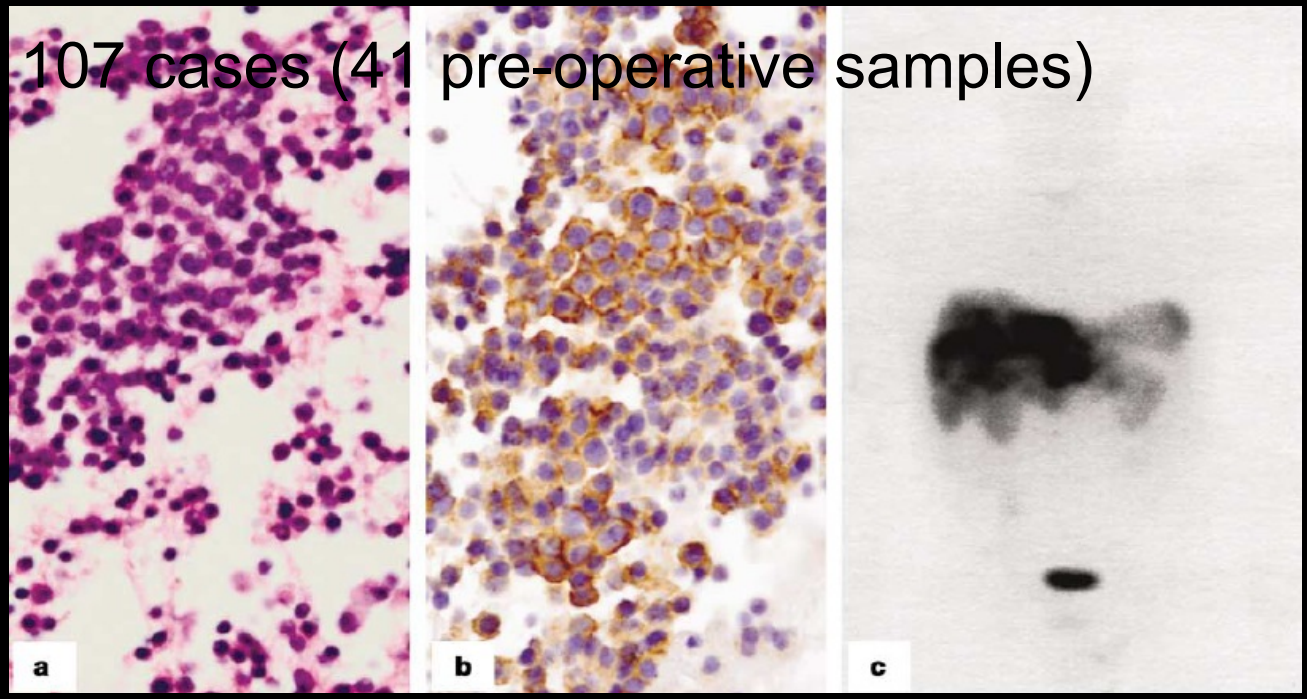
Correlazione tra ICC di SSTR e scintigrafia



Correlazione con:	
Scintigrafia (107 casi)	77%
Risposta ad analoghi (28 casi)	75%

Volante M. et al Mod Pathol. 2007 Nov;20(11):1172-82.

Integrazione tra SSTR IHC e scintigrafia (SRS):

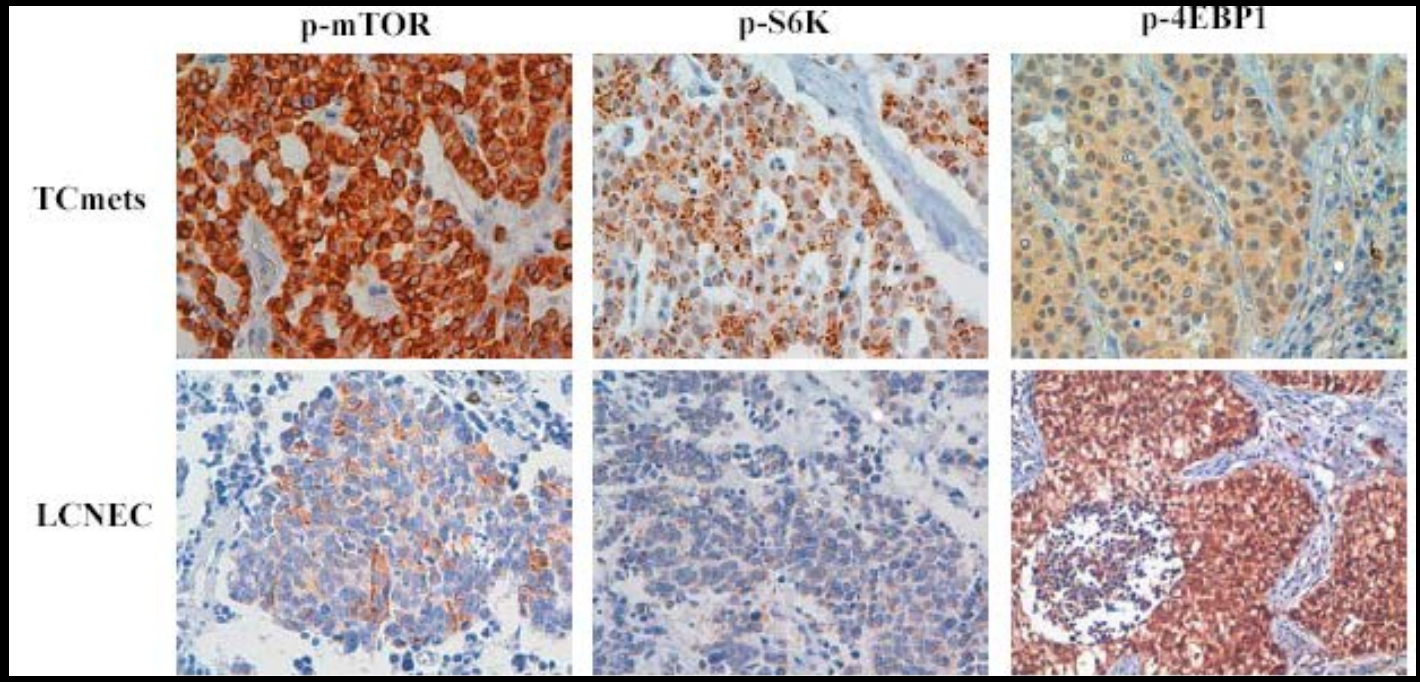
SSTR IHC

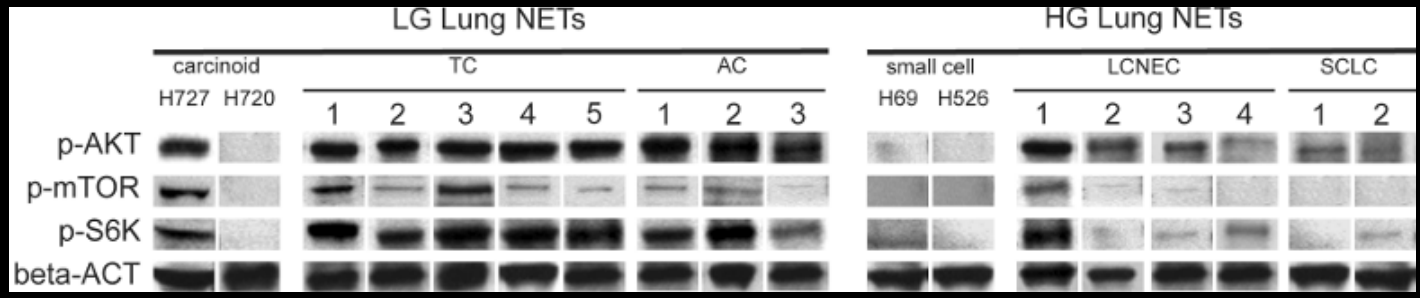
- ✓ poco costosa
- ✓ valutazione della proteina
- ✓ identificazione del sottotipo di SSTR
- ✓ identificazione del tipo cellulare esprimente SSTR
- ✓ applicabile retrospettivamente

SRS

- ✓ identificazione di recettori "funzionanti"
- ✓ determinazione della espressione di SSTR sulla intera "massa" tumorale

Mammalian target of rapamycin signaling activation patterns in neuroendocrine tumors of the lung





Luisella Righi, Marco Volante, Ida Rapa, Veronica Tavaglione, Frediano Inzani[1], Giuseppe Pelosi[2] and Mauro Papotti

Endocrine-Related Cancer (2010) **17** 977–987

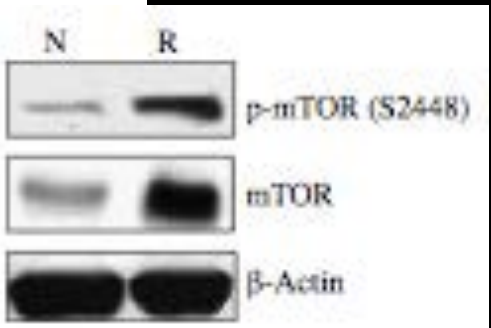
Everolimus as a new potential antiproliferative agent in aggressive human bronchial carcinoids

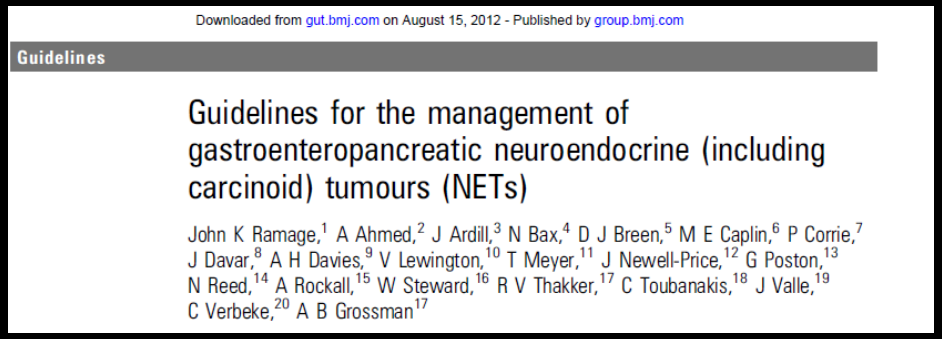
Endocrine-Related Cancer (2010) **17** 1–12

Maria Chiara Zatelli, Mariella Minoia, Chiara Martini[1], Federico Tagliati, Maria Rosaria Ambrosio, Marco Schiavon[2], Mattia Buratto, Fiorella Calabrese[3], Erica Gentilin, Giorgio Cavallesco[4], Lisa Berdondini, Federico Rea[2] and Ettore C degli Uberti

Table 2 Bronchial carcinoid characteristics according to response to everolimus

	Responders	Nonresponders	*P* (responders versus nonresponders
Age	53±5.4	48±4.7	NS
Gender (M/F)	8/7	5/4	NS
Smoking history (yes/no)	6/9	4/5	NS
Diameter (cm)	3.6±0.4	2.16±0.3	<0.05
Lymph node metastases (%)	10.4	3.1	<0.02
Typical/atypical	10/5	9/0	<0.05
Mitotic figures/mm^2	1.7±0.2	0.8±0.1	<0.01
CD105 (counts/mm^2)	43.3±9	25.3±4.3	<0.05
Plasma CgA levels (ng/ml)	496.8±144	57.6±2.1	<0.05
Plasma PP levels (ng/l)	116.6±21	51.2±7.8	<0.05
mTOR mRNA expression (fold versus nonresponders)	900	1	<0.01





Guidelines

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)

John K Ramage,[1] A Ahmed,[2] J Ardill,[3] N Bax,[4] D J Breen,[5] M E Caplin,[6] P Corrie,[7] J Davar,[8] A H Davies,[9] V Lewington,[10] T Meyer,[11] J Newell-Price,[12] G Poston,[13] N Reed,[14] A Rockall,[15] W Steward,[16] R V Thakker,[17] C Toubanakis,[18] J Valle,[19] C Verbeke,[20] A B Grossman[17]

✓ Pathology is currently the diagnostic gold standard

✓ Pathology reporting and review should be made by a patologist member of multidisciplinary team

✓ Pathological characterisation and classification of NETs should be based on the WHO 2010 classification, the UICC TNM 7th ed., and the ENETS site-specific T-staging system.

What is the role of cytology?

- WHO doesn’t recommend tumor grading on cytology speciments
- Different regions within a single tumor (or different sites of metastases) may display different grades
- No widely accepted cut-off on cytological material.

Something else?

Cytological Ki-67 in pancreatic endocrine tumours: an opportunity for pre-operative grading

Cecilia Piani, Giulia M Franchi, Chiara Cappelletti, Marina Scavini, Luca Albarello[1], Alessandro Zerbi[2], Paolo Giorgio Arcidiacono[3], Emanuele Bosi and Marco F Manzoni

General Medicine, Diabetes and Endocrinology Unit, San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, Via Olgettina 60, 20132 Milano, Italy
[1]Pathology Unit, [2]Pancreatic Unit, Department of Surgery, and [3]Gastroenterology and Endoscopic Unit, San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, 20132 Milano, Italy

(Correspondence should be addressed to M F Manzoni; Email: manzoni.marco@hsr.it)

C Piani and G M Franchi contributed equally to this work

Abstract

The cytological Ki-67 expression measured on cytological samples collected by endoscopic ultrasonography-guided fine needle aspiration cytology (EUS-FNAC) may provide pre-operative indications for pancreatic endocrine tumours (PETs) management. The aim of our study was to assess reliability of Ki-67 expression measured on cytological samples obtained by EUS-FNAC in patients with PETs. Eighteen patients with PETs underwent EUS-FNAC before surgery. Ki-67 expression was measured on FNACs and on histological sections. Using a cut-off of 2%, percent agreement of Ki-67 expression on cytological and histological samples was 89% (*k*-statistic: 0.78, 95% confidence intervals (95% CI): 0.5, 1.0). Using cut-off values of 2 and 10%, percent agreement was 78% (*k*-statistic: 0.65, 95% CI: 0.3, 0.9). Ki-67 expression measured on cytological samples obtained by EUS-FNAC before surgery showed good agreement with that measured on histological samples.

Endocrine-Related Cancer (2008) **15** 175–181

ORIGINAL ARTICLE: Clinical Endoscopy

EUS-FNA predicts 5-year survival in pancreatic endocrine tumors

Fátima A. F. Figueiredo, MD, PhD, Marc Giovannini, MD, PhD, Genevieve Monges, MD, PhD, Erwan Bories, MD, Christian Pesenti, MD, Fabrice Caillol, MD, Jean Robert Delpero, MD, PhD

Marseille, France

Capsule Summary

What is already known on this topic

- Recognition of the underlying and variable malignant potential of GI endocrine tumors has led to increased aggressiveness in their treatment.

What this study adds to our knowledge

- In 77 of 86 (90%) patients EUS-FNA was successful in diagnosing pancreatic endocrine tumors.
- It is possible to apply the WHO classification and to determine the potential malignant behavior of PETs in specimens obtained by EUS-FNA.

Gastrointest Endoscopy 2009; 70: 907-914

How to get a “complete” cytological report

- Morfological evaluation
- Immunocytochemical confirmation (chromogranin and synaptophysin)
- Grading evaluation (mitotic counting and Ki67 cell proliferation)
- Looking for primary site in metastatic disease

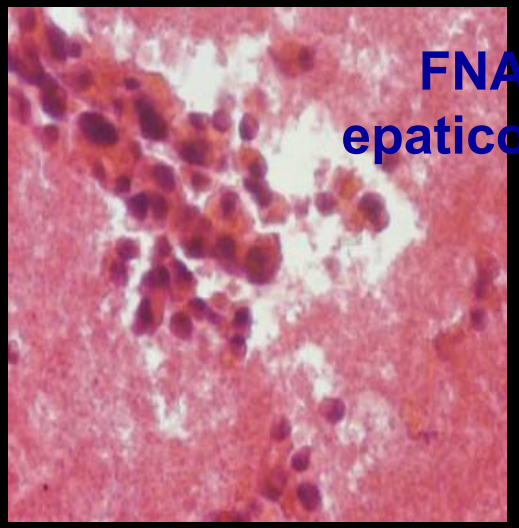
Remember

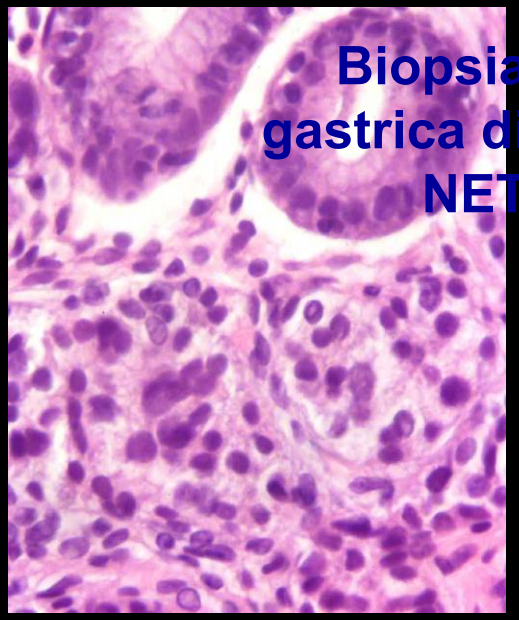
- Grading system should be applied at least to 500/2000 tumor cells
- Cytological material may be the only available information for clinical/therapeutic decisions in inoperable cases*
- In case of small number of tumor cells, don't try to "capture the moon".

Volante M et all. Virchow Arch (2011) 458: 393-402

Classificazione WHO 2010 in fase preoperatoria

- ✓ Definizione di NEN: sospetto + markers
- ✓ Differenziazione tra NET e NEC: incostantemente possible (dimensione cellulare, atipia, necrosi, pattern di crescita)
- ✓ Grading: applicabile ma con limiti tecnici rilevanti.





Classificazione dei NET polmonari (WHO)

"……The major categories of morphologically identifiable neuroendocrine tumors are

1. Small cell carcinoma (SCLC)
2. Large celle neuroendocrine carcinoma (LCNEC)
3. Typical carcinoid (TC)
4. Atypical carcinoid (AC)…….

"…..**Historical terms** such as well-differentiated neuroendocrine
carcinoma, neuroendocrine carcinoma (grade 1-3), intermediate cell
neuroendocrine carcinoma, malignant carcinoid and peripheral small
cell carcinoma resembling carcinoid, **should be avoided**."

Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC.
WHO classification of tumours. Pathology and genetics of tumours of the lung, pleura,
thymus and heart. IARC Press, Lyon, 2004.

Classificazione dei tumori neuroendocrini polmonari

- Grading basato su conta mitosi e presenza di necrosi.
- Ancora utilizzato il termine carcinoide per i tumori di basso grado
- Il primo organo per cui si è utilizzato il termine LCNC (Travis et al, 1991), entità ora distinta anche in altri organi non NE quali parotide, laringe, colecisti, retto, rene, vescica, utero, prostata.

Table 2. WHO criteria for diagnosis of neuroendocrine tumours of the lung.

Typical carcinoid	Well-differentiated neuroendocrine neoplasm with <2 mitoses per 2 mm^2 (10 HPF), lacking necrosis, and ≥ 0.5 cm
Atypical carcinoid	Well-differentiated neuroendocrine neoplasm with 2–10 mitoses per 2 mm^2 (10 HPF) and/or focal necrosis
Large-cell neuroendocrine carcinoma	Poorly differentiated neuroendocrine carcinoma (organoid nesting, palisading, rosettes, trabeculae) with high mitotic rate (11 per 2 mm^2 and 10 HPF; median of 20 per 2 mm^2 and 10 HPF) and necrosis (often large zones). Cytological features: large cell size, low nuclear/cytoplasmic ratio, vesicular, coarse or fine chromatin, and/or frequent nucleoli
Small-cell carcinoma	Poorly differentiated neuroendocrine carcinoma. Cytological features: small cells with scant cytoplasm, fine granular chromatin, absent or faint nucleoli, high mitotic rate (11 per 2 mm^2 and 10 HPF; median of 80 per 2 mm^2 and 10 HPF), frequent necrosis often in large zones

HPF, high-power field.
Modified from Travis et al (2004, *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart.* WHO classification of tumours. Lyon: IARC Press).

Carcinoide tipico:

1. Dimensioni: > 0.5 cm di diametro. Se < 0.5 cm si parla di **tumorlet**.

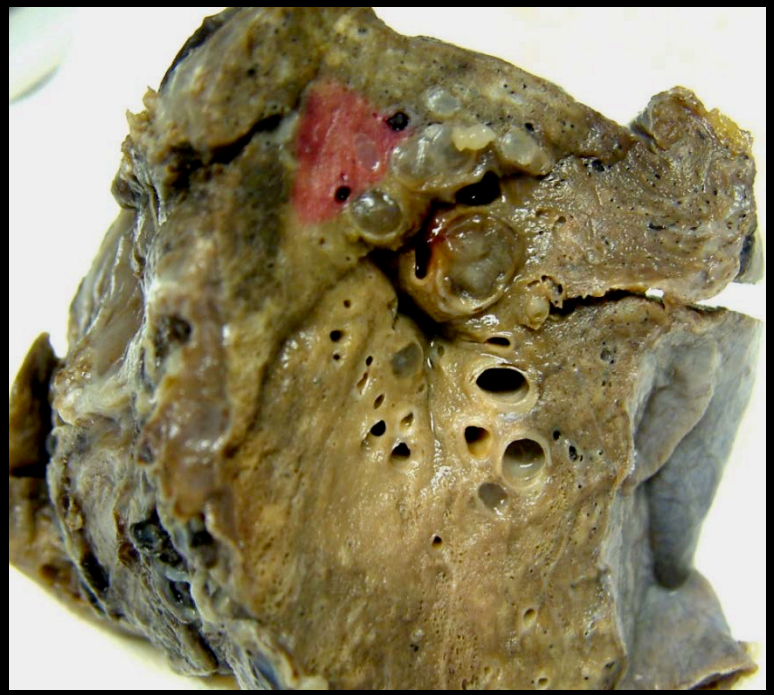
2. Attività mitotica:
   < 2 mitosi per 2 mm^2 (10 HPF)

   Le mitosi devono essere contate nelle aree con maggiore indice mitotico.

   I campi considerati devono essere occupati da cellule neoplastiche.

3. Necrosi: assente

4. Atipia citologica:
   caratteristica diagnostica non affidabile



Carcinoide atipico:

1. Attività mitotica:
   inizialmente compresa tra 5 e 10 mitosi per 10 HPF

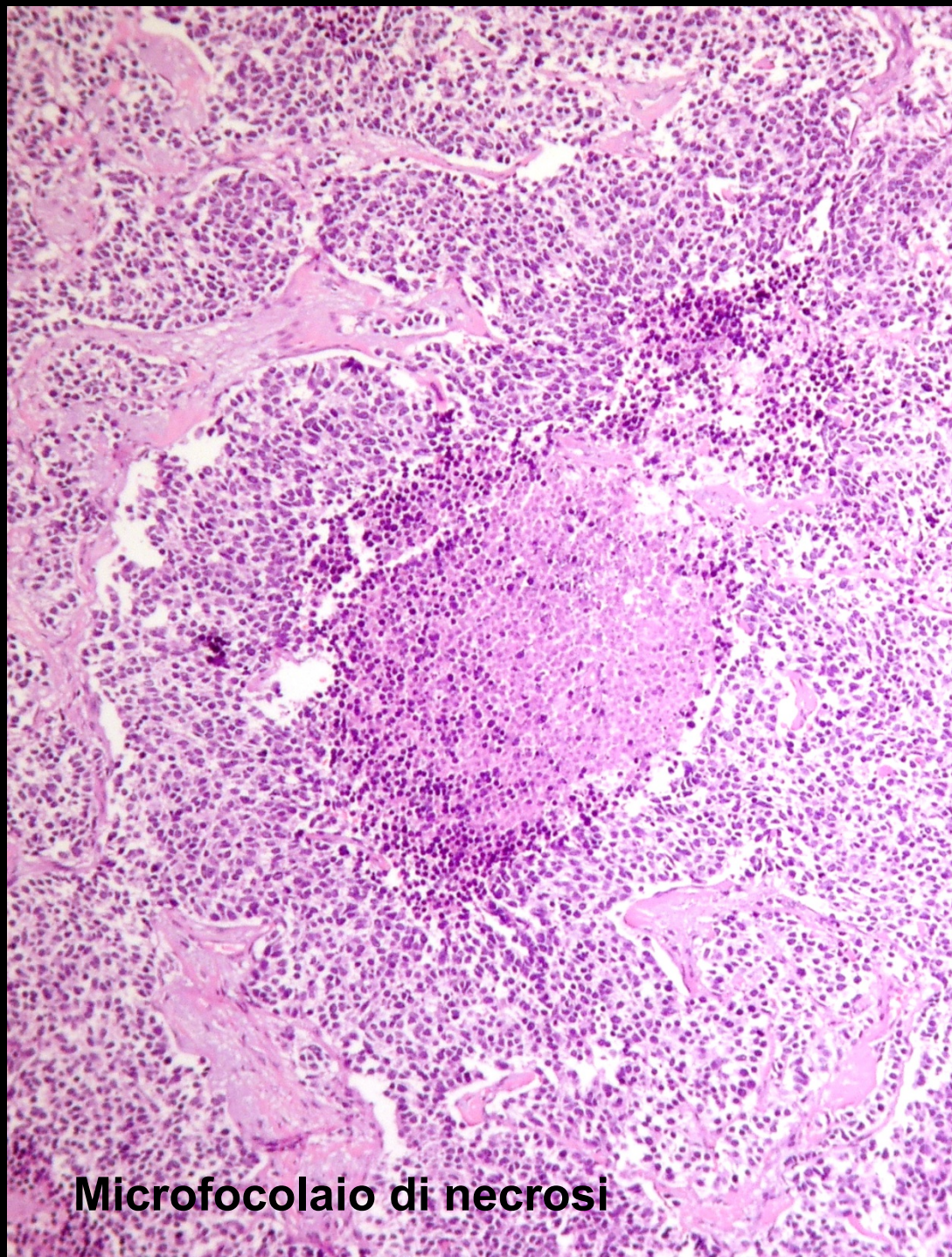
   Arrigoni MG et al. Atypical carcinoid tumours of the lung. J Thorac Cardiovasc Surg 1972; 64:413-421.

   Successivamente modificata a 2-10 mitosi per 2 mm^2 (10 HPF)

   Travis WD et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22:934-944.

2. O presenza di necrosi
   spesso piccoli focolai

3. Atipia citologica:
   caratteristica diagnostica non affidabile



Microfocolaio di necrosi

PROFILO MORFOLOGICO ED IHC	CARCINOIDE TIPICO	CARCINOIDE ATIPICO
DIMENSIONE	≥5mm	>5 mm
MONOMORFISMO CELLULARE	++	+/-
NUCLEOLO	-	-/+
MITOSI	<2/10HPF	2-10/10HPF
NECROSI	ASSENTE	PUNTIFORME
IHC	Cromo A+, Sin +, CD56+	Cromo A+, Sin +, CD56+

MORFOLOGIA	SCLC	LCNEC
PATTERN NEUROENDOCRINO	+/-	+++
CELLULARITA’	PICCOLA TAGLIA	GROSSA TAGLIA
ATIPIE	+++	+++
CITOPLASMA	SCARSO	ABBONDANTE
NUCLEOLO	ASSENTE	PROMINENTE
MITOSI	>11/10 HPF	>11/10HPF
NECROSI	ESTESA	AMPIE ZONE
IHC	CROMO+, SYN+, CD56+ TTF1+	CROMO+, SIN+, CD56+ TTF1+

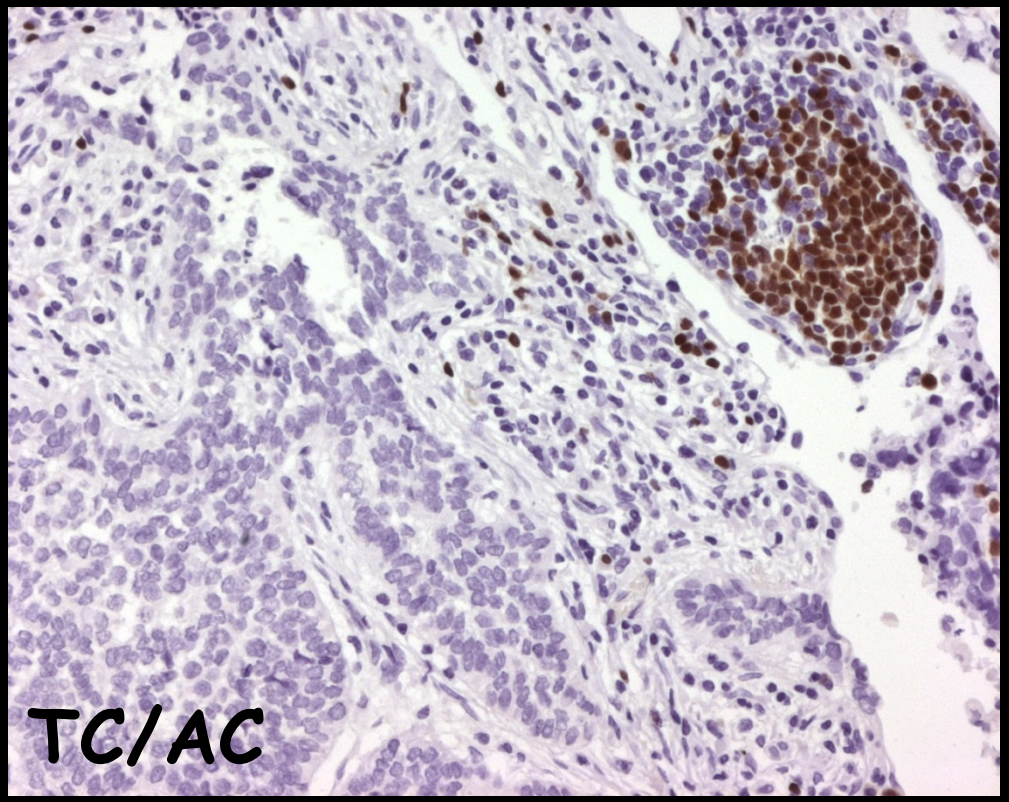
Am J Clin Pathol. 2008 Apr;129(4):556-62. MetaPress Links

PAX-5 expression in pulmonary neuroendocrine neoplasms: its usefulness in surgical and fine-needle aspiration biopsy specimens.

Sica G, Vazquez MF, Altorki N, Port J, Lee PC, Liu Y, Hyjek E, Saqi A.

Department of Pathology, Weill Cornell Medical Center, New York, NY, USA.

PAX-5 expression is a useful marker for the discrimination of high-grade NECs (78%) from low-to intermediate-grade NECs (0%)



Problemi aperti

- ✓ Applicabilità della nuova classificazione da verificare
- ✓ Grading da implementare (G2, sede)
- ✓ Sistema di staging migliore da validare
- ✓ Identificare e validare marcatori prognostici/ predittivi
- ✓ MEEC/MANEC
- ✓ Classificazione dei NET polmonari da omogenare