Erasmus MC
University Medical Center Rotterdam

Small cell lung cancer and large cell neuroendocrine tumours interobserver variability

Michael den Bakker

Erasmus MC

PPC London 2007

WEB presentation –
Pulmonary pathology Club presentation, London, November 2007

- The paper presented at the 2007 London PPC meeting contains early results of a Dutch interobserver study on small cell carcinoma and large cell neuroendocrine carcinoma.
- This data is currently being prepared for publication

Dr. Erik Thunnissen, VU MC, Amsterdam

Dr. Matthijs van Oosterhout, UMCU, Utrecht

Prof. Wim Timens, AZG, Groningen

Dr. Bart Vrugt, MZH, Leeuwarden

Dr. Arnold Noorduyn, AMC, Amsterdam

Dr. Anne Wiersma, Alysis, Arnhem

Dr. Katrien Grunberg, VU MC, Amsterdam

Dr. Robert-Jan van Suylen, AZM, Maastricht

Dr. Michael den Bakker, Erasmus MC, Rotterdam

PPC 2007 London

Erasmus MC

Annecdote

Case report

Vosika, JAMA (1979) 21;242(12):1258-9. Large cell-small cell bronchogenic carcinoma.

- Male 47, 4cm mass in hilum left lung, 1,5cm nodule left heart border, inguinal and axillary masses: "*Large cell undifferentiated carcinoma of the lung with metastases*"

Letter to the Editor: F.A. Gibbs, JAMA (1979) 10;242(6):514.

- *Diffuse histiocytic lymphoma*

Case sent off:

M. Matthews: small cell carcinoma, intermediate type

R. Yesner: intermediate small cell carcinoma, with large cell characteristics

J. Rosai: very undifferentiated tumor. Dd. Oat cell carcinoma, large cell undifferentiated carcinoma. *Room for disagreement*

SCLC history

1st description by Barnard 1926

THE NATURE OF THE "OAT-CELLED SARCOMA" OF THE MEDIASTINUM.

W. G. BARNARD.

University College Hospital Medical School, London.

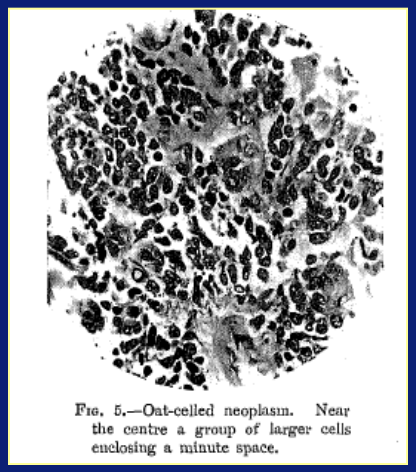
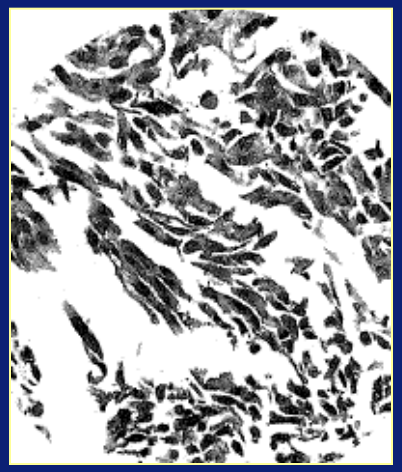
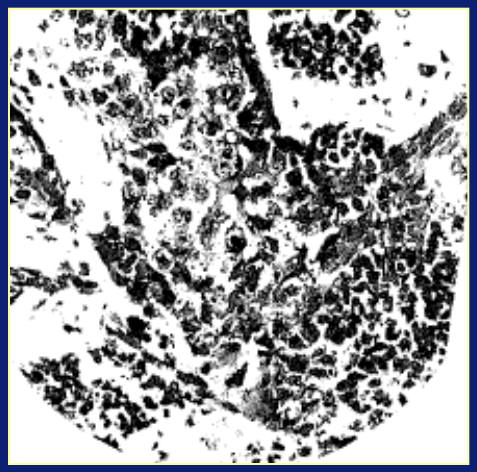


FIG. 5.—Oat-celled neoplasm. Near the centre a group of larger cells enclosing a minute space.





Barnard WG. J Pathol Bact (1926), 29:241-244

Small cell carcinoma (SCLC)

- Smoking-associated highly aggressive neuroendocrine carcinoma
- Frequently disseminated at presentation
- Set apart from all other types of lung cancer resulting in a dichotomous (treatment oriented) division: SCLC *vs* non-SCLC
- No precursor lesion identified
- Staging: limited *vs* extensive disease (with the option of surgery for limited disease)

SCLC classification history

TABLE 1. *Classification of small cell lung carcinoma*

Kreyberg[31] 1962	WHO[59] 1967	1973 WP-L WHO[60] 1981	IASLC[21] 1998	WHO/IASLC[50] 1999
Oat cell	Lymphocyte-like	Oat cell	Pure SCLC	SCLC
Polygonal	Polygonal	Intermediate		
	Fusiform		Mixed (with large cells)	
	Other (containing squamous and glandular foci)	Combined	Combined	Combined SCLC (containing any other NSCLC component)

Am J Surg Pathol 26(9): 1184–1197, 2002.

SCLC – diagnostic criteria (1)

Cytological features of paramount importance

Small cell size, <3 resting lymphocytes

Occasional large, pleomorphic nuclei accepted

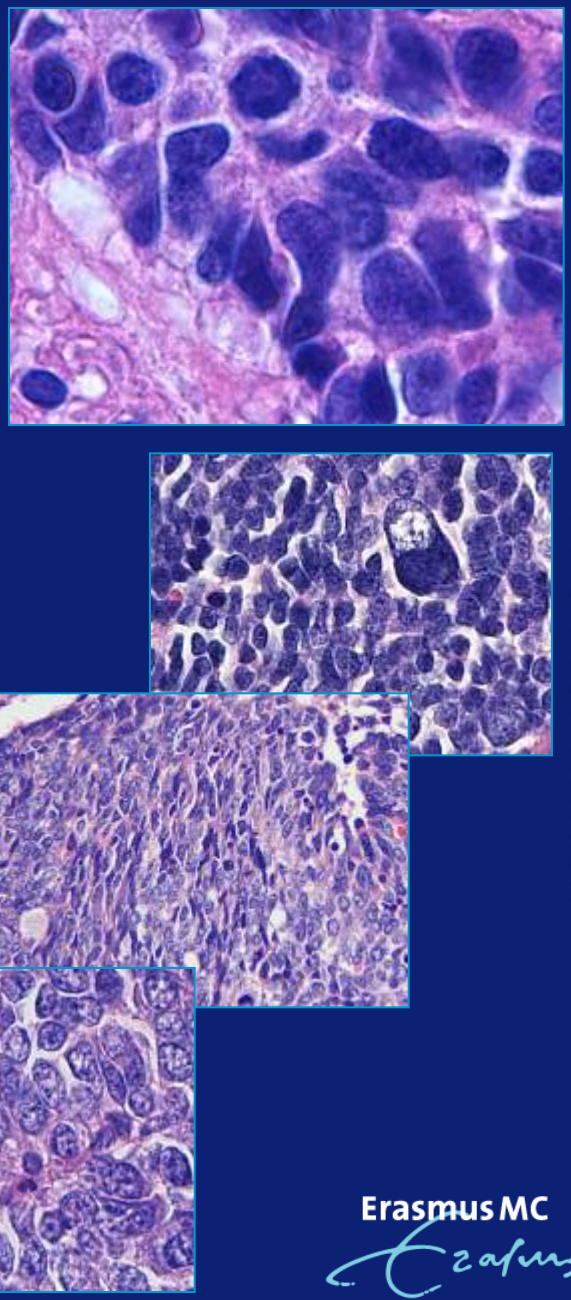
Cell borders not seen

High N/C ratio

Finely granular chromatin

Absent or at best inconspicuous nucleoli

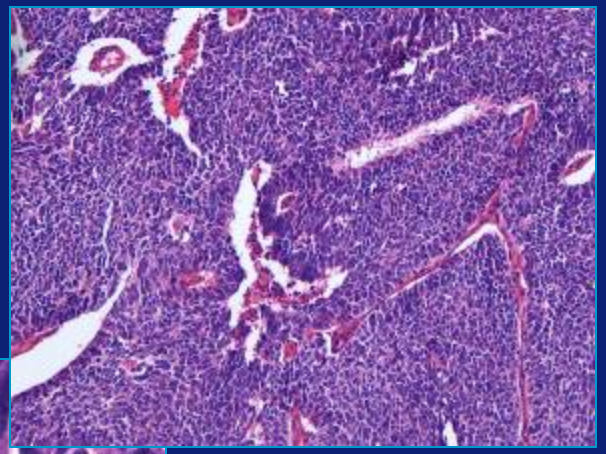
Cell shape varies from oval to spindled

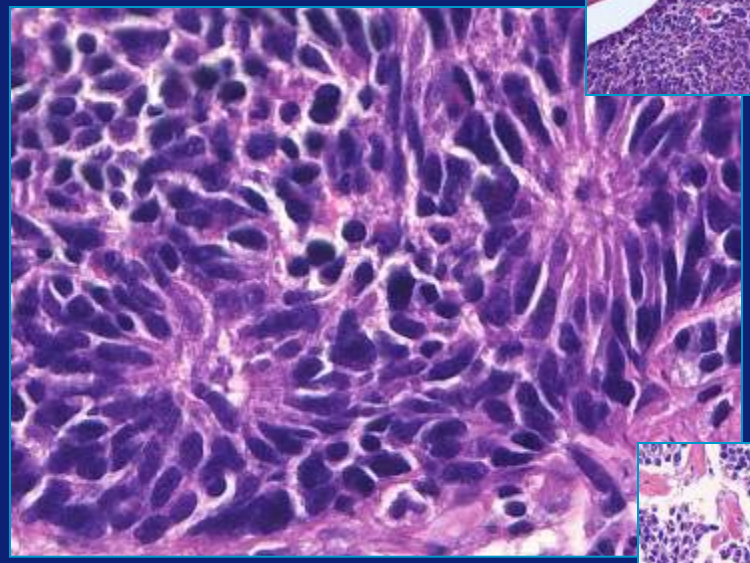


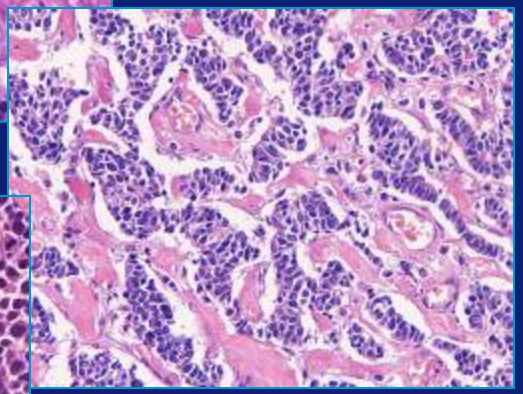
SCLC – diagnostic criteria (2)

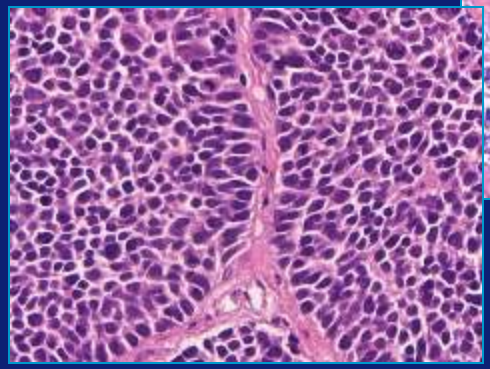
Architectural features

- Growth patterns:
  - Solid sheets
  - Nested
  - Trabecular
  - Rosettes
  - Palisading





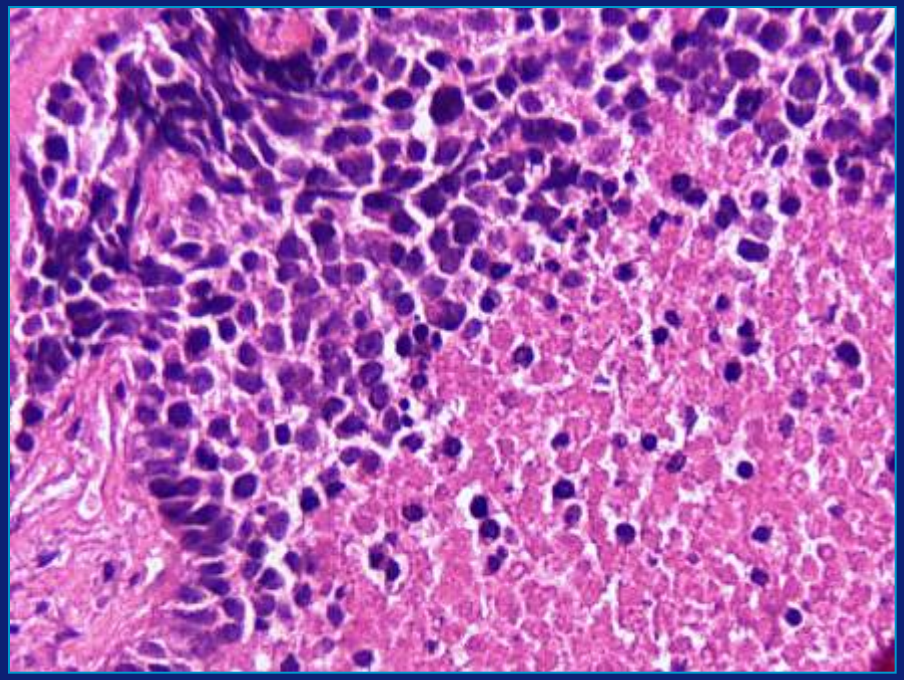


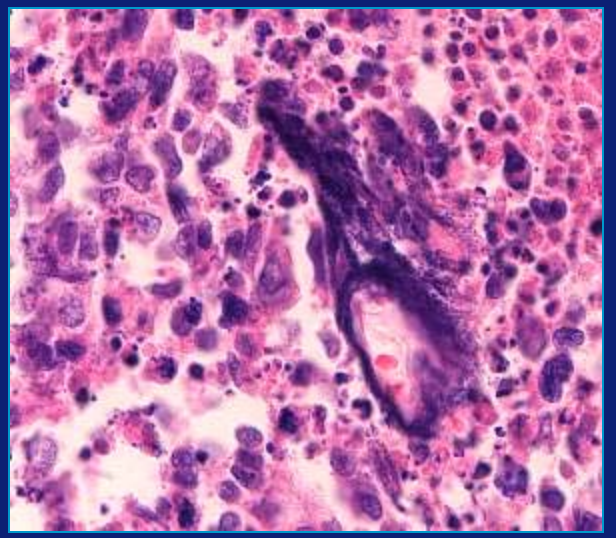


SCLC – diagnostic criteria (3)

Architectural features

- Necrosis
- Encrustation of nuclear material on vessel walls (Azzopardi phenomenon (10%)



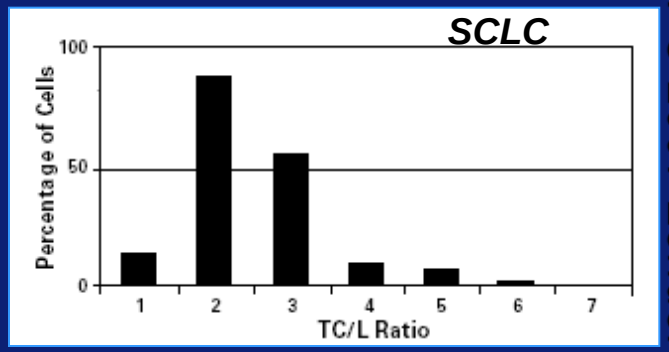


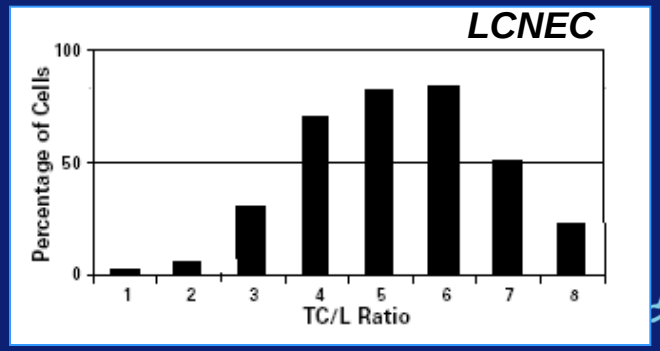
Cell size in SCLC

Marchevsky, Am J Clin Path 2001

28 resected HG NE carcinomas, 16 SCLC, 12 LCNEC

- *Measured tumor cell nucl diam. and lymphocyte, calculated ratios (TC/L)*
- *Histograms constructed type A-F*
  - *A-E → TC/L 2-6*
  - *F → no peak*





Expected:

SCLC → histogram type A/B

LCNEC → histogram C-F

Marchevsky, Am J Clin Path 2001

	SCLC	LCNEC
A (TC/L 2)	4	1
B (TC/L 3)	7	3
C (TC/L 4)	2	2
D (TC/L 5)	2	4
E (TC/L 6)	1	1
F (TC/L#)	0	1
	16	12

Nuclear size alone is not sufficient to diagnose SCLC

5/16 SCLC would be classified as LCNEC on nuclear size alone

4/12 LCNEC would be classified as SCLC on nuclear size alone

SCLC – diagnostic criteria

- Cyto-morphology dependent on biopsy size (i.e. method of acquiring sample)

  - In surgical biopsies and resections:
    - Cells appear larger
    - Chromatin more dispersed
    - Nucleoli may be identified

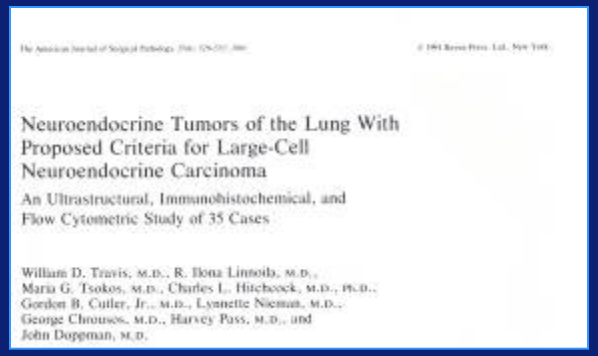
- Distinction of subtypes of SCLC (oat cell, intermediate, polygonal fusiform) to a certain extent results from morphological interpretation of biopsies obtained by different means.

Nicholson et al. Am J Surg pathol (2002) 26:1184-97)

Large cell neuroendocrine carcinoma (LCNEC)

Separate category 1991 (Travis)

- Cases not fitting in atyp carcinoid or SCLC



Neuroendocrine Tumors of the Lung With Proposed Criteria for Large-Cell Neuroendocrine Carcinoma

An Ultrastructural, Immunohistochemical, and Flow Cytometric Study of 35 Cases

William D. Travis, M.D., R. Ilona Linnoila, M.D., Maria G. Tsokos, M.D., Charles L. Hitchcock, M.D., Ph.D., Gordon B. Cutler, Jr., M.D., Lynnette Nieman, M.D., George Chrousos, M.D., Harvey Pass, M.D., and John Dopeman, M.D.

- Rare, <3,5% lung cancer cases

- NE morphology (palissading, trabecular, nested) *AND*
- NE differentation by IHC, (CD56 > Syn > Chr)
- Necrosis
- High mitotic rate (>10/2mm^2, usually >60)
- Large cell size (>3 x lymphocyte)

PPC 2007 London

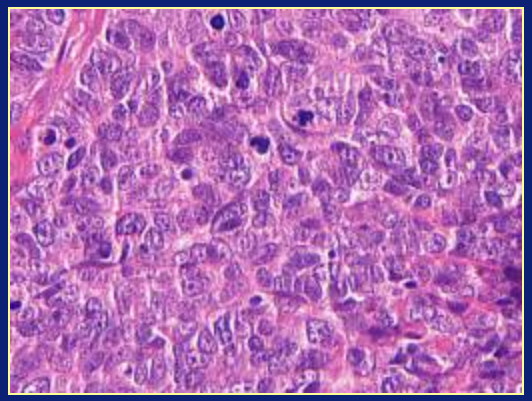
Travis et al. Am J Surg Pathol (1991) 15:529-553
Volmer. Cancer (1982) 50:1380-3

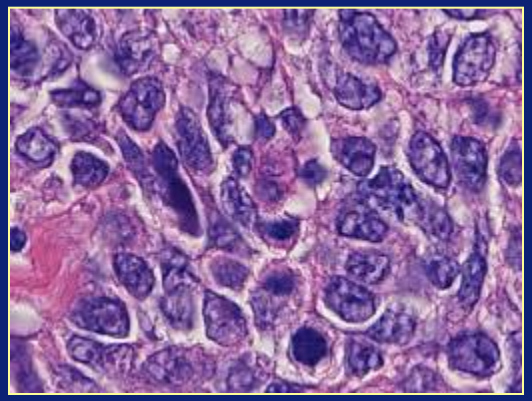
Erasmus MC

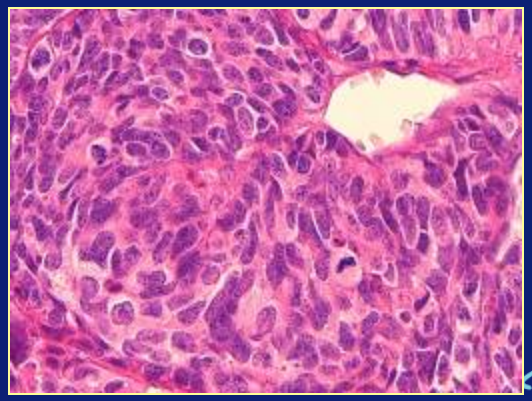
TABLE 9. *Light microscopic features for distinguishing small-cell carcinoma and large-cell neuroendocrine carcinoma*[a]

Histologic feature	Small-cell carcinoma	Large-cell neuroendocrine carcinoma
Cell size	Smaller (<3 lymphocytes)	Larger
Nuclear/cytoplasmic ratio	Higher	Lower
Nuclear chromatin	Finely granular, uniform	Coarsely granular or 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	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

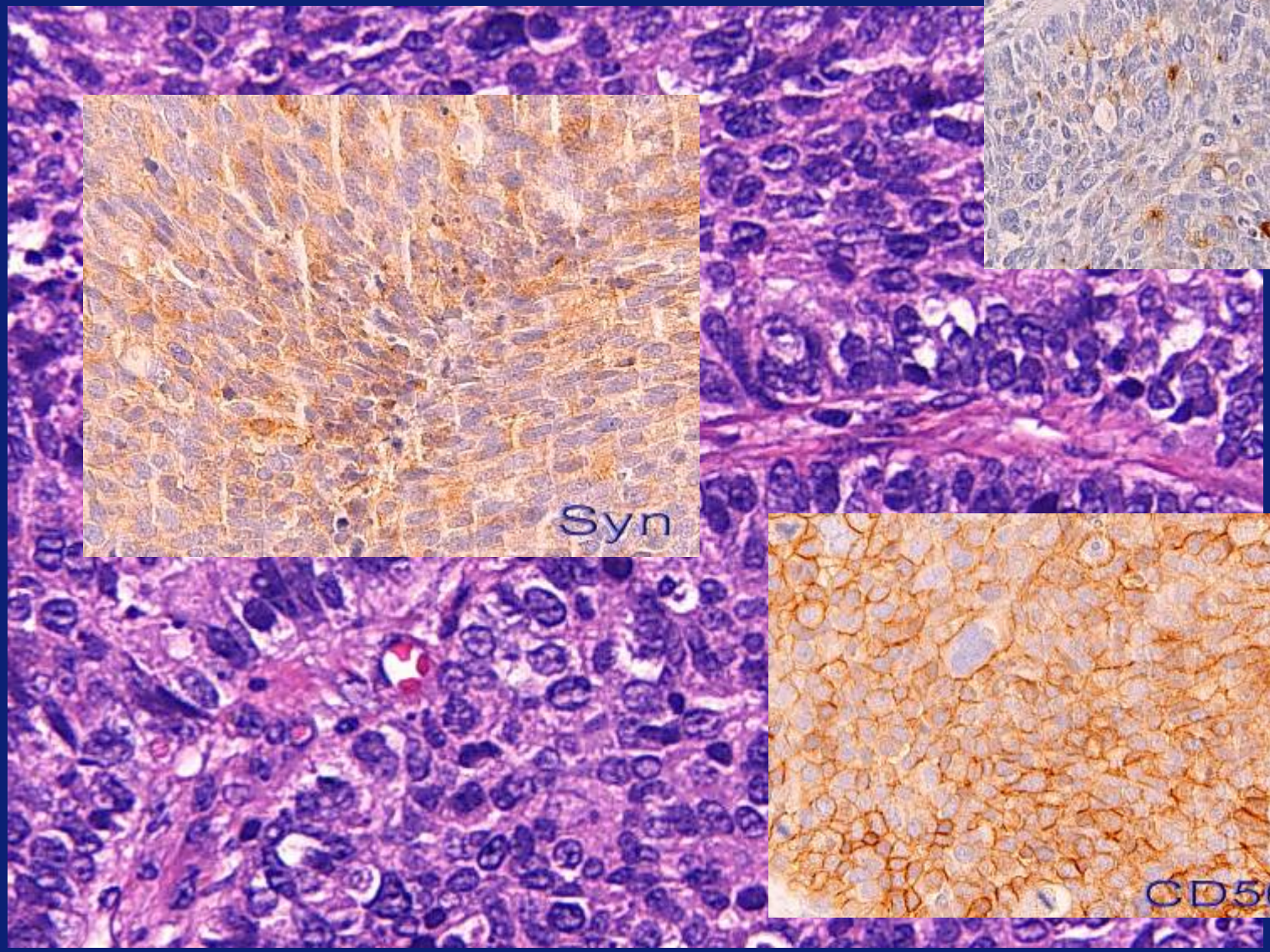
Travis et al. Am J Surg Pathol (1991) 15:529-553

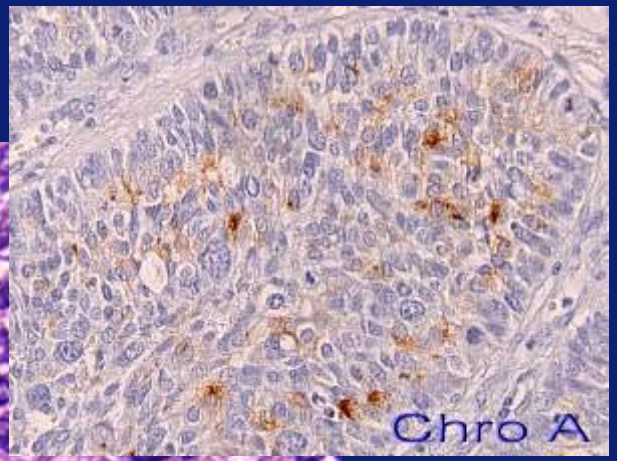






Large cell neuroendocrine carcinoma





How good are we at distinguishing SCLC and LCNEC?

TABLE 9. *Light microscopic features for distinguishing small-cell carcinoma and large-cell neuroendocrine carcinoma*[a]

Histologic feature	Small-cell carcinoma	Large-cell neuroendocrine carcinoma
Cell size	Smaller (<3 lymphocytes)	Larger
Nuclear/cytoplasmic ratio	Higher	Lower
Nuclear chromatin	Finely granular, uniform	Coarsely granular or 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	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

"Larger"

"Higher"

"Less unfiform"

"Often"

"Uncharacterisitc"

"Frequent"

"Rare"

PPC 2007 London

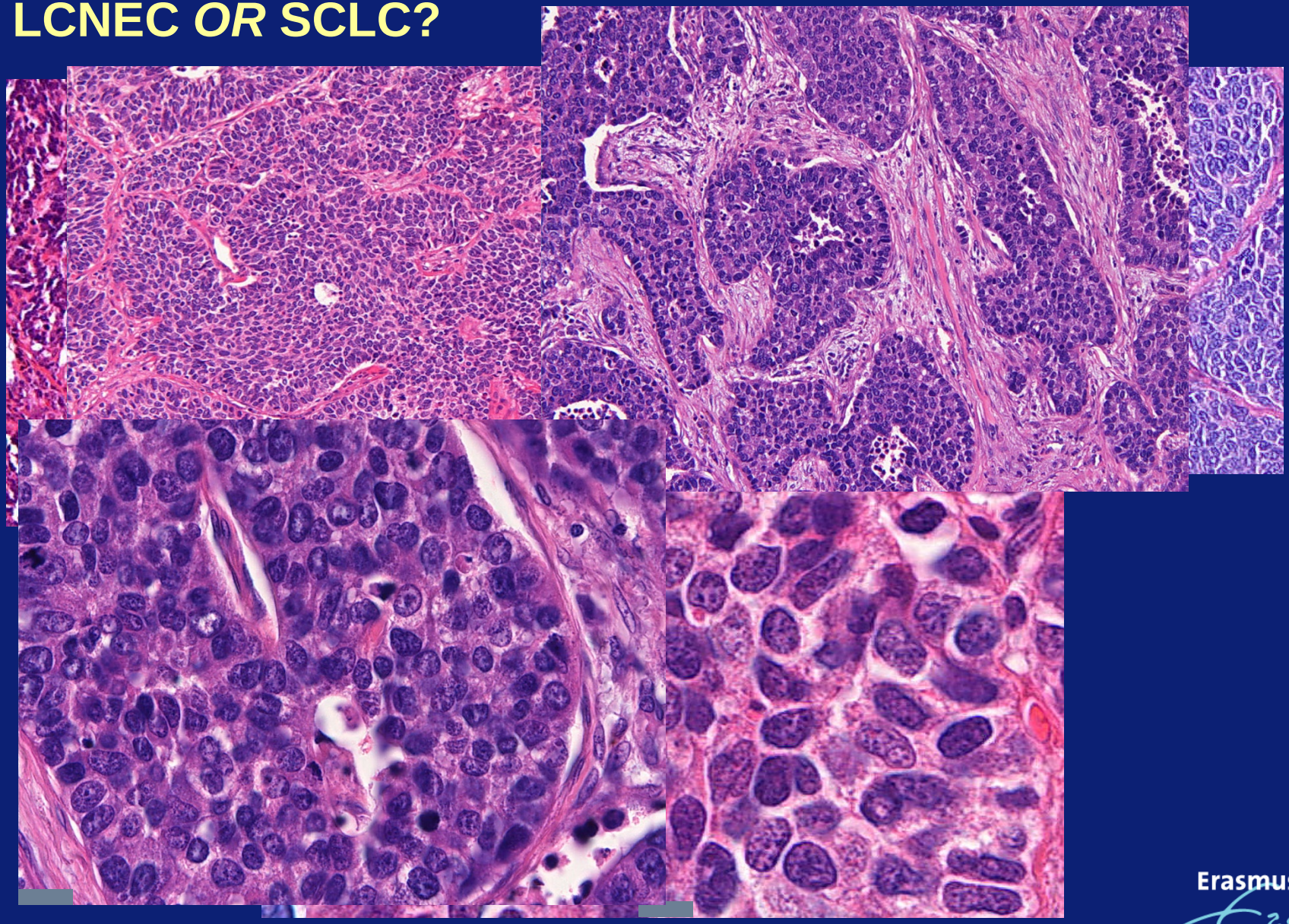
Erasmus MC

Interobserver variability SCLC - LCNEC

- 9 pathologists
- SCLC and LCNEC samples from archive, based on report
- Blinded and circulated
- Diagnostic categories:
  - SCLC
  - LCNEC
  - Combined
  - Carcinoid
  - Large cell carcinoma
  - Not suitable
- ~175 slides

Your turn!

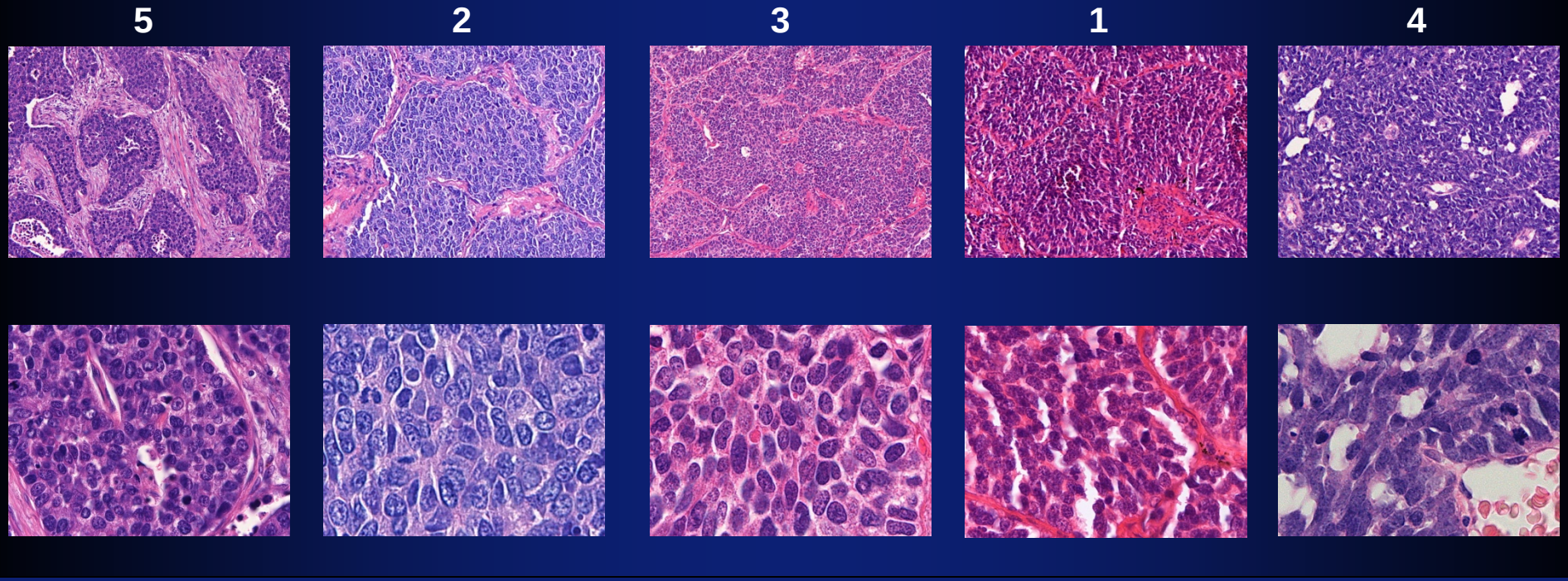
LCNEC *OR* SCLC?



PPC 2007 London

Erasmus MC

LCNEC *OR* SCLC?



LCNEC	LCNEC/sclc/comb	lcnec-sclc	SCLC/lcnec	SCLC
8/0	5/2/1	4/4	6/2	8/0

Erasmus MC

Preliminary analysis (172 cases)

Unanimous Dx 21 (9/9 agree)

- 17 SCLC
- 2 carcinoid
- 1 LCNEC
- 1 non NE carcinoma

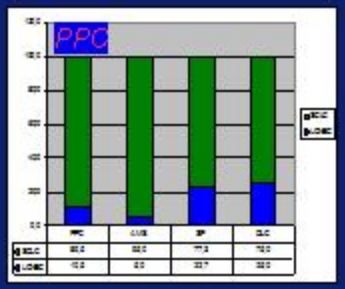
Majority reached in 116 cases (>4 agree)

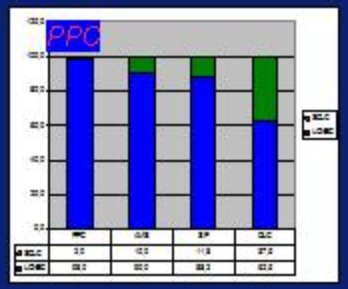
- SCLC 66
- LCNEC 27
- Combined SCLC 4
- Carcinoid 6
- Non NE carcinoma 8
- Unsuitable 5

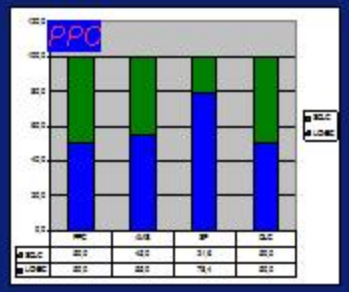
No consensus (< 5 identical Dx's)

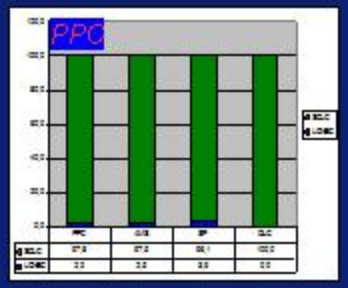
- 35

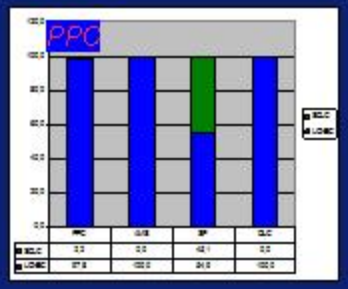
Ad hoc test result – 5 SCLC-LCNEC cases

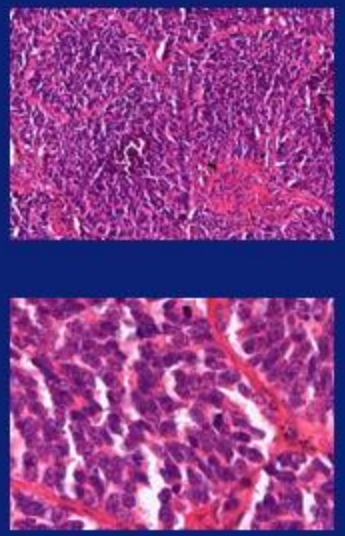


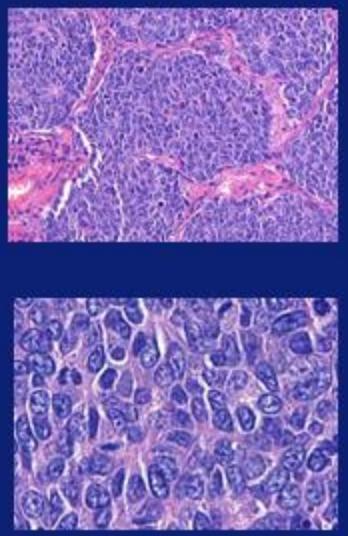


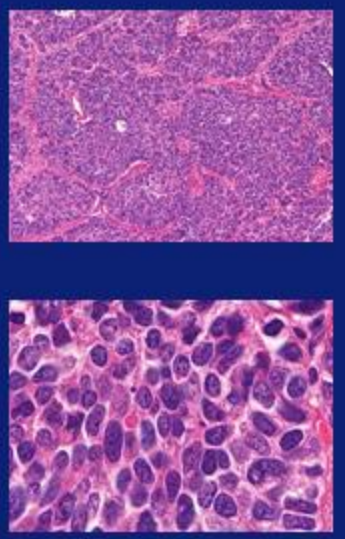


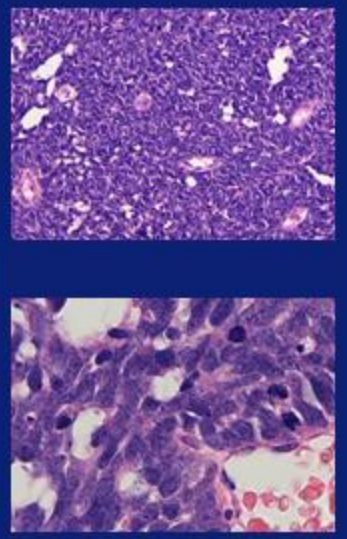


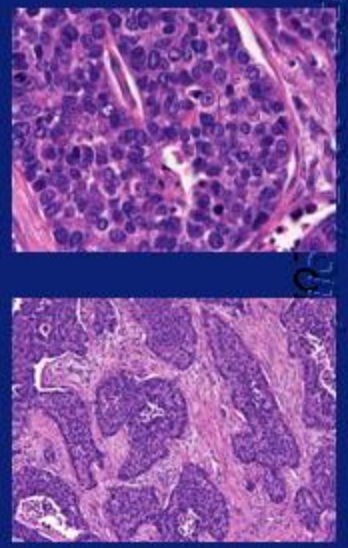












Case 1 | *Case 2* | *Case 3* | *Case 4* | *Case 5*

Lane 1 = ppc, 2= Amsterdam course, 3=Sao Paulo, 4=research group

Erasmus MC

Preliminary analysis

- Interobserver variability

SCLC
LCNEC
Combined
Carcinoid
Large cell carcinoma
Not suitable

kappa coefficient value	
< 0.00	poor agreement
0.00 to 0.20	slight agreement
0.21 to 0.40	fair
0.41 to 0.60	moderate
0.61 to 0.80	substantial
0.81 to 1.00	almost perfect agreement

Kappa value = 0,4

(combining categories SCLC and combined – kappa = 0,41)

SCLC – LCNEC

- Inter-observer variability is common in diagnosis SCLC:
  - 28% misdiagnosed in study by Nicholson[1]
  - In preselected SCLC cases 91% agreement[2]
  - 5-6% of experts do not reach consensus on SCLC *vs* LCNEC[1,5]

WHY?

- Overlap of nuclear size exists in SCLC *vs non-SCLC*[3,4]
- Nuclear morphology
- Nucleoli accepted in SCLC
- Biopsy *vs* resection

[1] *Nicholson et al. Am J Surg pathol (2002) 26:1184-97)*
[2] *Hirsch et al. Cancer (1982) 50:1360-66*
[3] *Volmer. Cancer (1982) 50:1380-3*
[4] *Marchevsky et al. Am J Clin Pathol (2001) 116:466-72*
[5] *Asamura et al. J Clin Oncol (2006) 24(1): 70-76*

BUT: Does it make sense to segregate SCLC and LCNEC?

- Survival similar in SCLC and LCNEC (identical in low stages)
- Both recognised as high-grade NE tumors
- To date analyses fail to show survival benefit with different treatment options
  - No prospective (controlled) studies exist
- This study demonstrates that with current morphologic criteria overlap exists between SCLC and LCNEC.

Demetri G, Oncology (Williston Park) 1996;10(11 Suppl):179-94.

Travis et al. Am J Surg Pathol (1998) 22:934-944