Pulmonary Carcinoid*

Presentation, Diagnosis, and Outcome in 142 Cases in Israel and Review of 640 Cases From the Literature

Gershon Fink, MD; Tali Krelbaum, MD; Alon Yellin, MD; Daniel Bendayan, MD; Milton Saute, MD; Mendel Glazer, MD; and Mordechai R. Kramer, MD, FCCP

Objective: To determine the characteristic features and outcome of pulmonary carcinoid tumors in Israel.

Methods: Retrospective analysis of the clinicopathologic data and outcome of patients from four major hospitals in Israel in the last 20 years.

Results: There were 142 cases of pulmonary carcinoid tumors: typical (n = 128) and atypical (n = 14). We calculated an annual incidence of about 2.3 to 2.8 cases per 1 million population. The ratio of female to male patients was 1.6:1. The prevalence of smoking was similar to the general population in patients with typical carcinoids and twice as high in the atypical group. Bronchial obstruction was the cause of most of the presenting symptoms and signs and included obstructive pneumonitis, pleuritic pain, atelectasis, and dyspnea (41%). Carcinoid syndrome was extremely rare and occurred in only one patient with metastatic disease. Most of the tumors (68%) arose in the major bronchi. Diagnosis was made using fiberoptic bronchoscopy in 52% of patients without evidence of endobronchial hemorrhage. Nodal involvement and distant metastases occurred in 57% and 21%, respectively, in the atypical group, and 10% and 3%, respectively, in the typical group. The treatment of choice was surgical: lobectomy (56%) or pneumonectomy (16%). The respective 5-year survival rates for patients with typical and atypical tumors were 89% and 75% (not significant), and the 10-year survival rates were 82% and 56% (p < 0.05). A review of large series from the literature is presented.

Conclusion: Pulmonary carcinoid is an uncommon tumor in the Israeli population. With early diagnosis and aggressive surgical therapy, long-term prognosis is excellent.

Key words: pulmonary carcinoid; pulmonary obstruction

Bronchial carcinoid tumors are considered a low-grade malignant neoplasm comprised of neuroendocrine cells. They account for 1 to 5% of all lung tumors.1,2 About 90% of the carcinoid tumors are well differentiated with rare mitoses, pleomorphism, and necrosis.3 These are referred to as “typical” carcinoid tumors, as described originally by Hamperl.4 The remaining 10% are characterized histologically by increased mitotic activity, nuclear pleomorphism, and disorganization; these lesions are designated “atypical” carcinoids. They tend to have a higher rate of metastasis and are larger at the time of diagnosis.5 Presenting symptoms in both types are cough, hemoptysis, or evidence of bronchial obstruction; some patients may be asymptomatic. The association of bronchial carcinoid tumors with carcinoid syndrome is rare, as well as ectopic production of adrenocorticotropic hormone and the occurrence of Cushing’s syndrome.6 The present multicenter retrospective study was conducted to determine the characteristic clinicopathologic features of carcinoid tumors in Israel.

Materials and Methods

We reviewed the medical records of 142 patients with carcinoid tumors treated at four major medical centers in Israel over
the last 20 years (from 1980 to 1999). Data were collected from Hadassah Medical Center, Jerusalem; Shaba Medical Center, Tel-Aviv; Carmel Medical Center, Haifa; and Rabin Medical Center, Petah-Tiqva. The data analyzed included patients’ age and sex, smoking history, presenting symptoms, mode of diagnosis, location and size of tumor, tumor spread, methods of treatment, immunohistochemical findings, and survival. Patients were analyzed for comparison by type of tumor: typical or atypical. Statistical analysis of the 5-year and 10-year survival rates between the groups was assessed with the proportion test.7

**Results**

The 142 patients consisted of 56 male and 86 female patients aged 12 to 80 years (mean ± SD, 52 ± 16 years). According to the histologic findings, 128 patients (48 male and 80 female patients; age range, 12 to 80 years) had a typical carcinoid tumor, and 14 patients (8 male and 6 female patients; age range, 22 to 75 years) had an atypical carcinoid tumor. The annual incidence is seven cases per year for a population of about 2.5 to 3 million people (the areas of referral for the four major hospitals in Israel). We calculate an annual incidence of about 2.3 to 2.8 cases per 1 million population. Our ratio of female to male patients was 1.6:1.

**Smoking**

Forty-two of the 128 patients with typical carcinoid tumor (33%) smoked > 10 pack-years at the time of diagnosis, as compared to 9 of the 14 patients with atypical tumors (64%; p < 0.05).

**Presenting Symptoms**

The majority of patients in our series presented with evidence of bronchial obstruction (n = 58; 41%): obstructive pneumonitis, pleuritic pain, atelectasis, and dyspnea (Table 1). This was followed by cough in 50 patients (35%), hemoptysis in 33 patients (23%), and a variety of other symptoms/signs, including weakness, nausea, weight loss, night sweats, neuralgia, hyperparathyroidism, and Cushing’s syndrome that occurred in 22 (15%). Forty-three patients (30%) were asymptomatic at presentation. Carcinoid syndrome was extremely rare and occurred in only one patient with metastatic disease.

**Methods of Diagnosis**

The diagnosis of carcinoid tumor was made using bronchoscopy in 72 patients (51%). Bronchoscopy was not diagnostic in 15 patients. No significant bleeding was reported in any of the bronchoscopies when endobronchial biopsies were performed. Fine-needle aspiration or biopsy was the mode of diagnosis in an additional 20 patients (14%); however, in 9 patients, fine-needle aspiration was nondiagnostic. Diagnosis was made at thoracotomy in 50 patients (35%).

**Tumor Size**

The lesions ranged in size (maximum dimension) from 0.3 to 7.5 cm, with 47% of the neoplasm having a maximum dimension of ≥ 3.0 cm. Mean lesion size was 2.8 ± 1.9 cm.

**Tumor Location**

Most of the carcinoid tumors (68%) arose in the major bronchi: approximately 13% in the mainstem bronchi and 55% in the lobar bronchi (Table 2). A third of the tumors (32%) originated in the periphery of the lungs, ie, at the segmental bronchi or beyond. In our study, the neoplasm was located in the right lung in 60% of patients and in the left lung in 40%. The most common site was the right middle lobe (23%).

**Tumor Spread**

Most patients underwent chest CT, abdominal CT or ultrasound, brain CT, and bone scan (Table 3). In the typical carcinoid group, involvement of the ipsilateral hilar lymph nodes (N1 disease) was found in 13 patients (10%) and of the mediastinal ipsilateral

| Table 2—Site of Origin of Bronchial Carcinoids* |
|-----------------|-----------------|-----------------|
| Site            | Central (68%)   | Peripheral† (32%) | Total‡ |
| Right           | 64              | 26              | 90   |
| Main bronchus   | 5               | 0               | 5    |
| Intermediate bronchus | 7       | 0               | 7    |
| Upper lobe      | 8               | 8               | 16   |
| Middle lobe     | 29              | 5               | 34   |
| Lower lobe      | 15              | 13              | 28   |
| Left            | 38              | 22              | 60   |
| Main bronchus   | 8               | 0               | 8    |
| Upper lobe      | 16              | 7               | 23   |
| Lingula         | 3               | 0               | 3    |
| Lower lobe      | 11              | 15              | 26   |

*Data are presented as No.
†A peripheral tumor was defined as a tumor arising in the segmental bronchus or beyond.
‡Eight patients had two ipsilateral sites of involvement.
lymph nodes (N2 disease) in 4 patients (3%). No patient in this group had N3 disease. Two patients (1.5%) with typical carcinoid had distant metastases (both in the liver). In the atypical carcinoid group, eight patients (57%) had lymph node involvement, including four patients (29%) with N1 disease, two patients (14%) with N2 disease, and two patients (14%) with N3 disease. Three patients (14%) in this group had distant metastases (liver, liver and spleen, or brain).

**Immunohistochemical Findings**

Information on immunohistochemical staining was available in 93 of the 142 patients in the study. The most common marker used was neuron-specific enolase, with positive findings in 78 specimens (84%). Chromogranin staining yielded positive findings in 69 specimens (74%), synaptophysin in 39 specimens (42%), and cytokeratin in 33 specimens (35%).

**Treatment**

Surgery was performed in 138 patients: lobectomy in 77 patients (56%), wedge resection in 18 patients (13%), bilobectomy in 9 patients (7%), pneumonectomy in 22 patients (16%), segmentectomy in 4 patients (3%), and sleeve resection in 4 patients (3%). One patient underwent endobronchial laser therapy. One patient refused surgery, and in three patients the tumor was considered inoperable.

**Survival**

We were able to assess 5-year survival in 102 patients (90 with typical carcinoid and 12 with atypical carcinoid) and 10-year survival in 73 patients (64 with typical carcinoid and 9 with atypical carcinoid; Fig 1). The overall 5-year and 10-year survival rates were 87% and 79%, respectively. The 5-year survival rate was 89% in the typical carcinoid group and 75% in the atypical carcinoid group (not significant), and 10-year survival was 82% and 56%, respectively (p < 0.05).

**Discussion**

The annual incidence of pulmonary carcinoid in Israel is quite low and is estimated to be 2.5 cases per 1 million people. Our female to male ratio of 1.6:1 contrasts with other studies in the literature, which reported an almost equal sex distribution.8,9 The relative rates of typical and atypical carcinoid tumors are similar to those reported by some authors, although in other series, the prevalence of atypical carcinoids was about 20%.10–12

The prevalence of smokers among the typical carcinoid group is close to that in the adult population of Israel for the last 20 years.13 However, the figure is twice as high in the atypical carcinoid group,
indicating a possible association between atypical carcinoids and smoking. This is supported by earlier studies as well.

Despite previous reports, endobronchial biopsies were quite safe in our hands without significant bleeding. In the peripheral lesions, the yield of fine-needle aspiration was 69% in our hands, which is slightly higher than that reported by Bertelsen and colleagues, but not reaching the impressive yield of 96% achieved by Anderson et al.

The occurrence of a third of our tumors in the periphery explains the high (43%) rate of asymptomatic patients at presentation. In the study of Okike et al, only 16% of 203 patients had peripheral carcinoid tumors, whereas Marty-Ane et al found more peripheral than central carcinoids in their small study of 23 patients. Right middle lobe involvement was high in our series, as was reported by Ranchod and Levine, but in contrast with Okike et al, in which the most common sites of tumors were the right and left lower lobes.

As in our series, previous reports pointed out that regional nodal involvement in typical carcinoid tumors is low and ranges from 3 to 20%, unlike the atypical carcinoids, in which nodal metastasis ranges from 48 to 75%. Distant metastases are quite rare in the typical group but less favorable in the atypical form.

Long-term results vary in the literature: Todd and colleagues, in a study conducted in 65 patients with carcinoid tumors, reported a survival rate of only 65% at 5 years, whereas Stamatis et al, in 210 patients with typical carcinoids, reported 5-year and 10-year survival rates of 98% and 95%, respectively. The 10-year survival in our atypical group is similar to that reported by Okike et al, which reached 57%. Table 4 summarizes 640 cases in the literature in the last 20 years (1984 to 2000) with sufficient data. Mean age is 52 years, and the male to female ratio is 1.1 in favor of the female patients. Location in most series is central (64%), and typical carcinoid is reported in 81% of cases. Lobectomy was sufficient in 42 to 69% of cases, and pneumonectomy was performed in 6 to 16% of cases. As seen, prognosis is excellent in most series, and survival is approximately 88% at 5 years and 81% at 10 years.

**Conclusion**

Carcinoid tumor is an uncommon tumor in Israel. It is more common in woman and occurs frequently in the central airways, causing obstruction of an airway. Diagnosis can be made easily using bronchoscopy, and surgical removal is the treatment of choice. Long-term results are excellent in the typical form but less favorable in the atypical form.

**References**


**Table 4—Data Collected From Large Series in the Literature**

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Mean Age, yr</th>
<th>Female/Male Patients, Ratio</th>
<th>Location, %</th>
<th>Histology, %</th>
<th>Surgery, %</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurt and Bates</td>
<td>1984</td>
<td>79</td>
<td>47</td>
<td>1.1/1</td>
<td>97</td>
<td>3</td>
<td>66</td>
<td>13</td>
</tr>
<tr>
<td>McCaughan et al</td>
<td>1985</td>
<td>124</td>
<td>55</td>
<td>1.2/1</td>
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<td>63</td>
<td>81</td>
<td>19</td>
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<tr>
<td>Bertelsen et al</td>
<td>1985</td>
<td>82</td>
<td>45</td>
<td>1.1/1</td>
<td>79</td>
<td>21</td>
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<td>21</td>
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<tr>
<td>Harpole et al</td>
<td>1992</td>
<td>126</td>
<td>53</td>
<td>1.1/1</td>
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<td>45</td>
<td>66</td>
<td>34</td>
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<tr>
<td>Gould et al</td>
<td>1998</td>
<td>57</td>
<td>55</td>
<td>1.1/1</td>
<td>Not available</td>
<td>74</td>
<td>26</td>
<td>69</td>
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<tr>
<td>Our study</td>
<td>2000</td>
<td>142</td>
<td>52</td>
<td>1.1/1</td>
<td>68</td>
<td>32</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>640</td>
<td>52</td>
<td>1.1/1</td>
<td>64</td>
<td>36</td>
<td>81</td>
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*Four-year survival.*