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*Accurate classification of this malignancy will help to guide management decisions regarding resection and adjuvant therapy.*

# Large-Cell Neuroendocrine Carcinoma of the Lung

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**Background:** Large-cell neuroendocrine carcinoma (LCNEC) of the lung displays morphologic and immunohistochemical characteristics common to neuroendocrine tumors and morphologic features of large-cell carcinomas. Because surgical resection of LCNEC in many series has been described with 5-year actuarial survival that is far worse than that reported for other histologic variants of non-small-cell lung cancer (NSCLC), considerable debate has emerged as to whether these tumors should be classified and treated as NSCLC or small-cell lung cancer.

**Methods:** The initial evaluation and diagnosis, tumor classification, surgical treatment, results of therapy, and long-term prognosis of patients with LCNEC based on our experience are discussed, and a review of the literature is presented.

**Results:** Patients with LCNEC are more likely to develop recurrent lung cancer and have shorter actuarial survival than patients with other histologic types of NSCLC, even in those with stage I disease.

**Conclusions:** Accurate differentiation of LCNEC from other types of NSCLC is important because it identifies those patients at highest risk for developing recurrent disease. Efforts to identify effective adjuvant therapies are needed to improve treatment outcomes with this aggressive type of lung cancer.

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**Abbreviations used in this paper:** SCC = small-cell carcinoma, ICC = large-cell carcinoma, NSCLC = non-small-cell lung cancer, LCNEC = large-cell neuroendocrine carcinoma.

## Introduction

Neuroendocrine tumors of the lung encompass a wide range of pathologic entities that display distinct biologic behaviors. In the 1970s, pulmonary neuroendocrine tumors were classified into three histologically defined categories. Typical carcinoid tumors, which metastasize infrequently and have an excellent prognosis, are at one end of the spectrum. At the other extreme are small-cell carcinomas (SCCs), which frequently metastasize and have a dismal prognosis. Between these two extremes are atypical carcinoid tumors, first reported

in 1972 by Arrigoni et al.<sup>1</sup> In 1991, Travis et al<sup>2</sup> were the first to propose large-cell neuroendocrine carcinoma (LCNEC) as a separate category of pulmonary neuroendocrine tumors, distinct from typical and atypical carcinoids and SCC. These tumors were described as having a cell size at least three times that of SCC, an organoid growth pattern, cellular palisading or rosette-like areas, a high mitotic rate, and a variably granular chromatin pattern.<sup>3</sup>

Dresler et al<sup>4</sup> classified the spectrum of neuroendocrine tumors on the basis of histologic characteristics and clinical behavior. Neuroendocrine tumors were classified as follows: grade I = classic typical carcinoid tumors, grade II = previously atypical carcinoids, and grade III = large- and small-cell types. However, in 1999, the World Health Organization International Association for Staging of Lung Cancer histologic classification of lung and pleural tumors grouped a number of histologic variants under the title "large-cell carcinoma (LCC)," including LCNEC, basaloid carcinoma, lymphoepithelioma-like carcinoma, and LCC with rhabdoid phenotype.<sup>5</sup> Such differences in classification have created confusion in the characterization of LCNEC of the lung.

Survival after resection of LCNEC appears to be substantially worse than for other non-small-cell lung cancer (NSCLC), resembling more the survival of SCC. Therefore, considerable debate has emerged as to whether these tumors should be classified and treated as NSCLC or considered together with SCC, given their aggressive behavior. The goal of this review is to clarify the existing literature on LCNEC to better classify this malignancy and help guide management decisions in terms of surgical resection and adjuvant therapy.

## Incidence and Epidemiology

The true incidence of LCNEC is in all probability low, although it has not been well defined. In a series reported by Jiang et al<sup>6</sup> of 766 patients with resected primary lung cancer, 22 (2.87%) were classified as LCNEC. In 4 of these, LCNEC was combined with another histologic type (combined LCNEC). Takei et al<sup>7</sup> reported a similar rate of 3.1% (87/2790) in their series, 5 of which were combined LCNEC. In the series of Iyoda et al,<sup>8</sup> 3.4% (72/2070) of resected lung cancers were LCC with neuroendocrine features, 50 of these were LCNEC, 9 were LCC with neuroendocrine differentiation, and 13 were LCC with neuroendocrine morphology. Paci et al<sup>9</sup> reported a frequency of LCNEC of 3.5% (53/1530). At our institution from July 1988 through December 2002, there were 45 LCNEC out of 2099 surgically resected primary lung cancers (2.1%).<sup>10</sup> Another 11 tumors were classified as "mixed LCNEC," demonstrating features of both LCNEC and NSCLC, which increases the incidence to 2.78% if these are

included. Therefore, the incidence of LCNEC in surgically resected lung cancers appears to be between 2.1% and 3.5% based on the available literature. The incidence of LCNEC in lung cancers not treated surgically is unknown but is likely to be higher, given the aggressive nature of these tumors.

As with other histologic variants of lung cancer, smoking appears to be the primary cause of LCNEC. Several series report that 85% to 98% of patients who underwent surgical resection for LCNEC had a history of habitual cigarette smoking.<sup>7,9,11,12</sup> The mean age of patients treated for LCNEC ranged from 62 to 68 years of age, with a median of 65.8 years.<sup>4,7-14</sup> In these same series, the preponderance of patients with LCNEC were men, with a range of 55% to 90% and a median of 85%. As recognition and reporting of LCNEC increases, the epidemiology of this neoplasm will be better defined, including possible associated environmental and genetic risk factors.

## Pathologic Characterization

Travis et al<sup>2</sup> proposed that the term LCNEC should be used for tumors with obvious neuroendocrine features by light microscopy that do not fit into the category of typical carcinoid, atypical carcinoid, or SCC. Histologic attributes include a cell size at least three times a large as SCC. Cells of these tumors have an organoid growth pattern with cellular palisading or rosette-like areas and patches of geographic necrosis. A variably granular pattern of chromatin in the nuclei with an absent or faint nucleolus has also been described (Fig 1).<sup>3</sup> It should be noted, however, that overlapping between nuclear dimensions of LCNEC and SCC has been reported.<sup>15</sup> A

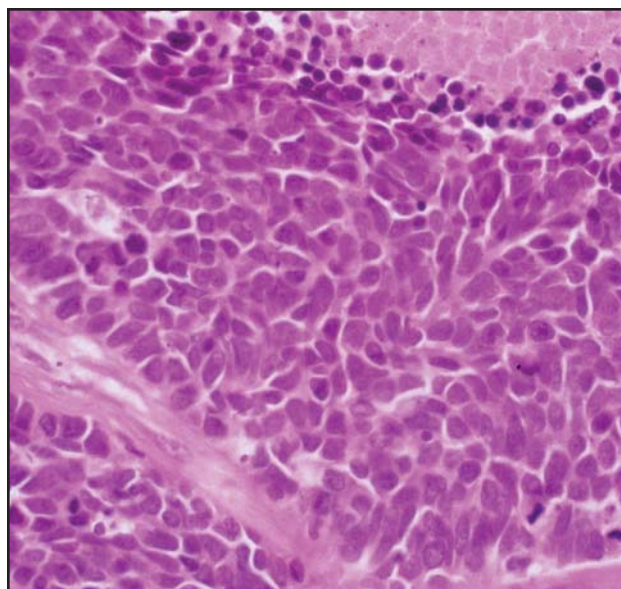


Fig 1. — Photomicrograph of large-cell neuroendocrine carcinoma. (Original magnification  $\times 40$ )

high mitotic rate approaching that of SCC is seen. The high mitotic index and the presence of areas of necrosis have been used by Travis et al<sup>3</sup> to aid in the differentiation of the tumors from atypical carcinoids. Finally, foci of squamous or adenomatous differentiation may also be seen in these tumors.

The electron microscopic and immunohistochemical features of these tumors have also been described by Travis et al.<sup>2</sup> These tumor cells have been shown to contain neurosecretory granules and occasional evidence of granular differentiation and intercellular junctions suggestive of squamous differentiation on electron microscopy. On immunohistochemistry, these tumors stain for neuron-specific enolase, carcinoembryonic antigen (CEA), and keratin as well as variably stain for chromogranin, Leu-7, synaptophysin, and adrenocorticotropin hormone. These immunohistochemical properties have also been confirmed by Wick et al.<sup>16</sup> The use of three neuroendocrine markers — neural cell adhesion molecule, chromogranin A, and synaptophysin — has been suggested by Takei et al<sup>7</sup> to identify a neuroendocrine tumor. Positivity for a neuroendocrine phenotype was determined by the presence of focal staining for at least one of these three markers.<sup>7</sup>

## Molecular Biology

At the cellular level, LCNEC has a higher proliferative rate compared to LCC. A study from Ab'Saber et al<sup>17</sup> found that LCNEC had greater staining than LCC for *p21<sup>waf1/cip1</sup>*, which is involved in the regulation of apoptosis and the cell cycle, as well as microvessel density, a marker of angiogenesis. Patients found to have greater than 3.5% staining for *p21<sup>waf1/cip1</sup>* and microvessel density staining of greater than 3.0% in their tumor specimens were found to be at high risk of death due to lung cancer. Further, Iyoda et al<sup>18</sup> analyzed the proliferative activity of stage I resected LCNEC compared with that of resected stage I LCC. They found that the mitotic rate of LCNEC was significantly higher than that of LCC. In addition, the Ki-67 labeling index (associated with cellular proliferation) and expression of Bcl-2 (an important inhibitor of apoptosis) were significantly higher in stage I LCNEC. Not surprisingly, disease-free survival was significantly lower for patients with LCNEC in this series.

Characterization of the patterns of expression of several molecular markers was carried out by Rusch et al.<sup>19</sup> They found that expression of Ki-67, p53, and Rb helped to distinguish LCNEC and SCC from typical and atypical carcinoid tumors. LCNEC and SCC demonstrated a high proliferative rate based on Ki-67 staining, abnormal p53, and absent Rb staining in comparison with typical carcinoid and atypical carcinoid, which had low proliferative rates, absent p53, and normal stain-

ing for Rb. These results suggest a sharp separation of high-grade neuroendocrine tumors from carcinoids and imply a close relationship between LCNEC and SCC. Further, an analysis of p53, *K-ras-2*, and *C-raf-1* expression has revealed that LCNEC is more genetically similar to SCC than NSCLC.<sup>20</sup> These molecular findings may help explain the higher recurrence rates observed after surgical resection of LCNEC.

## Clinical Presentation

LCNEC more frequently presents as a peripheral tumor as opposed to typical and atypical, which are generally central in location. Garcia-Yuste et al<sup>13</sup> reported that two thirds of LCNECs present in the periphery of the lung parenchyma. In a series by Paci et al,<sup>9</sup> only 1 out of 48 LCNECs was found to be in a central location. Accordingly, patients with LCNEC are less likely to present with symptoms such as cough, hemoptysis, or postobstructive pneumonia. In the series reported by Zacharias et al,<sup>14</sup> only 4 out of 21 patients presented with cough or hemoptysis. The remainder of patients presented with an asymptomatic nodule (5), chest pain (6), nonspecific flu-like symptoms (2), dyspnea (2), night sweats (1), and carcinoid syndrome (1). Paraneoplastic syndromes have not been frequently observed in patients with LCNEC.<sup>7,9,11</sup>

## Diagnosis

Because the accurate differentiation of LCNEC from other histologic subtypes of NSCLC requires careful review of the pathologic specimen, LCNEC is infrequently diagnosed preoperatively. Before the diagnosis of LCNEC is ascribed to these tumors, neuroendocrine differentiation must be confirmed by light microscopy and subsequently distinguished from typical carcinoma, atypical carcinoma, and SCC by size, presence or absence of necrosis, and mitotic rate.<sup>3</sup> It must be remembered, however, that there is significant overlap in nuclear dimensions between LCNEC and SCC.<sup>15</sup> Greater awareness of the distinct biologic behavior of LCNEC will likely increase the use of confirmatory immunohistochemical staining for neuroendocrine markers such as chromogranin, synaptophysin, neuron-specific enolase, and CD56 in many specimens. In difficult cases, evidence of neuroendocrine differentiation may also be determined ultrastructurally using electron microscopy.

Because somatostatin receptors are frequently expressed by neuroendocrine tumors,<sup>21-23</sup> OctreoScan (indium 111-tagged diethylenetriaminepentaacetic acid pentreotide scintigraphy) imaging can be useful for preoperative staging when LCNEC is suspected or confirmed, as well as for postoperative surveillance of

**Table 1. — Series Examining Overall Survival for Resected Large-Cell Neuroendocrine Carcinoma**

Author	Year	No. of Patients	5-yr Overall Survival Rate (%)	5-yr Overall Survival Rate Stage I (n)
Dresler et al <sup>4</sup>	1997	40	13	18% (25)
Travis et al <sup>3</sup>	1998	37	27	N/A
Jiang et al <sup>6</sup>	1998	22	44.8	N/A
Garcia-Yuste et al <sup>13</sup>	2000	22	21	33% (13)
Iyoda et al <sup>8</sup>	2001	50	~35*	N/A
Takei et al <sup>7</sup>	2002	87	57	67% (41)
Zacharias et al <sup>14</sup>	2003	18	47	88% (9)
Paci et al <sup>9</sup>	2004	48	21.2	27% (29)
Doddoli et al <sup>12</sup>	2004	20	36	N/A
Battafarano et al <sup>10</sup>	2005	45	30.2	32.1% (30)
Asamura et al <sup>11</sup>	2006	141	40.3	57.8% (63)

N/A = not available.  
\* Number estimated from survival curve.

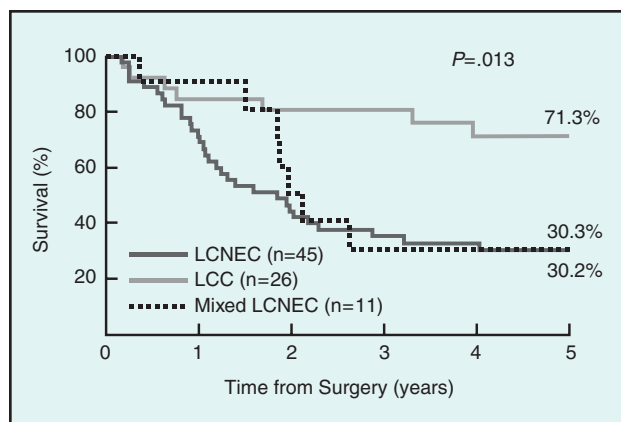
patients.<sup>24</sup> Although there has been some debate about the utility of (18)F-deoxyglucose-positron emission tomography (FDG-PET) imaging of neuroendocrine tumors, it has been our experience that LCNECs are universally FDG avid.

Gene expression profiling is a modality that in the future may serve to differentiate LCNEC from LCC on the basis of patterns of gene expression. In our laboratory, experiments are underway to characterize gene expression patterns capable of differentiating these two variants of lung cancer. Such characterization may work towards the development of clinically useful molecular biomarkers as well as a better understanding of the molecular biology behind the disparate clinical outcomes of these two tumors. Preliminary results suggest that gene expression profiling provides robust molecular signatures that can distinguish between these two tumors.<sup>25</sup>

## Survival

Compared with other histologic types of NSCLC, the 5-year overall survival rate after resection of LCNEC has been reported to range from 13% to 57% (Table 1).<sup>3,4,6-14</sup> In a series reported from our institution,<sup>10</sup> the 5-year overall survival rate for resected LCNEC was only 35% and was significantly worse than the survival rate of 71.3% observed for LCC with no evidence of neuroendocrine morphology or differentiation (Fig 2). Given this poor prognosis, we believe that LCNEC must be accurately differentiated from other forms of NSCLC.

As previously mentioned, the World Health Organization classified LCNEC as a variant of LCC. In this schema, LCCs were classified into four types: LCNEC, large-cell carcinoma with neuroendocrine differentiation (LCCND), large-cell carcinoma with neuroendocrine morphology (LCCNM), and classic large-cell carcinoma (CLCC).<sup>5</sup> Iyoda et al<sup>8</sup> sought to define the clinical relation of these four categories. Out of 119



**Fig 2. — Kaplan-Meier overall survival by cell type.** From Battafarano RJ, Fernandez FG, Ritter J, et al. Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2005;130:166-172. Reprinted with permission from American Association for Thoracic Surgery.

cases of LCC, 50 (42%) were classified LCNEC, 9 (7.6%) as LCCND, 13 (10.9%) as LCCNM, and 47 (39.5%) as CLCC. In this study, overall and disease-free survival rates for patients with LCC with neuroendocrine features, which combined LCNEC, LCCND and LCCNM, were significantly lower than for patients with CLCC. Multivariate analysis also identified the presence of neuroendocrine features as an independent predictor of poorer overall and disease-free survival. This study demonstrates that the presence of either neuroendocrine morphology or differentiation alone in LCCs portends a poor prognosis.

The observation that LCNEC has worse overall survival in many series cannot be explained by more advanced disease at the time of presentation. In our series,<sup>10</sup> there was a similar distribution of pathologic stage at the time of presentation in patients with LCNEC and NSCLC who underwent definitive surgical resection during the same time period (Table 2). Even in stage I disease, the overall survival for LCNEC remained significantly worse than observed for LCC<sup>10</sup> and for other histologic subtypes of NSCLC.<sup>26</sup> In other series,<sup>4,7,9,13,14</sup> the 5-year overall survival rate for resected stage I LCNEC has been reported to range from 18% to 88% (Table 1). The 32.1% 5-year survival rate in our series for stage I disease was similar to the rates report-

**Table 2. — Distribution of Stages for Resected Patients With LCNEC vs NSCLC**

	IA	IB	IIA	IIB	IIIA	IIIB	IV
NSCLC (n = 2,089)	34.4%	23.8%	3.4%	16.1%	13.9%	5.3%	3.1%
LCNEC (n = 45)	48.8%	17.9%	4.4%	20.0%	6.7%	0%	2.2%

From Battafarano RJ, Fernandez FG, Ritter J, et al. Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2005;130:166-172. Reprinted with permission from American Association for Thoracic Surgery.

ed by Dresler et al<sup>4</sup> (18%), Paci et al<sup>9</sup> (27%), and Garcia-Yuste et al<sup>13</sup> (33%). Takei et al<sup>7</sup> and Zacharias et al<sup>14</sup> have reported higher 5-year survival rates (67% and 88%, respectively), although stage I LCNEC had a worse prognosis than stage I NSCLC in the former. The higher 5-year survival rate for stage I LCNEC observed by Zacharias et al<sup>14</sup> may be attributable to the fact that patients in this study were highly selected and all carefully staged with a systematic nodal dissection. In total, these results appear to indicate that even stage I LCNEC has a worse prognosis than stage-equivalent NSCLC, reinforcing the aggressive biology of LCNEC.

Mixed or biphasic LCNEC tumors contain areas of LCNEC as well as histologic subtypes of other NSCLC. It has been uncertain as to whether these tumors behave as LCC or LCNEC. Although examined in only 11 patients, our data reveal that mixed LCNEC behaved poorly, having a 5-year overall survival rate of 30% that was similar to pure LCNEC and significantly worse than that of LCC.<sup>10</sup> The finding that mixed LCNEC has the same clinical behavior as LCNEC has also been observed by others,<sup>4,8,14,27</sup> whereas one group has found that LCCs with neuroendocrine features have a prognosis similar to other histologic subtypes of NSCLC.<sup>28</sup> Therefore, it appears that the presence of neuroendocrine differentiation in any portion of the tumor is associated with a poor prognosis. Given the poor prognosis of LCC that has any degree of neuroendocrine features, all LCC should be examined closely on pathology for evidence of occult neuroendocrine features.

## Treatment

As shown above, stage-for-stage survival is worse for LCNEC than for NSCLC. In efforts to improve cure rates of LCNEC, postoperative adjuvant chemotherapy or radiotherapy has been used in several series of this disease.<sup>4,13,19,29,30</sup> Unfortunately, a definitive survival advantage for postoperative adjuvant therapy has yet to be reported in these patients. One series from Iyoda et al<sup>31</sup> did find a survival benefit to adjuvant chemotherapy in a small subgroup of 5 patients with stage I disease treated with cisplatin, carboplatin, or cyclophosphamide. As a result of the small numbers in each study and the relative infrequency of LCNEC, no standard adjuvant therapy regimen has been developed. It has previously been suspected that LCNEC tumors are resistant to conventional chemotherapeutic agents. A majority of lung neoplasms with neuroendocrine markers were found to express the multidrug resistance gene (MDR1), a harbinger of resistance to chemotherapy, in a study reported by Lai et al.<sup>32</sup> The somatostatin analog octreotide represents a potential novel adjuvant biologic therapy. It has been shown to control metastatic growth while being well tolerated in the treatment of other neuroen-

docrine tumors.<sup>24,33</sup> The role of adjuvant therapy for early-stage LCNEC or mixed LCNEC should be examined in large-center prospective, randomized trials.

## Conclusions

LCNEC of the lung is an uncommon but aggressive neoplasm with a poor prognosis. Given the aggressive biology as well as pathologic and molecular features, these tumors should be classified separately from NSCLC and referred to as grade III neuroendocrine carcinoma large-cell type, part of the neuroendocrine spectrum of lung cancer. Any evidence of neuroendocrine differentiation in NSCLC appears to be associated with an increased risk for recurrence and decreased 5-year survival. Novel approaches are needed for the diagnosis, staging, and treatment of this increasingly recognized lung malignancy.

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