

**LARGE CELL  
NEUROENDOCRINE  
CARCINOMA**

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**PULMONARY NE TUMORS  
CLASSIFICATION**

- **LOW GRADE**
  - **TYPICAL CARCINOID**
- **INTERMEDIATE GRADE**
  - **ATYPICAL CARCINOID**

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- **HIGH GRADE**
  - **LARGE CELL NEUROENDOCRINE CARCINOMA**
  - **SMALL CELL CARCINOMA**

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**SPECTRUM OF NE LUNG LESIONS**

- **NE Cell hyperplasia & tumorlets (<5mm)**
- **Tumors with NE morphology**
  - **Typical carcinoid**
  - **Atypical carcinoid**
  - **Large cell NE carcinoma**
  - **Small cell carcinoma**
- **Non-small cell carcinoma with NE differentiation**
- **Other tumors with NE properties**

2004 WHO CLASSIFICATION OF LUNG AND PLEURAL TUMORS

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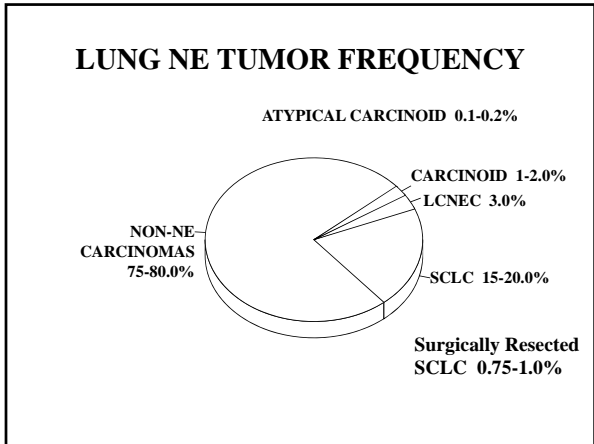
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### TYPICAL AND ATYPICAL CARCINOID DIAGNOSTIC CRITERIA

- **1.3.7.1 TYPICAL CARCINOID**
  - Less than 2 mitoses per 10 HPF (2 mm<sup>2</sup>) and No foci of necrosis
- **1.3.7.2 ATYPICAL CARCINOID**
  - 2-10 mitoses per 10 HPF (2 mm<sup>2</sup>)
  - OR
  - Foci of necrosis
- Pleomorphism, cellularity, and vascular invasion are more subjective

Travis WD, et al; Am J Surg Pathol 22:934-44, 1998

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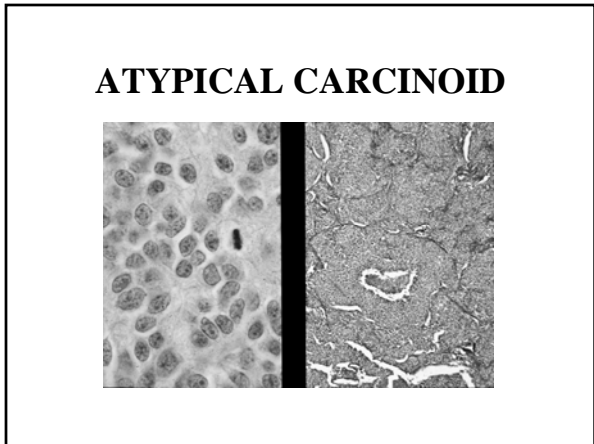
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**2004 WHO CLASSIFICATION  
SMALL CELL CARCINOMA**

**Variant  
Combined small cell carcinoma**

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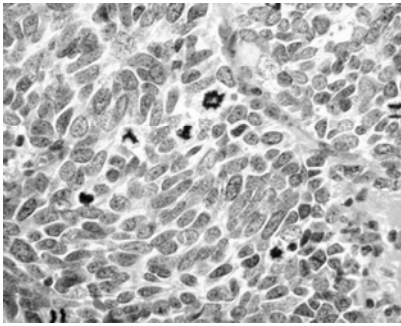
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**SCLC**



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**2004 WHO CLASSIFICATION  
LARGE CELL CARCINOMA**

**Large cell neuroendocrine carcinoma  
Combined large cell  
neuroendocrine carcinoma  
Basaloid carcinoma  
Lymphoepithelioma-like carcinoma  
Clear cell carcinoma  
Rhabdoid phenotype**

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**LARGE CELL NE CARCINOMA  
DIAGNOSTIC CRITERIA**

- **NE Morphology:** Organoid nesting, trabecular, palisading, rosette-like patterns
- **Increased Mitoses** (11 or more per 10 HPF or 2mm<sup>2</sup>; Avg. 60)
- **FEATURES OF A NON-SMALL CELL CARCINOMA**
  - Large cell size (> diameter 3 lymphocytes)
  - Low N/C ratio (abundant cytoplasm)
  - Round to oval or polygonal shape
  - Nucleoli frequent and prominent (not every case)
  - Chromatin usually coarse or vesicular, may be finely granular
- **NE Differentiation** by EM or Immunohistochemistry

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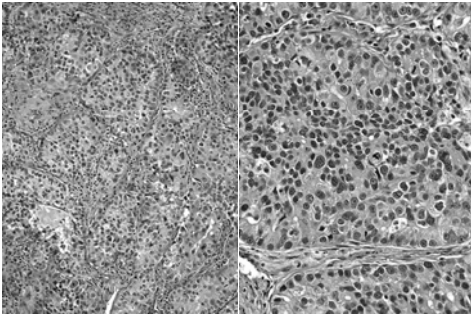
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**LCNEC**



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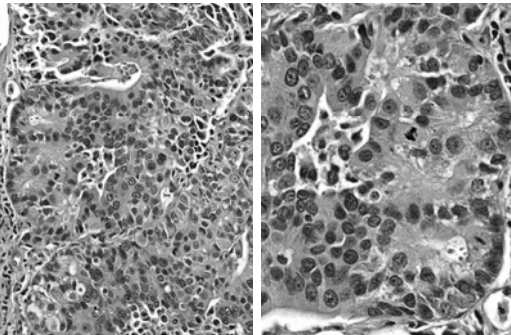
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**LCNEC**



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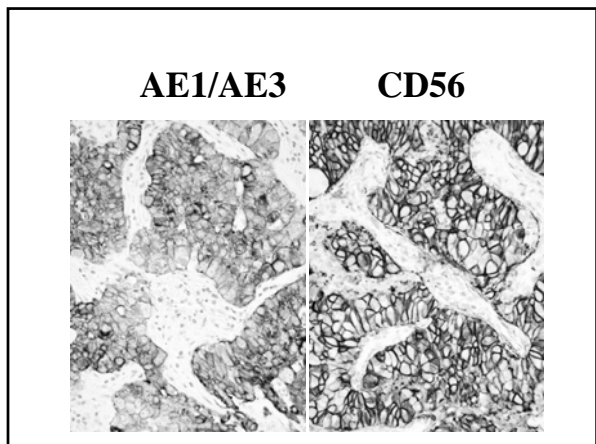
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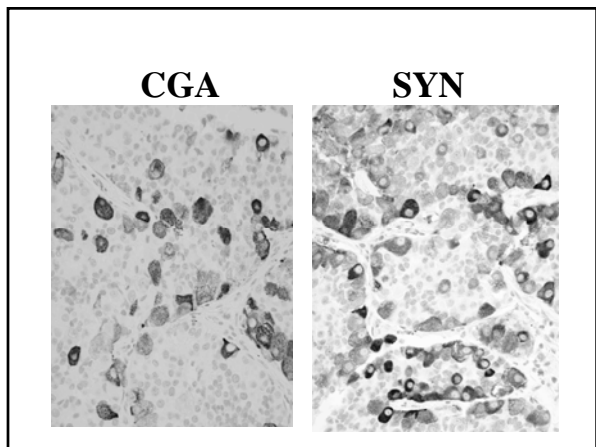
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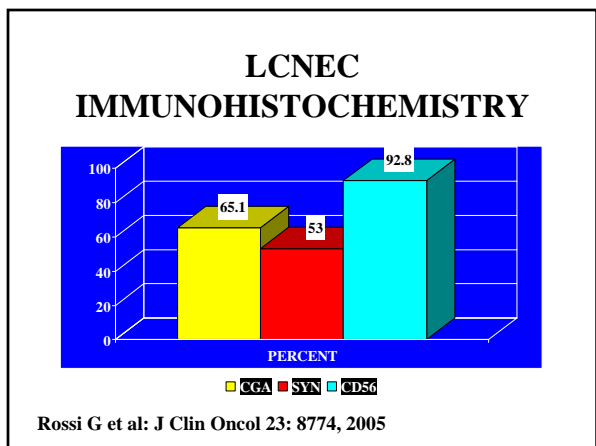
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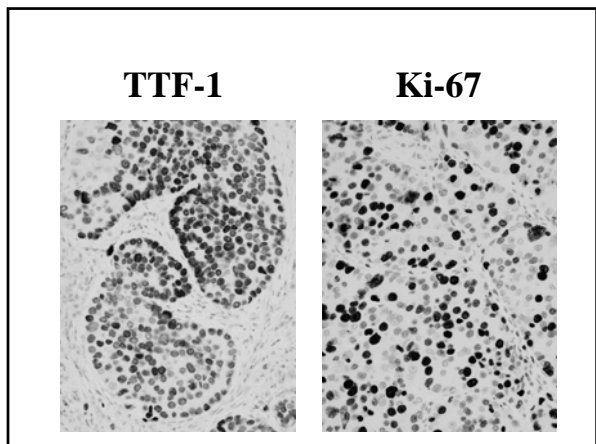
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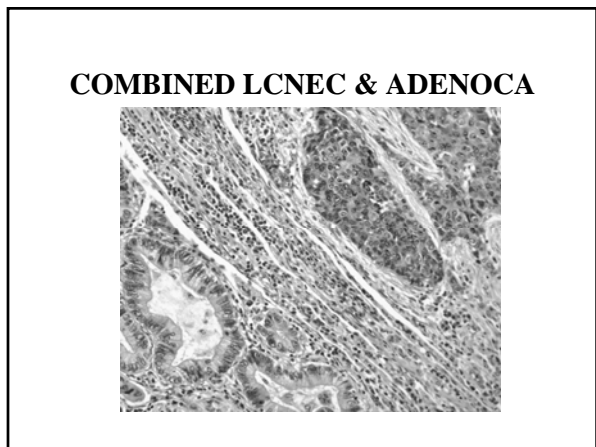
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**MSKCC: 86 LCNEC HISTOLOGY**

Type	Number (%)
Pure LCNEC	68 (79%)
Combined LCNEC/Adenoca	15 (19%)
Combined LCNEC/Squamous	2 (2%)
Combined LCNEC/Giant Cell	1 (1%)
<b>Total</b>	<b>86</b>

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**MSKCC: 86 LCNEC HISTOLOGY**

Type	Number (%)
<b>Pur Surgically Resected Specimens:</b>	
<b>Co</b>	<b>80% – Pure LCNEC</b>
<b>Co</b>	<b>20% – Combined LCNEC</b>
<b>Combined LCNEC/Giant Cell</b>	<b>1 (1%)</b>
<b>Total</b>	<b>86</b>

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**SCLC VS LCNEC: DDX**

FEATURE	SCLC	LCNEC/LCC
Cell Size	Smaller (< 3 small resting lymphocytes)	Larger
N/C Ratio	Higher	Lower
Nuclear Chromatin	Finely granular, uniform	Coarsely granular, vesicular, Less uniform
Nucleoli	Absent or faint	Often (not always) present, may be prominent or faint
Nuclear molding	Characteristic	Uncharacteristic
Fusiform shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Common	Uncommon
Basophilic staining of stroma and vessels	Occasional	Rare

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**SMALL  
CELL  
CARCINOMA**



**LARGE  
CELL  
NEUROENDOCRINE  
CARCINOMA**

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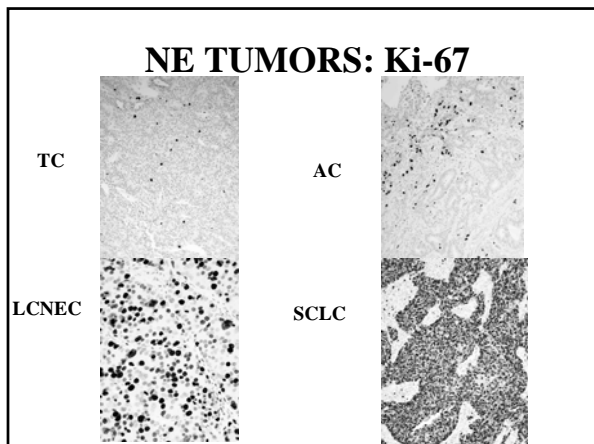
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**SPECTRUM OF NE DIFFERENTIATION  
LARGE CELL CARCINOMA**

DIAGNOSIS	NE MORPHOLOGY	NE IHC OR EM
LCNEC	YES	YES
LC WITH NE-MORPHOLOGY	YES	NO
LCC-NE DIFFERENTIATION	NO	YES
LCC (NON-NE)	NO	NO

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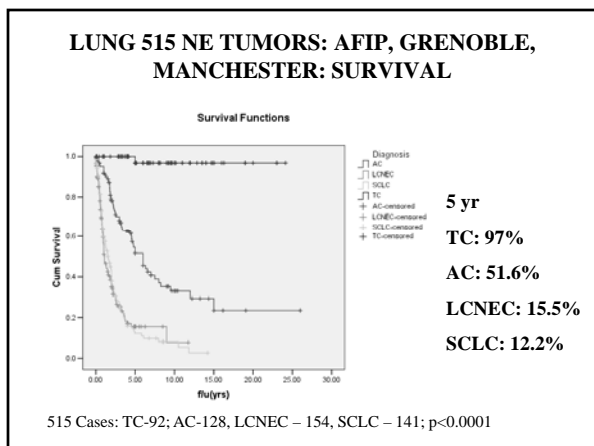
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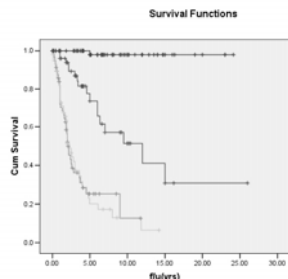
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### SURVIVAL STAGE I NE TUMORS



5 yr  
 TC: 98%  
 AC: 73.7%  
 LCNEC: 25.3%  
 SCLC: 20.1%

Travis W et al, unpublished AFIP data

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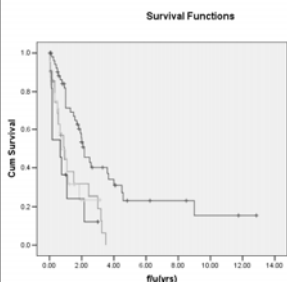
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### LARGE CELL NEUROENDOCRINE CARCINOMA



3-year Surv; N  
 Stg 1: 40.1%;54  
 Stg 2: 19.0%; 21  
 Stg 3: 23.6%;24  
 Stg 4:12.1%;11  
 P<0.001; Tot:110

Travis W et al, unpublished AFIP data

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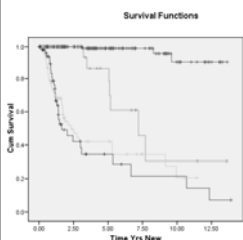
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### MSKCC 367 NE TUMORS: OVERALL SURVIVAL p<0.001



Survival: 5 & 10 yr  
 TC (n=190): 99 & 91%  
 AC (n=29): 87 & 31%  
 LCNEC (n=86):42 & 21%  
 SCLC (n=62): 34 & 22%

Roh MS et al, unpublished data

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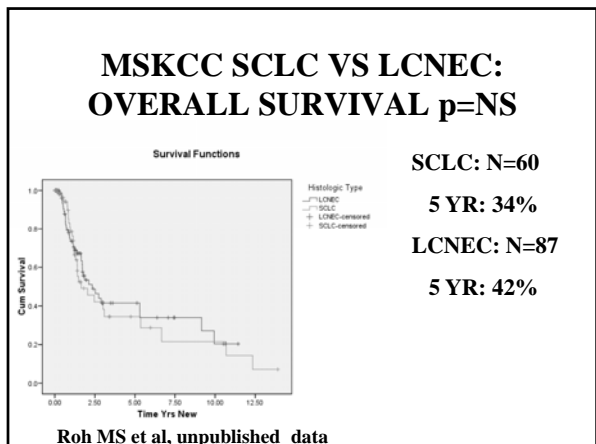
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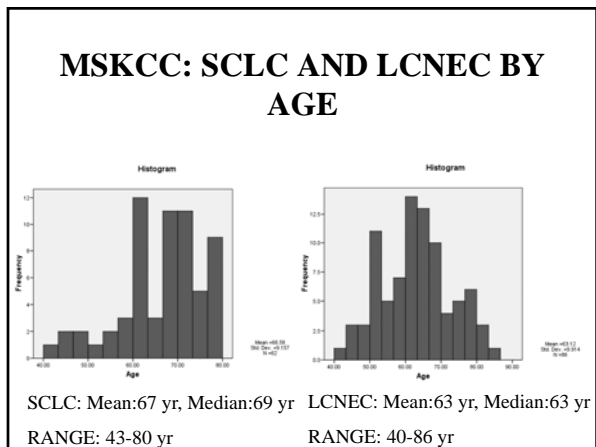
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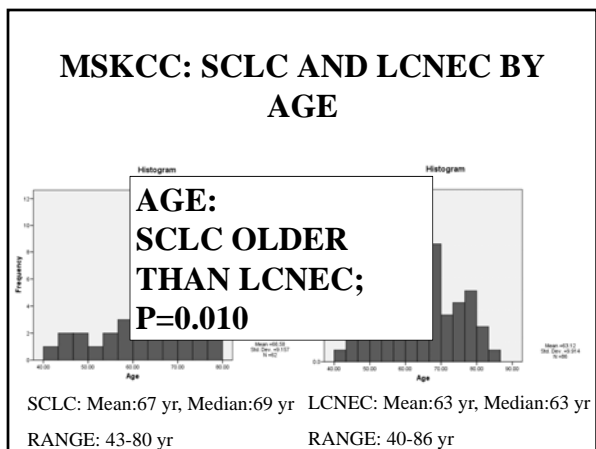
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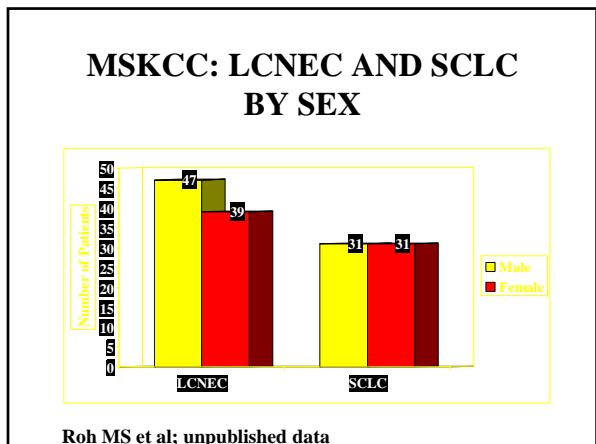
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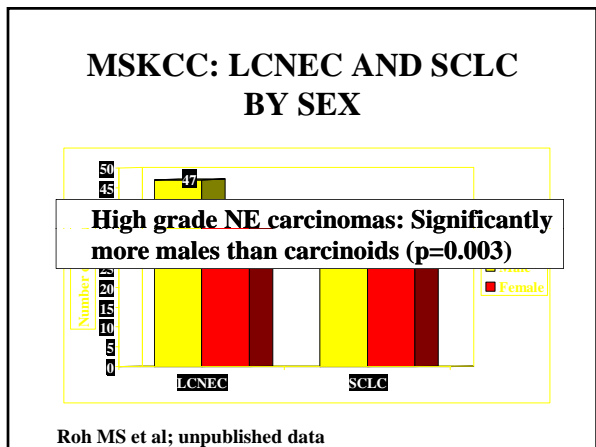
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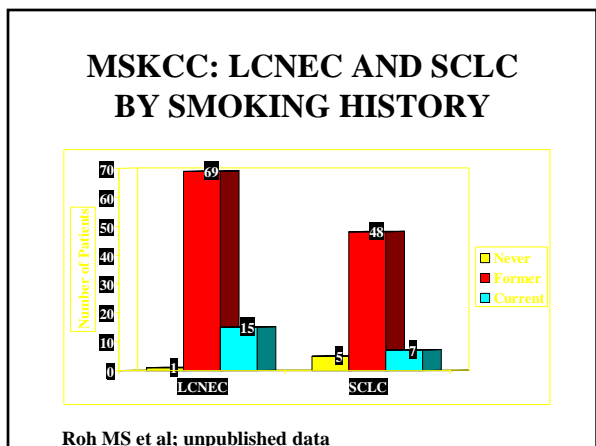
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**LCNEC & LCNEM  
(Brompton Hospital, London)**

- **21 pts (15 LCNEC, 6 LCNEM); 20 resected; 18 had systematic nodal dissection (SND)**
- **5 yr survival: 18 with SND: Overall: 47%**
  - All pts (+3 without SND): LCNEC – 52%; LCNEM – 63% (no significant difference)
- **Why better survival than others?**
  - Better staging: SND may be important in LCNEC
  - Three pts without SND: dead within 18 mo
  - 50% of pts – stage I; 25% asymptomatic

Zacharias et al: Ann Thorac Surg 75:348, 2003

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**LCNEC vs LCNEM (Chiba Japan)**

- **50 (2.4% resected lung cancers); 9 LCNEM**
- **42M (84%):8F; Age: 64 yrs (38-82)**
- **Mitotic rate LCNEC > CLCC (p=0.0108); LCNEM > LCNEC (p=0.0259)**
- **5 yr survival: LCNEC 35.3% LCNEM: 27.3%; CLCC:48.4%**
- **Disease free survival: Significantly lower for LCNEC and LCNEM than CLCC (p=0.031 and 0.0351)**

Iyoda A et al: Cancer 91:1992, 2000

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**LCNEC vs LCNEM (Chiba Japan)**

- **Clinical characteristics, behavior and pathology of LCNEC were similar to those of LCNEM (Age, gender, smoking, tumor size, LCH)**
- **Differences**
  - LCNEM: Higher proportion of cases with elevated, mitotic rates, rate of LN mets.
- **Suggest that LCNEM is more clinically aggressive than LCNEC; distinction may be important**

Iyoda A et al: Cancer 91:1992, 2000

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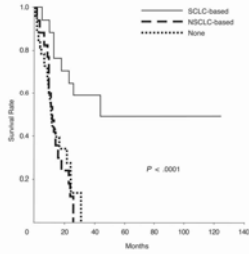
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### LCNEC: CHEMOTHERAPY



**ADJUVANT SETTING**  
**Platinum & Etoposide (44mo) vs**  
**Gemcitabine & Taxanes (12 mo) vs**  
**No chemotherapy (12 mo)**  
**P<0.0001**

Rossi G et al: J Clin Oncol 23: 8774, 2005

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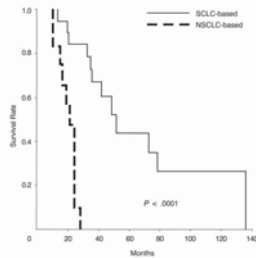
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### LCNEC: CHEMOTHERAPY



**METASTATIC SETTING**  
**Platinum & Etoposide (51mo) vs**  
**Gemcitabine & Taxanes (21 mo)**  
**P<0.0001**

Rossi G et al: J Clin Oncol 23: 8774, 2005

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### NON-SMALL CELL CARCINOMA WITH NE DIFFERENTIATION

- A NSCLC which does not show neuroendocrine morphology by light microscopy
- NE differentiation is demonstrated by immunohistochemical and/or electron microscopy
- NE differentiation can be shown by immunohistochemistry in 10-20 percent of NSCLC, mostly in adenocarcinomas

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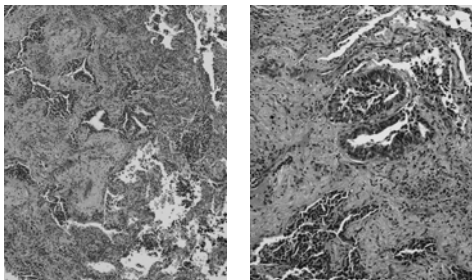
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### ADENOCARCINOMA WITH NE DIFFERENTIATION



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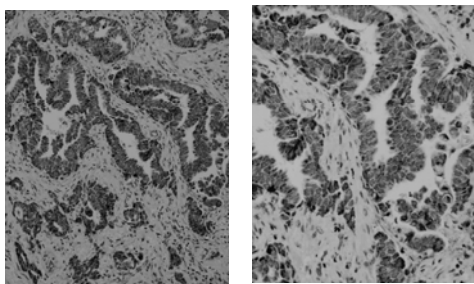
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### ADENOCARCINOMA WITH NE DIFFERENTIATION (SYNAPTOPHYSIN)



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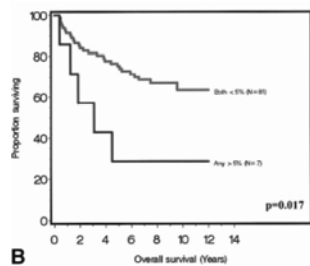
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### ADENOCARCINOMA WITH NE DIFFERENTIATION: REDUCED OVERALL SURVIVAL WITH >5% CGA &/or SYN



Pelosi G, et al: Cancer 97:2487-2497, 2003

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**NONSMALL CELL CARCINOMA WITH NE DIFFERENTIATION (NSCLC-NED)**

- **SURVIVAL**
  - Worse (Berendsen 89, Pujol 93, Hiroshima 2002, Iyoda 2002, Pelosi G 2003)
  - Better (Carles 93, Schleusener 96, Harada 2002)
  - Not significant (Skov 91, Graziano 93, Linnoila 94, Graziano 94), Gajra A 2002)
- **RESPONSE TO CHEMOTHERAPY**
  - Increased (Graziano 89, Linnoila 89)
  - Not increased (Neal 86, Carles 93, Schleusener 96, Gajra A 2002)

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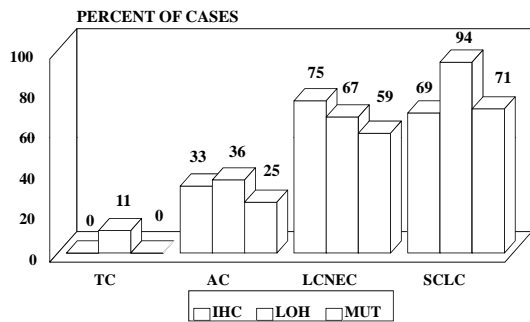
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**p53 IHC, LOH AND MUTATIONS IN LUNG TUMORS**



Onuki N, et al: Cancer 85:600, 1999

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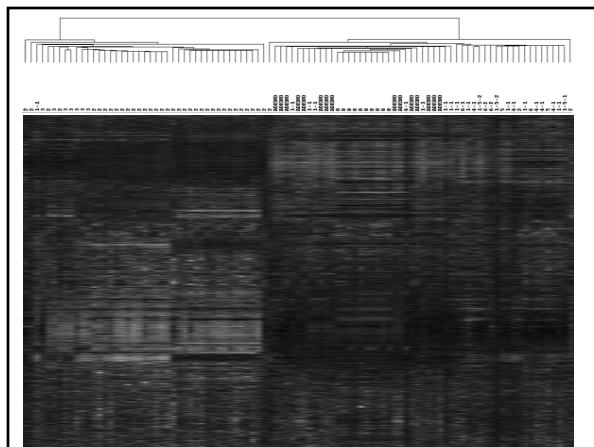
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## GOALS OF REGISTRY SCLC - LCNEC

- To Define Clinical, Pathologic and Molecular Characteristics of LCNEC and SCLC
- Better separate LCNEC and SCLC
- Due to Rarity of LCNEC and Surgically Resected SCLC – need to develop network of collaborations
- Learn how best to treat LCNEC
- Communication network – learn what others are doing
- Start Retrospective – become Propsective

Lim E, et al; JTO 3:1194, 2008

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