaths, and 8 were disease-related (LCNEC, 4 deaths; SCC, 2 deaths; LSNEC, 1 death; and AC tumor, 1 death). The mean disease-free intervals for patients with these neoplasms were the following: TC tumor, 41.3 months; AC tumor, 20 months; LCNEC, 20.4 months; LSNEC, 25 months; and SCC, 48 months. The overall 3-year survival rate was 45.2% (28 of 62 patients).

Conclusion: This report will emphasize the classification, surgical management, and treatment considerations of pulmonary neuroendocrine neoplasms. Despite the poor overall prognosis in high-grade neuroendocrine tumors of the lung, surgery remains a viable adjunct in the early stages of this disease.

Key words: carcinoid; lung; neoplasm; neuroendocrine

Abbreviations: AC = atypical carcinoid; LCNEC = large cell neuroendocrine carcinoma; LSNEC = large-small cell neuroendocrine carcinoma; SCC = small cell neuroendocrine carcinoma; TC = typical carcinoid

Neuroendocrine tumors of the lung comprise a heterogeneous group of tumors that represents a spectrum of disease from well-differentiated typical carcinoid (TC) tumors to poorly differentiated small cell carcinomas (SCCs). This report details our experience with neuroendocrine tumors, with an emphasis on the pathologic clas-
sification, oncologic treatment, and surgical treatment options for each type of neuroendocrine tumor.

The term carcinoid was first introduced in the literature by Oberndorfer in 1907 in his description of a class of malignant tumors that behaved less aggressively than the more common adenocarcinomas of the GI tract. In 1954, Thorson described a clinical syndrome of flushing, palpitations, fainting, abdominal pain, diarrhea, bronchospasm, and right heart valvular disease. This has now become known as the carcinoid syndrome.

Prior to the description of carcinoid tumors and the related syndrome, Langerhans in 1869 and Kultschitzky in 1897 identified the presence of neuroendocrine cells in the pancreas and gut mucosa, respectively. Over the course of the next several decades, histologic tests, immunohistochemical stains, electron microscopy, and biochemical assays for the detection of secretory products of neuroendocrine cells were developed.

The term neuroendocrine defines a specific group of cells by their secretory products and distinct staining characteristics and by their ability to uptake and decarboxylate amine precursors. The pathologic classification of neuroendocrine neoplasms has continued to evolve from the original distinction between carcinoid and atypical carcinoid (AC) tumors by Arrigoni et al to the current classification as outlined by Travis et al. The surgical spectrum of pulmonary neuroendocrine neoplasms includes TC tumors, AC tumors, large cell neuroendocrine carcinomas (LCNECs), mixed large-small cell neuroendocrine carcinoma (LSNECs), and SCCs. TC and AC tumors account for 80 to 90% of all pulmonary neuroendocrine neoplasms. Unfortunately, the more aggressive SCCs and LCNECs are infrequently amenable to surgical resection.

Carcinoids tend to be located centrally. Presenting symptoms include hemoptysis, wheezing, cough, and dyspnea. Endocrine manifestations in pulmonary carcinoids are rare but include the carcinoid syndrome, Cushing’s syndrome, hypercalcemia, and acromegaly. The carcinoid syndrome is more frequent in GI carcinoid tumors, particularly with hepatic metastases.

Most of the larger series of patients with carcinoid tumors report a slightly higher incidence in women. These tumors have a propensity for the right lung. More than 75% of these tumors may be visualized with bronchoscopy. They may appear as pedunculated masses or submucosal lesions. The foci of a hemorrhage dispersed against a yellowish-white background may be seen on the cut surface. Typical bronchial carcinoids have a tan, glistening appearance on bronchoscopy.

SCCs and LCNECs characteristically are more aggressive and frequently are widely disseminated at the time of diagnosis. The diagnosis of these high-grade neuroendocrine tumors can be elusive, as has been demonstrated in some of the early trials of surgical therapy for SCC. The role of surgery in the treatment of patients with these high-grade neoplasms remains controversial. From retrospective data, the overall reported survival rate in patients with surgically resected small cell lung cancer ranges from 0 to 29%. When studied in a prospective randomized fashion, Lad et al were unable to show any survival benefit in the surgical arm of the study. However, the peripheral small cell tumor may indeed be less aggressive and lend itself to surgical resection for long-term survival. Thus, aggressive surgical intervention in small (ie, <3 cm) small cell lung cancers with normal positron emission tomography scans may be warranted.

Materials and Methods

The purpose of our study is to review again the cases of all patients who had undergone surgical resection for a neuroendocrine neoplasm over a 10-year period. We retrospectively reviewed the records of patients who had undergone pulmonary resection for neuroendocrine tumors during an 11-year period from January 1985 to December 1995 on the general thoracic surgery service of Emory University Hospitals. Only patients who had undergone resection were included in this study. Patients who were treated with adjuvant therapy alone were excluded. This represents <1% of the lung cancer patients treated surgically during this same time period. Two patients underwent exploratory surgery but were not deemed to have surgically resectable conditions and, therefore, were excluded from the total in this review. All patients were identified through the oncology data bank of the Winship Cancer Center.

Data were obtained from a retrospective review of inpatient and outpatient records. Specific clinical information included patient demographics, presenting symptoms, preoperative diagnostic studies, type of procedure, pathologic conditions, staging, adjuvant therapy, morbidity, and mortality. Tumors were classified initially according to the classification of Arrigoni et al and Gould et al. Pathology slide blocks from 60 of the patients were reviewed and reclassified by one of the authors (A.G.G.) using criteria as outlined by Travis et al. Slides for the remaining patients were unavailable for review.

Follow-up information was obtained from phone interviews, medical records, primary physician contacts, and vital statistics records.

Results

Demographics

During the 11-year study period, patients underwent thoracotomy for resection of a pulmonary neuroendocrine tumor. Among these patients, there were 40 women (51.9%) and 37 men (48.1%). The average age was 57.9 years (range, 14 to 87 years).
Sixty patients (78%) had a history of tobacco abuse. Comorbid conditions included hypertension (53 patients), coronary artery disease (31 patients), diabetes mellitus (23 patients), and COPD (10 patients).

Presenting symptoms were invariably respiratory related, with hemoptysis, cough, weight loss, rhonchi, and dyspnea being the most notable. None of our patients had the carcinoid syndrome.

**Diagnostic Procedures**

All patients underwent preoperative pulmonary function testing, ECG, chest radiograph, and CT scanning of the thorax and abdomen, along with a cardiac evaluation as was deemed necessary from the patient’s medical history and physical examination.

Bronchoscopy was performed preoperatively in the majority of patients or just prior to the start of the procedure if a preliminary diagnosis had been made by physicians on the pulmonary service. The majority of the central carcinoid lesions were identified on bronchoscopy. Thirty-two of the 77 patients (42%) had lesions identified by bronchoscopy.

**Surgery**

Primary pulmonary resections included 52 lobectomies, 10 pneumonectomies, 13 limited or partial resections, 4 bilobectomies, 2 multiple wedge resections, 1 carinal resection, and 1 left main bronchus sleeve resection. Six patients had concomitant procedures, pericardiectomy, mediastinoscopy, chest wall resection, stapling of blebs, and transdiaphragmatic liver biopsy.

Tumors involved the right lung in 43 patients (56%). The right middle lobe was the most frequently resected lobe. Seventeen of these procedures were isolated middle lobectomies with four middle lobes resected as part of a bilobectomy.

None of the patients underwent any attempt at endobronchial resections. Our surgical goal was complete resection of all tumors with negative margins around the primary tumor site.

Perioperative complications occurred in 15 patients and were primarily pulmonary related, as is shown in Table 1. Two patients died as a result of respiratory failure. One patient required transfer to an outside facility for prolonged ventilatory care. Infectious complications included pneumonia in four patients, minor wound infection in one patient, and urinary tract infection in one patient.

**Pathology**

The spectrum of pathologic conditions is as shown in Table 2. In this series, 50 patients had TC tumors, 5 had AC tumors, 9 had LCNECs, 4 had LSNECs, and 9 had SCCs. In 60 cases, the original pathology report was reviewed and all tumors were reclassified according to the criteria outlined by Travis et al. Ten percent of the cases (6 of 60 patients) were reclassified. Two TC tumors were changed to AC tumors. Four patients originally classified as having LCNECs actually had poorly differentiated adenocarcinomas.

Lymph node metastases were present in eight of nine patients with SCCs, five of nine patients with LCNECs, two patients with TC tumors, and two patients with AC tumors. No patient had evidence of metastatic disease at the time of presentation for surgery.

Pathologic staging was performed according to the international system for lung cancer staging as proposed by Mountain. The nine patients who had a preoperative diagnosis of SCC were considered for surgery if they had limited disease.

**Adjuvant Therapy**

All nine patients with SCCs and seven of nine patients with LCNECs received adjuvant chemotherapy. One patient with an AC tumor had chemotherapy. Adjuvant radiation therapy was administered to six patients with SCCs, five patients with LCNECs, and one patient with an AC tumor. Additionally, two patients with LSNECs received chemotherapy and, three patients received radiation therapy (Table 3).

**Survival**

The hospital mortality rate was 2.6% (2 of 77 patients). Follow-up information was obtained from Table 2—The Spectrum of Pulmonary Neuroendocrine Pathology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC tumor</td>
<td>50</td>
</tr>
<tr>
<td>AC tumor</td>
<td>5</td>
</tr>
<tr>
<td>LCNEC</td>
<td>9</td>
</tr>
<tr>
<td>LSNEC</td>
<td>4</td>
</tr>
<tr>
<td>SCC</td>
<td>9</td>
</tr>
</tbody>
</table>
62 of 77 patients (81%) for an average of 38 months (range, 2 to 132 months). Thirteen patients died during the follow-up period. Eight of these deaths were confirmed to be as a result of the following distant metastases: LCNEC, four deaths; AC tumor, one death; LSNEC, one death; and SCC, two deaths. The remaining five deaths were not disease-related.

Twenty-eight of the 62 patients (45%) with follow-up data had survived for at least 3 years. The average follow-up period for TC tumor patients was 41 months; no patient in this group had evidence of disease during the follow-up period. AC tumor patients had an average disease-free interval of 20 months. One death occurred in this group, two of five patients had evidence of recurrence, and one patient was unavailable for follow-up. There were two confirmed disease-related deaths in the SCC group. The average disease-free interval was 48 months. Three of the remaining patients had evidence of recurrence. One patient with a confirmed SCC who had been treated with a right pneumonectomy and combined chemotherapy and radiation was alive and well through 8 years of follow-up.

**DISCUSSION**

Since the original description of carcinoid tumors in 1907, the spectrum of pulmonary neuroendocrine tumors has continued to evolve. The vast majority of these tumors that are resectable are low-grade TC tumors. As the malignant features become more prominent, lymph node and distant metastases occur more frequently. Certainly, the presence or absence of nodal involvement and histology are the major determinants of survival.

Our data are comparable to those previously reported in other series. The vast majority of our patients underwent lobectomy, in particular; we performed more lobectomies on the right middle lobe than on any other. Carcinoid tumors in general have a propensity to arise in the right lung; however, we are unclear as to the reason for higher numbers of tumors in the right middle lobe. We do not routinely perform biopsies on suspected carcinoid tumors due to their propensity for hemorrhaging, and their mere presence, especially endobronchially, is an indication for definitive resection. Sleeve lobectomy is reserved for patients with compromised lung function who would not otherwise tolerate a pneumonectomy.

Our overall 3-year survival rate for the entire cohort was 45%. The vast majority of these patients had TC tumors. The limited follow-up prevented extrapolation beyond 3 years. As expected, the patients with LCNECs and SCCs tended to have more extensive tumors, metastases, and recurrences.

In contrast with other reports, we report our experience with surgical resection across the entire spectrum of neuroendocrine neoplasms. In particular, we reclassified all of our tumors according to the new classification scheme reported by Travis et al. In doing so, we reclassified two TC tumors as AC tumors based on these criteria. Both of these patients were without any evidence of recurrent disease at the time of this review. This is significant since one patient had evidence of lymph node metastasis and may obtain long-term benefit from adjuvant radiation therapy. Although controversial, we believe that adjuvant radiation therapy is warranted in patients with lymph node metastases, regardless of the histology of the tumor (TC vs AC). Rarely, TC tumors with nodal metastasis may recur beyond 5 years and reoperative surgery should be considered. It remains to be proven whether adjuvant radiation therapy can prevent recurrences in node-positive TC tumors.

Two of five patients with AC tumors presented in this study had evidence of lymph node involvement at presentation; both received radiation therapy, and one received chemotherapy. One patient with recurrent disease was unavailable for follow-up. Since the 5-year survival rate in patients with AC tumors is much less than in those with TC tumors, we support aggressive management of these patients. Although the role of postoperative adjuvant therapy is unproven, the relatively poor overall survival and more frequent recurrences in this group of patients make such an approach justified.

As expected, the high-grade neuroendocrine tumors, namely LCNECs and SCCs, were associated with more frequent recurrences and death in this study. The vast majority of patients who were treated in the early years of the study received aggressive neoadjuvant chemotherapy (LCNECs, 9 patients; SCCs, 7 patients) and postoperative radiation therapy (LCNECs, 5 patients; SCCs, 6 patients). We agree that surgery has a limited role in the current management of these tumors. However, on the rare occasion that one encounters the limited-stage or peripheral high-grade neuroendocrine carcinoma, surgery should be considered in those patients with localized tumors.

**Table 3—Adjuvant Therapy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chemotherapy</th>
<th>Radiation</th>
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</thead>
<tbody>
<tr>
<td>AC tumor</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SCC</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>LCNEC</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>LSNEC</td>
<td>2</td>
<td>3</td>
</tr>
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</table>

*Values given as No. of patients.
Table 4—Treatment Recommendations for Pulmonary Neuroendocrine Neoplasms

<table>
<thead>
<tr>
<th>Type</th>
<th>Procedure</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Peripheral-wedge + LNR</td>
<td>Node +: Yes</td>
</tr>
<tr>
<td></td>
<td>Central-lobectomy + LNR</td>
<td>Node −: No</td>
</tr>
<tr>
<td>AC</td>
<td>Lobectomy + LNR</td>
<td>Node +: Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Node −: No</td>
</tr>
<tr>
<td>LCNCE</td>
<td>Lobectomy + LNR</td>
<td>Yes</td>
</tr>
<tr>
<td>LSNEC</td>
<td>Lobectomy + LNR</td>
<td>Yes</td>
</tr>
<tr>
<td>SCC</td>
<td>Lobectomy + LNR</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*LNR = lymph node resection; + = positive; − = negative.

Many questions remain to be answered regarding the optimal treatment of intermediate (AC) and high-grade neuroendocrine carcinomas, in particular, the role of adjuvant chemotherapy and radiation in AC tumors.24 In addition, as more advanced and effective treatment strategies are developed, the uniform classification of these tumors will become more important for the comparison of results across various reports.24–26

We acknowledge the limitations of this study in regard to its small number of patients, short length of follow-up, and retrospective design. We also acknowledge the controversial role of surgery in high-grade neuroendocrine tumors, although we do think that all of these patients should be evaluated as potential surgical candidates. Therefore, our approach to these tumors in the context of the spectrum of neuroendocrine neoplasms of the lung is supported by our experience and review of the current literature (Table 4).

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