Large Cell Neuroendocrine Versus Small Cell Carcinoma: When, Whether and How to Make the Distinction

Jeffrey L. Myers, M.D.
A. James French Professor and Director, Division of Anatomic Pathology
The University of Michigan, Ann Arbor, MI

Objectives
At the end of this presentation attendees will understand, 1) current criteria for separating large cell neuroendocrine from small cell carcinoma, and 2) the clinical, biological, histologic and phenotypic overlap between the two.

Key Points
• Small cell carcinoma (SCLC) is defined on basis of cytologic criteria.
• Large cell neuroendocrine carcinoma (LCNEC) is defined by a combination of histologic (i.e. neuroendocrine morphology, necrosis) and cytologic (i.e. large cell size, cytoplasm, nucleoli, coarse chromatin, high mitotic rate) criteria as well as the presence of neuroendocrine differentiation demonstrated using immunohistochemistry.
• LCNEC is separated from atypical carcinoid tumors based primarily on consistent presence of necrosis and higher mitotic rate.
• SCLC and LCNEC overlap in their clinical, biological, histopathologic, immunophenotypic, and genetic characteristics making separation difficult, and perhaps unimportant, in some patients.

INTRODUCTION
A revised WHO classification of lung tumors was published in 1999 and again in 2004, building on the popular foundation provided in the 1981 version. Like its predecessors, the updated WHO classification scheme relies heavily on routine light microscopy for tumor classification. Immunohistochemical stains have been established as an important diagnostic adjunct for certain tumor types, particularly tumors with neuroendocrine differentiation. The current scheme does not specifically categorize neuroendocrine neoplasms together, separating carcinoid tumors (typical and atypical) from more conventional forms of carcinomas. Small cell carcinoma (SCLC) remains a distinct carcinoma category, while large cell neuroendocrine carcinomas (LCNEC) are a subset of the larger group of large cell carcinomas. This review focuses on the two high grade variants of neuroendocrine neoplasms and those features that separate SCLC from LCNEC.

SMALL CELL CARCINOMA
Small cell lung cancer (SCLC) accounts for around 15% of all bronchogenic carcinomas, and is considered a high grade representative of the family of neuroendocrine lung tumors. Small cell carcinoma is strongly associated with cigarette smoking. Men are affected more commonly than women by a ratio of about 2:1, and most patients present in the 6th or 7th decade of life. Nearly all patients have advanced stage disease at presentation, and for that reason surgery is reserved for rare patients in whom tumor is
confined to the lung. In a review limited to patients who underwent some sort of surgical procedure, survival for stage I and II ("limited") disease was 50% at two years, but only 14% at 5 years. The survival at 5 years was not significantly different from that seen in patients with "extensive" (stage III and IV) disease. Combination chemotherapy with or without radiation remains the mainstay of therapy in most patients.

Small cell carcinoma is a highly malignant epithelial neoplasm composed of relatively small cells with distinctive round to oval nuclei characterized by a diffuse ("salt and pepper") chromatin pattern and inconspicuous nucleoli. Cell size is variable, however, and comprises a range that merges with that seen in non-small cell carcinomas. In addition, a minor population of larger cells with prominent but small nucleoli is common in surgical specimens and does not, by itself, exclude the diagnosis. The cells generally have only scant cytoplasm and are arranged in broad sheets which frequently show necrosis. Focal areas demonstrating various growth patterns associated with neuroendocrine neoplasia (*i.e.* nested/organoid, peripheral palisading, trabecular, rosettes) occur in a substantial number of sufficiently preserved tumors. Extensive crush artifact and basophilic staining of blood vessel walls (Azzopardi phenomenon) are characteristic but not pathognomonic of this tumor. Cytogenetic and molecular studies fail to demonstrate a single specific abnormality, although abnormalities in p53, bcl2/bax, cyclin D1, RB loss and LOH at 3p occur in a high percentage of both SCLC and large cell neuroendocrine carcinomas (see below).

Three variants of SCLC were recognized by the 1981 WHO classification: 1) oat cell ("lymphocyte-like") carcinoma which corresponds to the classically described small cell carcinoma, 2) intermediate cell type which differs in that the cells tend to have more cytoplasm, are less regular in contour, and are often polygonal or fusiform, 3) combined small cell carcinoma in which definite small cell carcinoma is admixed with a clearly identifiable squamous cell, adenocarcinoma or large cell component. The Pathology Committee of the International Association for the Study of Lung Cancer (IASLC) proposed separating SCLC into, 1) SCLC (pure or classical type), 2) mixed small cell/large cell carcinoma, and 3) combined small cell/non-small cell (*i.e.* squamous cell or adeno-) carcinoma. Although SCLC can be distinguished from non-small cell carcinomas with a great deal of consistency by light microscopy, subclassification using previously proposed categories was subject to frequent interobserver disagreement. Furthermore, a number of studies demonstrated no significant clinical, therapeutic, or prognostic differences between subtypes. The revised WHO classification scheme includes only combined SCLCs as a distinct variant.

Diagnosis of SCLC can be made with confidence and a high degree of interobserver agreement in greater than 90% of cases. In difficult cases the differential diagnosis includes other forms of intermediate and high grade neuroendocrine (*i.e.* atypical carcinoid tumors and large cell neuroendocrine carcinomas – see below) and non-neuroendocrine (*i.e.* squamous cell, adeno-, and large cell) carcinomas. Immunostains for neuroendocrine-associated proteins (*e.g.* chromogranin, synaptophysin) are of limited value since a substantial subset of SCLCs lack immunohistochemical evidence of neuroendocrine differentiation, and a minor subset of non-small cell carcinomas are
positive. Keratin profiles can be helpful in selected cases. In the end, however, there is no single stain and no combination of stains that consistently and categorically allows separation of these entities, a differential diagnosis that still hinges primarily on a combination of cytologic and histologic findings.

**LARGE CELL NEUROENDOCRINE CARCINOMA**

Small cell carcinoma and atypical carcinoid tumors can usually be diagnosed on the basis of light microscopy alone. Immunohistochemical staining for neuropeptides (*i.e.* neuron specific enolase, chromogranin, synaptophysin, serotonin, bombesin) can be helpful in difficult cases but are not required for diagnosis. Application of these techniques to non-small cell carcinomas will reveal neuroendocrine differentiation in two additional groups of tumors -- so-called *large cell neuroendocrine carcinomas (LCNEC)* and *non-small cell carcinomas with neuroendocrine differentiation*.

Large cell neuroendocrine carcinoma refers to a subset of high grade neuroendocrine tumors characterized by, 1) a "neuroendocrine" histological growth pattern (*i.e.* organoid, palisading, trabecular, rosette-like); 2) "large" polygonal cells with lower N:C ratio than SCLC, coarse vesicular chromatin, and conspicuous nucleoli; 3) high (> 10/2 mm²) mitotic rate; 4) necrosis; 5) immunophenotypic and/or ultrastructural evidence of neuroendocrine differentiation. Historically tumors of this type were referred to by a variety of terms (*e.g.* atypical carcinoid tumors, intermediate variant of SCLC, large cell neuroendocrine tumor, and large cell carcinoma with neuroendocrine differentiation), indicating the difficulty in identifying these poorly differentiated carcinomas as a distinct nosological entity. Nonetheless, LCNECs appear to be highly aggressive bronchogenic carcinomas with a prognosis similar to that for SCLC.

Rates of interobserver agreement for the diagnosis of LCNEC are low, a feature that sets it apart from SCLC. This likely reflects the considerable histologic and cytologic overlap between LCNEC and SCLC at one end of a spectrum, and overlap with other forms of non-small cell lung carcinoma at the other. Perhaps the most difficult criteria to apply is the presence of a "neuroendocrine" growth pattern, something that frequently resides within the eye of the beholder. Cytologic features by themselves do not reliably separate LCNEC from SCLC; several studies have shown substantial overlap in cell size. Immunohistochemical studies are of limited value in that certain proteins (*e.g.* CD117, bcl-2, PAX-5, CRMP5) are expressed more frequently in high grade rather than lower grade neuroendocrine lung tumors but do not consistently separate LCNEC from SCLC.

While difficulty in separating LCNEC from SCLC may be the bad news, the good news is that large retrospective case series suggest that there may be limited value in making the distinction at all. A number of studies have shown survival rates for patients who undergo surgery for early stage LCNEC that are superimposable on those reported for rare patients with early stage SCLC treated surgically. The survival rates for both are lower than that observed in patients with other forms of early stage but high grade non-neuroendocrine lung carcinoma. Comparisons of patients with late stage disease also show a similar survival experience that is different from lower grade forms of neuroendocrine lung tumors but similar to that seen in other types of late stage non-neuroendocrine lung carcinoma.
<table>
<thead>
<tr>
<th></th>
<th>typical carcinoid</th>
<th>atypical carcinoid</th>
<th>SCLC</th>
<th>LCNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>45</td>
<td>55</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>M:F</td>
<td>1:1</td>
<td>1:1</td>
<td>2:1</td>
<td>4:1</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>30-50%</td>
<td>60-70%</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Central</td>
<td>75%</td>
<td>60%</td>
<td>&gt;90%</td>
<td>40%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>90%</td>
<td>60%</td>
<td>&lt;10%</td>
<td>45%</td>
</tr>
<tr>
<td>≥ II</td>
<td>10%</td>
<td>40%</td>
<td>≥90%</td>
<td>55%</td>
</tr>
</tbody>
</table>
REFERENCES


47. Marchevsky AM, Gal AA, Shah S, Koss MN. Morphometry confirms the presence of considerable nuclear size overlap between "small cells" and "large cells" in high-grade pulmonary neuroendocrine neoplasms.[see comment]. American Journal of Clinical Pathology 2001;116(4):466-72.


Large Cell Neuroendocrine vs Small Cell Carcinoma
When, Whether and How to Make the Distinction

March 8, 2009

Jeffrey L. Myers, M.D.
A. James French Professor and
Director, Anatomic Pathology
University of Michigan, Ann Arbor, MI

myerjeff@umich.edu
Objective

At the end of this talk attendees will understand,

• current criteria for separating large cell neuroendocrine from small cell carcinoma, and

• the clinical, biological, histologic and phenotypic overlap between the two
WHO Classification of Lung Tumors*

Neuroendocrine Lung Neoplasms

- **small cell carcinoma**
- **large cell carcinoma**
  - large cell neuroendocrine carcinoma
- **carcinoid tumor**
  - typical carcinoid tumor
  - atypical carcinoid tumor

*Travis et al (editors). WHO Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press, Lyon 2004.*
# Neuroendocrine Lung Tumors Comparison*


<table>
<thead>
<tr>
<th></th>
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<th>SCLC</th>
<th>LCNEC</th>
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<td>75%</td>
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<td>40%</td>
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<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>I</td>
<td>90%</td>
<td>60%</td>
<td>&lt;10%</td>
<td>45%</td>
</tr>
<tr>
<td>≥ II</td>
<td>10%</td>
<td>40%</td>
<td>≥90%</td>
<td>55%</td>
</tr>
</tbody>
</table>

SMALL CELL CARCINOMA

General

- cigarette smoking
- ~ 15% of incident cases
- men ≥ women (~1-2:1)
- central >> peripheral
SMALL CELL CARCINOMA

small cell ca rates in US

- ↓ in men
- ↑ in white women
- ↓ in black women (since 1990)

from Devesa Int J Cancer 2005; 117: 294
# SMALL CELL CARCINOMA

## Survival*

<table>
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<tr>
<th>cStage</th>
<th>% of pts</th>
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<th>5 years</th>
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<tbody>
<tr>
<td>I</td>
<td>7%</td>
<td>41%</td>
<td>28%</td>
</tr>
<tr>
<td>II</td>
<td>4%</td>
<td>73%</td>
<td>21%</td>
</tr>
<tr>
<td>III</td>
<td>32%</td>
<td>54%</td>
<td>11%</td>
</tr>
<tr>
<td>IV</td>
<td>57%</td>
<td>22%</td>
<td>1%</td>
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</table>

*from Shepherd et al. J Thorac Oncol 2007*
SMALL CELL CARCINOMA
WHO Definition

malignant epithelial tumor consisting of,

- *small* cells with scant cytoplasm, ill-defined cell borders

“usually less than the size of three small resting lymphocytes”
WHO “size rule”
\[ \leq 3 \times \text{lymphocyte diameter} \]
SMALL CELL CARCINOMA

WHO Definition

• small cells with scant cytoplasm, ill-defined cell borders
SMALL CELL CARCINOMA
WHO Definition

• small cells with scant cytoplasm, ill-defined cell borders

• finely granular nuclear chromatin, and absent or inconspicuous nucleoli
- finely granular chromatin
- absent/inconspicuous nucleoli
“In 29 cases, a varying percentage of cells demonstrated nucleoli that were conspicuous but small.”

Nicholson et al. AJSP 2002
SMALL CELL CARCINOMA

WHO Definition

• small cells with scant cytoplasm, ill-defined cell borders

• finely granular nuclear chromatin, and absent or inconspicuous nucleoli

• cells are round, oval and spindle-shaped; prominent nuclear molding
round, oval and spindle-shaped
prominent nuclear molding
high mitotic count (>10/2 mm²)
SMALL CELL CARCINOMA
WHO Definition

- small cells with scant cytoplasm, ill-defined cell borders
- finely granular nuclear chromatin, and absent or inconspicuous nucleoli
- cells are round, oval and spindle-shaped; prominent nuclear nuclear molding
- mitotic count is high (>10/2 mm²)
## SMALL CELL CARCINOMA
### Histologic Variants

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<td></td>
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</tr>
<tr>
<td>mixed small/large cell</td>
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<td></td>
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</tr>
<tr>
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SMALL CELL CARCINOMA

Immunohistochemical Profile

<table>
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<tr>
<th></th>
<th>small cell</th>
<th>squamous cell ca</th>
<th>adca</th>
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</thead>
<tbody>
<tr>
<td>keratin</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

dot-like, perinuclear staining pattern
# SMALL CELL CARCINOMA

**Immunohistochemical Profile**

<table>
<thead>
<tr>
<th></th>
<th>small cell ca</th>
<th>squamous cell ca</th>
<th>adca</th>
</tr>
</thead>
<tbody>
<tr>
<td>keratin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CRG</td>
<td>+/–</td>
<td>–/+</td>
<td>–/+</td>
</tr>
<tr>
<td>SYN</td>
<td>+/–</td>
<td>–/+</td>
<td>–/+</td>
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</table>
"NE" Differentiation in Non-small Cell Lung Carcinomas Using TMAs*

<table>
<thead>
<tr>
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<th>Sq cell ca</th>
<th>Adenocarcinoma</th>
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<tbody>
<tr>
<td>CRG</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>SYN</td>
<td>10 (4.3%)</td>
<td>23 (11.2%)</td>
</tr>
<tr>
<td>CD56</td>
<td>29 (12.4%)</td>
<td>11 (5.1%)</td>
</tr>
</tbody>
</table>

**“NE” Differentiation in Non-small Cell Lung Carcinomas**

<table>
<thead>
<tr>
<th></th>
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<th>Adenocarcinoma</th>
</tr>
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<tbody>
<tr>
<td>CRG*</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>SYN*</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>CRG/SYN/CD57 (leu 7)*</td>
<td>41%</td>
<td>35%</td>
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</tbody>
</table>

*Data collected from 10 peer reviewed publication, 1990 – 2005
# SMALL CELL CARCINOMA

**Immunohistochemical Profile**

<table>
<thead>
<tr>
<th></th>
<th>small cell ca</th>
<th>squamous cell ca</th>
<th>adca</th>
</tr>
</thead>
<tbody>
<tr>
<td>keratin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CRG</td>
<td>+/−</td>
<td>−/+/+</td>
<td>−/+/+</td>
</tr>
<tr>
<td>SYN</td>
<td>+/−</td>
<td>−/+/+</td>
<td>−/+/+</td>
</tr>
<tr>
<td>34βE12</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>p63</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TTF-1</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
</tbody>
</table>
combined small cell + squamous cell ca

TTF-1

p63

34βE12 (ker903)
# SMALL CELL CARCINOMA

## Immunohistochemical Profile

<table>
<thead>
<tr>
<th></th>
<th>small cell ca</th>
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</thead>
<tbody>
<tr>
<td>keratin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CRG</td>
<td>+/−</td>
<td>−/+</td>
<td>−/+</td>
</tr>
<tr>
<td>SYN</td>
<td>+/−</td>
<td>−/+</td>
<td>−/+</td>
</tr>
<tr>
<td>34βE12</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>p63</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>TTF-1</td>
<td>+</td>
<td>−</td>
<td>+</td>
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</table>
Large Cell Carcinoma

WHO 2004

• poorly differentiated NSCLC that lacks cytologic and architectural features of SCLC and glandular or squamous differentiation

• 5 variants:
  – *large cell neuroendocrine*
  – basaloid carcinoma
  – lymphoepithelioma-like carcinoma
  – clear cell carcinoma
  – large cell ca with rhabdoid phenotype
Large Cell Neuroendocrine Carcinoma

Definition

• neuroendocrine morphology
• necrosis (extensive)
Large Cell Neuroendocrine Carcinoma

Definition

• *neuroendocrine* morphology
• necrosis (extensive)
• >10 mitosis/2 mm² (10 hpf)
• cytologic features of NSCLC:
  – large size, low N:C, nucleoli, coarse chromatin
large cell neuroendocrine carcinoma

vs.

atypical carcinoid tumor
**ATYPICAL CARCINOID TUMOR**

**Definition***

- “neuroendocrine” growth pattern
- uniform cytology ± “atypia”
- 2-10 mits/2 mm²
- ± necrosis

*Travis et al (editors). WHO Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press, Lyon 2004.*
Asamura et al. J Clin Oncol 2006; 24: 70-6

<table>
<thead>
<tr>
<th></th>
<th>atypical carcinoid</th>
<th>LCNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE morphology</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>necrosis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>atypia</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>mitotic rate</td>
<td>2-10/2 mm²</td>
<td>&gt;10/2 mm²</td>
</tr>
</tbody>
</table>
**ATYPICAL CARCINOID TUMOR**

**Definition***

- "neuroendocrine" growth pattern
- uniform cytology ± "atypia"
- 2-10 mits/2 mm²

9 (8.5%) of 106 cases had < 2 mits/2 mm²

Beasley et al. Hum Pathol 2000; 31: 1255

- 2-10 mits/2 mm²

*Travis et al (editors). WHO Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press, Lyon 2004.*
ATYPICAL CARCINOID TUMOR

Definition*

- “neuroendocrine” growth pattern
- uniform cytology ± “atypia”
- 2-10 mits/2 mm²
- ± necrosis

71 (67%) of 106 cases had necrosis
Beasley et al Hum Pathol 2000; 31: 1255

Large Cell Neuroendocrine Carcinoma
Comparison with Atypical Carcinoid

10 mits/2 mm²
Large Cell Neuroendocrine Carcinoma

Definition

- neuroendocrine morphology
- necrosis (extensive)
- >10 mitosis/2 mm² (10 hpf)
- cytologic features of NSCLC:
  - large size, low N:C, nucleoli, coarse chromatin
- immunohistochemical confirmation
**Large Cell Neuroendocrine Carcinoma**

**Definition**

- *neuroendocrine* morphology
- necrosis (extensive)
- >10 mitosis/2 mm² (10 hpf)
- cytologic features of NSCLC:
  - large size, low N:C, nucleoli, coarse chromatin
- immunohistochemical confirmation

---

**LCNEC vs other NSCLC**

**LCNEC vs SCLC**
Large Cell Neuroendocrine Carcinoma

**Definition**

Is cell size a reliable criterion for separating **large cell** neuroendocrine carcinoma from **small cell** carcinoma?
SCLC vs LCNEC
Nuclear Size Overlap*

- n = 12 LCNEC and 16 SCLC
- measured tumor cell (TC) and lymphocyte (L) nuclear areas
- histograms for each peak TC/L:
  A = 2
  B = 3
  C = 4
  D = 5
  E = 6
  F no peak

SCLC vs LCNEC
Nuclear Size Overlap*

5 (31%) of 16 “SCLC” had predominant population of cells 4-6 times larger than lymphocytes

SCLC vs LCNEC

Nuclear Size Overlap*

The frequency distribution of tumor nuclear diameter/lymphocyte size ratios in SCLC (2.75 ± 0.86) overlaps with LCNEC (3.22 ± 0.86)

*Hiroshima et al. Mod Pathol 2006; 19: 1358
Is cell size a reliable criterion for separating large cell neuroendocrine carcinoma from small cell carcinoma?

NO!
Is immunohistochemistry useful for separating large cell neuroendocrine carcinoma from small cell carcinoma?
SCLC vs LCNEC
Role of Immunohistochemistry*

CRG  SYN  CD56  mASH1  NeuroD  TTF  p63  p16  PTEN

*p.0018  p.0422  p.0022  p.0369  p.0150

*Hiroshima et al. Mod Pathol 2006; 19: 1358
SCLC vs LCNEC
Role of Immunohistochemistry*

c-kit/bcl-2 expression in SCLC & LCNEC

SCLC vs LCNEC
Role of Immunohistochemistry*

*PAX-5 expression in SCLC & LCNEC

Neither cell size nor immunohistochemistry are useful for separating large cell neuroendocrine carcinoma from small cell carcinoma?
## Neuroendocrine Lung Tumors

### Diagnostic Reproducibility

<table>
<thead>
<tr>
<th></th>
<th>Unanimous (5 of 5)</th>
<th>Majority (4 of 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical carcinoid</td>
<td>58%</td>
<td>92%</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>SCLC</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>LCNEC</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Travis et al. Hum Pathol 1998; 29: 272*
Does separating LCNEC from SCLC have value?
If so, when?
LCNEC versus SCLC?
Survival

Asamura, 2006

P = .9147

J Clin Oncol 24: 70-6
Large cell neuroendocrine histology has a significant adverse prognostic impact on pathologic stage Ia non-small cell carcinoma.

Iyoda 2006

Impact of LCNEC Histology on Survival in Early Stage Disease?
LCNEC versus SCLC? Survival in Stage I Disease

Takei 2002

P = .1851

Asamura 2006
Fig 5. Kaplan-Meier curves for overall survival stratified according to chemotherapeutic protocols in the adjuvant setting and tumor stage

LCNEC is more likely to respond to chemotherapeutic strategies targeting SCLC

“SCLC-based” = platinum-etoposide

SCLC vs LCNEC

Summary

of cytological “criteria” for LCNEC, only the presence of cytoplasm is useful
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no consistent difference at level of protein expression

low rates of interobserver agreement among experts

no difference in therapeutic response or natural history
Large Cell Neuroendocrine Carcinoma
Practical Approach?

any way to make this SCLC?
• finely dispersed chromatin?
• inconspicuous nucleoli?
• scant cytoplasm?
• is cell size the only issue?
• clinical context?
  – central mass in smoker with mediastinal adenopathy?
Large Cell Neuroendocrine Carcinoma
Practical Approach?

any way to make this SCLC?

YES!
Large Cell Neuroendocrine Carcinoma
Practical Approach?

any way to make this SCLC?

• LCNEC already diagnosed
• IHC stains and it really, really looks neuroendocrine but ≠ atypical carcinoid
• been called SCLC but it isn’t

compelling reason to acknowledge neuroendocrine differentiation?

NO
Large Cell Neuroendocrine Carcinoma
Practical Approach?

any way to make this SCLC?

NO

compelling reason to acknowledge neuroendocrine differentiation?

YES!
Large Cell Neuroendocrine Carcinoma
Practical Approach?

LCC, sq cell ca, adca

any way to make this SCLC?

NO

compelling reason to acknowledge neuroendocrine differentiation?

NO

NO
SCLC vs LCNEC

Key Points

• SCLC is defined on the basis of cytologic criteria
• LCNEC is defined by a combination of histologic and cytologic criteria + “proof” of NE differentiation (immunohistochemistry)
• LCNEC is separated from atypical carcinoid based on consistent presence of necrosis and higher mitotic rate
• SCLC and LCNEC overlap in clinical, biological, histopathologic, immunophenotypic and genetic characteristics