Neuroendocrine Neoplasms of the Lung

Allen Burke, MD and Kristin Stashek, MD

Abstract: In this review, we discuss the clinical and pathologic aspects of epithelial neuroendocrine neoplasms of the lung and compare the current classification with that of gastrointestinal (GI) neuroendocrine neoplasms. Endocrine neoplasms can be broken down into 2 major categories, which, as currently believed, are not part of a continuum, but rather distinct pathogenetic entities. Well-differentiated neuroendocrine tumors (NETs) are low-grade malignancies. In the lung, the term “carcinoid” is still applied for these, which are classified as typical or atypical. In the pancreas and GI tract, well-differentiated NETs are graded based on Ki-67 proliferative index into 3 numeric categories. Poorly differentiated neuroendocrine carcinomas (NECs) are classified in both organ systems into small cell carcinoma and large cell NEC. In this review, “NET” is used interchangeably with “well-differentiated NET.” Although often used in the GI tract, “poorly differentiated NEC” is not a term used in the lung, where the distinction between small cell carcinoma and LCNEC is more clear-cut than in the GI tract.

Key Words: lung, carcinoid tumor, atypical carcinoid, spindle cell carcinoid, neuroendocrine tumor, large cell neuroendocrine carcinoma, small cell carcinoma, combined small cell carcinoma

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tial neuroendocrine neoplasms are a heterogeneous group of tumors, previously defined by the presence of cytoplasmic endocrine polypeptides within neurosecretory granules. Currently, in the lung, defining criteria include the diffuse expression of 1 or more of 4 antigens: chromogranin, CD56, synaptophysin, and recently INSM1. The least differentiated neuroendocrine carcinomas (NECs), small cell carcinomas, may lose endocrine features and are defined largely by histologic features.

Neuroendocrine tumors are generally separated into 2 groups, which differ greatly in histologic features, clinical aggressiveness, and treatment. Carcinoid tumors, or well-differentiated NETs, are low-grade epithelial neoplasms with a relatively indolent clinical course. Poorly differentiated NECs, which comprise small cell carcinomas and large cell neuroendocrine carcinoma (LCNEC), are aggressive tumors that usually spread rapidly causing the death of the patient. The relationship, if any, between these 2 groups of tumors is unclear, as combined low- and high-grade endocrine carcinomas in the lung have not been reported.

The classification of neuroendocrine lung tumors still includes use of the term “carcinoid tumor,” the equivalent of which, in the gastrointestinal tract, is “well-differentiated NET, grade 1.” “Atypical carcinoid tumor” of the lung would be represented in the gastrointestinal classification as “well-differentiated NET, grades 2 and 3” (Table 1).

Neuroendocrine tumors of the lung should be designated as such based on established diagnostic criteria. The term “neuroendocrine differentiation” should be avoided, because it has no specific meaning and causes confusion among clinicians. When positivity of 1% of cells or more are used on tissue microarray specimens, approximately 15% of non–small cell carcinomas express endocrine markers (ie, show neuroendocrine “differentiation”), with no clinical significance. Another study showed that 15% of adenocarcinomas expressed synaptophysin, with a mean of 16% or tumor cells positive. Currently, it is not recommended to perform endocrine markers, unless the differential diagnosis includes a NET based on histologic appearance.

Precursor endocrine lesions in the lung include carcinoid tumorlet and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. The former will be discussed below as a subset of carcinoid tumors.

WELL-DIFFERENTIATED NEUROENDOCRINE TUMORS

General Aspects

Carcinoids of the lung were historically defined as “foregut carcinoids” based on the origin of the lung bud from the foregut. They contrast with the midgut carcinoids of the jejunum ileum, which are characterized by the presence of endocrine granules that contain serotonin. Carcinoid syndrome is a rare complication of lung carcinoids because they uncommonly secrete vasoactive amines and are less likely to metastasize to the liver, a requirement in most cases of carcinoid syndrome. Histologically, pulmonary carcinoids are similar to low grade NETs elsewhere and can be divided into 2 types. Typical carcinoids are usually central (bronchial) and have a nested or trabecular growth pattern with abundant pink to amphophilic cytoplasm and by definition show low proliferation. Atypical carcinoids are usually peripheral but are otherwise similar in histologic appearance to typical carcinoids and by definition have increased proliferation. A (not officially recognized) subset of typical carcinoid is the spindle cell carcinoid, which is a small, usually multiple, tumor with a very low proliferation rate and diffuse TTF-1 positivity (unlike other lung carcinoids) (Table 2).

Carcinoid Tumor

Carcinoids are typically submucosal masses that are smooth surfaced with maintenance of the overlying respiratory epithelium. These are typically proximal to the segmental bronchi, accessible by endobronchial biopsy. They often present with symptoms due to infections or airway obstruction (cough, hemoptysis). The typical specimen is a lobectomy following a prior diagnosis, generally provided by transbronchial biopsy or transbronchial needle aspiration. Lymph node staging is generally performed prior to surgery, and in approximately 13% of cases, there are positive lymph nodes. Tumors tend to be well circumscribed and have a homogeneous cut surface (Figs. 1, 2). Because desmoplasia or fibrosis is absent, they are softer than most carcinomas. Histologically, tumors are homogenous and cellular, without fibrosis, necrosis, or cavitation (Figs. 3, 4). A proportion of typical carcinoids are not proximal but occur as peripheral subpleural masses (Fig. 2). For this reason, a distinction between proximal-type and peripheral-type carcinoid is not
uniformly possible; hence, there is no current scheme that incorporates location into classification. Immunohistochemically, carcinoids are positive for endocrine markers (synaptophysin, chromogranin, and CD56) and generally negative for TTF-1. Like other epithelial malignancies, they are positive for pancytokeratins and, similar to other pulmonary epithelial tumors, cytokeratin-7.

In resected specimens, there is usually no difficulty with the diagnosis, especially as most are previously diagnosed by biopsy or cytology. In small biopsies, the differential diagnosis includes adenocarcinomas and high-grade NECs. TTF-1, Ki-67, and endocrine marker panel are useful in establishing a diagnosis in this setting. Metastatic carcinoids in extrapulmonary sites can sometimes pose a diagnostic dilemma, if there is no history of a lung tumor. Rarely, calcitonin-secreting carcinoids can be difficult to distinguish from a metastatic medullary carcinoma of the thyroid.4

Variants of bronchial carcinoid tumors include Hurthle cell (Fig. 4) or oncocytic type, and melanocytic carcinoid. These are rare, and there is no effect on treatment or prognosis. Ossification is another feature that may occur and can be massive.5,6

“Spindle Cell” Carcinoids

There is no current classification of “spindle cell carcinoids” because there is overlap between morphology, location, and behavior between carcinoids with spindled cells and those with rounded cells. Current studies on prognosis make no attempt to subcategorize carcinoids by morphology.3 Historically, “spindle cell carcinoids” are usually incidental peripheral masses that are more often multiple than central carcinoids. When multiple, especially bilateral, spindle cell carcinoids can clinically be mistaken for metastases. They are more often diagnosed on frozen sections, when they can be mistaken for adenocarcinomas or metastatic tumors. If a tumor is uniformly cellular, lacks pleomorphism or fibrosis, and has a solid growth pattern, carcinoid tumor should be high on the differential diagnosis.

<p>| TABLE 1. Comparison of the Classification of NETs of the Lung and GI Tract |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Classification</th>
<th>Diagnostic Features</th>
<th>Classification</th>
<th>Diagnostic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated NET (carcinoid)</td>
<td>&lt;2 mitoses in 10 high-power field (2 mm²)</td>
<td>Well-differentiated NET grade 1</td>
<td>Up to 2% Ki-67; carcinoid morphology</td>
</tr>
<tr>
<td>Atypical NET (atypical carcinoid)</td>
<td>2–10 mitoses/2 mm²; necrosis (usually “pinpoint”)</td>
<td>Well-differentiated NET grade 2</td>
<td>3%–20% Ki-67; carcinoid morphology</td>
</tr>
<tr>
<td>[<em>LCNEC with carcinoid morphology]</em></td>
<td>&gt;10 mitoses/2 mm² with carcinoid morphology</td>
<td>Well-differentiated NET grade 3</td>
<td>&gt;20% Ki-67; carcinoid morphology†</td>
</tr>
<tr>
<td>Poorly differentiated LCNEC</td>
<td>Zonal necrosis, “endocrine” growth pattern, diffuse NE marker expression, &gt;10 mitoses/2 mm²</td>
<td>Poorly differentiated NEC, subset LCNE</td>
<td>&gt;55% Ki-67; high grade with “endocrine” growth pattern but without well-differentiated (carcinoid-like) morphology, diffuse endocrine marker expression</td>
</tr>
<tr>
<td>SCC</td>
<td>Histologic features of SCC</td>
<td>Poorly differentiated NEC, subset SCC</td>
<td>Histologic features of SCC</td>
</tr>
</tbody>
</table>

In the GI tract, the distinction between poorly differentiated carcinomas into small cell and large cell neuroendocrine is not clear cut, or at least less so than in the lung.

*Not an established entity, only case reports.
†Organoid growth pattern, nests with central necrosis, regular capillary network in direct contact to tumor cells, peripheral palisading; desmoplastic stroma is more typical of SCC or squamous carcinomas.

<table>
<thead>
<tr>
<th>TABLE 2. Carcinoid Tumors</th>
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<tbody>
<tr>
<td>Conventional Central Carcinoid</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Nuclear shape</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Proliferation rate</td>
</tr>
<tr>
<td>TTF-1 expression</td>
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<tr>
<td>Multiplicity</td>
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<tr>
<td>Course</td>
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</table>

*Currently not a diagnostic entity, but a subset of typical carcinoids that encompasses small, peripheral tumors with ovoid nuclei and relatively little cytoplasm.
Spindle cell carcinoids have elongated nuclei, but rarely truly elongated spindle cells. There is usually less cytoplasm than centrally located carcinomas, and the cytoplasm is pinker. Nuclear features are similar to central carcinoids and include the absence of nucleoli and fine dispersed chromatin. In contrast to central carcinoids, spindle cell carcinoids are TTF-1 positive (Fig. 5).

When smaller than 5 mm, spindle cell carcinoids are called carcinoid tumorlets. Tumorlets are the presumed precursor for spindle cell carcinoid tumors. They have the same immunohistochemical profile. Histologically, they form nests or clusters of cells surrounding a bronchiole. This feature helps distinguish them from meningothelial nodules, which are primarily interstitial and not associated with airways.

Atypical Carcinoid Tumor

Atypical carcinoids of the lung are characterized by mitotic activity and, sometimes, pinpoint necrosis. They are more often peripheral than central. Most would be the equivalent to well-differentiated NETs grade 2 of the pancreas. In 41% of resections, there are positive lymph nodes, much higher than typical carcinoids. Grossly, atypical carcinoids resemble typical ones but may have slightly more irregular edges. Histologically, atypical carcinoids should be very similar to typical carcinoids, unless necrosis is present. Nuclei retain features of typical carcinoid (Fig. 6). The definition of atypical carcinoid is a carcinoid-like tumor with 2 or more mitotic figures per 10 high-power fields. Tumor necrosis (to be distinguished from needle biopsy artifact) is another feature that places the tumor in the atypical carcinoid group, but in

Spindle cell carcinoids are indolent tumors. Although bronchial lymph nodes can be involved, no cases of distant metastasis have been reported in older series when this subtype was recognized. With the recognition that TTF-1 positivity may identify this subset, it is possible that spindle cell carcinoid will reemerge as a diagnostic entity.

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FIGURE 3. Carcinoid tumor, histologic features. Carcinoid tumors often distend and fill airways (top left). The tumor at the top right has a prominent trabecular pattern and an eosinophilic cytoplasm because of the presence of abundant endocrine granules, which are rare in lung carcinoids, in contrast to the jejunileum. As is the case with many types of endocrine tumors, multinucleated and bizarre cells can be seen (arrow, bottom left). The tumor at the bottom right has finely granular cytoplasm (oncocytic or Hurthle cell change).

FIGURE 4. Carcinoid tumor, histologic features. Ossification may be prominent (top left). A cord-like growth pattern is often a component (top right). The tumors at the bottom have a combined nested/trabecular pattern. Carcinoid tumors are very homogeneous typically without stroma.
practice, tumors with this feature reliably have mitotic counts comfortably above the threshold.

Rare NETs of the lung with histologic features of carcinoid can demonstrate more than 10 mitotic figures in 10 high-power fields. These tumors would correspond to well-differentiated NET, grade 3, in the pancreas. The term “(large cell) neuroendocrine carcinoma with carcinoid morphology” has been used for such lesions.\textsuperscript{10,11} The designation “LCNEC” for this type of tumor goes back to the proposed cutoff of 10 mitotic figures per 10 high-power fields to distinguish atypical carcinoid from LCNEC.\textsuperscript{9}

**ROLE OF KI67 IMMUNOLABELING IN WELL-DIFFERENTIATED NETS**

Unlike in the gastrointestinal tract, where 2% is the upper limit allowed for a NET grade 1 diagnosis,\textsuperscript{12} Ki-67 indexing does not form the basis for grading well-differentiated pulmonary NETs. In lung carcinoids, various studies have found cutoffs from 4%\textsuperscript{13,14} to 5%\textsuperscript{15} and as high as 7%\textsuperscript{16} to reliably separate carcinoids from atypical carcinoids. In practice, the values vary depending on the intensity of nuclear staining required for inclusion as positive and the presence of tumor infiltrating lymphocytes, which can stain positive. For example, when automated software is used for determining Ki-67 proliferation index, a 3-tiered positivity rate can be assessed, depending on weak, moderate, or strong nuclear positivity. The debate over which method (mitotic rate, “eyeballed” Ki-67 proliferative index, and automated Ki-67 proliferative index) is ongoing, but at this time the World Health Organization recommends mitotic activity as the primary method of separating the 2 entities.

**Prognosis**

Many studies have shown the favorable outlook for typical carcinoids, compared to one that is only marginally better (stage for stage) than non–small cell lung cancer for atypical carcinoids.\textsuperscript{17–21} A recent study from the National Cancer Institute registry data of 4645 patients showed that for typical carcinoids the 10-year disease-specific survival was approximately 95% for stage I patients, 85% for stages II and IIIA, 60% for stage IV, and 49% for stages IIB and IIIC.\textsuperscript{3} For atypical carcinoids, there was an 88% 10-year survival for stage I, which decreased respectively by stages II to IV to 76%, 48%, and 19%. Metastases for typical carcinoids tend to be delayed and may occur in a variety of sites, including in addition to lymph nodes, liver, brain, pleura, and heart (Fig. 7). Patients with typical carcinoids with
distant metastasis can live for prolonged periods as the follow-up data have shown.

POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMAS

Poorly differentiated NECs have been classified into 2 groups since the 2004 World Health Organization classification, namely, small cell carcinomas and LCNEC. In the 2015 classification, LCNEC was taken out of the “large cell” category and grouped with other neuroendocrine neoplasms. “Large cell carcinoma” as a diagnosis is currently a wastebasket category, limited to poorly differentiated carcinomas without expression of p40 or TTF, and after pleomorphic carcinoma and poorly differentiated neuroendocrine carcinoma have been ruled out.

As noted previously, there is little evidence of a spectrum between well- and poorly differentiated neuroendocrine neoplasms of the lung. Ki-67 immunolabeling demonstrates a large gap between atypical carcinoid and LCNEC, for example. Although metastases from typical carcinoids may demonstrate increased mitotic rates and Ki-67 indices that would put them in a poorly differentiated category, they maintain the molecular profile of well-differentiated tumors and are not thought to represent progression to a poorly differentiated carcinomas.

Small Cell Carcinoma

Small cell carcinoma is usually diagnosed on small biopsies or cytologic specimens. Resections are uncommon because of frequent involvement of mediastinal lymph nodes and responsiveness to chemotherapy.

Histologically, it had been recognized for more than 50 years that there is heterogeneity in the size of the cells in small cell carcinomas, which led to subtypes (long abandoned) such as oat cell, lymphocyte-like, and intermediate categories. Because the diagnosis ultimately rests on histologic appearance and some of the features are somewhat subjective, small cell carcinoma (along with large cell neuroendocrine) is probably the subtype of lung cancer with the most frequent diagnostic difficulty.

Small cell carcinomas, when typical, are easy to diagnose, especially on large pieces of tissue (Figs. 8, 9). The diagnostic histologic features of small cell carcinoma reside primarily in the nucleus. Eosinophilic nucleoli are always absent and indicate that another diagnosis is more appropriate or that there is a combined tumor. Small chromocenters or basophilic nucleoli in scattered nuclei may be seen in small cell carcinoma, provided that the chromatin is generally dispersed and coarse, without areas of vesiculation. The most characteristic feature is that of nuclear molding, which is otherwise seen to any degree only in LCNECs and high-grade lymphomas. Nuclear molding is often associated with “crush artifact,” as both features reflect the lack of rigidity of the nuclear membrane.

In addition to the definition of “prominent” nucleoli (which exclude the diagnosis), there is also variability in the interpretation of the degree of cytoplasm accepted for a diagnosis. Significant amounts of cytoplasm should lead to the consideration of LCNEC, although it is generally held that nuclear features are more important diagnostically than cytoplasmic features.

Immunohistochemical stains that are useful in the diagnosis of small cell carcinomas of the lung are listed in Table 3. More than 90% of small cell carcinomas express TTF-1, as well as 1...
endocrine marker (chromogranin is the most specific but least sensitive). There may be focal positivity for p40, but areas of diffuse strong nuclear positivity do not occur. Although the vast majority express at least 1 neuroendocrine markers and/or TTF-1, the tumors that pose the most diagnostic difficulty on routine stains are often those that are negative for both. In these cases, it is essential to exclude lymphoma by immunostains, and TTF-1 negative adenocarcinoma and LCNEC by histologic features. Newer endocrine markers, such as INSM1, may be more sensitive than established markers in small cell carcinomas and may soon be added to the list of routine stains (Fig. 8). On cytologic samples, p16 has been reported to show cytoplasmic and nuclear positivity in the majority of small cell carcinomas, with absent staining in squamous carcinomas (Svajdler). The vast majority of SCLCs show loss of RB1 protein and p53 overexpression or null expression, although these findings are nonspecific.

The differential diagnosis of small cell carcinoma is generally an issue on small biopsy samples. Table 4 highlights the major entities that can be mistaken for small cell carcinoma. The most common difficulties include distinguishing squamous cell carcinoma (SqCC) from LCNEC, nonkeratinizing basaloid carcinomas, and solid adenocarcinomas. Carcinoid tumors may show areas of nuclear molding and crush artifact, and in such instances, paucity of mitotic figures and low Ki-67 immunolabeling is very helpful. In addition to those listed in the table, the differential diagnosis can also include mediastinal small round blue cell sarcomas, because small cell carcinoma can involve mediastinal lymph nodes to such an extent that the primary lung tumor is obscured or the site of biopsy unclear (mediastinum vs mediastinal lymph node). Thoracic location of small round blue cell sarcomas is rare. They include Ewing sarcoma (CD99, NKX2.2 positive with EWSR1-ETS gene family fusion), CIC-rearrangement sarcoma (WT1 positive, CIC-DUX rearrangement), and BCOR-CCNB3 fusion sarcoma (bcor positive).

Combined Small Cell Carcinoma

Because small cell carcinomas are not often resected, the incidence of tumors with non–small cell components is not precisely known. The most common combined component is LCNEC, followed by adenocarcinoma, squamous carcinoma, and spindled cell or giant cell carcinoma (Figs. 10–12). A study of resected small cell carcinomas found that 16% of small cell carcinomas have areas of LCNEC; an arbitrary cutoff point for the designation of combined tumor was proposed at 10% LCNEC areas. The current terminology for the diagnostic line is “combined small cell
FIGURE 8. Small cell carcinoma, resected specimens. The top panel shows a 5.5-cm tumor resected from the peripheral lower lobe, with 1 positive bronchial lymph node. The bottom panels show a 1.7-cm peripheral tumor, with negative lymph nodes. The Ki-67 proliferative index was 80%, and there was diffuse CAM5.2 positivity. Chromogranin, synaptophysin, and CD56 were negative, but there was focal INSM1 positivity (bottom right).

FIGURE 9. Small cell carcinoma, histologic features. The top panel shows a small cell carcinoma with extensive necrosis and desmoplasia, the latter feature also common in LCNEC (and not seen in carcinoids). The bottom panel shows a primary small cell (left) that recurred in the adrenal 2 years later (right). The morphology is acceptable for small cell, although there is very slight vesiculation to the nuclear, and the cytoplasm is unusually abundant.
carcinoma, with [other component, such as adenocarcinoma]." The reason that "small cell" should be emphasized in the diagnosis is that these patients are treated with small cell regimens.

Histologically, there can be a sharp demarcation between the morphologic subtypes, or they can be more intermingled. Immunohistochemical stains can be useful to delineate the different components. It is not necessary to approximate the amount of tumor of each type. There is no percent cutoff for adenocarcinoma or SCCs, as there is for LCNEC.

It is believed that distant metastases are usually of the small cell component, although there have been no reports of a series of histologically proven cases. In a series of resected specimens with lymph node dissections, approximately one-half of patients have positive lymph nodes, with the non–small cell component present nearly as often as the small cell component.27

Combined small cell carcinomas are thought to derive from a single origin, based on genetic studies, and therefore are not collision tumors. Compared to pure small cell carcinomas, they are more often peripheral tumors and likewise amenable to surgical therapy.28 Other studies have shown no clinical differences and a shorter survival.29

The criteria for diagnosing a squamous component have sometimes included the requirement for keratinization, although if there are histologic distinct areas with absence of endocrine markers and positivity for p40, the diagnosis of combined carcinoma has been applied even in the absence of keratinization.29

Small Cell Carcinoma After Tyrosine Kinase Inhibitor Therapy for Adenocarcinoma

Patients with adenocarcinomas of the lung that harbor epidermal growth factor receptor mutations are often never-smokers and are treated with tyrosine kinase inhibitors. Between 3% and 15% of these patients will have a recurrence in the form of small cell carcinomas, either locally or as distant metastasis, between several months to years after initial diagnosis. The transformation to small cell carcinoma in recurrences is associated with rapid clinical deterioration, disease progression, and change in oncological management. Histologically, the findings are typical of small cell carcinoma, although epidermal growth factor receptor mutations may be present, which are rare in de novo small cell cancers.30

Large Cell Neuroendocrine Carcinoma

There are 3 requirements for a diagnosis of LCNEC. First, there has to be evidence of diffuse expression (in at least large areas of the tumor) of neuroendocrine markers chromogranin, synaptophysin, CD56, and/or INSM1. The chromogranin positivity rate is somewhat higher than in small cell carcinoma. Second, there has to be a neuroendocrine "growth pattern" to the tumor. Lastly, the tumor has to be high grade, with the presence of zonal necrosis and/or a brisk mitotic rate, at least 1 mitotic figure per millimeter squared.31 (Fig. 13).

Neuroendocrine histologic features include organoid or trabecular growth pattern, a regular tumoral vascular pattern, and abundant granular cytoplasm. In contrast to small cell carcinoma, nucleoli tend to be prominent and often eosinophilic (Table 5). On low magnification, LCNEC is typically much more homogeneous than adenocarcinomas or SqCCs, is relatively circumscribed, and is often composed of large cell nests with central necrosis, which are often surrounded by areas of loose fibrosis (desmoplasia).

### TABLE 3. Immunostains That Are Helpful in the Differential Diagnosis of Small Cell Carcinoma

<table>
<thead>
<tr>
<th>Marker</th>
<th>Staining</th>
<th>Diagnostic Relevance</th>
</tr>
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<tbody>
<tr>
<td>Ki-67 proliferation index</td>
<td>&gt;75%</td>
<td>Compatible with SCC, LCNEC</td>
</tr>
<tr>
<td></td>
<td>&lt;50%</td>
<td>Excludes SCC</td>
</tr>
<tr>
<td>CG/CD56/synaptophysin/INSM1</td>
<td>Areas of diffuse cytoplasmic positivity</td>
<td>LCNEC, SCC, well-differentiated NETs (carcinoids and atypical carcinoid)</td>
</tr>
<tr>
<td>Pancytokeratins (panCK, CAM5.2)</td>
<td>Areas of diffuse cytoplasmic positivity</td>
<td>Useful in SCC negative for TTF-1 and endocrine markers, differentiates from diffuse large B-cell lymphoma and SRBL sarcoma</td>
</tr>
<tr>
<td>CD20 or pax5</td>
<td>Membranous positivity</td>
<td>B-cell lymphoma, helpful in undifferentiated SCC</td>
</tr>
<tr>
<td>Napsin A</td>
<td>Negative</td>
<td>Compatible with SCC, LCNEC</td>
</tr>
</tbody>
</table>

Endocrine markers can be positive in some small round blue cell sarcomas as well as some adenocarcinomas.

*Remember that the ultimate diagnosis rests on cytomorphic features.

### TABLE 4. Differential Diagnosis of Small Cell Carcinoma

<table>
<thead>
<tr>
<th>Entity</th>
<th>Distinguishing Histologic Features</th>
<th>Distinguishing Immunohistochemical Features</th>
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</thead>
<tbody>
<tr>
<td>LCNEC</td>
<td>Nucleoli, more abundant cytoplasm</td>
<td>None</td>
</tr>
<tr>
<td>Combined small cell carcinoma (with adenocarcinoma, squamous carcinoma, or LCNEC)</td>
<td>Distinct areas of adenocarcinoma, squamous carcinoma, LCNEC</td>
<td>Distinct areas of loss of endocrine markers (squamous or adenoc); distinct areas of p40+ (squamous)</td>
</tr>
<tr>
<td>Solid type adenocarcinoma</td>
<td>Nucleoli, areas of cribriform/sheet-like growth, mucin vacuoles</td>
<td>None for LCNEC</td>
</tr>
<tr>
<td>Nonkeratinizing/basaloid poorly squamous carcinoma</td>
<td>Nucleoli; although may occasionally have dispersed coarse chromatin</td>
<td>Absent endocrine markers (usually)</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Can be difficult on small samples</td>
<td>p40 positivity (areas with diffuse staining), lack of NE markers</td>
</tr>
<tr>
<td>Carcinoid tumor with nuclear molding and crush artifact on biopsy</td>
<td>Lack of mitoses, necrosis</td>
<td>Pax5</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ki-67 immunolabeling low</strong></td>
</tr>
</tbody>
</table>
TTF-1 positivity is less frequent than in small cell carcinoma and usually less diffuse. As is the case with small cell carcinoma, napsin-A is negative in the vast majority of cases. Similarly, p40 is either positive or isolated to scattered cells. By definition, there is expression of NECs, which are generally not present in squamous carcinomas.

In resected specimens, the main entity in the differential diagnosis is SCC, because of the relatively abundant cytoplasm and lack of acinar, papillary, or cribriform patterns that are characteristic of adenocarcinomas. Immunohistochemical stains and familiarity with the histologic features of LCNEC readily distinguish these entities. The other entity in the differential diagnosis is small cell carcinoma, with which it is often intermixed. Histologic nuclear criteria are essential in this distinction. On small biopsies, it can be difficult to confirm a diagnosis on a small sample, and a common difficulty is the distinction from adenocarcinoma. Because LCNECs are usually peripheral lesions that are treated similar to adenocarcinomas, a change in diagnosis from non–small cell carcinoma favoring adenocarcinoma (usually because of positive TTF-1) to LCNEC is of little clinical consequence.

A scoring system has been devised for small biopsy samples that separates LCNEC from adenocarcinomas and SCCs. This system uses 7 markers (3 neuroendocrine, napsin A, ttf-1, and p40).
As noted previously, the distinction may not be as critical as the distinction from small cell carcinoma, which may be treated differently. Unfortunately, only the nuclear features discussed previously will allow this discrimination.32

In general, LCNEC is still clinically considered a non–small cell carcinoma, which causes considerable confusion, as it is classified in the same group as small cell carcinoma pathologically. Molecular studies that have tried to elucidate its pathogenesis have shown that LCNEC is heterogeneous. A significant proportion show RB1/TP53 inactivation and MYCL (MYCL1) amplification, which are hallmarks of small cell carcinoma. However, this molecular subset of LCNECs is associated with an ASCL1-low/DLL3-low/Notch-high profile, which is not usually found in small cell carcinoma. Conversely, another large subset of LCNECs is associated with RAS pathway genetic alterations characteristic of adenocarcinoma, but these tend to have an ASCL1-high/DLL3-high/Notch-low expression profile more typical of small cell carcinoma. These findings suggest that there are 2 large groups of LCNECs, each with select molecular findings of both small cell and adenocarcinomas. Unfortunately, attempts to correlate histologic features with molecular subtypes have as yet been unfruitful. Whether the 2 molecular subsets of large cell carcinoma respond to different types of treatment regimens is a matter of ongoing study.33 An update on molecular studies and morphologic features of LCNEC has recently been published.31

Similar to small cell carcinomas, combined neuroendocrine carcinoma may occur, although less frequently. The 2 histologic types derive from the same clone, like combined small cell carcinoma, and adenocarcinoma is the most common histologic type, followed by SCCs. In a large series, 23% of resected LCNECs had components of adenocarcinoma or SCC.34 By definition, if

FIGURE 11. Combined small cell carcinoma with squamous carcinoma. The top figure shows the small cell element, and the middle the squamous (with some small cell areas as well). The bottom figure shows a metastatic deposit in a regional lymph node (squamous cell component).

FIGURE 12. Combined small cell carcinoma with adenocarcinoma. The top figure shows typical small cell carcinoma, and the bottom an area of adenocarcinoma. There were other growth patterns as well, including lepidic.
there is a small cell component, the tumor is diagnosed as combined small cell carcinoma (see above).

Prognostically, LCNECs are bad tumors. Stage 4 tumors have a similar prognosis as stage 4 small cell carcinomas. Surgically resected tumors have a worse stage-per-stage prognosis than other non–small cell cancers.35

Patients with LCNECs that present with distant metastases have been variably treated with either small cell or non–small cell regimens.35 Surgically resected tumors have shown a good initial response with platinum-based treatment similar to those used for non–small cell carcinomas.34 There are few results of trials including immunotherapy regimens: programmed death ligand 1 expression (>50% tumor cells) is found in only 15% of LCNEC.

REFERENCES


