LUNG CANCER PATHOLOGY: UPDATE ON NEUROENDOCRINE LUNG TUMORS

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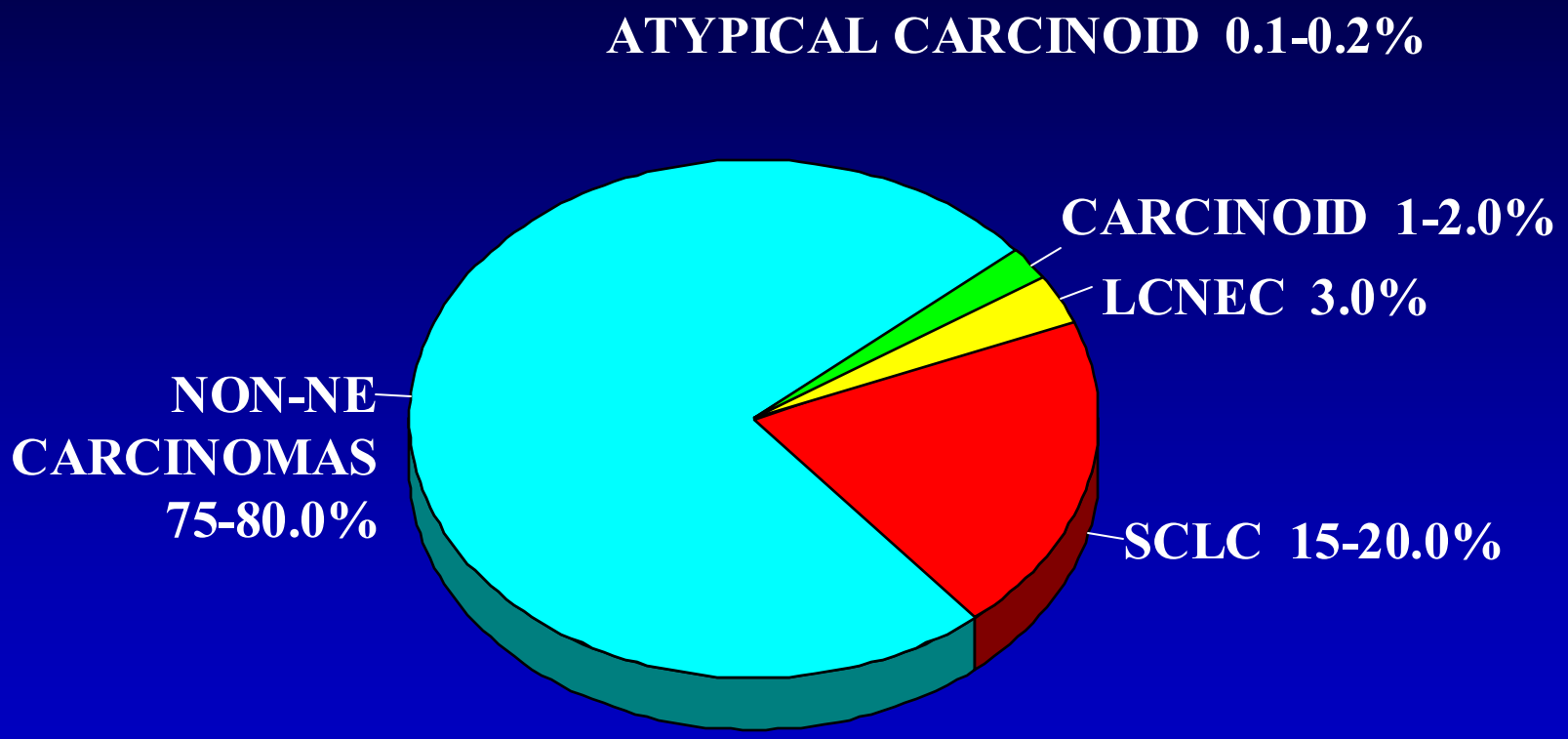
PULMONARY NE TUMORS
CLASSIFICATION

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

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

LUNG NE TUMOR FREQUENCY

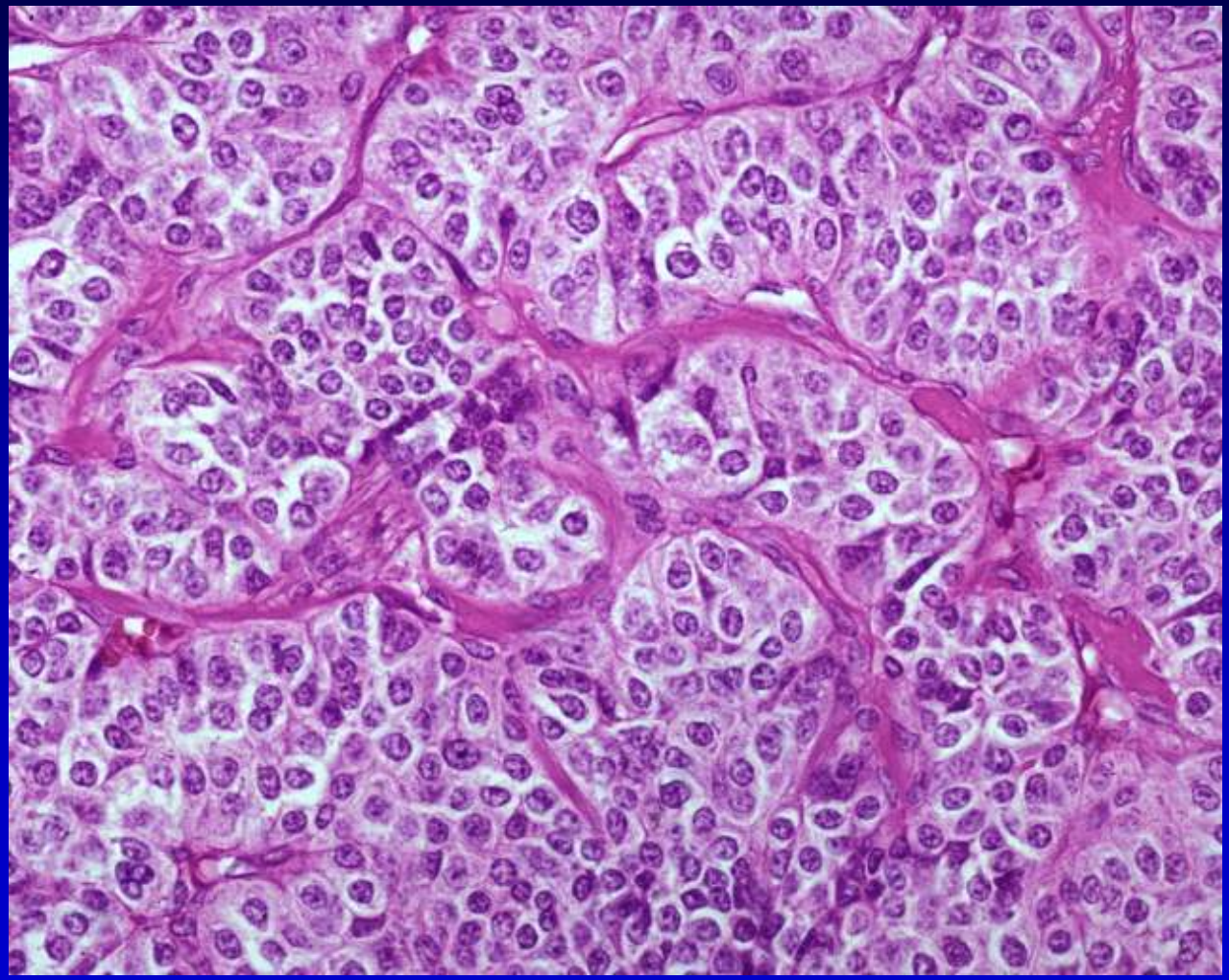


NE TUMORS: CLINICAL FEATURES: JAPANESE REGISTRY

	TC	AC	LCNEC	SCLC
AGE: Mean (Range) yr	52 (17-83)	63 (38-73)	67 (40-84)	65 (17-88)
SEX: % M	58.2	44.4	89.4	79.7
PARANEO-PLASTIC %	1.8	0	0	2.7
% SMOKERS	54.6	55.6	98.6	93.8

Asamura H et al: J Clin Oncol 24: 70, 2006

CARCINOID: ORGANOID NESTING

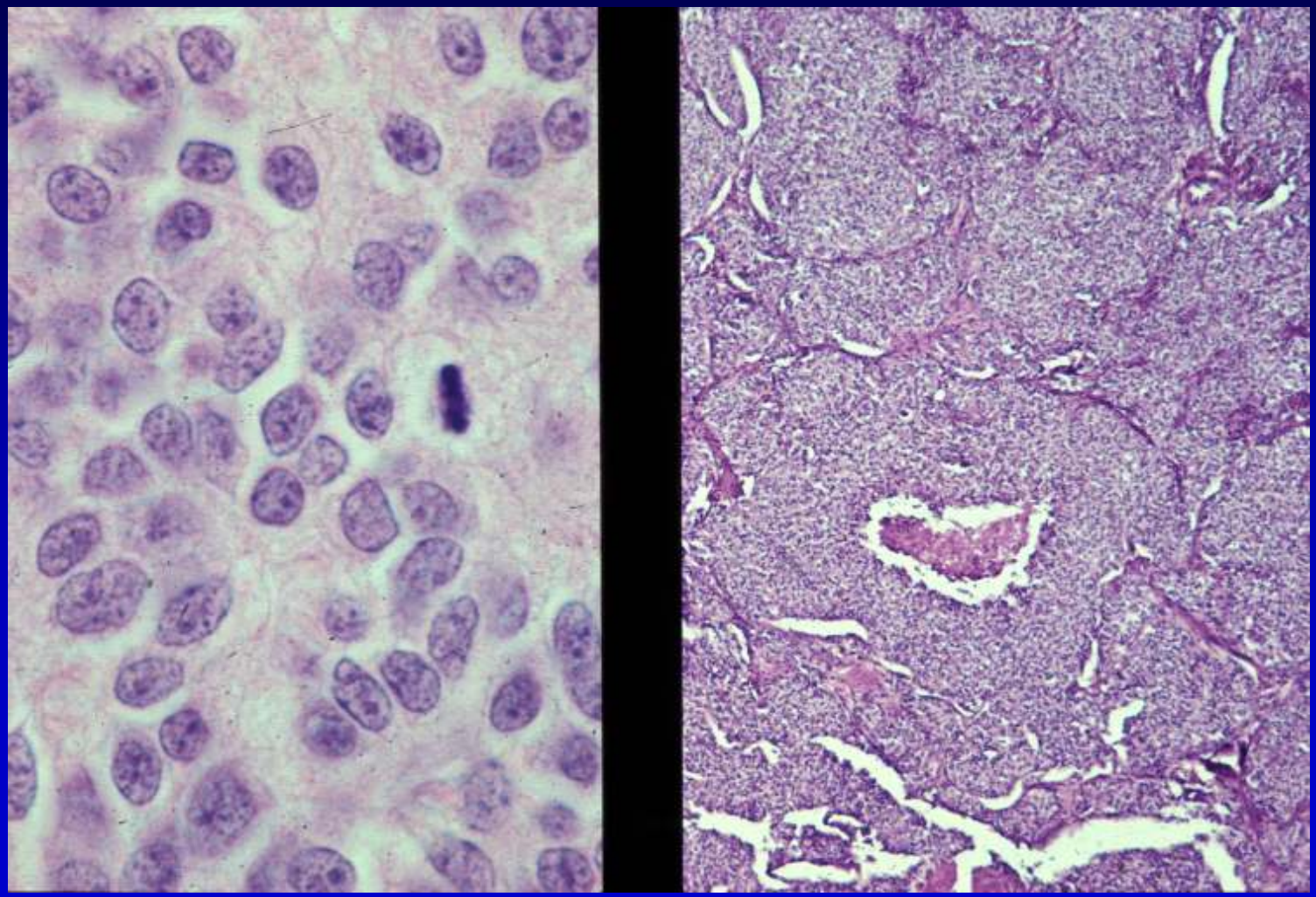


TYPICAL AND ATYPICAL CARCINOID DIAGNOSTIC CRITERIA

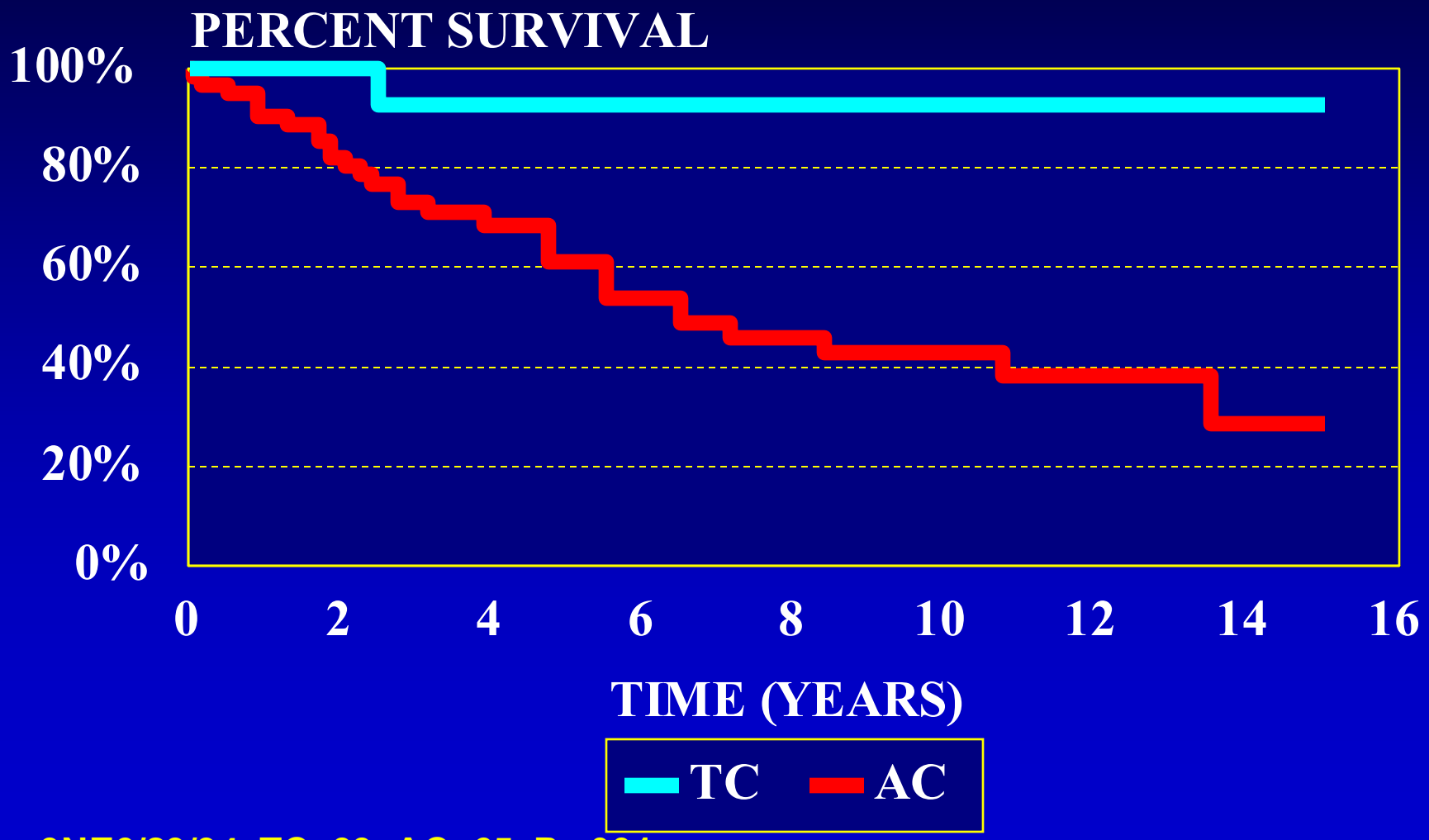
- 1.3.7.1 TYPICAL CARCINOID
  - Less than 2 mitoses per 10 HPF (2 mm^2) and
    No foci of necrosis
- 1.3.7.2 ATYPICAL CARCINOID
  - 2-10 mitoses per 10 HPF (2 mm^2)
    OR
  - Foci of necrosis
- Pleomorphism, cellularity, and vascular invasion are more subjective

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

ATYPICAL CARCINOID

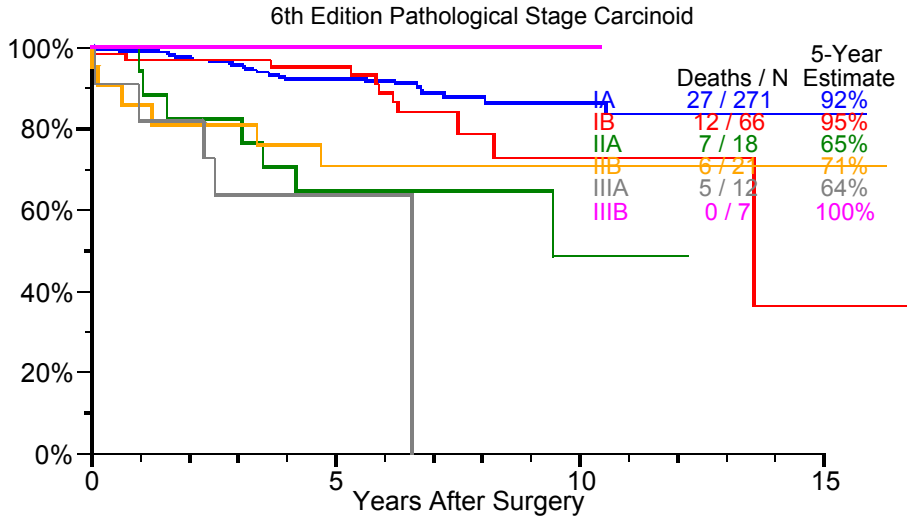


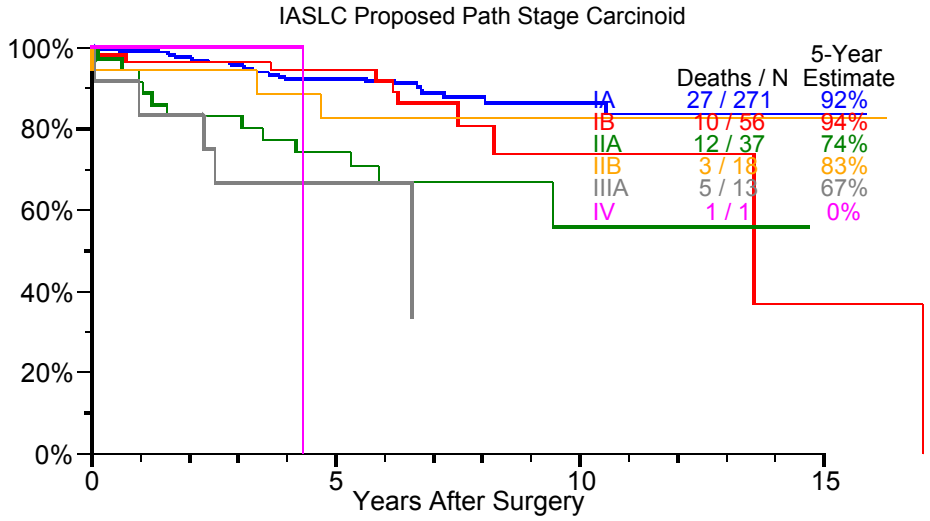
TYPICAL VS ATYPICAL CARCINOID SURVIVAL



3NE6/23/94 TC=33; AC=65 P<.001

IASLC CARCINOID CASES BY DETAILED PATHOLOGIC STAGE





IASLC DATA: Problem in both IASLC proposed and UICC6:

Survival for IIB is better than IIA: Why? Multiple same lobe nodules (n=7) 100% survival; Within 2 cm of carina (n=2); >3cm (n=2); visceral pleural invasion (n=1); unknown T factors (n=7)

TNM FOR LUNG CARCINOIDS

- TNM is a useful predictor of survival
- N and M factors are strong predictors of survival
- T factor details are limited in both IASLC and SEER databases
- T factors that need more detailed evaluation:
  - Size
  - Multiple nodules (ipsilateral same/separate lobe vs contralateral)
  - < 2 cm distal to carina
  - Atelectasis
  - Pleural invasion
- Cannot assess typical vs atypical carcinoid in these datasets
- Need for International Registry for Pulmonary NE Tumors
  - Brompton Hospital; London, December 13-14, 2007

Travis WD, et al: JTO 3:1213, 2008

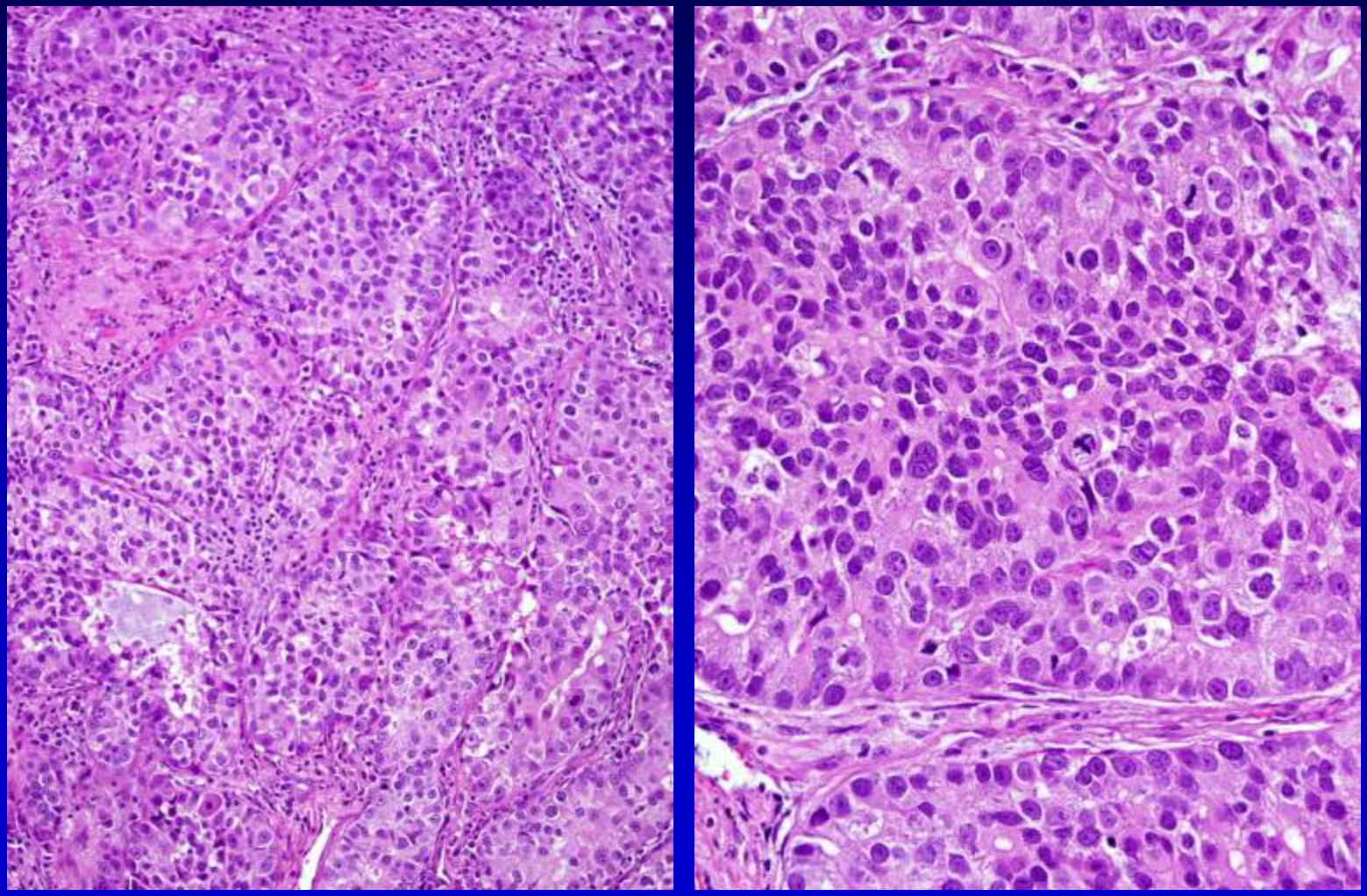
2004 WHO CLASSIFICATION LARGE CELL CARCINOMA

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

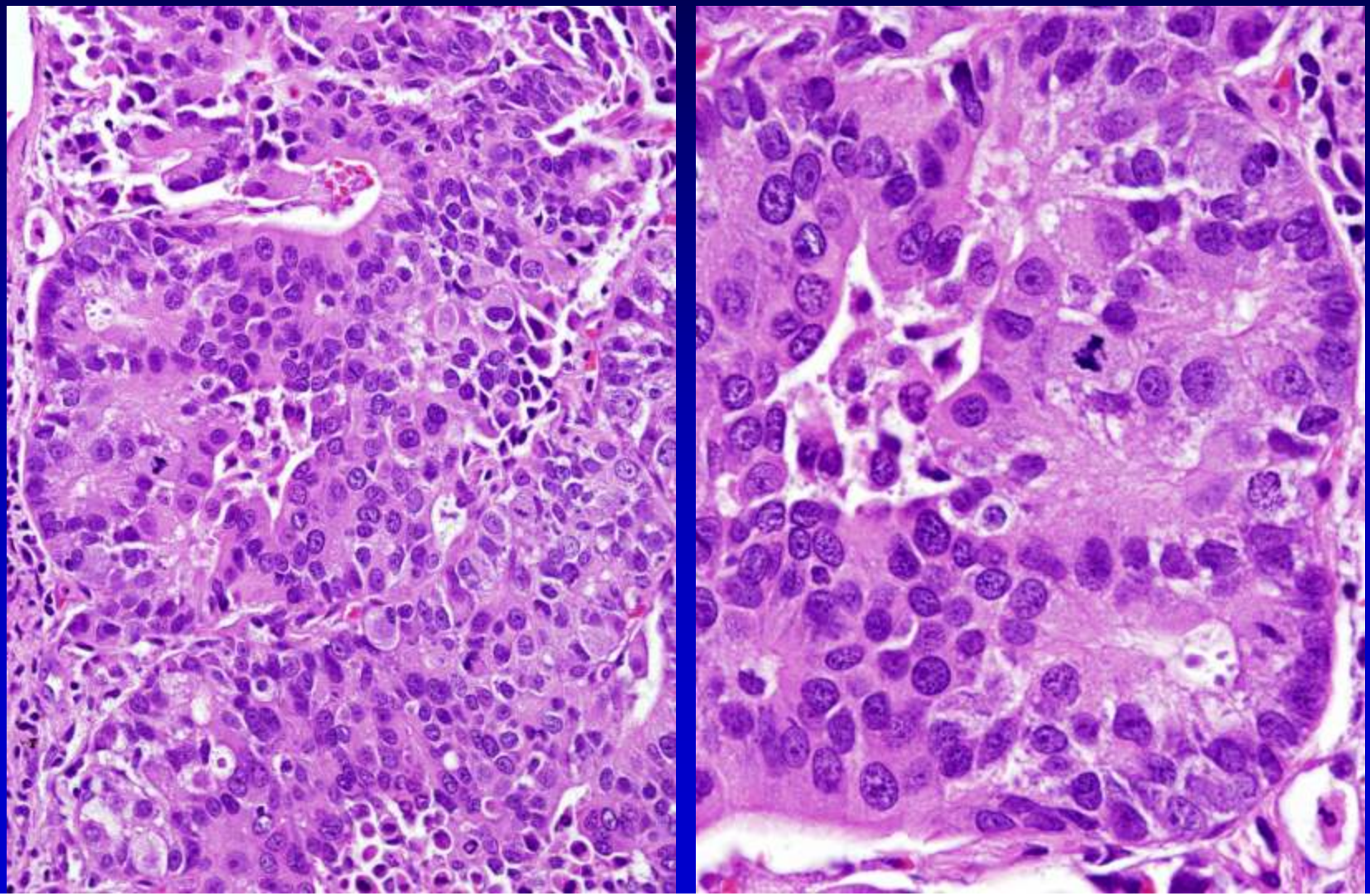
LARGE CELL NE CARCINOMA
DIAGNOSTIC CRITERIA

- NE Morphology: Organoid nesting, trabecular, palisading, rosette-like patterns
- Increased Mitoses (11 or more per 10 HPF or 2mm^2; 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

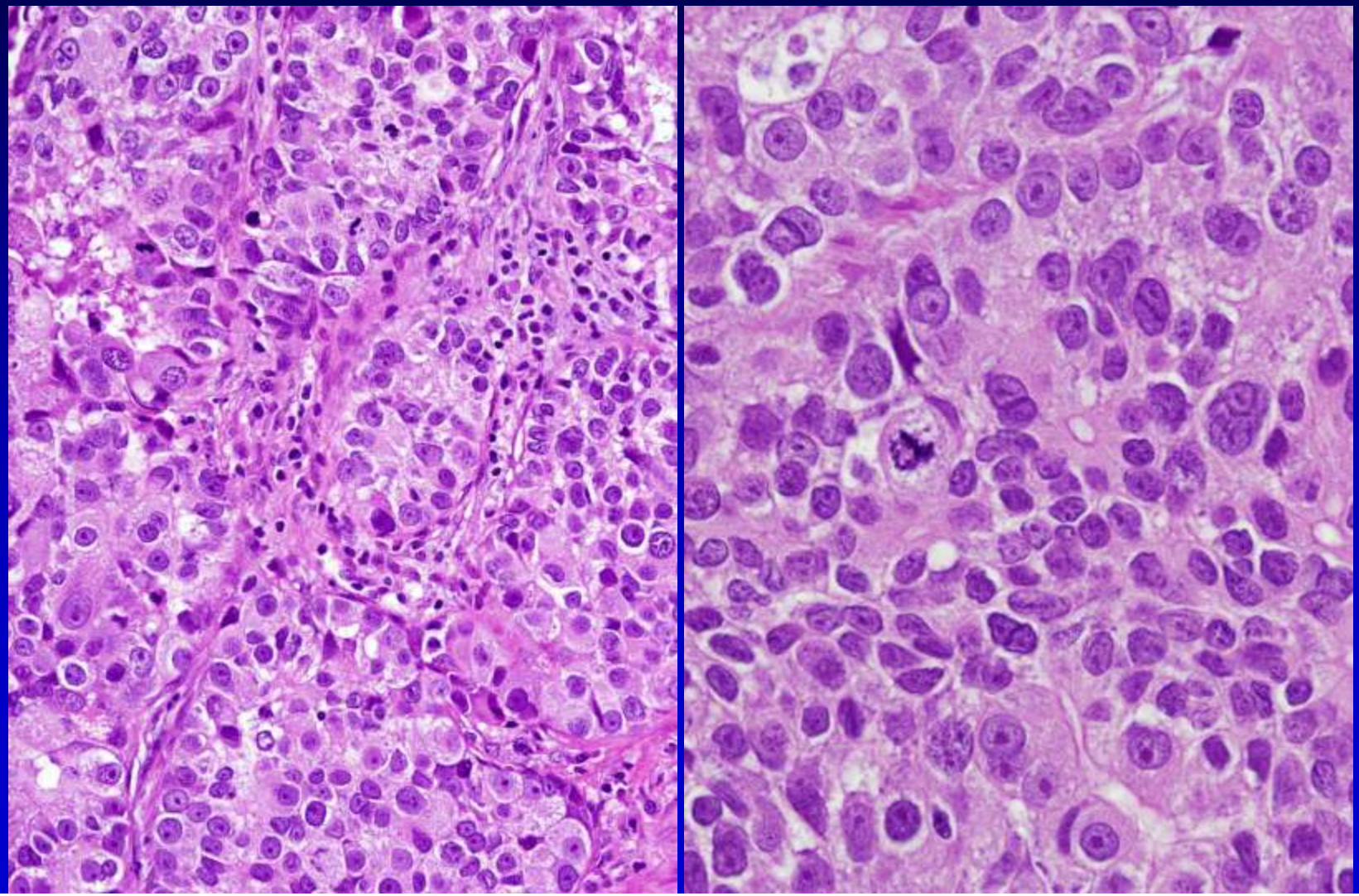
LCNEC



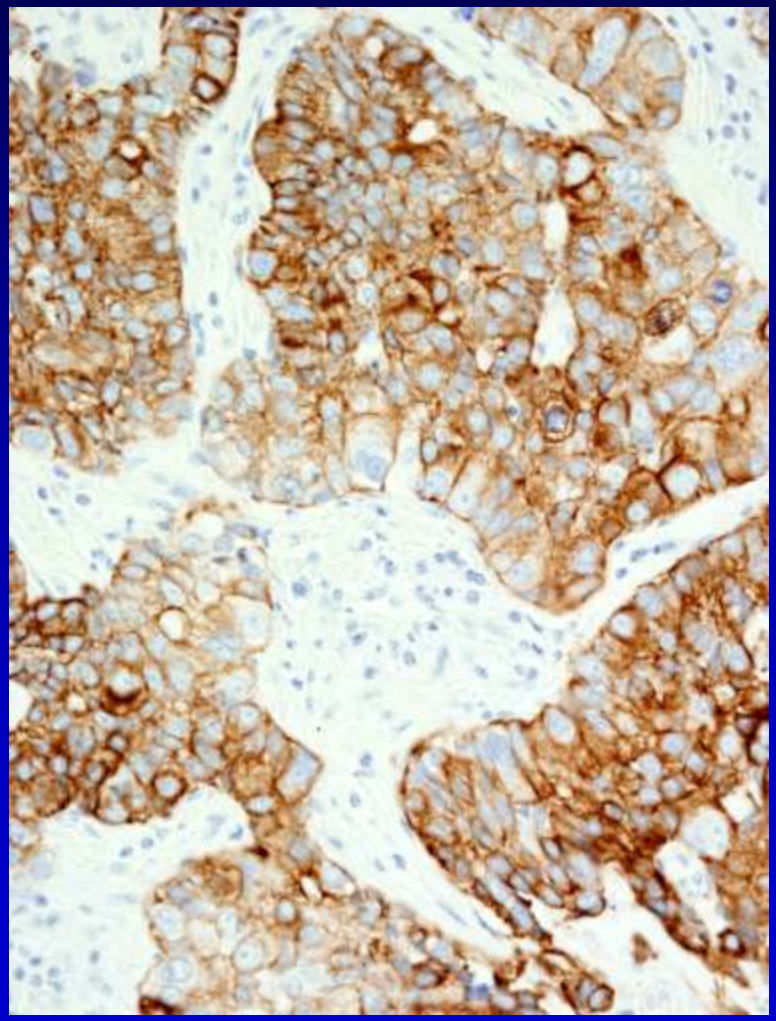
LCNEC



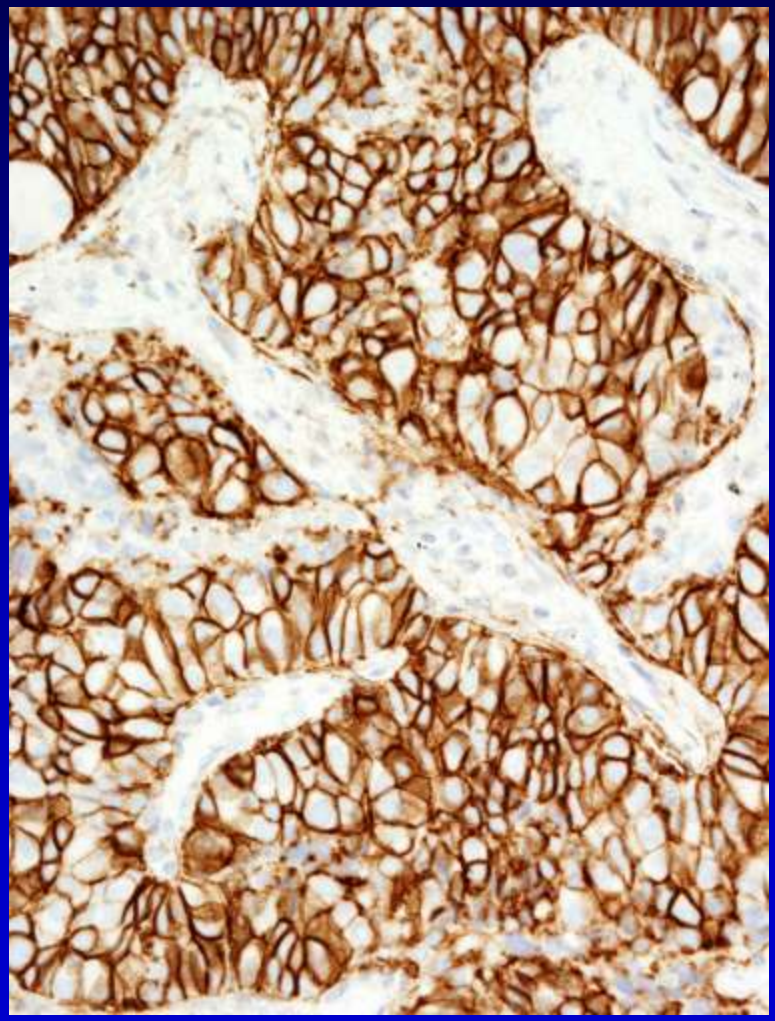
LCNEC



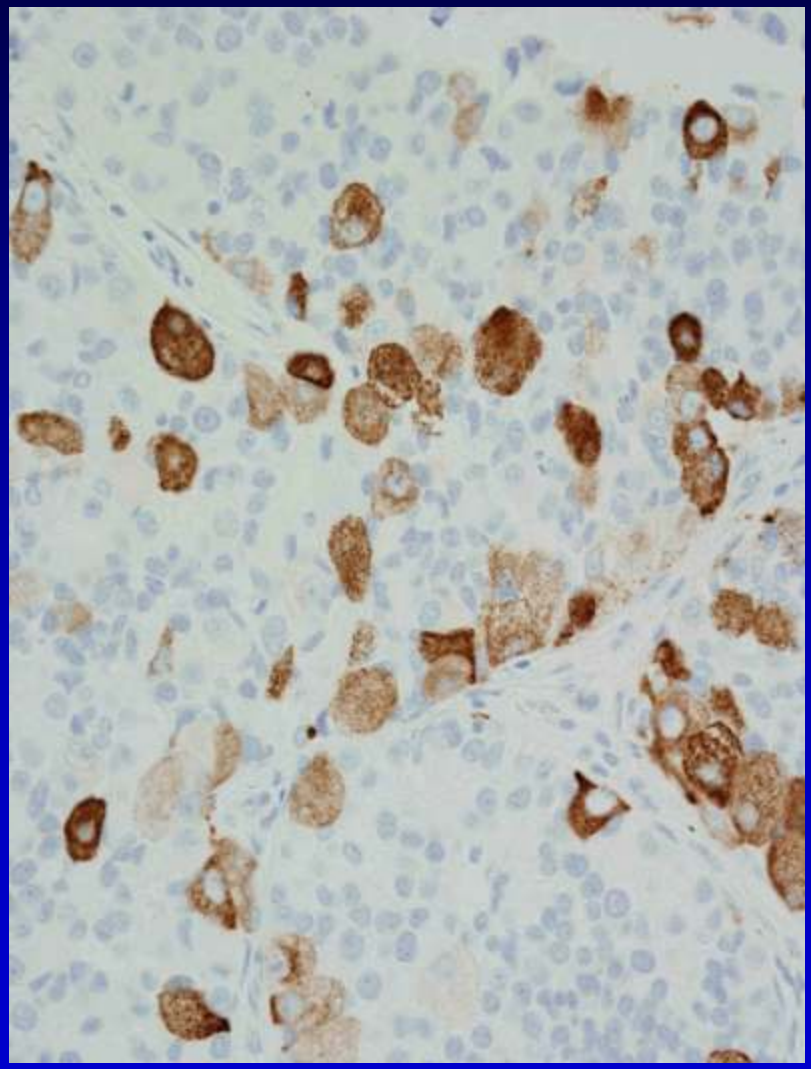
AE1/AE3



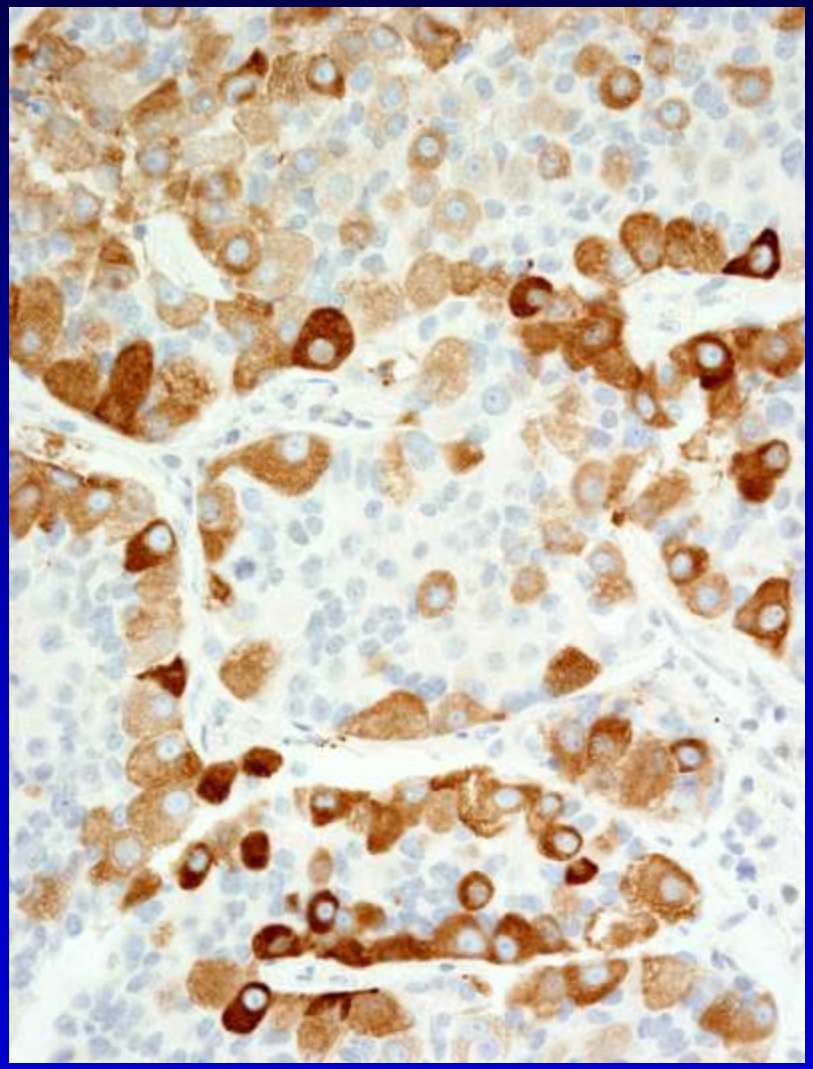
CD56



CGA



SYN



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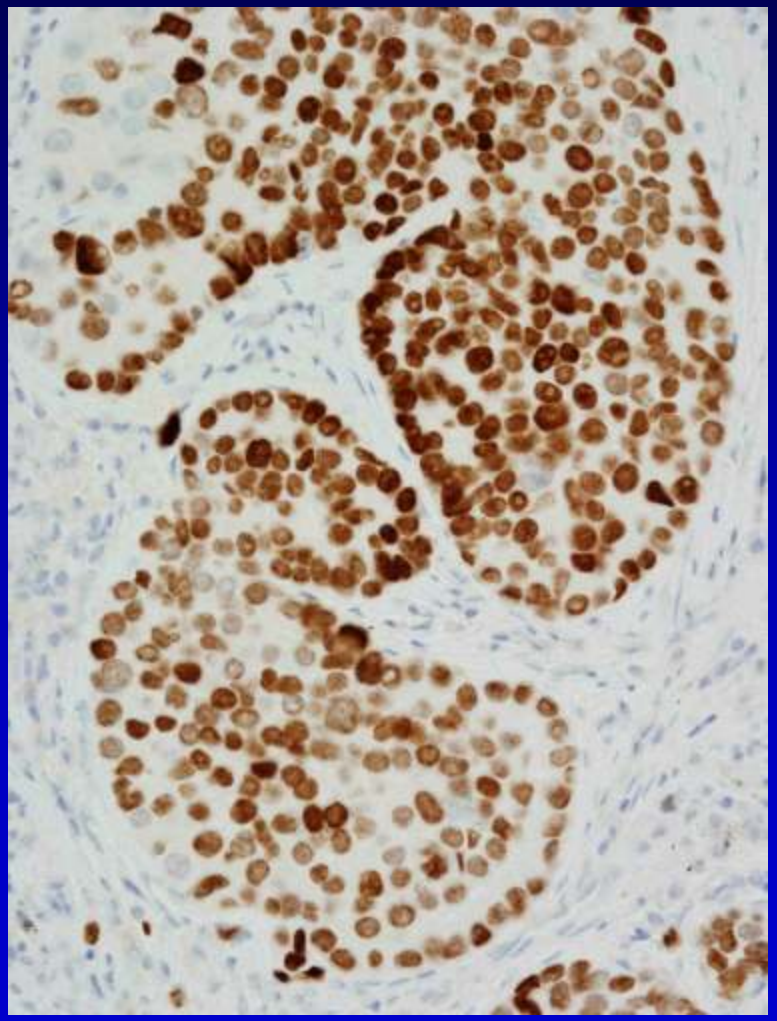
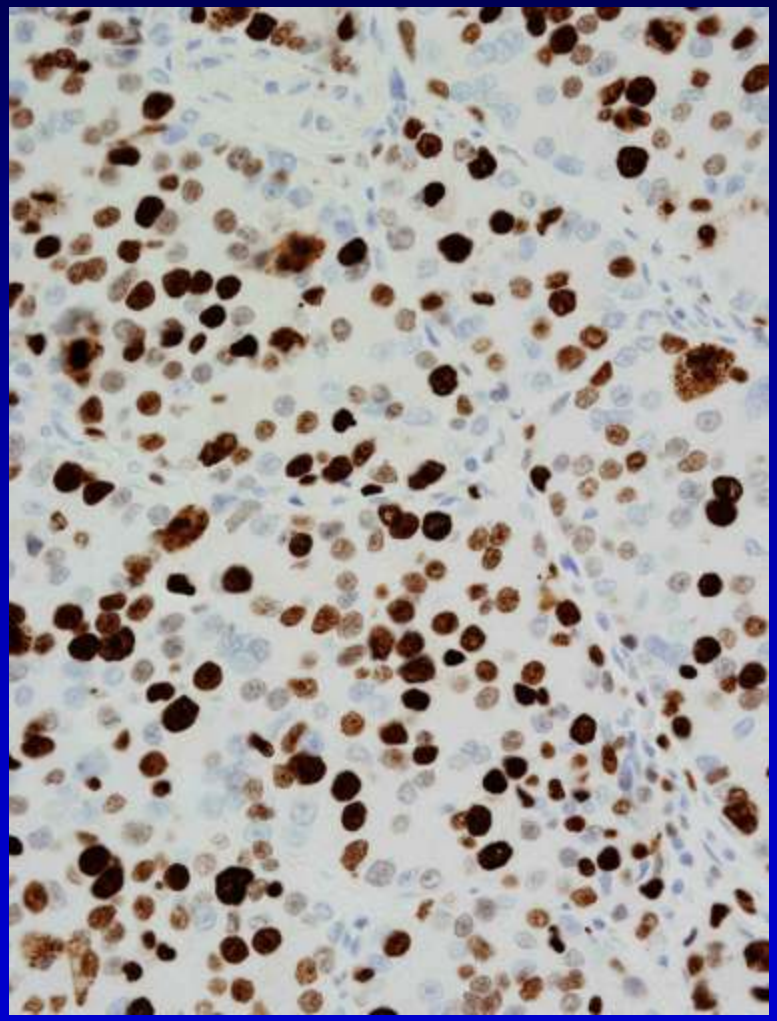
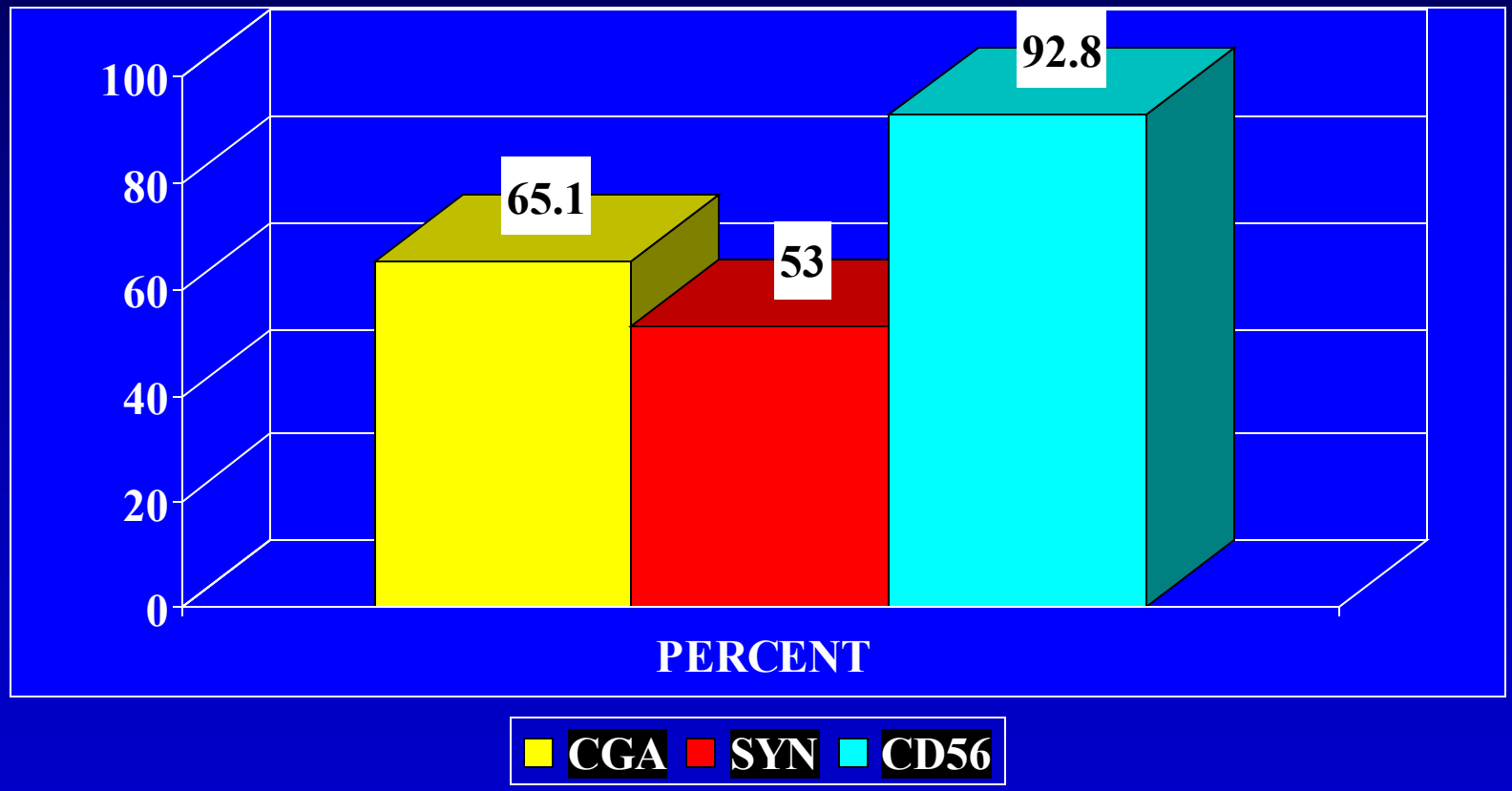


Ki-67



LCNEC IMMUNOHISTOCHEMISTRY



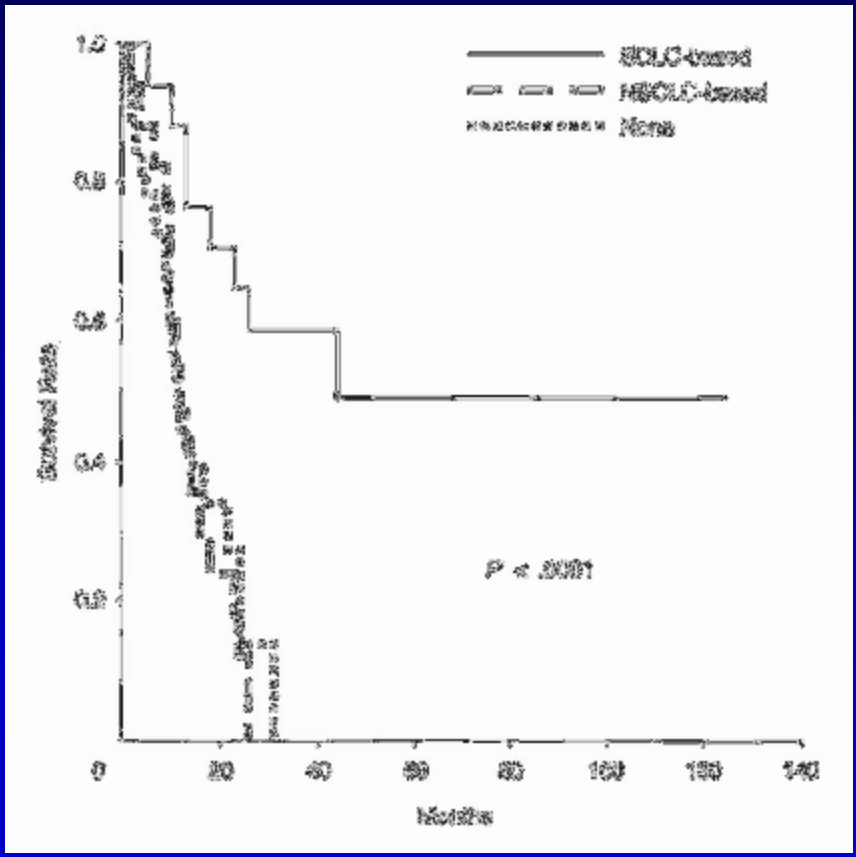
Rossi G et al: J Clin Oncol 23: 8774, 2005

LCNEC: NCC Research Institute, Tokyo

- 87 cases (3.1% resected lung cancers)
- Sex:77M (89%); 10F; Mean age 68 yr (37-82)
- Smoking: 98%; No paraneoplastic syndrome
- 5-yr survival – overall: 57%
  - Stage 1: 67%; II:75%; III:45%;IV:0%
  - Stage I LCNEC:67%; PD NSCLC:88%, LCC:92% (p=0.003)
  - No difference between Stage I SCLC and LCNEC

Takei H et al: J Thorac Cardiovasc Surg 24:285, 2002

LCNEC: CHEMOTHERAPY



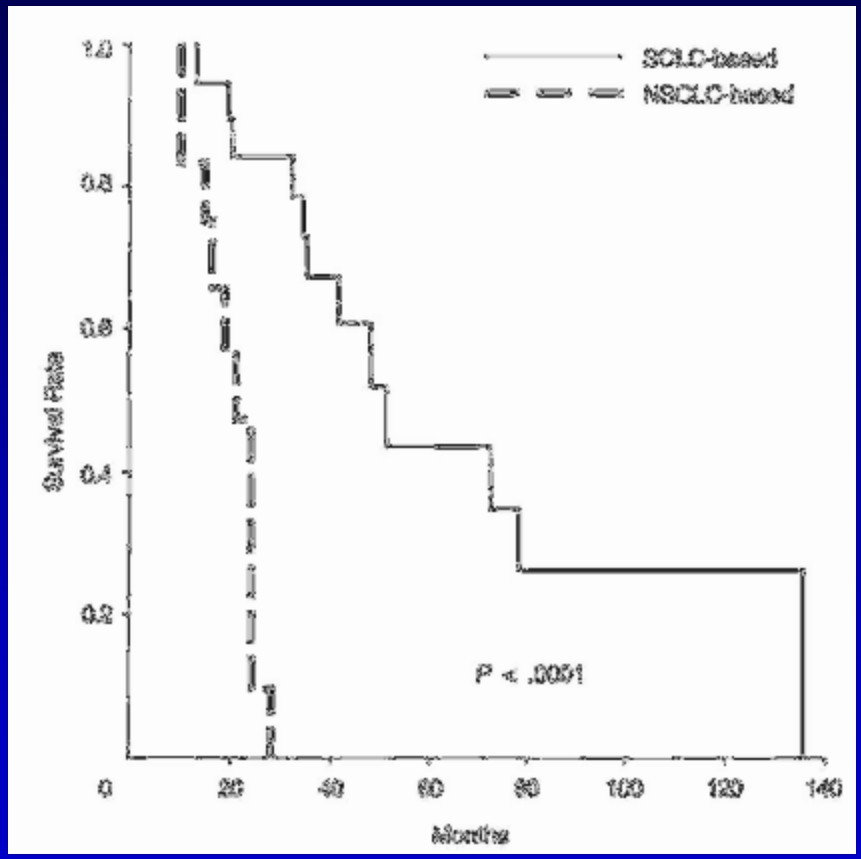
ADJUVANT SETTING

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

LCNEC: CHEMOTHERAPY

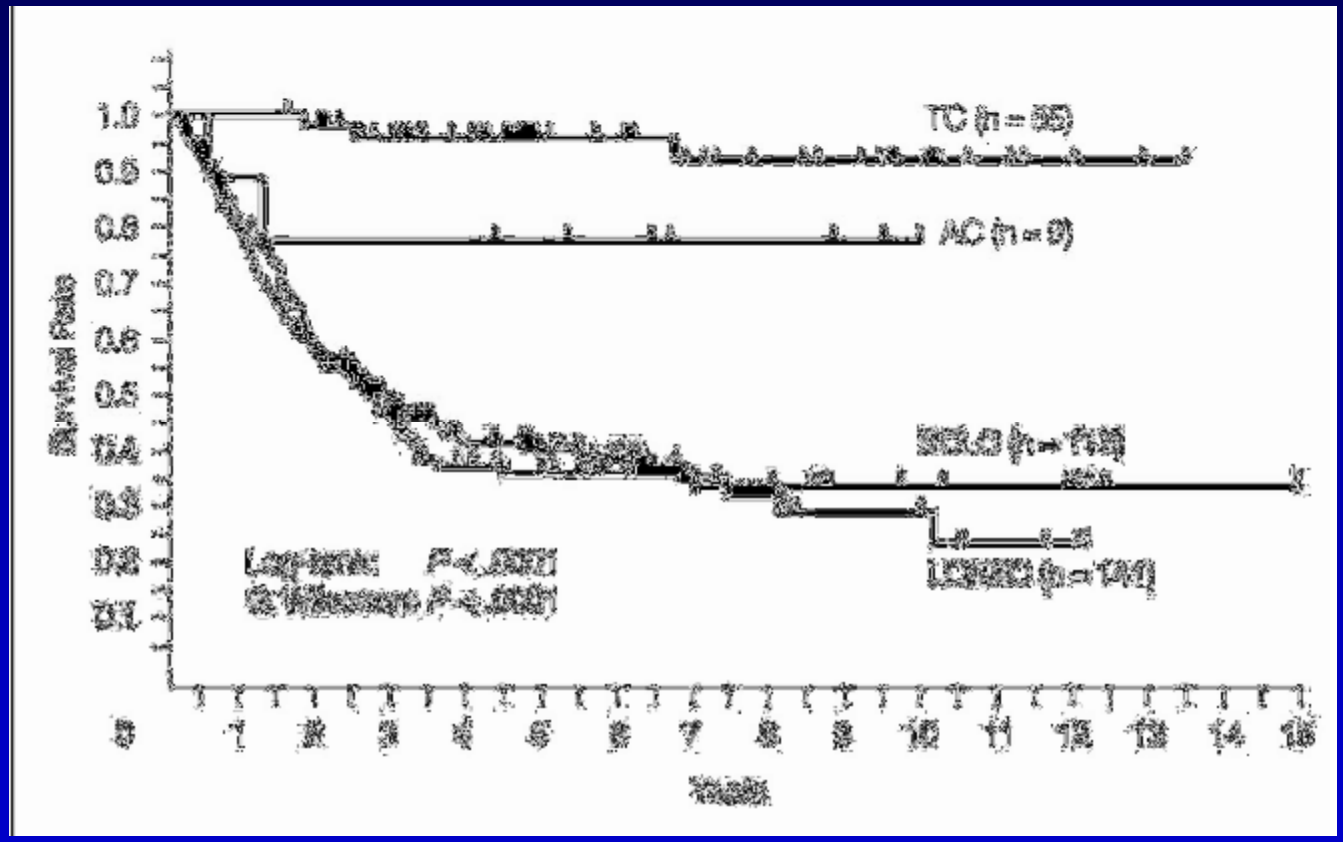


METASTATIC SETTING

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

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

PULMONARY NE TUMORS



5-yr Survival

TC: 87%

AC: 56%

LCNEC: 27%

SCLC: 9%

Asamura H et al: J Clin Oncol 24: 70, 2006

NONSMALL CELL CARCINOMA WITH NE DIFFERENTIATION (NSCLC-NED)

- LIGHT MICROSCOPY
  - Ordinary squamous cell, adenocarcinoma, or large cell ca
  - No morphologic NE features
- ELECTRON MICROSCOPY
  - NE Granules in 5-10% of NSCLC
- IMMUNOHISTOCHEMISTRY
  - Positive NE markers in 10-20% of NSCLC
  - Definition varies:
    - EM: dense core granules
    - IHC: Antibodies , % staining, # of pos Ab (1 VS 2)

NONSMALL CELL CARCINOMA WITH NE DIFFERENTIATION (NSCLC-NED)

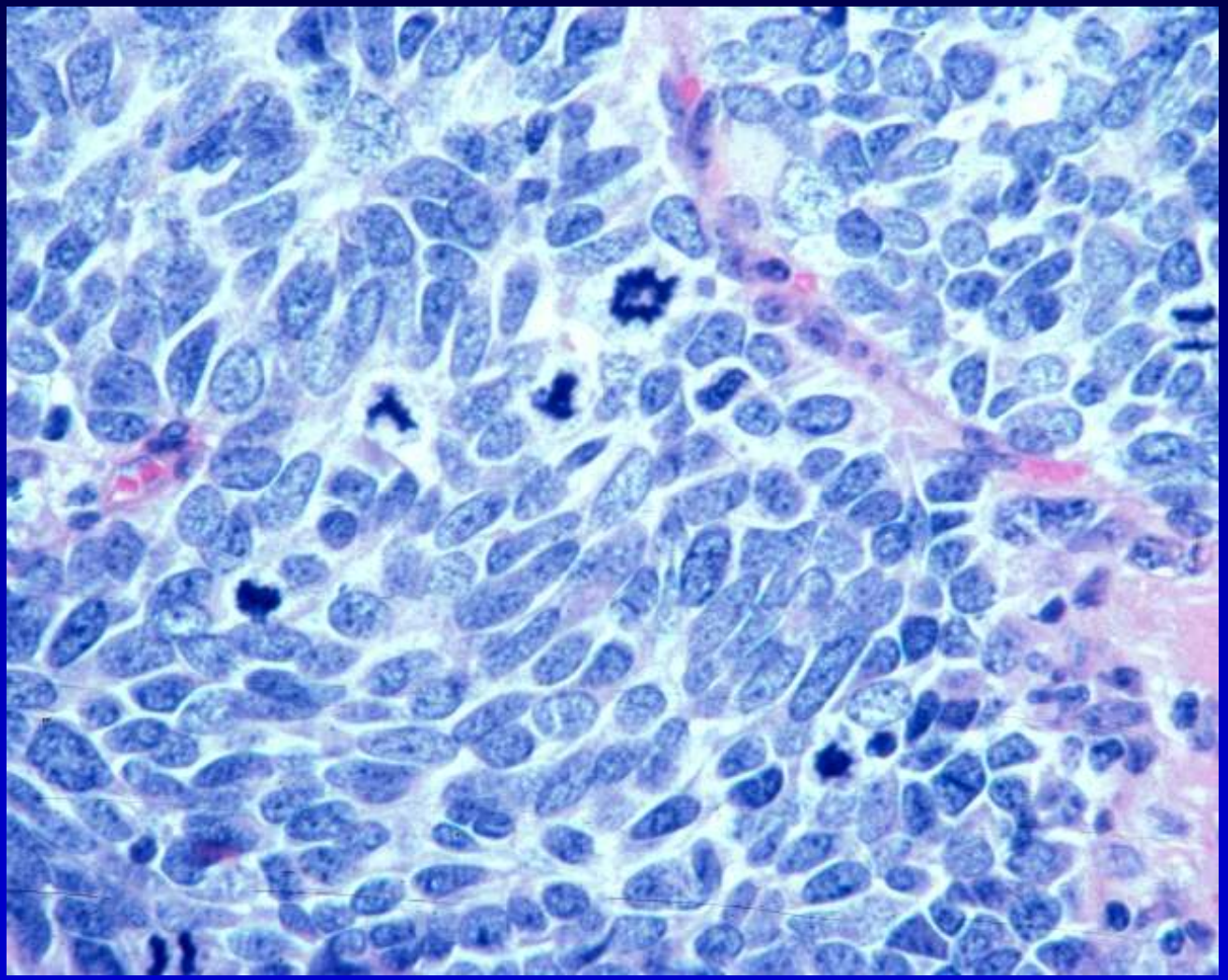
- SURVIVAL
  - Worse (Berendsen 89, Pujol 93, Hiroshima 2002, Pelosi G 2003)
  - Better (Carles 93, Schleusener 96, Harada 2002)
  - Not significant (Skov 91, Graziano 93, Linnoila 94, Graziano 94), Gajra A 2002)
- RESPONSE TO CHEMOTHERAPY
  - Increased (Graziano 89, Linnoila 89)
  - Not increased (Neal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

2004 WHO CLASSIFICATION SMALL CELL CARCINOMA

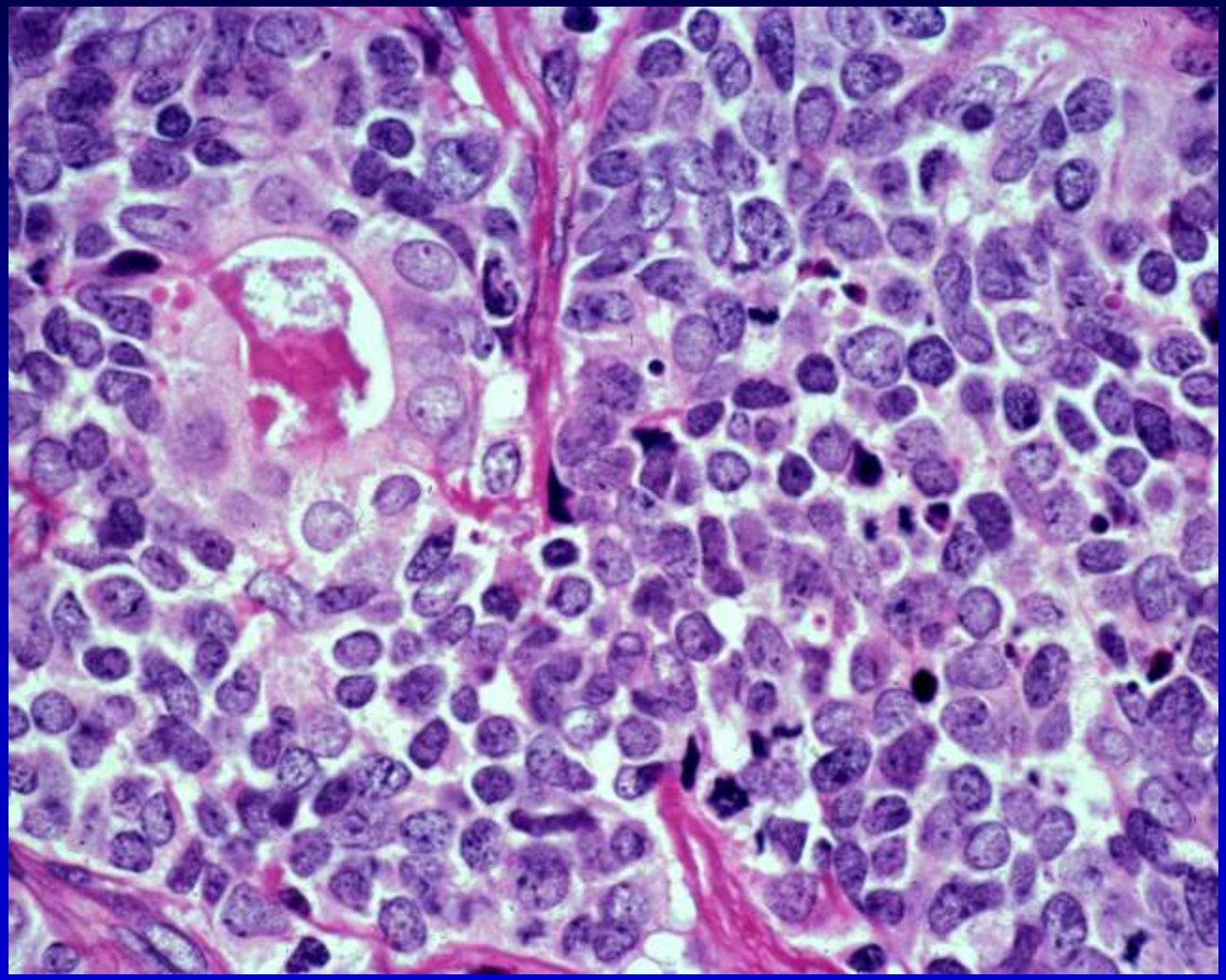
Variant

Combined small cell carcinoma

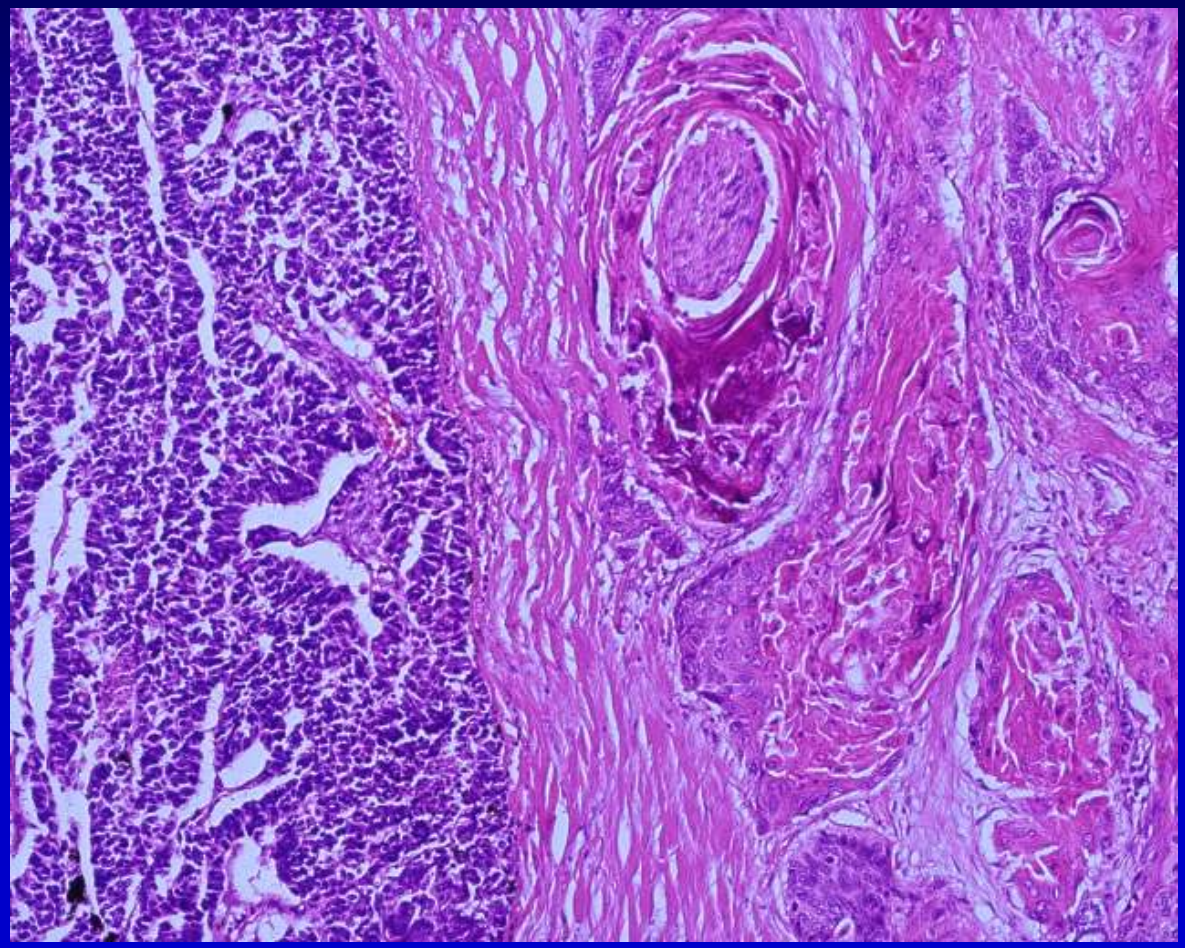
SCLC



COMBINED SCLC & ADENOCA

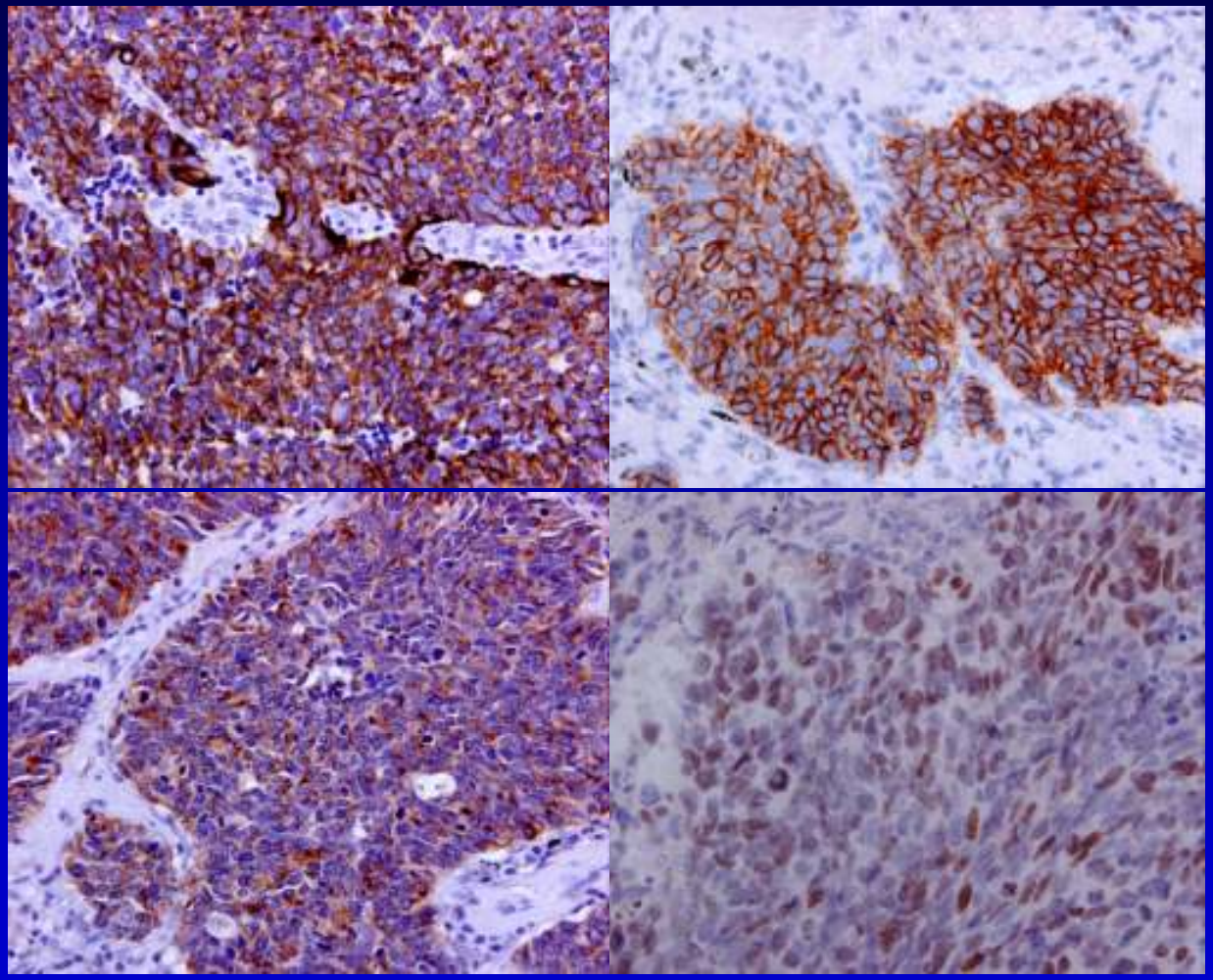


COMBINED SCLC & SQUAMOUS CELL CA



SMALL CELL CARCINOMA IMMUNOHISTOCHEMISTRY

KERATIN



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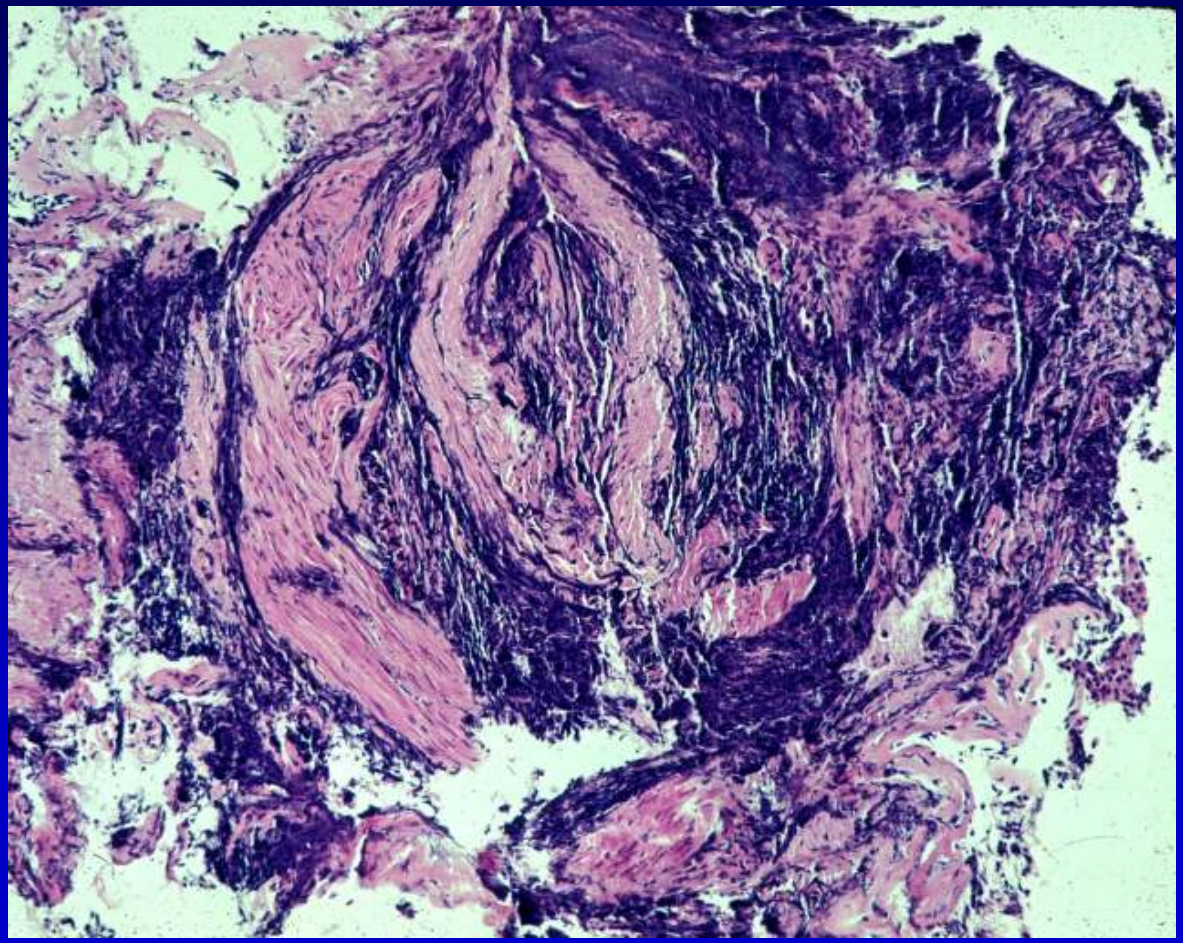
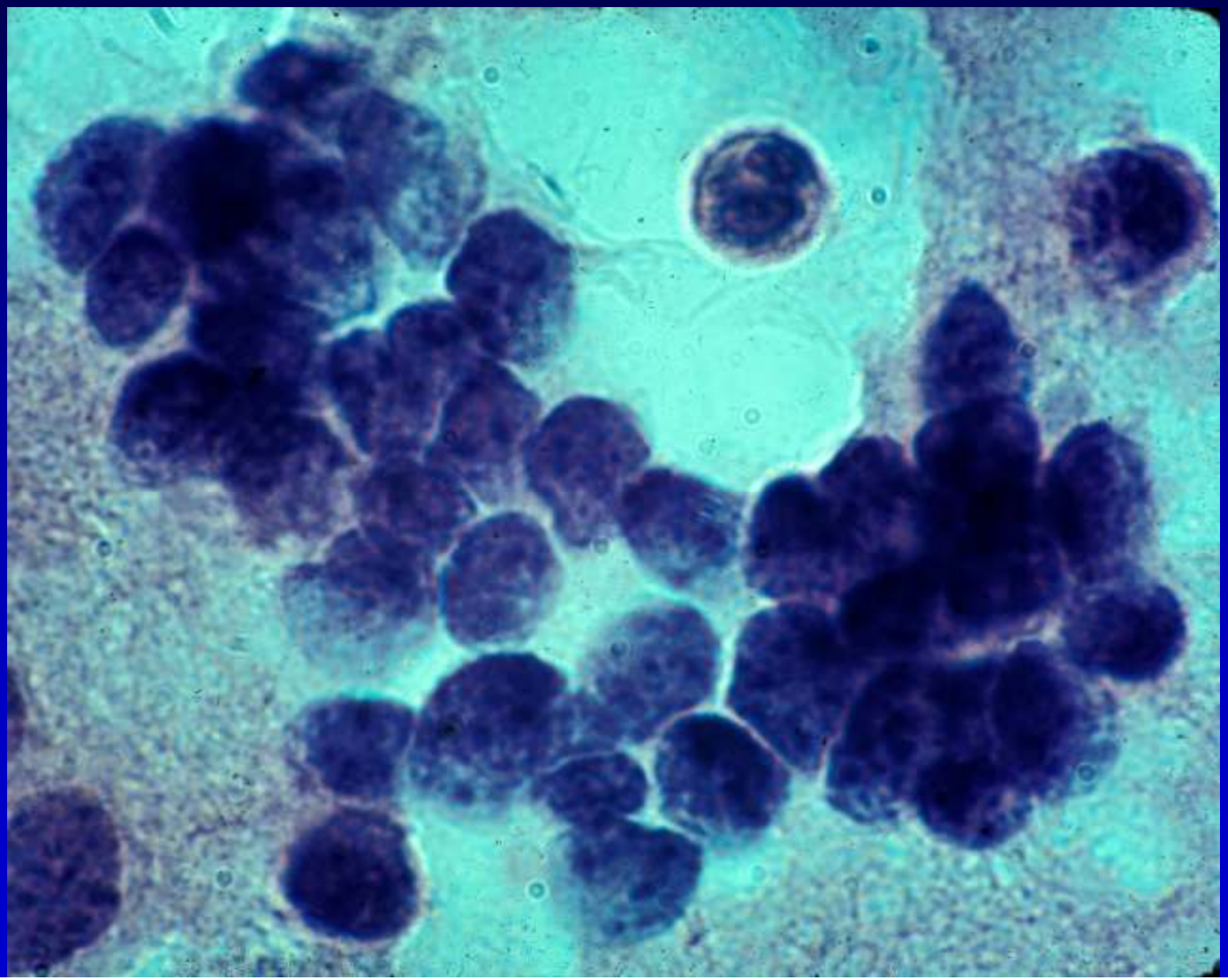
CHROMO-GANIN A

TTF-1

SCLC: CRUSH ARTIFACT



SCLC: CYTOLOGY



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 vesssels	Occasional	Rare

SMALL

CELL

CARCINOMA

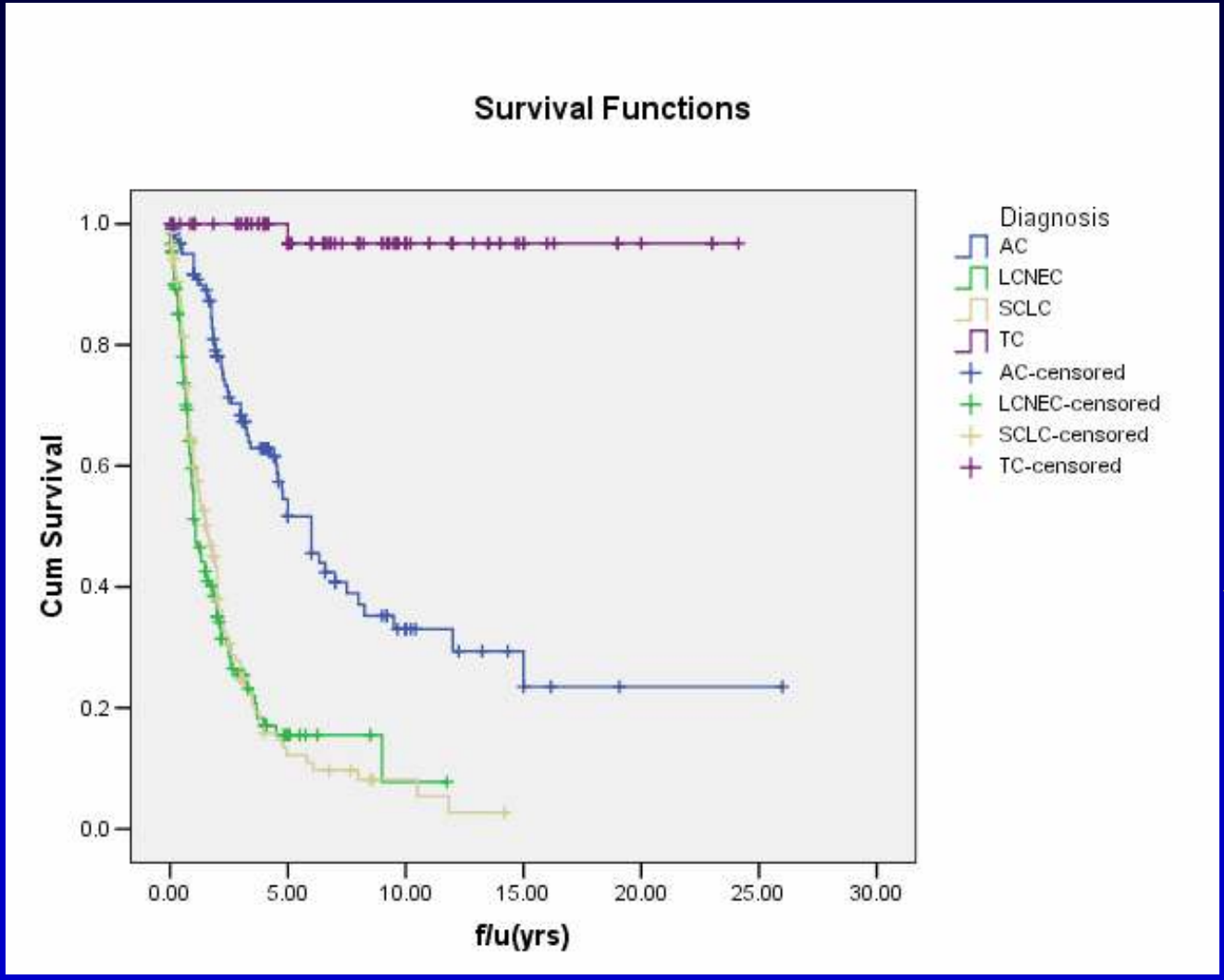
LARGE

CELL

NEUROENDOCRINE

CARCINOMA

LUNG NE TUMORS: SURVIVAL



5 yr

TC: 97%

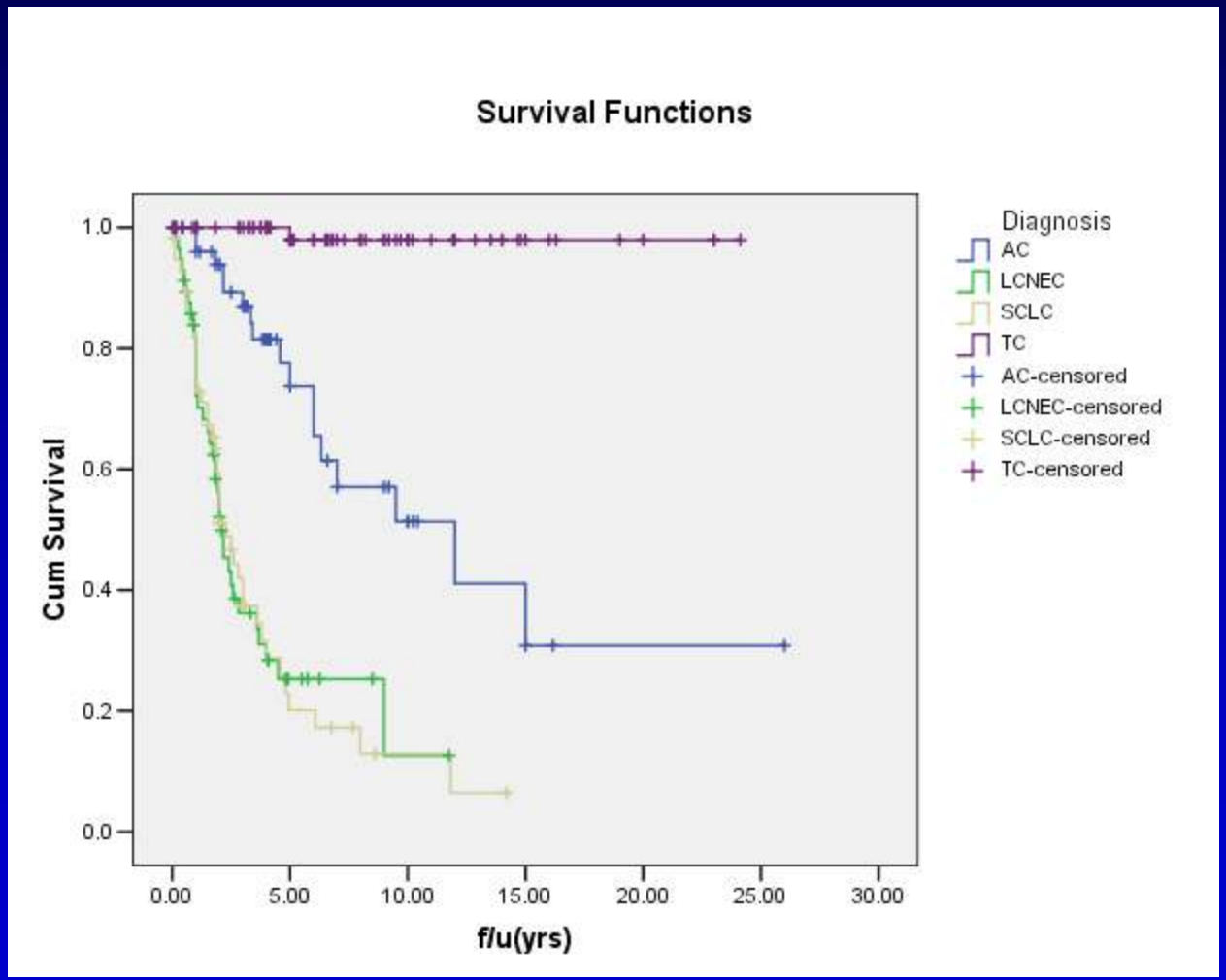
AC: 51.6%

LCNEC: 15.5%

SCLC: 12.2%

515 Cases: TC-92; AC-128, LCNEC – 154, SCLC – 141; $p<0.0001$

SURVIVAL STAGE I NE TUMORS



5 yr

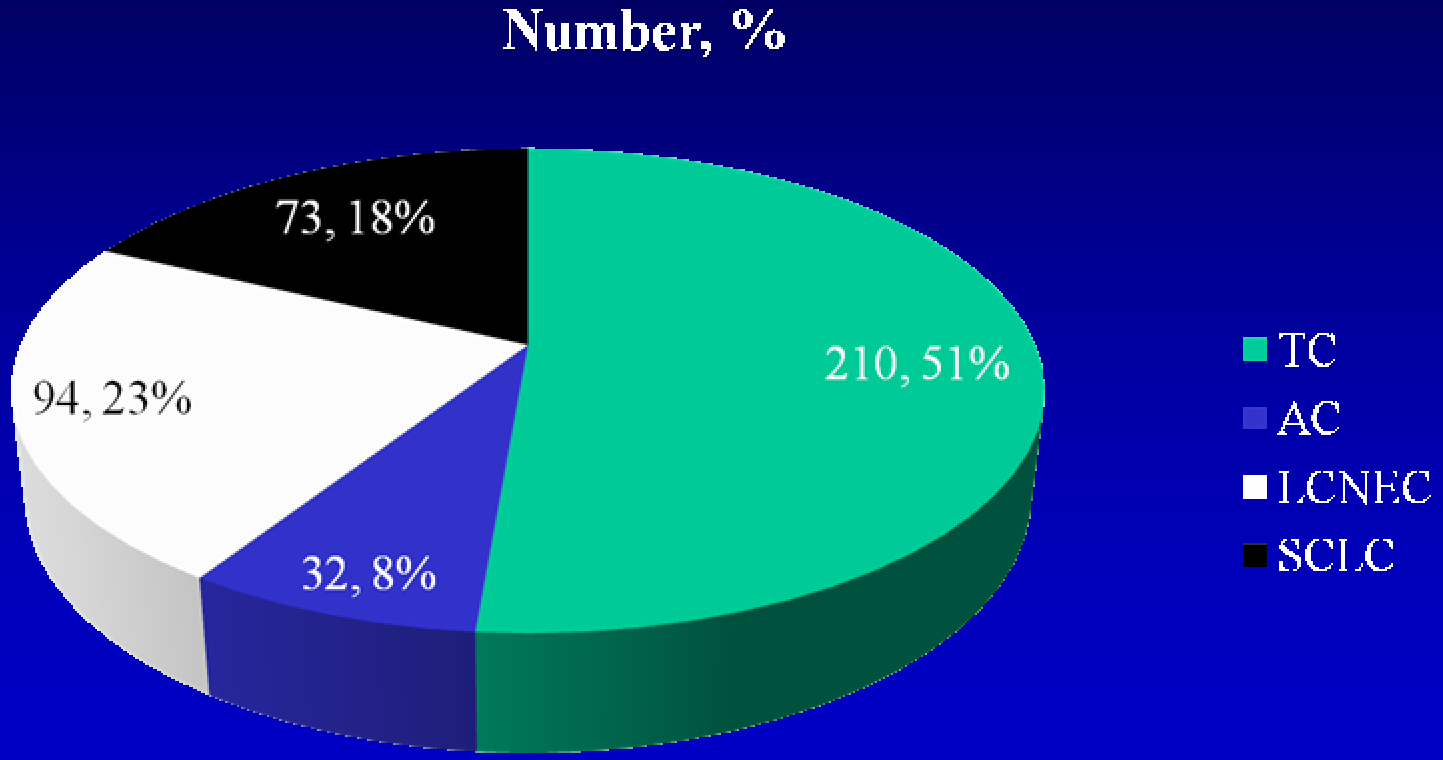
TC: 98%

AC: 73.7%

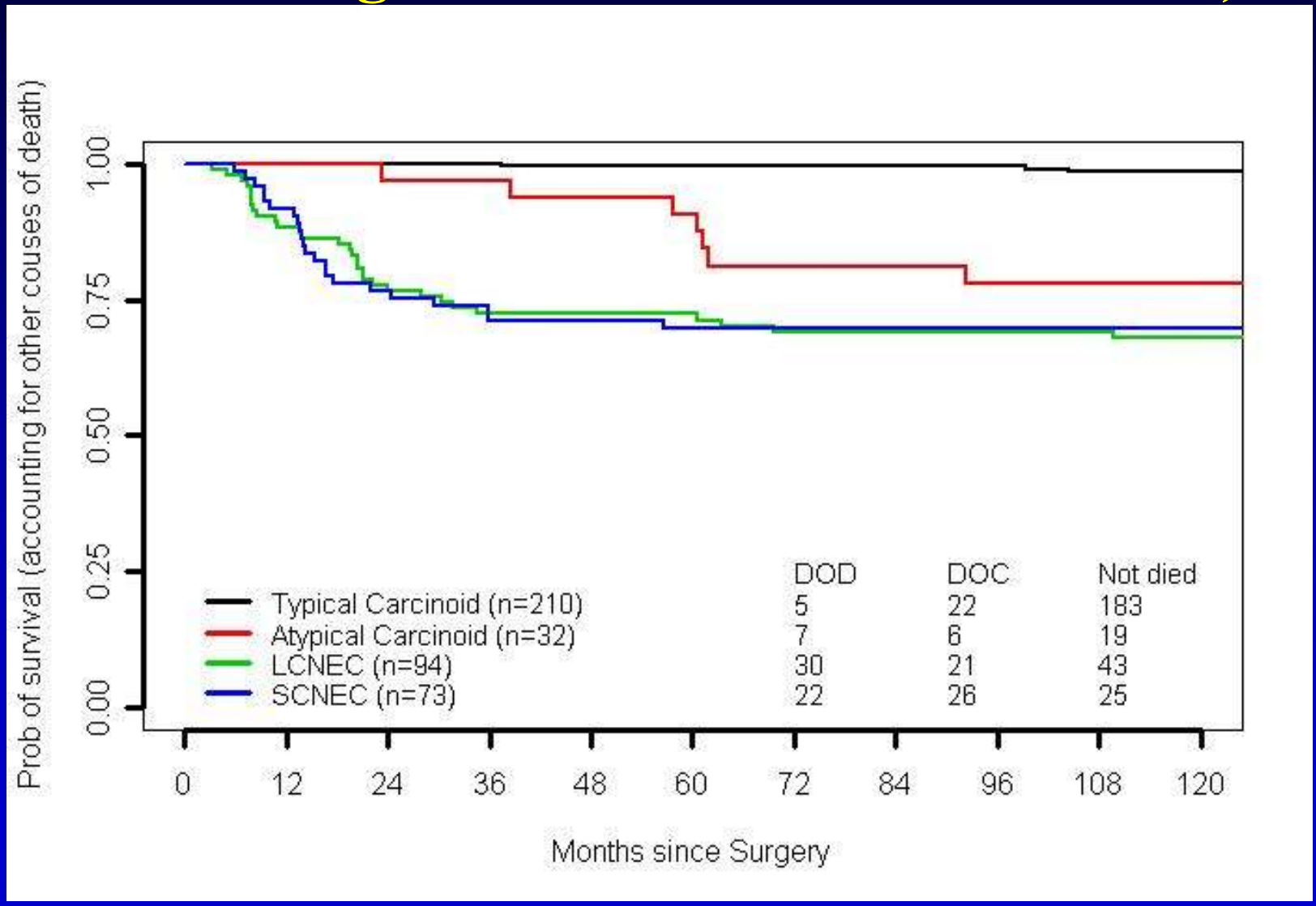
LCNEC: 25.3%

SCLC: 20.1%

408 MSKCC NE LUNG TUMORS SURGICAL CASES (1992-2008)



Competing Risks (probability of Survival, accounting for death from other causes)



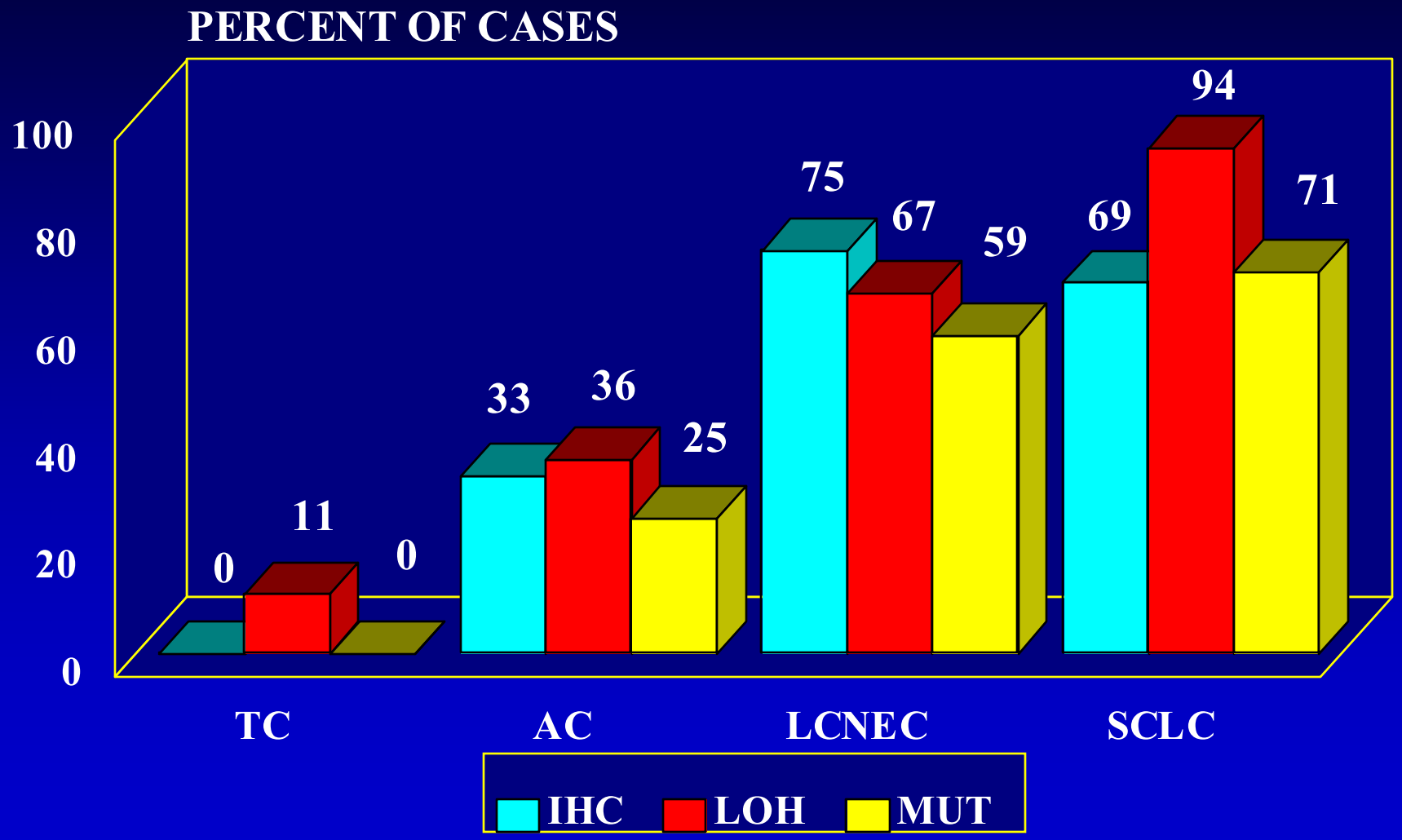
PULMONARY NE TUMORS
TREATMENT

HISTOLOGY	SURGERY	CHEMO-THERAPY	RADIATION
TC	Primary approach	Not proven	Not proven
AC	Primary approach	Not proven	Not proven
LCNEC	If resectable	Probably needed	Effective locally
SCLC	Controversial	Primary approach	Effective locally

NE LUNG TUMORS

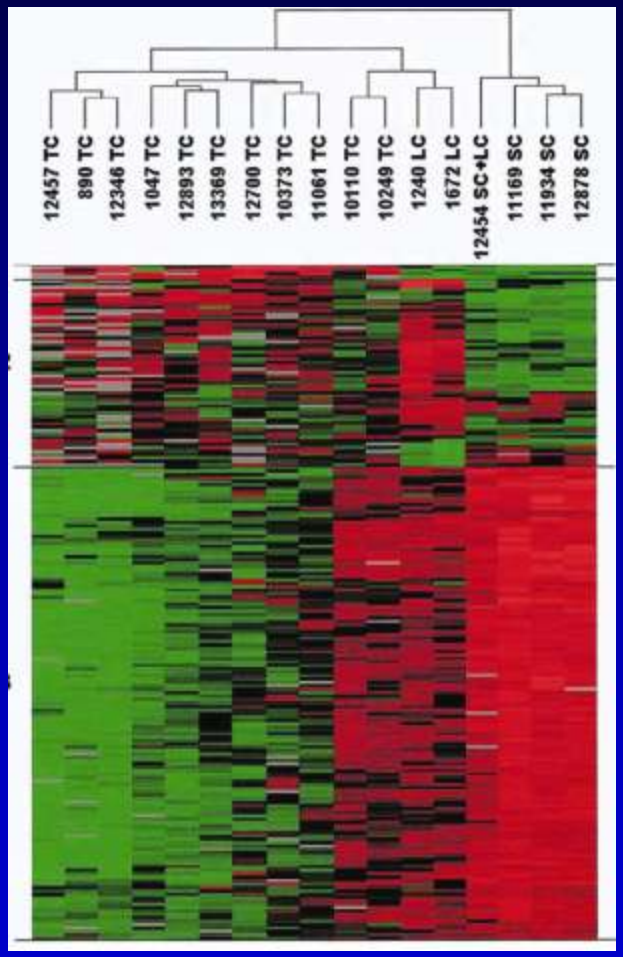
	TC	AC	LCNEC	SCLC
Mitoses per $2mm^2$	<2	2-10	>11 (median-70)	>11 (median-80)
Necrosis	No	Yes	Yes	Yes
Histologic heterogeneity	No	No	Yes	Yes
MEN I Mutation Syndrome	No Yes	Yes Yes	Rare No	No No

p53 IHC, LOH AND MUTATIONS NE LUNG TUMORS



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

GENE PROFILING: NE TUMORS



He P, et al: Hum Pathol 35: 1196, 2004

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INTERNATIONAL REGISTRY OF NE LUNG TUMORS

- Will collect
  - TC with metastases
  - AC
  - LCNEC
  - Resected SCLC
- Tissue archive (slides, blocks, frozen tissue)
- Pathology panel consensus review
- Clinical Data: Therapy & Response?
- National Registries Exist in Spain and Japan
- Encourage Collaboration

INTERNATIONAL NE LUNG TUMOR REGISTRY OVERALL GOALS

- To develop collaborations that allow for combining data on rare NE tumors to answer difficult questions that none of us can answer by ourselves
- To encourage existing (Japan, Spain) and the development of new national registries of pulmonary NE tumors
- To establish an international consensus and a worldwide uniform approach to diagnosis (2004 WHO classification)
- To develop a tissue network for study of molecular changes with hope of identifying molecular therapeutic targets