

A Historical Appreciation of Bronchopulmonary Neuroendocrine Neoplasia Resolution of a Carcinoid Conundrum



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KEYWORDS

- Atypical carcinoid • APUD • Azzopardi • Bronchial adenoma • Bronchopulmonary carcinoid
- Capella • Carcinoid • Chevalier Jackson

KEY POINTS

- In the three-quarters of a century that have elapsed since the first description of a bronchial carcinoid, the field has progressed from serendipitous radiological or bronchoscopic diagnosis to computed tomography, magnetic resonance imaging, and somatostatin receptor imaging identification. Similarly, pathologic techniques have advanced from a naïve assessment of neoplasia to a delineation of several tumor subtypes and an understanding of the neuroendocrine basis of the disease process.
- Endoscopic therapy has evolved from bronchoscopic resection to laser ablation and surgical ablation from sleeve resection to lobectomy and lymph node clearance.
- The recent usage of somatostatin receptor targeted Lutetium-177 or Yttrium-90 peptide receptor radiotherapy to treat residual disease or metastases represents the full turn of the circle because radiation, which initiated diagnosis at the turn of the nineteenth century, has now, a century later, become the novel therapeutic strategy.
- Current pathologic analyses are limited in their ability to precisely define the malignancy of a lesion and predict the likelihood of recurrence.
- The issues of the future that remain to be resolved are early detection of tumors by molecular blood biomarkers, establishment of the individual genomic tumor patterns that define the biologic behavior of each tumor, and the identification of the tumor interactome and master regulators that will precisely facilitate targeted therapy.
- A key unresolved question is the identification of the genetic and environmental activators that are responsible for the initiation of pulmonary neuroendocrine cell proliferation and neoplastic transformation.

FROM GNOSIS TO SUNESIS

In the eighteenth and nineteenth centuries, lung disease was difficult to diagnose and even more

difficult to treat. Visualization of the lung was only possible postmortem and operative intervention was impossible in the absence of anesthesia and positive pressure ventilation. The stethoscope

The authors have nothing to disclose.

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Thorac Surg Clin 24 (2014) 235–255

<http://dx.doi.org/10.1016/j.thorsurg.2014.05.008>

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described by Laennec (1781–1826) in 1816 had replaced the percussive technique of Auenbrugger (1722–1809) as a clinical tool but neither yielded great insight into pulmonary pathology (Fig. 1). Diseases of the chest were for the most part infectious and tuberculosis (TB) remained the scourge of the time as the most prevalent cause of lung pathologic abnormality. Almost all knowledge was gleaned from the extensive autopsy series of Rokitsansky (1804–1878), but minimal clinical diagnostic tools were available other than visual

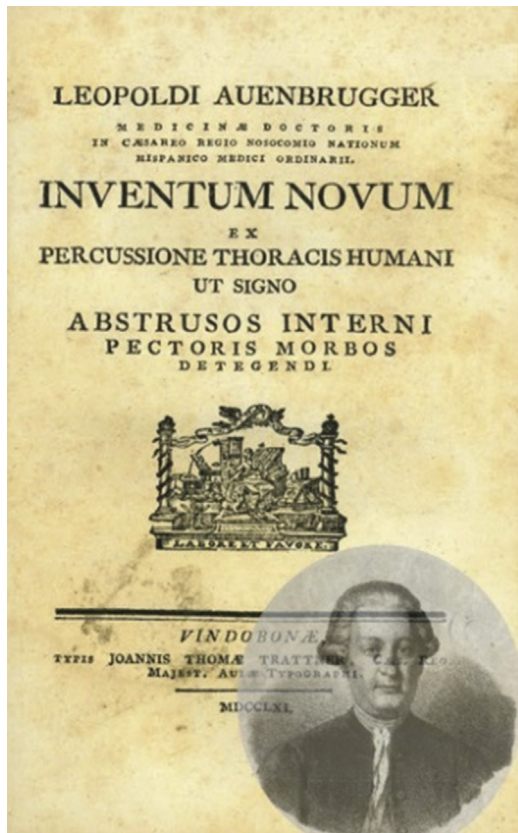


Fig. 1. Josef Leopold Auenbrugger (1722–1809), born in Graz, invented percussion as a diagnostic technique. This skill was initially acquired in testing the level of wine casks in the cellar of his father's hotel but was translated into the first diagnostic test for pulmonary disease. His published text, *Inventum Novum ex Percussione Thoracis Humani Interni Pectoris Morbos Detegendi* (A New Discovery that Enables the Physician from the Percussion of the Human Thorax to Detect the Diseases Hidden Within the Chest) has been regarded as a book that defines a new epoch in the modern history of medicine. Auenbrugger's method of diagnosis at first met with indifference but was noted by the French physician René Laennec (1781–1826), who, pursuing a similar train of thought, thereafter developed the technique of auscultation. (Courtesy of Irvin M. Modlin, MD, New Haven, CT.)

examination of the sputum. Given the low life expectancy and the limitations of hygiene and ventilation, infections and TB were the dominant pulmonary diseases. By the end of the nineteenth century, tumors of the lung were considered a rarity, although attention was focused on them as observant physicians began to note their relationship to inhaled agents, such as radon, asbestos, tobacco, and silica, based on industrial exposure. The advent of radiology and bronchoscopy at the beginning of the twentieth century combined with the advance of histology dramatically amplified the ability to diagnose pulmonary disease, identify tumors, and begin to characterize them. Thus, lung neoplasia became a source of increasing clinical focus as public health techniques improved TB management and the disease focus began to shift. The consideration of lung cancer as a rare disease in the first decade of the twentieth century had dramatically shifted by the mid-century to a realization of its major clinical impact. A further issue was the evolving understanding that such tumors were substantially different in clinical behavior and could be differentiated by their histopathological patterns. Although most attention was focused on the highly aggressive squamous and adenocarcinoma variants, it became apparent that a subset of tumors initially designated bronchial adenomas behaved differently and required reassessment. The elucidation of the neuroendocrine cell system and the description by Oberndorfer (1876–1944) of a gastrointestinal tumor termed, *Karzinoide* (1907), led to the recognition that such lesions might have a pulmonary equivalent.

Armed with this knowledge, pathologists addressed the question of identifying and categorizing such tumors to best inform clinicians, in particular surgeons, as to the optimal management of pulmonary carcinoid tumors. The crux of the matter related to the delineation of specific pulmonary neuroendocrine tumor subtypes, each of which carried a substantially different prognosis and therefore required a significantly different management strategy. This article documents the evolution of the understanding of bronchopulmonary neuroendocrine tumor disease and the elucidation of the stratagems that have led to the current understanding of its genesis and management.

EARLY OBSERVATIONS ON LUNG TUMORS

Early literature indicates that the first description of a neoplastic lesion of the lung emanates from Morgagni (1682–1771), who in 1761, described an *ulcus cancrosum* of the right lung in an autopsy on a 60-year-old man (Fig. 2).¹ In 1821, Andral² suggested that examination of the color of sputum

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