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Treatment and prognosis in bronchial carcinoids involving regional lymph nodes

From 1953 to 1992, 25 patients were surgically treated for bronchial carcinoids with metastases to regional lymph nodes (N1 or N2). The tumors were located centrally, involving main or lobar bronchi in 12 patients and were peripheral in 13. Histologically, 12 of the carcinoids were classified as typical and 13 as atypical (neuroendocrine carcinoma). Pneumonectomy was performed in 11 patients, sleeve lobectomy in one, lobectomy in seven and bilobectomy in six. A formal mediastinal lymph node dissection was done in 20 patients. At final staging, 10 had N1 disease and 15 had N2. No adjuvant treatment was given to the 10 patients with N1 disease. External radiation therapy was given after the operation to 9 of 15 patients with N2 disease. The overall 5-year survival (Kaplan-Meier) was 75 % (median 62 months). No difference in survival was found between patients with N1 or N2 disease. However, survival and recurrence rate differed between typical and atypical carcinoids. In typical carcinoids, the 5-year survival was 92% and, in atypical carcinoids, it was 60% ($p = 0.02$). We conclude that complete resection for bronchial carcinoids results in long-term survival despite the presence of regional lymph node metastases. Recurrence appears to depend more on cell type than nodal status. Postoperative radiation therapy does not appear to be beneficial. (J THORAC CARDIOVASC SURG 1994;107:1-7)

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Bronchial carcinoids constitute less than 3% to 5% of all lung tumors.¹⁻³ The prevalence is even lower (less than 1%) in cigarette smokers because lung cancer is most prevalent in smokers.⁴ Most carcinoids are confined to the lung or bronchus, but 10% to 15% of patients have regional lymph node metastases at diagnosis. Because nodal involvement is uncommon, little has been published regarding their optimal treatment.

Because of repeated inquiries on how to best manage

Fig. 1. Location of the primary tumor. 1, 2, and 3, correspond to the number of tumors found at these specific locations.

Fig. 2. Location of involved N1 and N2 nodes.

carcinoids with lymph node metastases, we reviewed the experience at the Memorial Sloan-Kettering Cancer Center with this subset of tumors and report our findings.

Patients and methods

From 1953 to 1992, 25 patients (15 men and 10 women) were treated surgically at the Memorial Sloan-Kettering Cancer Center for histologically confirmed bronchial carcinoids with metastases to regional lymph nodes (N1 or N2). This sample represents 15% of the 167 patients who had carcinoid tumors diagnosed during this time frame. Pathologic confirmation was based on routine light microscopy, argyrophilic staining techniques (Grimelius), and the demonstration of neurosecretory granules by electron microscopy. The tumors were located centrally, involving main or lobar bronchi, in 12 patients and peripherally in 13. Sixteen tumors were in the right lung and nine in the left (Fig. 1).

Tumors were detected on routine chest roentgenograms in 14 patients in the absence of pulmonary symptoms. Cough, hemoptysis, dyspnea, wheezing, and upper respiratory infection were present in 11 patients. None had carcinoid syndrome or distant metastases. Four of 12 patients with central tumors were without symptoms, whereas 10 of 13 patients with peripheral tumors had no symptoms associated with the chest.

Fig. 3. *Top*, Typical central carcinoid with organoid pattern, extreme uniformity of nuclear size, and absence of mitosis or necrosis (hematoxylin and eosin stain, original magnification $\times 100$). *Bottom*, Atypical carcinoid with markedly hyperchromatic and pleomorphic nuclei with scanty cytoplasm. Necrosis is evident on both sides (hematoxylin and eosin stain, original magnification $\times 100$).

Ten of 25 patients had preoperative computed tomographic scanning of the chest, five of whom had enlarged mediastinal lymph nodes whose conditions were staged clinically as N2 disease. Additionally, one patient underwent mediastinoscopy and positive N2 nodes were found. Twenty-four patients underwent no mediastinoscopy. Before the operation, 16 patients were not suspected of having regional lymph node involvement (N0), and three patients were suspected of having N1 disease (Table I). At operation, 10 had N1 disease and 15 had N2 disease. The locations of the N1 and N2 nodes are shown in Fig. 2.

A histologic diagnosis of carcinoid was obtained at thoracotomy in 11 of 13 patients with peripheral tumors, by means of transcutaneous needle biopsy in one patient, and by means of thoracoscopy in one patient. In 12 patients with central tumors, the diagnosis of carcinoid was obtained before the operation by means of mediastinotomy in two and bronchial biopsy in six. Tissue diagnosis was postponed until thoracotomy in four pa-

tients with visible but friable tumor observed at bronchoscopy.

The histologic slides were reviewed by one pathologist (M. Z.) in all patients. The tumors were classified as typical carcinoid in 12 and atypical (neuroendocrine carcinoma) in 13 patients. The definition of the two histologic groups was based on the classification of Arrighi and associates.⁵ The basis for diagnosis of typical carcinoid was as follows: (1) characteristic, tan, fish-flesh gross appearance and relationship to major bronchi often with endobronchial component; (2) microscopically organoid or "neuroendocrine" pattern also described as nesting, insular, trabecular, glandular, or mixed; (3) extreme uniformity of cells with moderate pale pink or granular cytoplasm, round to oval nucleus, and stippled chromatin pattern; nucleoli were small or unappreciable and mitoses were rare (Fig. 3, A).

Tumors were classified as atypical when they exhibited one or more of the following characteristics: (1) areas of necrosis; (2) pleomorphism and irregularity of nuclei with hyperchromasia and increased nuclear/cytoplasmic ratio (Fig. 3, B); (3) areas of increased cellularity with disorganized structure; (4) increased mitotic activity (more than 5 per 10 high-power fields).

Some of the tumors were composed predominantly of spindle cells without any of the four previously noted characteristics for atypical tumors; they were classified as typical carcinoid. Most, but not all (three cases, blocks not available), of the tumors were stained by argyrophilic (Grimelius) and immunohistochemical (chromogranin) stains for dense-core neurosecretory granules. All were strongly positive for neurosecretory granules except three atypical carcinoid tumors in which only focal positivity was seen. Electron microscopy, performed in some of the cases, demonstrated dense-core granules of approximately 200 nm.

Survival was calculated by the Kaplan-Meier method, considering postoperative deaths and tumor-related deaths. The log-rank test was used for comparisons and was considered significant at $p \leq 0.05$.

Results

All patients underwent complete resection of their tumor. Pneumonectomy was performed in 11 patients, sleeve lobectomy in one, lobectomy in seven, and bilobectomy in six. Mediastinal lymph node sampling was done in five patients treated before 1972, but a formal lymph node dissection was done in the 20 patients who underwent operation after 1972.

No correlation was found between smoking history and the type of carcinoid detected. Six of 12 patients with typical carcinoids were nonsmokers and 7 of 13 patients with atypical carcinoids were nonsmokers. Although the overall age range was 18 to 79 years with a median age of 50, the median age for patients with typical carcinoids was 42 years, with none older than 55 years of age. In patients with atypical carcinoids, the median age was 62 years with an age range of 24 to 79 years.

Lymph node metastases were confined to hilar and bronchial lymph nodes (N1) in 10 patients and involved mediastinal lymph nodes (N2) in 15. The patients with N1 or N2 disease were nearly equally divided between the

Table I. Clinical and postoperative nodal status by tumor type

	Typical	Atypical	Overall
Clinical			
N0	8	8	16
N1	1	2	3
N2	3	3	6
Total	12	13	25
Postoperative			
N1	5	5	10
N2	7	8	15
Total	12	13	25

two types of carcinoids. Postoperative external radiation therapy was given to 9 of 15 patients with mediastinal lymph node metastases, oral cyclophosphamide to one patient with T2 N2 disease, and levamisole to one with T3 N1 disease. No patient with N1 nodes received postoperative radiation therapy.

No significant difference was found between tumor types with respect to size. In patients with typical carcinoids, the primary tumor ranged in size from 1 to 10 cm in maximum diameter with a median of 3 cm. Five of these tumors were associated with N1 nodes and seven with N2. In atypical carcinoids, the tumor size ranged from 1.6 to 6.5 cm with a median of 3.5 cm. Of these, five were associated with N1 disease and eight with N2 disease.

All patients were followed up for a minimum of 2 years, and 20 (80%) were followed up for 5 or more years. The overall 5-year survival (Kaplan-Meier) of the 25 patients was 75%, with a median of 8.8 years (Fig. 4). A significant difference in survival was found between patients with typical versus those with atypical carcinoids (92% alive at 5 years with typical carcinoids, 60% alive at 5 years with atypical carcinoids; $p = 0.02$) (Fig. 5). In typical carcinoids, the 5-year disease-free survival was 100%. One patient died after the operation and one had recurrence at 8½ years. In atypical carcinoids, the 5-year disease-free survival was 57% ($p = 0.025$).

Patients with N2 disease showed a trend toward poorer overall survival than did patients with N1 disease, but this difference did not reach statistical significance ($p = 0.12$) perhaps because of the small number of patients available for analysis (Fig. 6). Extent of resection, tumor size, or use of postoperative radiation therapy also did not appear to influence overall survival.

An apparent difference in survival was found by location of the tumor. Patients with central tumors had a better 5-year survival than did those with peripheral tumors

Fig. 4. Overall survival after resection (95% confidence interval at 60 months: 52% to 92%, standard deviation 0.09).

Fig. 5. Survival by tumor type (95% confidence interval at 60 months for typical carcinoids: 51% to 100%, standard deviation 0.15; for atypical carcinoids: 38% to 95%, standard deviation 0.14).

(92% versus 58%). However, this survival difference was due to tumor type because most peripheral tumors were atypical carcinoids (10/13) and most central tumors were typical carcinoids (9/12).

The tumor size did not influence the prevalence of recurrence in patients with typical carcinoids. Only one patient with a 3 cm lesion had recurrent disease at 8½ years. However, the tumor size influenced the prevalence of recurrence in patients with atypical carcinoids. Excluding one postoperative death, no recurrence occurred in three patients with tumors of 2 cm or less in diameter; one of six patients with tumors 3 cm or less in diameter had recurrence, whereas all six patients with tumors greater than 3 cm had recurrence.

Local recurrence was observed in only one patient who had N1 disease. All other recurrences were at distant sites in patients with N2 disease. Because of the small number

of patients, it was not possible to assess the effect of mediastinal radiation on recurrence.

Two patients died after the operation. With a median follow-up of 8 years (range 2 to 28 years), 15 of the remaining 23 patients were alive and disease-free at the time this article was written, four died of unrelated causes, and eight died of recurrent disease. Only 5 of the 12 patients with atypical carcinoids were alive and disease-free at the time this article was written.

Discussion

Bronchial carcinoids are now recognized as malignant tumors because of their potential to metastasize. Most authors suggest that the primary treatment is surgical when the disease is confined to the chest, but no article has addressed whether adjuvant treatment after resection is either necessary or helpful.⁶⁻¹⁰

Fig. 6. Survival by nodal status (95% confidence interval at 60 months for N1: 73% to 100%, standard deviation 0.16; for N2: 44% to 96%, standard deviation 0.13).

There has been considerable controversy regarding the nomenclature that best reflects this group of patients. Typical and atypical carcinoids appear to share with small-cell lung cancer a common neuroectodermal stem cell. Electron microscopic findings and biochemical markers common in carcinoids, as well as in small-cell cancer, have led to the postulation of a neoplastic continuum among these tumors.^{11,12} As a result, Wain, Pak, and Benfield¹³ have suggested that these tumors be called KCC I, II, and III to reflect their origin from Kulchitsky cells. Others have opted to refer to them as neuroendocrine carcinomas of different degrees of differentiation.¹⁴ There is now mounting evidence that nuclear deoxyribonucleic acid studies can be helpful in differentiating the typical and atypical carcinoids from small-cell carcinoma.^{15,16}

Clinically, carcinoids and small-cell lung cancer are distinctly separate entities. Bronchial carcinoids are generally uncommon lung cancers, and their natural history is long, whereas small-cell cancers represent nearly 15% to 20% of all lung cancers and patient survival is measured in months.

In carcinoids, no correlation exists between the history of smoking and the development of these tumors. Surgical resection is the accepted treatment even when mediastinal nodal metastases are present. They are generally unresponsive to radiation or chemotherapy, and the long-term prognosis is excellent for both typical and atypical carcinoids treated with resection. Because of these reasons, we favor the term carcinoid tumor (typical or atypical) over the terms neuroendocrine carcinoma or KCC that group small-cell lung cancer with carcinoids.

Although bronchial carcinoids can occur at any age,

typical carcinoids usually occur at a younger age. The median age for patients with typical carcinoids in the current series was far lower than for those with the atypical variants (42 years versus 62 years). No patients with typical carcinoids was older than 55 years of age in this review.

Computed tomographic scans are helpful in staging bronchial carcinoids, but mediastinoscopy is not essential once a carcinoid diagnosis is established. Less than 15% of cases have nodal involvement; more importantly, even if lymph node metastases exist, their presence does not preclude surgical treatment because long-term survival is still possible. In our series, 75% of patients with nodal involvement who were treated surgically were alive at 5 years, and local control was effective in 22 of 23 patients.

It is evident from the data presented that both typical and atypical carcinoids, though malignant, are far more favorable tumors prognostically than any histologic type of lung cancer with nodal involvement. Resection remains the only effective treatment for this group of tumors, despite the presence of nodal metastases.

Controversy exists regarding the extent of resection necessary to obtain the most favorable results. Provided there is sufficient pulmonary reserve, we recommend a pulmonary resection with mediastinal lymph node dissection in patients with lymph node involvement to achieve the best local control. With such treatment, only 1 of 23 patients who survived the operation had local recurrence, despite lymph node metastases.

The apparent prevalence of pneumonectomies as opposed to sleeve lobectomies in this series is explained by the fact that most pneumonectomies were done either for large tumors (≥ 5 cm in diameter) or because of exten-

sive hilar and mediastinal disease. We believe that, on the basis of hindsight, two patients might have been adequately treated by sleeve lobectomy.

The estimated 10-year survival of patients with typical carcinoids is 76%, but this percentage drops to 24% in those with atypical carcinoids because of the increased prevalence of recurrence in this group. Only 5 of 12 patients with atypical carcinoids remained free of tumor after resection. For these patients, adjuvant treatment may be beneficial, but the specific adjuvant or group of adjuvants proved to be helpful still eludes us because of the small number of cases seen with this condition.

No local recurrence was observed in the patients with N2 disease, regardless of whether they were treated with postoperative mediastinal radiation. Most recurrences were at distant sites.

In summary, complete resection including a mediastinal lymph node dissection provides excellent local control and results in long-term survival for bronchial carcinoids despite the presence of regional lymph node metastases. Recurrence is generally late and in distant sites and appears more dependent on histologic subset than on nodal status. There is no indication that postoperative radiation therapy is beneficial in local control or overall survival, and we are unable to assess the merit of systemic adjuvants because no patients had effective systemic treatment.

REFERENCES

- World Health Organization. The W.H.O. histologic typing of lung tumors. 2nd ed. Am J Clin Pathol 1982;77:123-36.
- Rosai J. Ackerman's surgical pathology. 6th ed. St. Louis: CV Mosby, 1981:277.
- Carter D, Eggleston JC. Tumors of the lower respiratory tract. Washington DC: Armed Forces Institute of Pathology, 1980:95-113, 177-80.
- Melamed MR, Flehinger BJ, Zaman MB. Impact of early detection on the clinical course of lung cancer. Surg Clin North Am 1987;67:909-23.
- Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. J THORAC CARDIOVASC SURG 1972;64:413-21.
- Jensik RJ, Faber LB, Brown CM, Kittle CF. Bronchoplastic and conservative resectional procedures for bronchial adenoma. J THORAC CARDIOVASC SURG 1974;68:556-65.
- McCaughan BC, Martini N, Bains MS. Bronchial carcinoids. J THORAC CARDIOVASC SURG 1985;89:8-17.
- Okike N, Bernatz PE, Payne WS, Woolner LB, Leonard PF. Bronchoplastic procedures in the treatment of carcinoid tumors of the tracheobronchial tree. J THORAC CARDIOVASC SURG 1978;76:281-91.
- Pairolero PC, Trastek VF, Payne WS, Bernatz PE. Carcinoid tumors of the lung. In: Martini N, Vogt-Moykopf I, eds. International trends of general thoracic surgery. vol. 5. St. Louis: CV Mosby, 1989;258-62.
- Wilkins EW, Scannell JG, Grillo HC, Moncure AC, Scannell JG. Changing times in the management of bronchial carcinoid tumors. Ann Thorac Surg 1984;38:339-44.
- Bensch KG, Corrin B, Pariente R, Spencer H. Oat-cell carcinoma of the lung: its origin and relationship to bronchial carcinoid. Cancer 1968;22:1163-72.
- DeCaro LF, Paladugu R, Benfield JR, Lovisatti L, Pak H, Teplitz RL. Typical and atypical carcinoids within the pulmonary APUD tumor spectrum. J THORAC CARDIOVASC SURG 1983;86:528-36.
- Wain JC, Pak SHY, Benfield JR. Immunohistochemistry and new trends in the diagnosis of carcinoids. In: Martini N, Vogt-Moykopf I, eds. International trends of general thoracic surgery. vol. 5. St. Louis: CV Mosby, 1989;249-57.
- Faber LP. Discussion of DeCaro et al.¹²
- El-Naggar AK, Ballance W, Abdul Karim FW, et al. Typical and atypical bronchopulmonary carcinoids: a clinicopathologic and flow cytometric study. Am J Clin Pathol 1991;95:828-34.
- Larimont D, Kiss R, de Launoit Y, Melamed MR. Characterization of the morphonuclear features and DNA ploidy of typical and atypical carcinoids and small cell carcinomas of the lung. Am J Clin Pathol 1990;94:379-83.

Discussion

Dr. Safuh Attar (Baltimore, Md.). Over the past 22 years, we have had 43 cases of bronchial carcinoids at the University of Maryland Medical Center. Of the cases, 31 (72%) were typical, and 12 (28%) were atypical.

In the typical cases, only one of 31 patients had positive mediastinal nodes—a prevalence of 3.3%—compared with six cases—a prevalence of 50%—in the atypical group.

Our data illustrate the prognostic significance of positive lymph nodes, with significant reduction in the survival in patients with positive nodes.

The survival of patients who had typical carcinoids was 92% at 5 years and 88% at 10 years, compared with 59% (at 5 years) in the atypical carcinoids. These results compare favorably well with Dr. Martini's.

I have two questions for Dr. Martini. I realize that you do not favor mediastinoscopy in most of your practice; however, specifically in these patients, because the prognosis of patients who have positive mediastinal nodes is different from those who have negative lymph nodes, would not a positive mediastinoscopy predispose you to perform a radical dissection instead of doing a radical dissection of the mediastinum for all cases?

The second question is, do you believe that further characterization of these tumors with the use of methods besides electron microscopy, such as immunohistochemical studies, would be helpful in the ultimate differentiation between the neuroendocrine tumors and these tumors?

Dr. Martini. Dr. Attar, I do not believe that a mediastinoscopy could be advantageous before the operation when dealing with a typical or an atypical carcinoid. I have just shown that in typical carcinoids, despite the presence of nodal metastases, the 5-year survival was essentially 100%. In atypical carcinoids, the survival is lower—60% at 5 years with resection; but this is

a far better survival than any observed after resection for lung cancer. Both typical and atypical carcinoids are hence best treated with surgical resection and a lymph node dissection. Moreover, I have not been able to acquire from our pathologists a firm diagnosis, on frozen section examination at the time of operation, between these two variants to justify doing a lesser resection and not evaluate the mediastinum. Therefore, I treat these tumors as I do any lung cancer and do a systematic lymph node dissection at the time of resection.

In answer to your second question, I concur that immunohistochemical studies now far outweigh electron microscopy studies; in fact, we do not use electron microscopy studies routinely to separate typical from atypical carcinoids. We rely heavily on the Grimelius and chromogranin stains.

Dr. William H. Warren (*Chicago, Ill.*). We agree that the distinction between the classic or typical bronchial carcinoid and the so-called atypical carcinoid has clinical significance, including the prognostic significance of regional lymph node metastases. The central message of your article is that the presence of lymph node metastases does not invalidate the diagnosis of typical bronchial carcinoid, does not qualify to label a carcinoid as atypical, and does not alter the generally favorable prognosis in

typical bronchial carcinoids. I wholeheartedly agree that these classic or typical bronchial carcinoids should be distinguished from more aggressive neuroendocrine tumors, as we proposed in our 1983 classification of pulmonary neuroendocrine neoplasms.

Did the presence of lymph node metastases influence the surgeon at the time of the procedure, and should it have? We noted that 11 of these patients had a pneumonectomy, and only one had a sleeve resection. Is that appropriate for these otherwise low-grade tumors?

Dr. Martini. Dr. Warren, I will confine my response to your two questions. Many of these patients were treated at a time when pneumonectomy was the gold standard for central lesions. I have gone back over the 11 pneumonectomies, assessing whether a sleeve lobectomy might have been possible, and found that 9 of the 11 patients had peribronchial disease of an extent that would have precluded a resection less extensive than a pneumonectomy, but two would have benefited from a sleeve lobectomy. In answer to your second question, for none of the cases did positive lymph nodes deter the surgeon taking care of the patient from completing the resection, including the nodal dissection.