Pulmonary Neuroendocrine Tumors: What (Little) Do We Know?

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Key Words
Neuroendocrine tumors, lung cancer, carcinoid, small cell lung cancer

Abstract
Pulmonary neuroendocrine tumors are a distinct subset of tumors composing approximately 20% of all lung cancers. The major categories of pulmonary neuroendocrine tumors include typical and atypical carcinoids, large cell neuroendocrine carcinoma, and the more common small cell lung cancer. They are classified into different categories in the 2004 World Health Organization system, but share structural and morphologic features. Despite these shared features, their clinical characteristics range from indolent to aggressive, and therefore the approach to treatment depends on the histologic subtype. This article discusses the current understanding of the epidemiology, pathologic characteristics, treatment, and prognosis of this spectrum of diseases. (JNCCN 2006;4:623–630)

Lung cancer is one of the most frequently diagnosed cancers worldwide, with an estimated 1.1 million deaths occurring annually. In 2006, an estimated 170,000 people in the United States will be diagnosed with lung cancer.1 Most of these diagnoses will be non-small cell lung cancer (NSCLC), of which adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most common. Approximately 20% of patients are diagnosed with small cell lung cancer (SCLC), and fewer with large cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC) tumors, or atypical carcinoid (AC) tumors. According to data from the American Cancer Society, approximately 25,000 to 30,000 people will be diagnosed with SCLC, 1700 to 3000 with pulmonary carcinoid tumors, and 5000 with LCNEC. Of the estimated 10,000 to 12,000 carcinoid tumors diagnosed annually, more than half are of gastrointestinal origin and up to 25% are of pulmonary origin.2

Because these malignancies share morphologic, ultrastructural, molecular, and immunohistochemical features, they are believed to derive from a common cell of origin but have dissimilar clinical courses. Bronchial carcinoids were originally described as indolent tumors. However, as carcinoids became more widely recognized, clinicians began to realize that some patients had less benign courses, and therefore the distinction between typical and atypical carcinoids became more apparent. SCLC and LCNEC behave very aggressively, with high rates of metastases and low survival rates. In 1991, Travis et al.3 described a group of large-cell carcinomas with features characteristic of neuroendocrine differentiation, proposing it as a separate entity, which was subsequently incorporated into the World Health Organization (WHO) classification.4 Asamura et al.5 showed that 5-year survival rates for LCNEC were similar to those for SCLC, supporting the hypothesis that LCNEC should also be considered an aggressive disease when comparing overall survival. Researchers must understand the differences between these entities to determine the optimal approach to therapy and to improve cure rates.

Nomenclature/Classification
The nomenclature used for this spectrum of tumors has evolved, reflecting the development of improved cyto logic, pathologic, and histologic methods, with several classification schemes proposed.3,6-10 Efforts to standardize the nomenclature and classification system have led the WHO to recognize 4 general categories: SCLC, LCNEC, AC, and TC. Despite its neuroendocrine features,
LCNEC is a morphologic variant of large cell carcinoma, which is grouped under the NSCLCs.  

**Epidemiology**

In 1937, Hamperl first described pulmonary carcinoid tumors as low-grade malignant bronchial tumors. As more data and reports accumulated, these tumors were further categorized as TC or AC tumors. These tumors account for 1% to 2% of primary lung tumors and seem to have equal gender distribution. In retrospective series, the median age of patients diagnosed with carcinoid tumors is younger than for those diagnosed with LCNEC or SCLC. Some series suggest that TC is more frequently diagnosed at a younger age compared with AC, and metastasizes in approximately 15% of cases. AC tumors account for approximately 10% of pulmonary carcinoid tumors, and 30% to 50% of individuals develop lymph node or distant metastatic disease.

LCNEC and SCLC are more frequently diagnosed than the pulmonary carcinoids. LCNEC comprises 3% of diagnosed primary lung tumors, whereas SCLC accounts for approximately 15% of primary lung tumors in the United States and approximately 20% worldwide. The median age at diagnosis for LCNEC and SCLC is in the seventh decade, and LCNEC occurs slightly more frequently in men than women. Investigators have reported 5-year overall survival rates of approximately 90% for TC, 40% to 60% for AC, 13% to 47% for LCNEC, and 9% to 15% for SCLC.

Studies have addressed the role of smoking in pulmonary carcinoid tumor development. Smoking is known to be a major risk factor for SCLC. Virtually all SCLC patients have a history of cigarette smoking. Patients diagnosed with LCNEC are likely to have a more than 50 pack-year smoking history. Small studies suggest a correlation between tobacco exposure and AC tumors. Fink et al. retrospectively studied 142 Israeli patients diagnosed with pulmonary carcinoid tumors between 1980 and 1999. Of the 128 patients with TC, 42 (33%) smoked more than 10 pack-years at diagnosis compared with 9 of the 14 patients (64%) diagnosed with AC. However, a Japanese study that included 64 patients with resected pulmonary carcinoid tumors does not show the same correlation. Other environmental exposures have not been identified.

Recent studies have attempted to identify genetic changes associated with neuroendocrine lung tumors. Familial clusters of pulmonary carcinoid tumors have been associated with multiple neuroendocrine neoplasia (MEN). This has been associated with inactivation of the MEN1 gene located on chromosome 11q13. However, these genetic alterations were not found in LCNEC or SCLC. A few reports of familial pulmonary carcinoid in the absence of MEN suggest a distinct germline mutation. Mutation patterns in K-ras and p53 and gene expression profiles suggest closer similarities between LCNEC and SCLC than between LCNEC and other NSCLC types. Confirmatory studies by Onuki et al. showing different patterns of p53 mutations between AC and the high-grade neuroendocrine tumors LCNEC and SCLC support the hypothesis that TC and AC are genetically distinct from LCNEC and SCLC. These recent studies support the concept that these tumors represent a spectrum of tumors from low-grade TC to the high-grade neuroendocrine carcinomas. TC and AC seem to be closely related, but are clinically, morphologically, epidemiologically, and genetically distinct from LCNEC and SCLC.

**Pathology**

The lung is composed primarily of respiratory and structural cells. However, a network of neuroendocrine cells includes the submucosal nerves, ganglion cells, individual neuroendocrine cells, and neuroepithelial bodies. These cells are capable of synthesizing, storing, and using biologic amines or neuropeptides. Common histologic features of neuroendocrine differentiation are organoid nesting, rosette-like structures, trabecular growth, and peribulbar palisading patterns. Diagnosis of carcinoid cancer can be difficult and may be mistaken for SCLC, whereas LCNEC can be difficult to distinguish from poorly differentiated adenocarcinoma, squamous cell carcinoma, and basaloid carcinoma. SCLC may be confidently diagnosed with cytologic specimens and fine needle aspirates, although adequate tissue specimens may be needed for identifying carcinoids and LCNEC. Asamura et al. reported that the grade of malignancy was associated with the histology and was a significant prognostic factor.

Carcinoid tumors show growth patterns that are suggestive of neuroendocrine differentiation. Cells usually display uniform features of moderate eosinophilia,
fine granular cytoplasm, and nuclei with finely granular chromatin. Mitotic rates distinguish typical and atypical carcinoid. The 2004 WHO criteria defines TC with absent necrosis and having less than 2 mitoses per 2 mm² (10 hpf) of tumor (Figure 1). AC tumors show 2 to 10 mitoses per 2 mm² (10 hpf) and may have necrotic foci. They generally are more poorly differentiated and exhibit higher atypia than TC (Figure 2).

Neuroendocrine carcinomas with more than 10 mitoses per 2 mm² (10 hpf) are considered high grade and include LCNEC and SCLC. LCNEC is considered an undifferentiated non–small cell carcinoma. Cells are generally large with abundant cytoplasm and prominent nucleoli. Mitotic counts are usually more than 10 with an average of 75 per 2 mm² (10 hpf). Confirmation of neuroendocrine differentiation with at least 1 immunohistochemical marker, such as chromogranin, synaptophysin, or neural cell adhesion molecule (NCAM or CD56) is necessary for diagnosis. Cytokeratin expression/staining is uncommon (Figure 3). In contrast, SCLC is usually diagnosed by light microscopy. Histologically, the cells are described as small with scanty cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or ill-defined nucleoli (Figure 4). The mitotic rate is comparable to LCNEC, averaging more than 80 mitoses per 2 mm² (10 hpf).

Neuroendocrine differentiation can be identified using immunohistochemistry or electron microscopy. Common immunohistochemical stains for diagnosis of neuroendocrine origins include synaptophysin, chromogranin A, NCAM, and cytokeratins. Neuron specific enolase (NSE) has been described as a neuroendocrine marker. However, this is not a reliable marker because up to 60% of NSCLC will stain positive for NSE.40,41 Although not all tumors express these markers, certain patterns are most consistent with neuroendocrine tumors. Most SCLC and LCNEC tumors will stain for cytokeratins and at least 1 neuroendocrine marker. Large cell carcinomas without evidence of neuroendocrine differentiation on light microscopy or immunohistochemistry occasionally contain dense core granules as evidence of neuroendocrine features.

**Figure 1** Typical carcinoid. The tumor is composed of organoid nests of uniform tumor cells with moderate amount of eosinophilic cytoplasm and nuclei with finely granular nuclear chromatin.

**Figure 2** Atypical carcinoid. (A) In the center of a nest of tumor cells is a punctate focus of necrosis. (B) The tumor is composed of uniform tumor cells arranged in organoid nesting arrangements with moderate amount of eosinophilic cytoplasm, and finely granular nuclear chromatin. A single mitosis is present (center).
Clinical Presentation and Evaluation

Patients may present with various symptoms depending on the tumor location, size, and growth pattern. Typical carcinoids and SCLC are usually centrally located, whereas AC and LCNEC are frequently found in the peripheral lung. The most common presenting symptoms are cough, dyspnea, pneumonitis, and hemoptysis, with weakness, nausea, and weight loss being less common, although many patients with bronchial carcinoids are asymptomatic and their tumors are found incidentally. Paraneoplastic syndromes, including ectopic hormone secretion (syndrome of inappropriate antidiuretic hormone secretion, Cushing’s syndrome), and paraneoplastic neurologic degeneration, are more frequently associated with SCLC, although one series reported Cushing’s syndrome in 15% of patients with pulmonary carcinoid cancer.

Carcinoid syndrome is an entity seen in 10% of patients with gastrointestinal carcinoid tumors and 2% of pulmonary carcinoid patients. This syndrome manifests with flushing, copious diarrhea, wheezing, and tachycardia and is caused by the release of serotonin, 5-hydroxytryptophan, histamine, kallikrein, and prostaglandins. The interval from development of symptoms to diagnosis is variable. In bronchial carcinoids, the estimated interval ranges from 29 to 37 months, but has been reported to be up to 14 years. In contrast, patients with LCNEC and SCLC often present with acutely developing symptoms of dyspnea, dysphagia, or superior vena cava syndrome. Evaluation of a suspicious nodule is identical for other lung neoplasms. Radiographic imaging of the chest and upper abdomen is standard. Tissue diagnosis may be obtained by surgical resection or through less-invasive methods, such as video-assisted thoracoscopic surgery, bronchoscopy, core needle biopsy, fine needle aspiration, or thoracentesis for patients with pleural effusions. Additional workup is dictated by the tissue diagnosis and radiographic results. Staging for carcinoid tumors and LCNEC follows the TNM staging guidelines, although the International Contre le Cancer and American Joint Committee on Cancer have not formally adopted TNM staging for carcinoid tumors. And although TNM stag-
ing is possible for SCLC, the more practical system has been the limited- or extensive-stage designations, based on whether disease is confined to the ipsilateral hemithorax and can be encompassed in a tolerable radiation field (limited stage). Patients with SCLC who have malignant pleural or pericardial effusions or other sites of metastases are considered extensive stage.

**Treatment**

**Surgery**

Treatment for these tumors is determined by histology, stage, and performance status. Because of the larger number of patients diagnosed with SCLC, most studies have focused on this group, and therefore data on optimal treatment of LCNEC and the pulmonary carcinoid tumors are scarce.

Surgery plays a major role in treating the pulmonary carcinoid tumors and LCNEC, but is inadequate as the sole therapy for SCLC. Most studies in carcinoid tumors and LCNEC have been reported in surgical series. Generally more indolent in course, carcinoid tumors have been followed-up for up to 25 years after resection. Retrospective analyses suggest that TC can be treated successfully with conservative parenchymasparing procedures such as wedge resection, segmentectomy, and sleeve resections, but that AC should be resected using surgical principles for carcinomas, such as lobectomy and pneumonectomy.

Resection, if possible, is also preferred for patients with early-stage LCNEC. Most patients who have resectable disease undergo a lobectomy or pneumonectomy. Patients without lymph node metastases after careful mediastinal lymph node sampling seem to experience improved survival.

Because of the propensity for early hematogenous spread, surgery alone for SCLC was abandoned in the 1970s after studies showed the inadequacy of this approach. For patients who have clinical stage T1-2, N0 disease, a treatment plan consisting of resection with mediastinal dissection followed by adjuvant chemotherapy with or without radiation therapy can be considered. Data conflict on the role of resection of minimal disease.

**Chemotherapy**

SCLC is generally extremely sensitive to chemotherapy and thus all patients undergo chemotherapy as part of their treatment plan. Patients with limited stage disease undergo chemotherapy in combination with radiation therapy. The combination of etoposide with either cisplatin or carboplatin is most widely used, with response rates of 60% to 80%. Noda et al. reported higher survival in Japanese patients treated with a cisplatin/irinotecan regimen. The Southwest Oncology Group is leading an ongoing confirmatory trial in the United States. However, another follow-up study using a different treatment schedule of irinotecan/cisplatin showed equal, but not superior, survival rates when compared with cisplatin/etoposide.

Other combinations, such as cyclophosphamide, doxorubicin, and vincristine (CAV), are also commonly used.

Despite a high rate of response to initial therapy, relapse is common among patients with SCLC in the first 2 years after induction treatment. Studies addressing prolonged courses of chemotherapy have shown no improvement in relapse or survival, but increased toxicity. At relapse, the efficacy of treatment is poor. Topotecan, the FDA-approved treatment for relapsed SCLC, has a 10% to 20% response rate, but survival averages only 6 months.

Unlike SCLC, optimal chemotherapy regimens have not been determined for TC, AC, and LCNEC. Pulmonary carcinoids and LCNEC are much less sensitive to available chemotherapy agents. Most studies have described treatment for metastatic carcinoid tumors or LCNEC with regimens effective for SCLC; however, conclusions regarding efficacy are difficult to make because these studies are small. A retrospective analysis of 31 patients with metastatic pulmonary carcinoid tumors treated patients with multiple agents, including α-interferon, octreotide, streptozocin/5-FU, or doxorubicin, or cisplatin/etoposide regimens, showing no significant responses or improvement in survival. Wirth et al. confirmed the lower response rates in carcinoid patients. Partial responses in patients with relapsed LCNEC were reported in only 2 of 10 patients. Kozuki et al. described their experience in 7 patients with LCNEC. Of the patients treated with cisplatin and etoposide or docetaxel with concomitant radiation, 3 showed partial response. Other regimens, including single-agent vinorelbine, gemcitabine combinations, and salvage regimens with docetaxel and irinotecan were ineffective. Some clinicians suggest that the SCLC regimen of cisplatin and etoposide may have some benefit, although response rates are not comparable to those for
SCLC. Octreotide is potentially therapeutic in patients with carcinoid tumors whose tumors are positive on octreotide scan or have carcinoid syndrome.

Since the IALT and JBR.10 studies showed improved survival in patients who underwent adjuvant chemotherapy for NSCLC, clinicians now commonly recommend adjuvant chemotherapy for patients with stage II and IIIA disease. Data on adjuvant therapy in carcinoid and LCNEC are scarce. Retrospective series in TC suggest that patients with stage I–III disease do well and need not be subjected to the risks associated with chemotherapy. Patients diagnosed with AC are more likely to develop metastatic disease. However, no studies show the benefit of adjuvant chemotherapy in AC. Risk factors such as lymph node involvement, bulky tumor, or positive resection margins may be indications for adjuvant therapy in AC. Iyoda et al. reported that adjuvant chemotherapy prolonged survival in early-stage LCNEC, but not stage II or III disease. Whether this is because these patients have a more favorable prognosis regardless of adjuvant therapy is unclear.

**Radiation**

Concomitant chemotherapy and thoracic radiation are commonly used for curative intent in limited stage SCLC. Randomized studies of chemotherapy and radiation have shown that radiation administered concurrently with chemotherapy improves survival. Turrisi et al. reported that twice-daily thoracic radiation was superior to once-daily treatment. Prophylactic cranial irradiation in patients with complete or near-complete responses has been shown to decrease the risk for brain metastases and to improve overall survival.

Data on the efficacy of radiation therapy in the other neuroendocrine tumors are lacking. Radiation has been reported in some patients with LCNEC and carcinoid tumors, but data are insufficient to draw conclusions. For patients who are unable to undergo surgical resection, definitive radiation therapy is recommended (see the guidelines).

A few studies have addressed the role of adjuvant radiation in patients who have undergone resection and surgical staging for carcinoid tumors. One retrospective report by Kaplan et al. addressed the pattern of recurrence in patients with resected stage I tumors. Patients with AC (22.7% for both) had a significantly higher rate of locoregional recurrence and distant metastases compared with those with AC (8.4% and 7.4%). Thus, researchers are interested in the role of adjuvant radiation in improving local control, even in these earliest stage patients. Unfortunately, because of the low incidence of these tumors, prospective clinical trials addressing these issues are difficult to conduct.

**Prognosis and Future Research**

The overall prognosis for patients with pulmonary neuroendocrine carcinomas is variable. Patients with typical carcinoid have the most favorable prognosis, with 5-year survival rates generally more than 90% with surgery alone. Atypical pulmonary carcinoid tumors are more aggressive, with 40% to 60% 5-year survival rates. Lymph node involvement and distant metastasis, although uncommon, decrease survival further. Survival for patients with high-grade neuroendocrine tumors is poor. Reports have shown 5-year overall survival for LCNEC ranging from 15% to 57%. Data show that LCNEC and SCLC have no significant difference in survival. However, survival for LCNEC seems to be substantially lower than for non-neuroendocrine NSCLC.

Relapse is common in SCLC and LCNEC and less frequent in TC and AC. Relapse in patients with SCLC usually occurs within 2 years of diagnosis, with distant disease developing most commonly in the brain, liver, lung, and bone. Similar patterns were noted in LCNEC. Bronchial carcinoid tumors behave more indolently. Patients with TC do well and experience few relapses, although late relapse up to 42 years after primary resection has been reported. Metastatic disease is more common in AC, ranging from 15% to 64%. However, because TC accounts for most carcinoid tumors, the combined recurrence rate is considered to be less than 5%.

Much research is needed to better understand and treat this group of pulmonary malignancies. More effective treatment for metastatic carcinoid tumors, LCNEC, and relapsed SCLC is desperately needed. The role of radiation for carcinoid tumors and LCNEC has not been determined. Therapy to prevent or delay recurrence would be beneficial. Clarifying the similarities and differences at the molecular level of this spectrum of diseases will form the foundations for better therapies.

**References**

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