Advances in neuroendocrine lung tumors

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Pulmonary neuroendocrine (NE) tumors include a spectrum of tumors from the low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to the high-grade large-cell neuroendocrine carcinoma (LCNEC) and small-cell carcinoma (SCLC). Nodular NE proliferations \( \geq 0.5 \) cm are classified as carcinoid tumors and smaller ones are called tumorlets. When NE cell hyperplasia and tumorlets are extensive they represent the rare preinvasive lesion for carcinoids known as diffuse idiopathic pulmonary NE cell hyperplasia. Carcinoid tumors have significant clinical, epidemiologic and genetic differences from the high-grade SCLC and LCNEC. Multiple endocrine neoplasia type I can be found in TC and AC patients but not those with LCNEC and SCLC. Also both LCNEC and SCLC can demonstrate histologic heterogeneity with other major histologic types of lung carcinoma such as adenocarcinoma or squamous cell carcinoma, but is not characteristic of TC or AC. Genetic changes are very high in SCLC and LCNEC, but usually low for TC, intermediate for AC. The diagnosis of SCLC, TC and AC can be made by light microscopy without the need for special tests in most cases, but for LCNEC it is required to demonstrate NE differentiation by immunohistochemistry or electron microscopy.

**Key words:** Atypical carcinoid, carcinoid, large-cell neuroendocrine carcinoma, lung, neuroendocrine, neuroendocrine body, neuroendocrine cell hyperplasia, small-cell carcinoma, tumorlet, typical carcinoid

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**introduction**

Pulmonary neuroendocrine (NE) tumors include a spectrum of tumors from the low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to the high-grade large-cell NE carcinoma (LCNEC) and small-cell carcinoma (SCLC) (Table 1) [1]. NE lung tumors comprise \( \sim 20\% - 25\% \) of all invasive lung malignancies. The most common NE lung tumor is SCLC, which accounts for \( 15\% - 20\% \) of invasive lung malignancies [2]. In surgical series, LCNEC represents \( \sim 3\% \) of lung cancers. Carcinoid tumors represent \( 1\% - 2\% \) of invasive lung malignancies and only \( \sim 10\% \) of carcinoids represent AC, so these account for only \( \sim 0.1\% - 0.2\% \) of invasive lung cancers [3]. Diffuse idiopathic pulmonary NE cell hyperplasia (DIPNECH) is a very rare condition that represents a preinvasive lesion for carcinoid tumors. Treatment of SCLC is usually chemotherapy. It is difficult to diagnose AC and LCNEC in small biopsies or cytology and a definitive diagnosis usually requires a surgical specimen. These tumors are also clinically problematic because the optimal therapy for AC and LCNEC is not established [3].

The purpose of this article is to summarize the spectrum of pulmonary NE tumors with emphasis on the pathology and diagnostic criteria. A summary of the spectrum of NE lung neoplasms is presented in Table 1 and the diagnostic criteria in Table 2.

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**tumorlets and DIPNECH**

Nodular proliferations of NE cells that measure \( < 0.5 \) cm in greatest diameter are tumorlets. These are usually incidental histologic findings of no clinical significance encountered in lung specimens showing various inflammatory and/or fibrotic conditions such as bronchiectasis, interstitial fibrosis, chronic abscesses or tuberculosis.

When patients are found to have widespread peripheral airway NE cell hyperplasia and/or multiple tumorlets, the diagnosis of 'DIPNECH' can be made. Since a subset of these patients has one or more carcinoid tumors, DIPNECH is thought to represent a preinvasive lesion for carcinoid tumors [4, 5]. This must be distinguished from NE cell hyperplasia and tumorlets found associated with inflammation/fibrosis and local proliferation found in lung surrounding up to 75% of carcinoid tumors.

DIPNECH may present as a form of interstitial lung disease with airway obstruction due to the frequent association with bronchiolar fibrosis or it can present as multiple pulmonary nodules often mistaken for metastatic cancer. Davies et al. [5] reported 19 cases with 15 females and 16 nonsmokers. There were two major types of clinical presentation: one \( (n = 9) \) presenting with mild interstitial lung disease such as symptomatic cough and/or dyspnea averaging 8.6 years before diagnosis and the second \( (n = 10) \) in patients found incidentally to have pulmonary nodules on routine radiologic evaluation for another disorder, mostly cancer. Tumorlets and TC were found in nine patients. Three patients had AC and one had multiple endocrine neoplasia type I (MEN1) syndrome. Most
of these patients had a stable clinical course, but a few progressed to severe airflow obstruction [5].

Histologically DIPNECH is characterized by prominent NE cell hyperplasia and tumorlets. Some patients also have carcinoid tumors. Tumorlets may cause airway narrowing and/or obliteration. The surrounding lung parenchyma is generally normal.

carcinoid tumors

clinical features

There is no marked sex predilection for pulmonary carcinoids [1, 6, 7]. TC and AC occur at any age with an average of 45–55 years and they occur equally in both sexes.

Approximately half of patients with TC and AC are asymptomatic at diagnosis [1]. Patients typically present with dyspnea, hemoptysis, cough and post-obstructive pneumonia [7]. Carcinoids situated in the lung periphery are more likely an incidental radiologic finding. The most common paraneoplastic syndromes include the carcinoid syndrome [7], and Cushing’s syndrome [8, 9]. MEN1 patients can have lung carcinoids, which occur in ~5% of cases [10]. The recently published seventh edition UICC/AJCC TNM system, recommended TNM for staging of pulmonary carcinoids [11, 12].

pathologic features

Carcinoid tumors present in the lung periphery in ~40% of cases. Endobronchial growth is common in central carcinoids. Tumors average 2–3 cm in size and are usually round. The cut surface is tan to yellow.

An organoid growth pattern is the most common histologic pattern in both TC and AC. Tumor cells have uniform cytologic features with a moderate amount of eosinophilic cytoplasm with an eosinophilic hue (Figure. 1). Nuclear features usually consist of finely granular chromatin. In TC nucleoli are inconspicuous or absent, but they can be seen in AC.

The criteria for diagnosis of AC includes a carcinoid tumor with mitoses between 2 and 10 per 2 mm² area or the presence of necrosis (Figure. 2) [13]. The necrosis usually consists of small punctate foci. Other features such as pleomorphism,

Table 1. The spectrum of neuroendocrine lung tumors

<table>
<thead>
<tr>
<th>I. Tumors with NE morphology</th>
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<tbody>
<tr>
<td>A. Typical carcinoid (≥0.5 cm)</td>
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<tr>
<td>B. Atypical carcinoid</td>
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<tr>
<td>C. Large-cell neuroendocrine carcinoma</td>
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<tr>
<td>Combined large-cell neuroendocrine carcinoma</td>
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<td>D. Small-cell carcinoma</td>
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<td>Combined small-cell carcinoma</td>
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<td>II. Non-small-cell carcinomas with NE differentiation</td>
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<td>A. Other tumors with NE properties</td>
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<tr>
<td>B. Primitive neuroectodermal tumor</td>
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<tr>
<td>C. Desmoplastic round cell tumor</td>
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<tr>
<td>D. Carcinomas with rhabdoid phenotype</td>
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<tr>
<td>E. Paraganglioma</td>
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</tbody>
</table>

NE, neuroendocrine.

*Modified from [4].

The histological type of the other component of non-small-cell carcinoma should be specified.

Table 2. Criteria for diagnosis of neuroendocrine tumors [4]

<table>
<thead>
<tr>
<th>Typical carcinoid</th>
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<tr>
<td>A tumor with carcinoid morphology and &lt;2 mitoses per 2 mm² (10 HPF)*, lacking necrosis and ≥0.5 cm</td>
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Atypical carcinoid

A tumor with carcinoid morphology with 2–10 mitoses per 2 mm² (10 HPF) OR necrosis (often punctate)

Large-cell neuroendocrine carcinoma

A tumor with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)

High mitotic rate ≥11 per 2 mm² (10 HPF), median of 70 per 2 mm² (10 HPF)

Necrosis (often large zones)

Cytologic features of a non-small-cell lung carcinoma (NSCLC): large-cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli. Some tumors have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm.

Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/or neuroendocrine granules by electron microscopy.

Small-cell carcinoma

Small size (generally less than the diameter of three small resting lymphocytes)

Scant cytoplasm

Nuclei: finely granular nuclear chromatin, absent or faint nucleoli

High mitotic rate ≥211 per 2 mm², median of 80 per 2 mm²

Frequent necrosis often in large zones

*10 high-power fields (HPF) in a microscope with field of view of 0.2 mm²; however the number of HPF to reach 2 mm² vary depending on the field of view, see [13].

Figure 1. Typical carcinoid. This tumor shows an organoid nesting pattern with a prominent vascular stroma. The tumor cells are uniform with a moderate amount of eosinophilic cytoplasm and finely granular nuclear chromatin. No necrosis or mitoses are seen.
vascular invasion and increased cellularity are not as helpful in separating TC from AC [13, 14].

immunohistochemistry
Chromogranin, CD56 and synaptophysin are the most helpful NE immunohistochemical markers. A low proliferation rate ($\leq 5\%$) is seen in TC by Ki-67 staining compared with AC where it is usually between 5% and 20% [15, 16]. In small crushed biopsies Ki-67 staining can be helpful to separate TC or AC from high-grade LCNEC or SCLC, which have very high proliferation rates [15, 16].

treatment and prognosis
Carcinoids are treated primarily by surgical resection [7, 17]. Patients with TC have an excellent prognosis and rarely die of tumor [7]. Lobectomy is the treatment of choice in most cases, particularly central tumors. For peripheral tumors limited resection may be possible. Even patients with TC who have lymph node metastases have an excellent survival [18].

AC patients have a significantly reduced 5-year survival of 61%–88% compared with TC (92%–100%) [6, 19–21]. In TC, lymph node metastases are present in 4%–14% of cases compared with 35%–64% in AC. These tumors are relatively resistant to chemotherapy and radiation therapy; therefore, when possible, metastatic disease is sometimes best managed surgically. There is no proven optimal therapy for metastatic unresectable TC or AC.

LCNEC
LCNEC is a high-grade non-small-cell NE carcinoma classified as a variant of large-cell carcinoma in the 1999 and 2004 WHO classifications [4, 22]. There are four major categories of NE phenotypes in large-cell carcinomas: (i) LCNEC with NE features by light microscopy as well as immunohistochemistry and/or electron microscopy, (ii) large-cell carcinoma with NE morphology (LCNEM) with NE morphology but no NE differentiation by electron microscopy or immunohistochemistry, (iii) large-cell carcinomas with NE differentiation (LCC-NED) with no NE morphology but NE differentiation by immunohistochemistry or electron microscopy and (iv) classic large-cell carcinoma (LCC), which lacks both NE morphology and NE differentiation by special studies [14, 22].

clinical features
In surgical resected series, LCNEC accounts for $\sim 3\%$ of cases [23, 24]. There is a very high frequency of cigarette smoking with heavy smoking histories [14]. Most LCNEC patients are males and the median age is $\sim 60$ years [24]. Paraneoplastic syndromes such as ectopic hormone production are rare [24, 25]. Chest pain is the most common symptom, followed by hemoptysis, dyspnea, cough, fever and weight loss with up to 24% of patients being asymptomatic [26]. By computed tomography, tumors occur mostly in the lung periphery (84%) and the upper lobes (63%) [27].

pathology
LCNECs are usually peripheral tumors with a mean size of 3–4.0 cm (range 0.9–12 cm) [13, 28, 29]. Grossly the tumor is circumscribed with a necrotic, tan–red cut surface [27].

LCNECs are diagnosed according to the following criteria: (i) NE morphology with organoid nesting, palisading or rosette-like structures (Figure. 3A), (ii) high mitotic rate >10 mitoses per 2 mm$^2$ (average 60–80 mitoses per 2 mm$^2$), (iii) non-small-cell cytologic features including large-cell size, low nuclear/cytoplasmic ratio, nucleoli or vesicular chromatin (Figure. 5B) and (iv) NE differentiation by immunohistochemistry with antibodies such as chromogranin (Figure. 3B), CD56 or synaptophysin, or by electron microscopy [4, 13].

The diagnosis of LCNEC is difficult to establish based on small biopsies or cytology. [24, 30]. This is because the NE pattern is difficult to see morphologically in small tissue samples or cytology. Also NE differentiation can be difficult to demonstrate by immunohistochemistry in small pieces of tissue. For these reasons the diagnosis of LCNEC requires a surgical lung biopsy.
When a LCNEC has components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma and/or spindle cell carcinoma it is called combined LCNEC [4, 13]. The most common component is adenocarcinoma, but squamous cell, giant cell or spindle cell carcinoma can also occur. If the second component is SCLC the tumor becomes a combined SCLC and LCNEC.

**Immunohistochemistry/electron microscopy**

NE differentiation must be demonstrated by immunohistochemistry or electron microscopy to diagnose LCNEC [4, 13]. NE immunohistochemical markers are usually best performed as a panel of chromogranin (Fig. 3B), CD56/NCAM and synaptophysin [14]. In 41%–75% of cases, thyroid transcription factor-1 (TTF-1) will be positive [31, 32]. The proliferation index by Ki-67 staining is very high with staining of 50%–100% of tumor cells.

**Large-cell carcinoma with NE morphology.** Some large-cell carcinomas have NE morphology, but no NE differentiation can be demonstrated by immunohistochemistry or electron microscopy (LCC-NEM) [22]. Only a few papers have reported clinical data on these patients but they are generally similar to those for LCNEC [26, 28].

**Small-cell carcinoma**

The most common pulmonary NE tumor is SCLC and it accounts for an estimated 28 000 of the 219 440 lung cancer cases diagnosed in the United States in 2009 [39]. The frequency of SCLC cases among all lung cancers cases over the past 30 years in the USA decreased from 17% to 13% according to the US National Cancer Institute’s Surveillance, Epidemiologic, and End Results (SEER) database [40]. There is a strong association with cigarette smoking [41]. SCLC presents with four major types of manifestation: constitutional, pulmonary, the result of extrathoracic spread or due to paraneoplastic disorders [41]. The most common symptoms are fatigue, cough, dyspnea, decreased appetite, weight loss, pain and hemoptysis. Chest images demonstrate a large mass invading or compressing the mediastinum with mediastinal or hilar adenopathy. Superior vena cava syndrome can be found in 10% of patients [41]. SCLC can present as a solitary pulmonary nodule in <5% of cases. Metastases to extrathoracic locations such as the bone, brain, liver and adrenals are present in most patients at presentation [41]. Several paraneoplastic syndromes are known to occur in SCLC patients: syndrome of inappropriate antidiuretic hormone, Cushing’s syndrome or neurologic paraneoplastic syndromes such as autoimmune neuropathies and encephalomyelitis [41].

A distinct limited versus extensive staging system exists for SCLC as recommended by the Veterans Administration Lung
Study Group (VALSG) for SCLC [42]. According to this system, two-thirds of patients have extensive disease at diagnosis, and one-third have limited-stage disease [40]. The recent seventh edition AJCC/UICC TNM staging system proposes the use of TNM for SCLC based on an analysis of a large database of >8000 patients demonstrated that TNM staging is effective for SCLC [12, 43].

**pathology**

The diagnosis of SCLC is established based on small specimens such as bronchoscopic biopsies, fine needle aspirates, core biopsies and cytology in almost all cases, because of the presentation in advanced stages. Fortunately these specimens are diagnostic in most all cases. In resected cases, the tumor is usually a circumscribed peripheral lung nodule measuring 2–4 cm in size with a tan, necrotic cut surface. SCLC is diagnosed histologically primarily based on light microscopy (Figure. 4). Tumor cells are round to fusiform and they grow in sheets and nests with frequent necrosis that is often extensive. Necrosis is common, frequently with large areas. Tumor cells typically have scant cytoplasm and measure less than the diameter of three small resting lymphocytes with finely granular nuclear chromatin. Nucleoli are inconspicuous or absent [4, 44]. The mitotic rate is high, averaging 60–80 per 2 mm²; however, mitoses can be difficult to identify in small biopsy specimens.

When there is also a component of NSCLC such as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, spindle cell carcinoma or giant cell carcinoma the tumor is classified as combined SCLC. This diagnosis should be accompanied by a description of the non-small-cell component(s) [4, 44]. Combined SCLC may occur in up to 28% of surgically resected cases [4, 44]. For combined SCLC/large-cell carcinoma there should be at least 10% large or giant cells, but for the components of adenocarcinoma, squamous cell or spindle cell carcinoma the amount does not matter [4, 44].

There are two settings in which diagnostic difficulties are encountered by pathologists: crush artifact and surgically resected specimens. Crush artifact is common in small transbronchial or mediastinal biopsy specimens. Lesions other than SCLC that can cause confusion include NSCLC, lymphoma, carcinoid and chronic inflammation. Immunohistochemistry can be very helpful in this setting. In resected specimens the tumor cells of SCLC appear larger than in small biopsies because of better fixation [45].

While a panel of immunohistochemical stains is often helpful in the diagnosis of SCLC the most important special stain is a good quality hematoxylin and eosin stain. The most common cause of problems in diagnosis results from sections that are too thick or poorly stained. If the histologic features are classic, it may not be needed. The optimal panel of stains for diagnosis of SCLC includes a pancytokeratin antibody such as AE1/AE3, CD56, chromogranin and synaptophysin, TTF-1 and Ki-67. If keratin is negative, other tumors need to be excluded including lymphoma (CD45 and CD20), primitive neuroectodermal tumors (PNETs, CD99) and melanoma (S100). In 70%–80% of SCLCs TTF-1 is positive [31, 32]. Ki-67 is most helpful in separating SCLC from carcinoids because the proliferation is very high (80%–100%).

It is well known that the diagnosis of SCLC can be difficult in ~5% of cases even for expert lung cancer pathologists in the separation from non-small-cell carcinoma [46, 47]. In problematic cases it is best to use a consensus approach among other pathology colleagues. If this does not lead to a consensus diagnosis, such a problem case may need to be referred for extramural consultation.

**treatment and prognosis**

SCLC patients have a very poor survival of 12%, 7% and 5%, at 2, 3 and 5 years, respectively [48]. Factors that are associated with adverse outcome include performance status, Cushing’s syndrome, continued smoking and metastases to sites such as the liver, brain, bone marrow and bone [41].

The primary approach to therapy for SCLC is combination chemotherapy, typically with etoposide plus either cisplatin or carboplatin [41]. Patients with limited stage disease are usually given chemotherapy concurrently with radiation. Some early stage patients undergo surgical resection.

**molecular changes in pulmonary NE tumors**

NE lung tumors show a spectrum of molecular changes that largely reflect the differences in histologic grade. Many molecular abnormalities are found in LCNEC and SCLC compared with fewer in the carcinoids. These are reviewed in more detail elsewhere [15, 49, 50].

In a study of loss of heterozygosity (LOH) for 3p, RB, 5q21, 9p and p53 in pulmonary NE tumors, Onuki et al. [51] found at a higher frequency of LOH in the high-grade LCNEC and SCLC compared with the carcinoids. SCLC also showed significantly more frequent 5q21 LOH compared with LCNEC. p53 showed an increasing frequency of changes by immunohistochemistry, LOH and mutation analysis from TC to AC and high-grade SCLC and LCNEC [51]. No p53 mutations were found in TC, with 25% in AG, 59% in LCNEC.
and 71% in SCLC. These results are similar to data reported by others in high-grade NE carcinomas with p53 expression ranging between 40% and 86% and p53 mutations from 27% to 59% [15, 49, 50].

**international registry of pulmonary NE tumors**

An International Registry of Pulmonary NE Tumors is being organized by the International Association for the Study of Lung Cancer due to need for collaboration to gather sufficient numbers of cases to better advance our understanding of the rare subtypes of pulmonary NE tumors including TC with metastases, AC, LCNEC and surgically resected SCLC [52]. It is hoped that this will lead to the development of novel molecular targeted therapies for these tumors.

**disclosures**

The author has declared no conflict of interest.

**references**


