Pulmonary Carcinoid Tumors With Cushing's Syndrome: An Aggressive Variant or Not?
Subrato J. Deb, Francis C. Nichols, Mark S. Allen, Claude Deschamps, Stephen D. Cassivi and Peter C. Pairolero

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Background. Adrenocorticotropic hormone (ACTH)-secreting pulmonary carcinoid is considered an aggressive variant of carcinoid tumors. Current knowledge is based upon a limited number of reports with few patients.

Methods. All patients with Cushing’s syndrome (CS) resulting from pulmonary carcinoid (PC) who underwent pulmonary resection at our institution from November 1966 through April 1998 were reviewed.

Results. The group studied consisted of 10 males and 13 females. The median age was 39 years (range: 14–71). Pulmonary symptoms were present in 4 patients. Chest radiographs identified an abnormality in 13 patients (57%) and chest computerized tomography (CT) identified an abnormality in all 20 patients examined. Before pulmonary resection, hypophysectomy and bilateral adrenalectomy were performed in 7 patients (30%) each. Median time interval from presentation to pulmonary resection was 17 months (range: 1–228). Lobectomy was performed in 16 patients, segmentectomy was performed in 4 patients, and bilobectomy, pneumonectomy, and wedge excision was performed in 1 patient each. There were no operative deaths. Typical carcinoid was identified in 21 patients (91%) and atypical carcinoid was identified in 2 patients (9%). The median tumor diameter was 1.3 cm (range: 0.3–10). Nineteen patients (83%) underwent mediastinal lymphadenectomy and lymph node metastasis was found in 6 patients (32%) (N1 in 4 patients, N2 in 2 patients). The median follow-up was 78 months (range: 1–432). CS resolved in all of the patients. CS with PC recurred in 4 patients and CS alone recurred in 1 patient. Two patients underwent curative re-resection. Two patients, one with disseminated PC, died at last follow-up.

Conclusions. Despite long delays in surgical therapy, pulmonary resection for ACTH-secreting PCs results in a favorable prognosis. Anatomic resection with complete mediastinal lymphadenectomy decreases local recurrence. Although rare these tumors do not seem to be as aggressive a variant of typical carcinoid tumors as previously reported.

Material and Methods

Between November 1966 through April 1998, 441 patients underwent pulmonary resection for PC. Of these, 23 patients (5.2%) were diagnosed with associated CS and they form the basis of this report.

Patient records were reviewed for age, gender, symptoms, preoperative laboratory and radiologic findings, surgical treatment, histopathology, postsurgical stage, and follow-up. Operative mortality included patients who died within 30 days after pulmonary resection and those who died later but during the same hospitalization. Follow-up information was obtained from patient interviews, outpatient clinic visits, and correspondence from the patient’s referring physician. This study was approved by the Mayo Foundation’s Institutional Review Board.

Clinical Findings

The study group consisted of 13 females and 10 males. The median age was 39 years and ranged from 14–71 years. All patients presented with glucocorticoid excess and signs and symptoms of CS including an extreme sensitivity to bruising, facial swelling, fatigue, hirsutism, striae, and weight...
gain. Ten patients indicated a history of smoking; 8 were nonsmokers, and the smoking status was unknown in the remaining 5 patients. Pulmonary symptoms were present in only 4 patients (17%). Dyspnea was the most common symptom and occurred in 3 patients (13%). Other symptoms included wheezing, chest pain, and coughing. No patient exhibited hemoptysis. One patient who had undergone a wedge excision, which was performed elsewhere 5 years earlier for ACTH-secreting PC, presented with recurrent PC and CS. Twenty-two patients had not undergone previous thoracic surgery. The median time interval from diagnosis of CS to pulmonary resection was 17 months and ranged from 1–228 months. Seven patients (30%) underwent hypophysectomy before pulmonary resection, 7 patients (30%) underwent adrenectomy, and 1 patient (4%) underwent pituitary irradiation.

A chest radiograph was obtained for the entire study group and was abnormal in 13 patients (57%). An isolated pulmonary nodule was identified in 11 patients, a lung mass with pleural effusion was identified in 1 patient, and a focal infiltrate was identified in 1 patient. Twenty patients (87%) were examined using computed tomography (CT) of the chest and all were abnormal. A peripheral nodule was found in 18 patients and a central mass in 2 patients. Five patients (22%) were examined using magnetic resonance imaging (MRI) of the chest and all were abnormal. A peripheral mass was observed in 3 patients and a central mass was observed in 2 patients. An indium-111 labeled octreotide scan was used to examine 2 patients and only 1 of these patients demonstrated increased focal thoracic uptake in the lesion. Mean preoperative serum cortisol levels were 35.3 µg/dL for morning samples and 34.6 µg/dL for evening samples (normal: 7–25 µg/dL and 2–14 µg/dL, respectively). Preoperative bronchoscopy was performed in 14 patients and an endobronchial lesion was found in only 1 patient (7%). This patient presented with a hemotorax and a 10-cm mass in the right hilar region.

The PC was on the right in 14 patients (61%) and on the left in 9 patients (39%). Specific locations included the right upper lobe in 1 patient, middle lobe in 7, right lower lobe in 6, left upper lobe in 7, and left lower lobe in 2. The median PC diameter was 1.3 cm and ranged from 0.3–10 cm. A lobectomy was performed in 16 patients, segmentectomy was performed in 4 patients, and either pneumonectomy, bilobectomy, or wedge excision was performed in 1 patient each. A left hilar recurrence exhibited N2 metastasis. None of these 17 patients underwent pituitary irradiation.

Results

There were no operative deaths. Complications occurred in 6 patients (26%) and included prolonged air leak in 3 patients, pneumonia in 1 patient, hemothorax requiring reoperation in 1 patient, and Addisonian crisis in 1 patient. Hospitalization ranged from 4–28 days with a median stay of 8 days. Mean postoperative serum cortisol levels decreased to 3.6 µg/dL for morning samples and to 4.1 µg/dL for evening samples (normal: 7–25 µg/dL and 2–14 µg/dL, respectfully). Follow-up was complete in all patients and ranged from 1–432 months with a median of 78 months. At last follow-up 21 patients (91%) were still living and 17 patients (81%) were living without either recurrent PC or CS. This includes the patient whose second operation was a lingulecctomy with mediastinal lymph node dissection for recurrence. In these 17 patients, the pulmonary resection performed was a lobectomy in 13 patients, segmentectomy in 2 patients, and a bilobectomy and pneumonectomy in 1 patient each. Atypical histopathology was present in 1 patient. Four patients exhibited N1 lymph node metastasis and the patient from elsewhere who was operated on for local recurrence exhibited N2 metastasis. None of these 17 patients underwent adjuvant radiation or chemotherapy.

Two deaths occurred, however the cause of death in 1 of these patients was unrelated to either PC or CS 9 years after pulmonary resection. The second death was caused by recurrent, unresectable mediastinal carcinoid. This patient initially exhibited a 10 cm (T3NX) atypical PC and died 18 years after lobectomy with diffuse PC. In addition to the 1 patient who died with diffuse PC, 3 patients exhibited recurrent CS with PC and 1 patient exhibited recurrent CS alone without PC. All recurrences were 48 months or longer after pulmonary resection. The initial pulmonary resection in these 4 patients included lobectomy and segmentectomy in 2 patients each. The initial pathologic stage was classified as IA in 2 patients, IIA in 1 patient, and was unknown (T1NX) in the remaining patient. Two of these patients underwent curative re-resection. This included right completion pneumonectomy for hilar recurrence in 1 patient and resection of mediastinal recurrence in the other. Both patients remain alive without CS and PC. An unresectable mediastinal recurrence that was subsequently treated with radiation and chemotherapy developed 10 years later in 1 patient who, at initial resection, exhibited stage IIIA disease (T1N2). However, this patient is alive and without CS 3 years later. CS alone recurved in 1 patient. Although the initially resected PC was immunohistochemically posi-
N2 disease occurred in only 5.5%. Both these percentages are much lower than any of the other reported studies. In contrast 2 of our patients exhibited unresectable recurrence and all three remain asymptomatic at follow-up. Common to all three reports is the long duration of CS symptomatology before surgical resection. This likely reflects multiple factors including the rarity of the condition, the paucity of pulmonary symptoms, and the difficulty in diagnosis. This is in contrast with the majority of hormonally quiescent PCs where presenting symptoms often include wheezing, coughing, hemoptysis, and pneumonia [11, 12]. PC with associated CS rarely occurs with pulmonary symptoms. Also complicating the diagnosis is that CS resulting from ectopic ACTH-secreting tumors may be biochemically indistinguishable from pituitary-dependent CS [9]. The introduction of inferior petrosal sinus sampling for corticotropin, however, has helped with regard to ascertaining a diagnosis. This procedure involves the simultaneous sampling of petrosal sinuses and a peripheral vein for plasma ACTH both before and after the administration of bovine corticotropin releasing hormone (CRH). Patients with an ectopic source of ACTH exhibit no gradient between the pituitary and peripheral samples as compared with patients with an ACTH-secreting pituitary tumor where petrosal levels exceed peripheral ACTH levels [9].

The chest CT identified PC in all of our patients, whereas routine chest radiographs identified the PC in only 57%. Therefore we along with others believe that CT should be considered for all patients with corticotropin-dependent CS [7, 10, 13]. The observation that 30% of our patients underwent hypophysectomy and another 30% underwent adrenalectomy before identification of the PC further reinforces this diagnostic recommendation. Similarly nearly half of the patients in the report by Shrag & associates underwent hypophysectomy before pulmonary resection [7].

Unlike the report by Pass and associates [10], where 43% of patients received postoperative radiation therapy, none of our patients received radiation after initial resection. Recurrent PC after pulmonary resection developed in 18% of our patients and CS alone developed in 4%, all 48 months or longer after pulmonary resection. This rate of recurrence is far less than the 43% reported by Shrag & associates [7]. Formal anatomic resection and complete mediastinal lymphadenectomy likely accounts for our lower recurrence rate. In our series recurrence was more common after segmental resections. Three of our patients underwent curative re-resection after local recurrence and all three remain asymptomatic at follow-up. In contrast 2 of our patients exhibited unresectable recurrent carcinoid. One patient received both radiation

### Table 1. Comparison Between Series of Pulmonary Carcinoid and Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Mean Tumor Size (cm)</th>
<th>Typical PC (%)</th>
<th>N2 Nodes (%)</th>
<th>Thoracic Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>14</td>
<td>1.1</td>
<td>92</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>MGH</td>
<td>7</td>
<td>1.5</td>
<td>71</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Mayo</td>
<td>22</td>
<td>1.3</td>
<td>91</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

a This number excludes one patient in each study who had recurrent CS without intrathoracic tumor recurrence. b One patient had thymic carcinoid. All patients with N2 disease received adjuvant radiation therapy. c Excludes one patient who presented with recurrent intrathoracic disease after surgery elsewhere and was found to have N2 metastasis at reoperation.

CS = Cushing’s syndrome; MGH = Massachusetts General Hospital; NIH = National Institutes of Health; PC = pulmonary carcinoid.
and chemotherapy and the other received chemotherapy alone. Only one patient remains alive and is currently asymptomatic.

We conclude that ACTH-secreting PC is a rare but distinct clinical entity. Delayed diagnosis almost always occurs. We believe that PC associated with CS should be treated with formal anatomic resection and mediastinal lymphadenectomy. Although they may be more aggressive than hormonally quiescent typical PCs, they are not as aggressive as previously reported. Prognosis after pulmonary resection for these patients is regarded as excellent.

**References**


**DISCUSSION**

**DR SUDHIR R. SUNDARESAN** (Ottawa, Ontario, Canada): I would like to ask you regarding the considerable majority of patients in your series who exhibited typical carcinoids. I do not remember the exact frequency of lymph node metastases that you described, but it seems a little high for the frequency we would expect in the case of a typical carcinoid. Can you explain that discrepancy?

**DR DEB:** We did include 6 patients that exhibited lymph node metastases, of which 4 patients exhibited N1 and 2 patients exhibited N0 metastases. Of the 2 patients that exhibited N2 disease, 1 exhibited recurrent carcinoid that we reoperated on for cure. In reviewing the literature on this subject, the nodal metastasis rate with hormonally active carcinoids has been reported as approaching 50% and what we determined was that it was much lower than that—closer to 30%.

**DR GIUSEPPE CARDILLO** (Rome, Italy): You indicated that there were 2 patients with an atypical carcinoid. Is there a relationship between atypical carcinoid and a positive lymph node status?

**DR DEB:** I am sorry. Can you repeat that?

**DR CARDILLO:** Have you ascertained any relationship between the histology and the lymph node status? What I am referring to is that 2 patients were diagnosed with atypical carcinoid. What about the lymph node status in these 2 patients?

**DR DEB:** One patient actually did not undergo a lymphadenectomy at the time of surgery, so we do not know what the nodal status of that patient was. The other patient did undergo a complete lymphadenectomy and did not exhibit any nodal metastasis.

**DR JOSEPH SHRAGER** (Philadelphia, PA): As the author of one of the smaller series you mentioned and that your data contradicts, I am compelled to say something. I am not sure, as has been mentioned, why you forge the argument that these tumors are not more aggressive than typical carcinoids, because, although your nodal disease rates are lower than what I and several other authors have previously reported, they are still definitely higher than in most of the published series regarding typical carcinoids. Your recurrence rate is 4 out of 23, your N1 rate is 16%, and your N2 rate is 8%. These numbers are higher than in almost every series pertaining to typical carcinoids. I am not so sure that your data supports your conclusions.

The specific question I want to ask is, did the recurrences occur in the 30% of patients who did not undergo complete mediastinal lymphadenectomies? I ask this because, as you stated with regard to your last slide, an important conclusion is that these patients should definitely undergo mediastinal lymphadenectomies.

**DR DEB:** Thank you for those good questions. The number of patients in our series is certainly much higher than in other reported series—your series and then the one from NIH by Dr Pass. Clearly we attained, and I do not know why, a much lower rate of mediastinal nodal involvement. As I mentioned, the mediastinal nodal involvement between your series and Dr Pass’ series was between 40% and 50%, whereas we obtained closer to 32%. Perhaps the reason we encountered such a discrepancy is because we are studying a larger number of patients. In terms of the patients that recurred, 3 patients did undergo complete mediastinal lymphadenectomy and 1 patient exhibited N2 disease; the others did not exhibit any nodal involvement.

**DR SHRAGER:** Is everything still performed on frozen section at the Mayo Clinic? Also, are all the pathologic diagnoses performed on frozen section?

**DR DEB:** Yes.
DR SHRAGER: I do not know if it has ever been compared with performing permanent sections, but, for example, in lymph nodes, it is possible that frozen sections miss a certain percentage of the true positive nodes. Thus, if frozen sections are the only sections reported about, this may influence your rate of reported nodal involvement.

DR DEB: The numbers I presented today are based on the permanent sections. The nodal status and the T status was based on the final pathology reports.

DR JEAN DESLAURIERS (Saint Foy, Ottawa, Canada): Just for my own interest, you mentioned that before pulmonary surgery a number of patients had undergone brain surgery for this problem and some underwent adrenalectomies. Is that because the carcinoid tumor of the lung was missed or was that performed for some other reason? Was there a relationship between these operations and Cushing’s syndrome? And, if it was missed, why was it missed?

DR DEB: Thank you for the excellent questions. That is one of the dilemmas regarding this tumor—the difficulty in diagnosing the thoracic source for Cushing’s syndrome and, as in Dr Shrager’s, Dr Pass’, and also another series out of the Mayo Clinic, there was a large fraction of patients that underwent a previous pituitary resection for that reason. For most of these patients, the biochemical differentiation between pituitary and ectopic sources is not always accurate and other methods need to be resorted to.

I do not know exactly why the patients in our series that underwent pituitary resection were pushed toward that avenue of treatment. They all presented with elevated ACTH and some of the patients did exhibit petrosal sinus samplings. The carcinoid tumor was eventually located based on a radiographic finding on a CT scan when the patients represented with Cushing’s syndrome.

DR STEPHEN C. YANG (Baltimore, MD): Should these patients be followed-up more aggressively? Also, there have been some reports using the octreotide scan in these patients. What is the role of that?

DR DEB: That is a good question, that is, the more aggressive follow-up. I think that they should perhaps be followed more aggressively. All the recurrences that transpired occurred 48 months or later after the initial pulmonary surgery.

In terms of the role for the octreotide scan, I did not include the data, but we did have 2 patients who had undergone an octreotide scan—one was positive and one was negative. I know there have been some reports, particularly in the radiology literature, that this scan should be augmented with some sort of imaging modality, either an MRI or a CT scan.
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