XV Corso di aggiornamento
per operatori dei registri tumori

I tumori polmonari: diagnosi cito-istologica

MODENA

6-8 ottobre 2015
Sala Oratorio
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Pamela Sighinolfi

Anatomia Patologica
Azienda Ospedaliero-Universitaria di Modena

Modena, 7 ottobre 2015

editorial

Clinical Lung Cancer, Vol. 10, No. 3, 148-150, 2009
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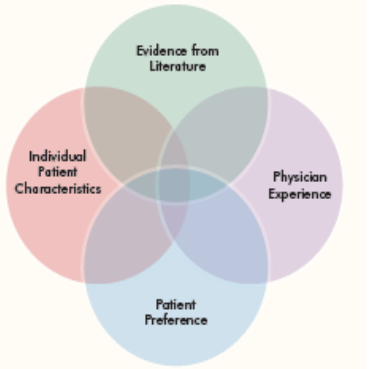
David R. Gandara, MD[1]
Primo N. Lara, Jr, MD[1]
Philip Mack, PhD[1]
Giorgio Scagliotti, MD[2]

[1]University of California, Davis Cancer Center, Sacramento
[2]University of Turin, Italy

Individualizing Therapy for Non–Small-Cell Lung Cancer: A Paradigm Shift from Empiric to Integrated Decision-Making

New basic and clinical research findings in non–small-cell lung cancer (NSCLC) are revolutionizing both our concepts about this malignancy and our clinical practice patterns. Current practice for selection of therapy in patients with advanced-stage NSCLC, and many other tumor types as well, is largely empiric. In general, each time a treating oncologist selects therapy, 4 different dimensions (Figure 1) are considered in the decision-making process: (1) evidence from the literature (ie, therapeutic ratio of different regimens); (2) individual patient characteristics (ie, age, sex, performance status, smoking status); (3) patient preference (ie, desire for longer life versus quality of life); and (4) physician experience and preference. Although this empiric process serves most patients well, in 2009 a paradigm shift has begun in which decision-making is beginning to move from "empiric" to what can be called an "integrated" approach. As summarized in the Table 1, a variety of emerging selection factors now make it possible to consider customizing therapy in individual patients with NSCLC by integrating clinical, histologic, and molecular factors. Because possible selection factors now list in the hundreds, only representative examples for which data appear most robust are listed in Table 1.

Figure 1 Empiric Approach to the Selection of Therapy for Non–Small-Cell Lung Cancer



First and foremost, previous studies have documented that clinical factors such as female sex, never-smoking status, and East Asian ethnicity are associated with response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Despite this clear association, the recently reported IPASS trial, performed entirely in East Asian patients with adenocarcinoma (94% never smoking and about 80% female) strikingly demonstrates that a molecular selection factor (EGFR TK domain mutation) "trumps" clinical features in predicting benefit from the EGFR TKI gefitinib.[1] In this study, in which East Asian patients with advanced NSCLC were randomized to gefitinib or chemotherapy, response and progression-free survival were highly associated with EGFR mutation status. Those patients with tumors harboring EGFR TK domain mutations did much better with gefitinib, whereas those with wild-type EGFR tumors fared better with chemotherapy, despite near uniformity in clinical factors that would have suggested superior outcomes with gefitinib. Because approximately 85% of North American NSCLC tumors are wild type for EGFR, this finding has significant implications for individualizing therapy. As discussed further below, other molecular factors (eg, *K-ras* mutation, EGFR gene copy number by fluorescence in situ hybridization [FISH]) have also recently been reported to have predictive value in the selection of EGFR-directed therapies.

Additional clinical factors are now being used in day-to-day practice to select patients for various treatment approaches. For example, although chemotherapy plus bevacizumab is generally accepted in North America as a standard of care for advanced NSCLC, bevacizumab-containing regimens are contraindicated in patients with NSCLC of the squamous cell subtype (SCCA), because of an increased risk of inducing life-threatening hemoptysis.[2] Recent data from the E4599 trial also suggested reduced benefit and more toxicity in patients aged > 70 years, approximating 50% of all NSCLC patients in the United States.[3]

Sciencexpress Report

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

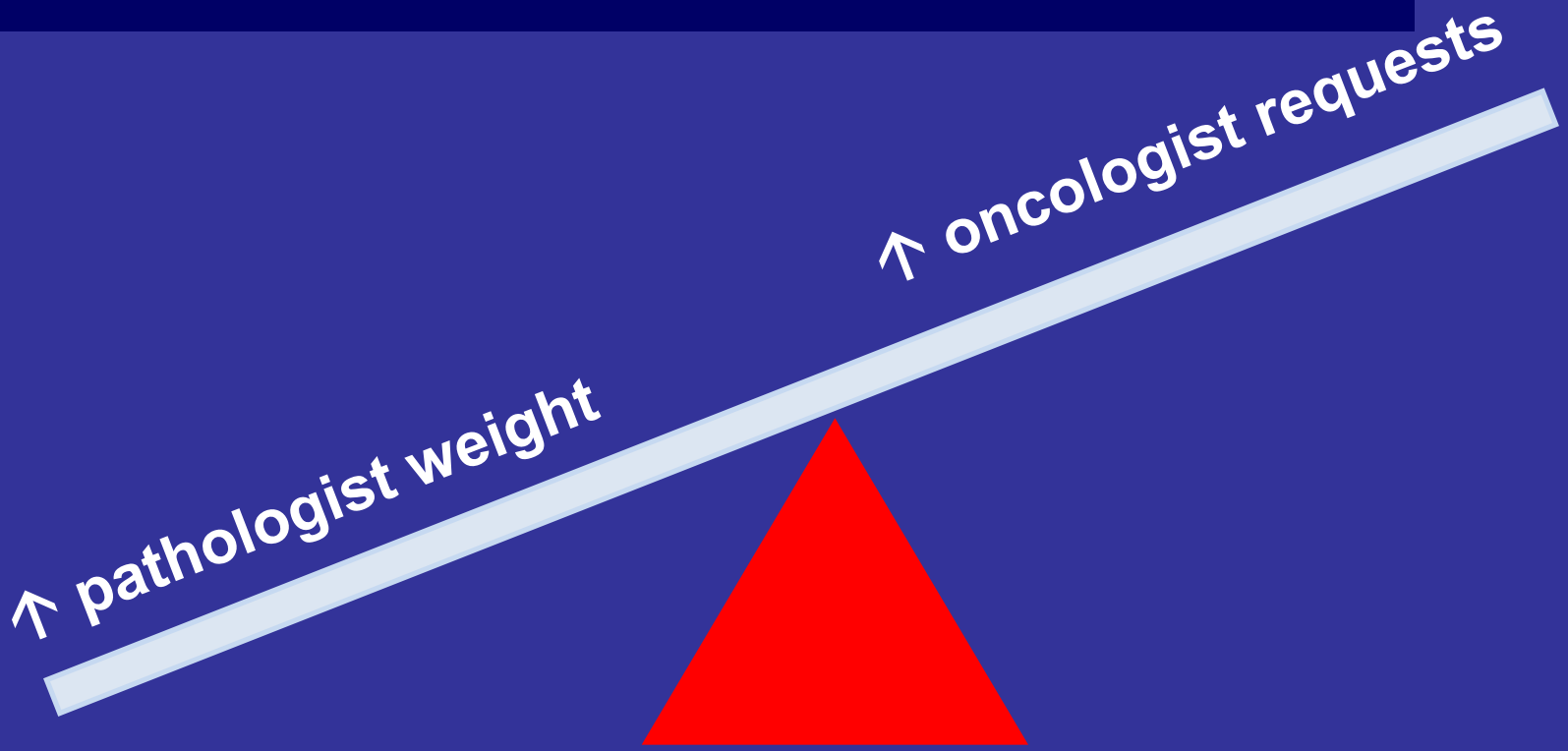
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*†‡, Vincent Miller‡§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis‡‡, Doris Kupfer‡‡, Richard Wilson‡‡, Mark Kris‡§, and Harold Varmus*

The advent of targeted therapies

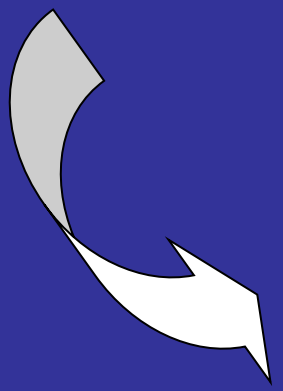
- Classify NSCLC
- Elegibility for molecular testing



The past

- **SCLC vs NSCLC**

2008



2015

The present

- **SCLC vs NSCLC**
- **NSCLC subtype**
- **EGFR (+/-KRAS) muts**
- **ALK**
- **ROS-1**
- **c-met**
- **Others (BRAF, HER2, RET …..)**

mandatory **optional**

WHY to subtype NSCLC ?

Histology Matters: Individualizing Treatment in Non-Small Cell Lung Cancer

JOEL W. NEAL

The Oncologist 2010

Therapy	Histologic subtype	Notes
Erlotinib, gefitinib	Adenocarcinoma; nonmucinous bronchioloalveolar carcinoma	Higher response rates in tumors with *EGFR* mutations; negligible response rate in tumors with *KRAS* mutations; intermediate effects in some patients with other histologic types.
Pemetrexed	Nonsquamous NSCLC	Adenocarcinoma may be more susceptible because of lower thymidylate synthase levels.
Bevacizumab	Predominantly nonsquamous NSCLC	Higher risk for fatal pulmonary hemorrhage with squamous cell histology; risk may be lower with small peripheral squamous tumors.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

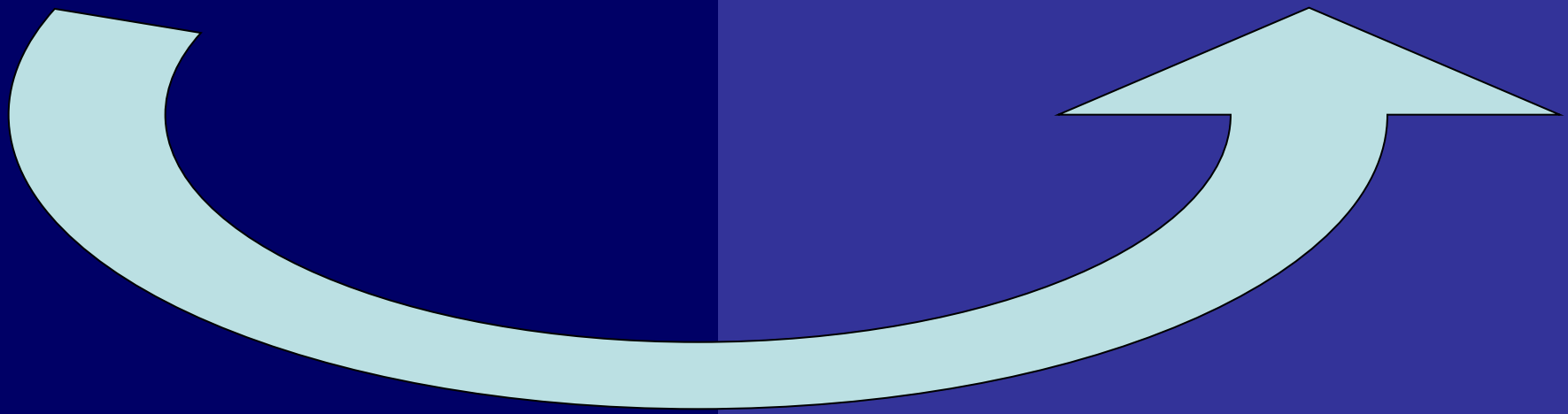
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

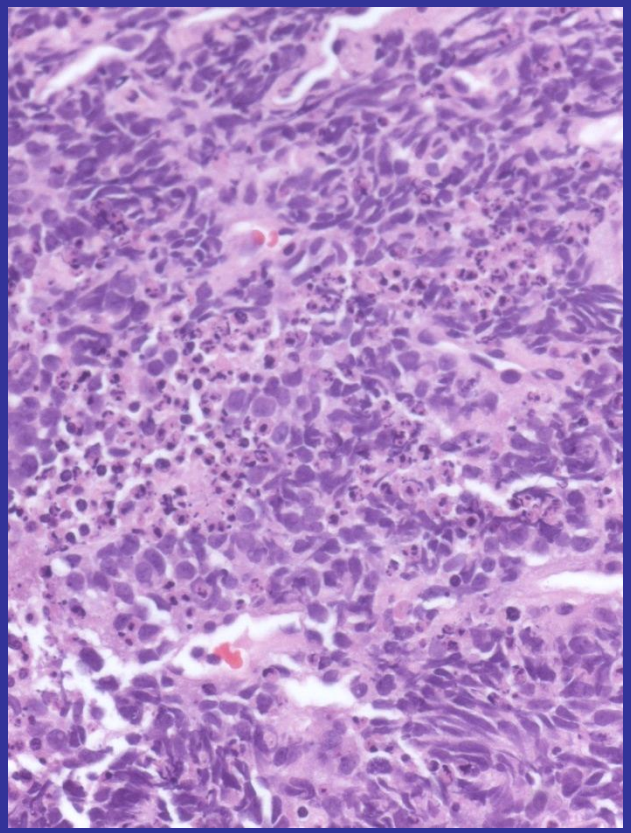
N Engl J Med 2015; 373:123-135 | July 9, 2015 | DOI: 10.1056/NEJMoa1504627

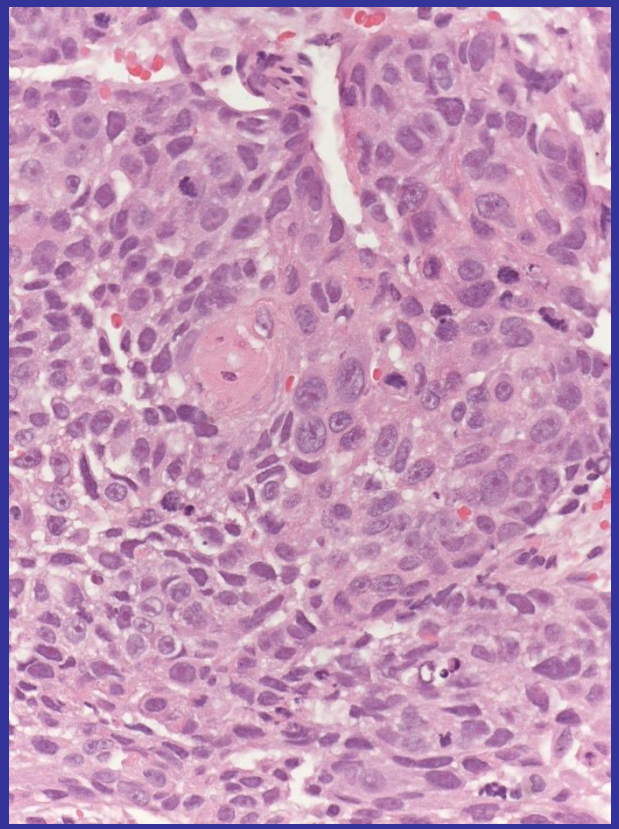
Pathologists for Pathologists

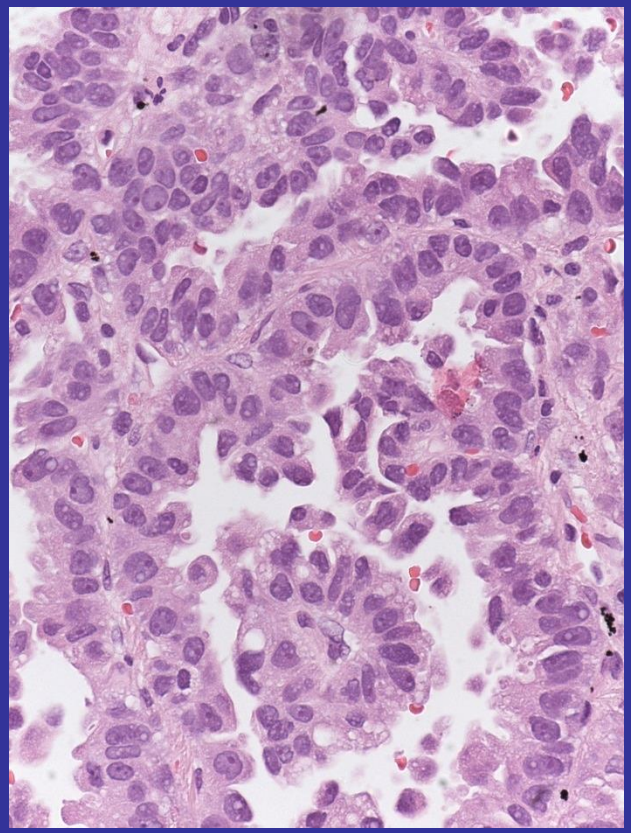
Pathologists for Clinicians



Once upon a time … histotype







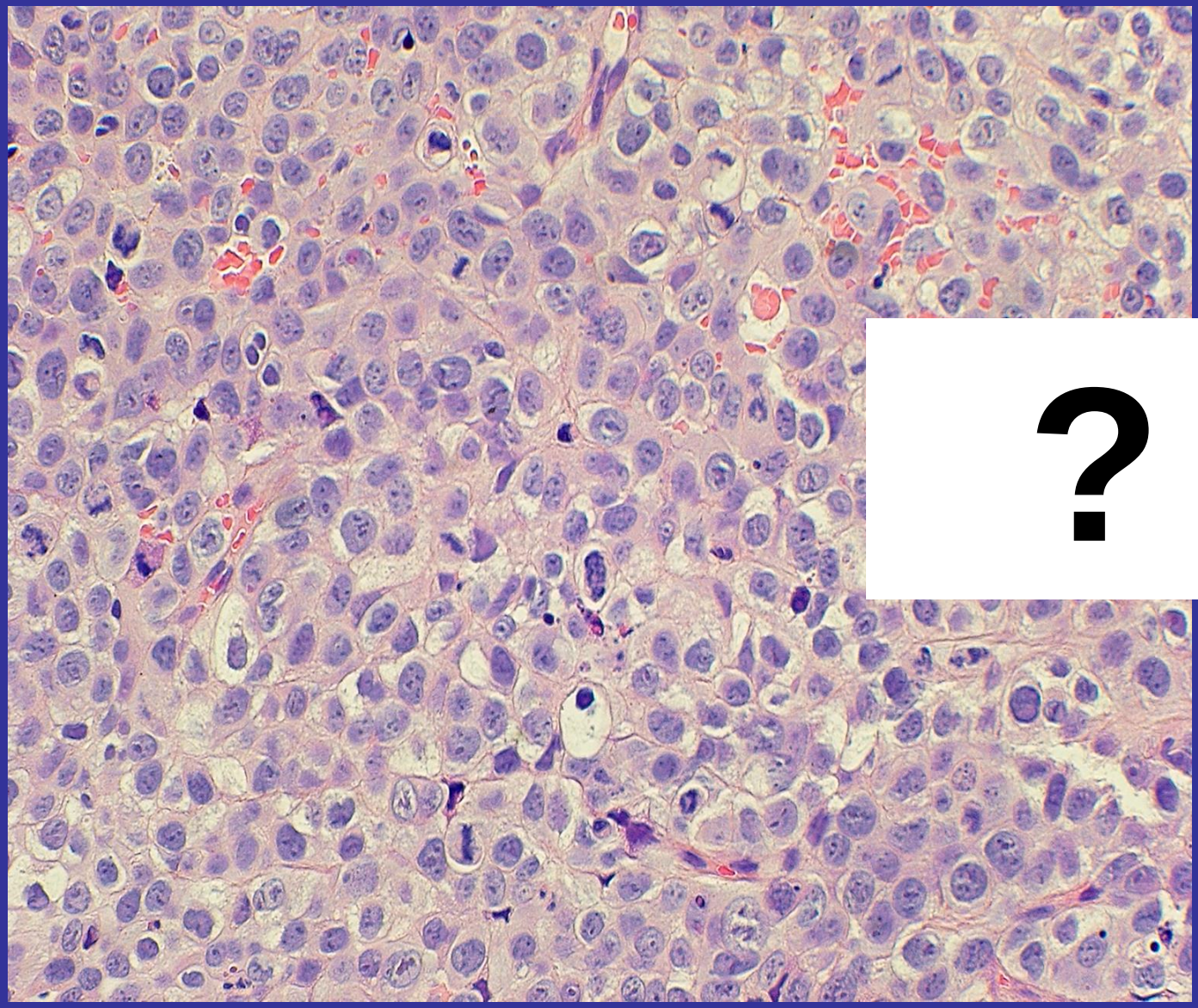
SCLC

SqCC

ADC

NSCLC

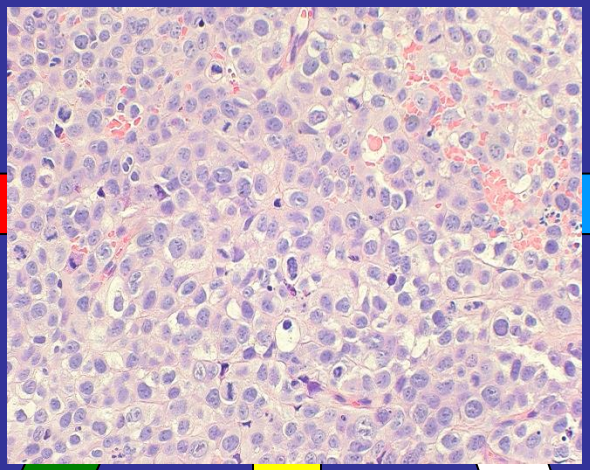
NSCLC poorly differentiated



?

What does NSCLC mean ?

25%
Squamous
cell carcinoma



50%
Adenocarcinoma

Large cell carcinoma
10%

Metastatic carcinoma
5%

Others (salivary gland-type, sarcomatoid, others)
10%

Subtyping NSCLC

3 basic lung cancer IHC patterns

- TTF-1
- Surfactant (A & B)
- Napsin A
- CK7

Adenocarcinoma

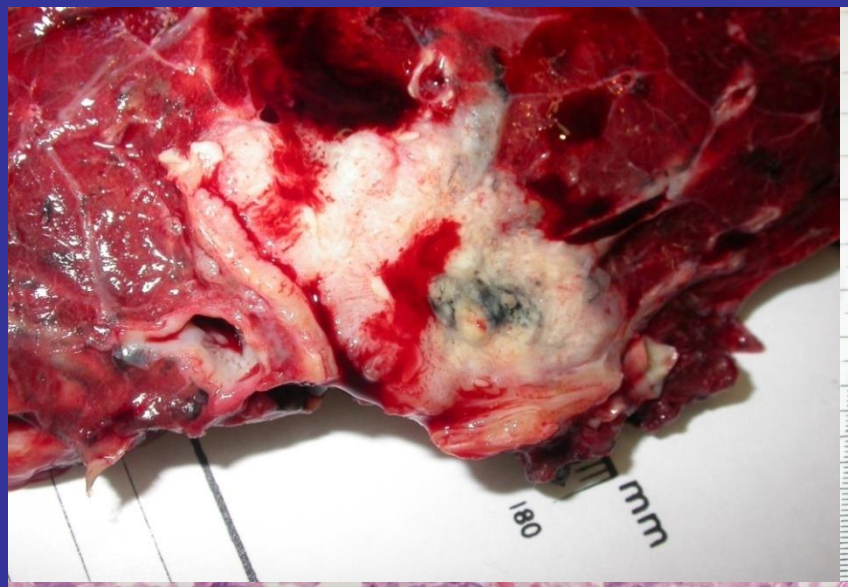
- p63/p40
- HMWCKs (CK5/6 or 34betaE12)
- Desmo-3
- S100A7

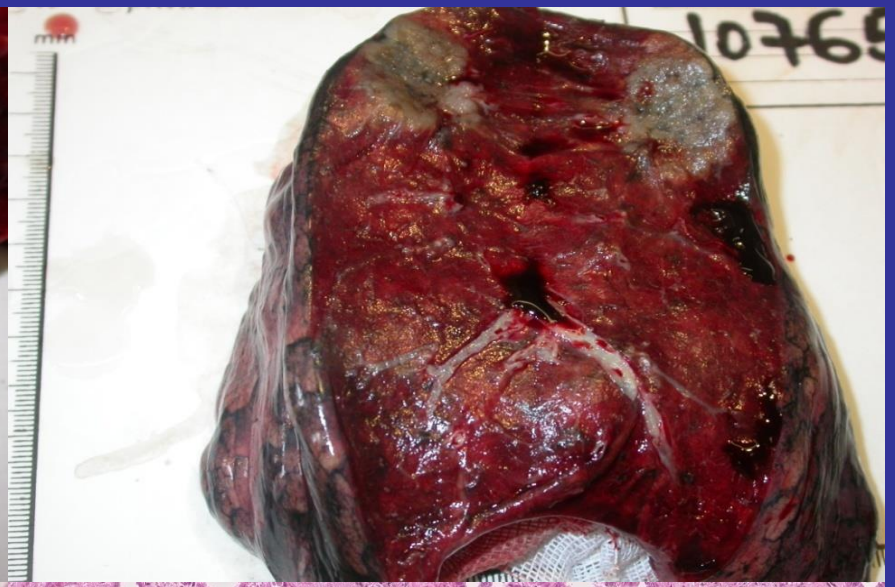
Squamous cell carcinoma

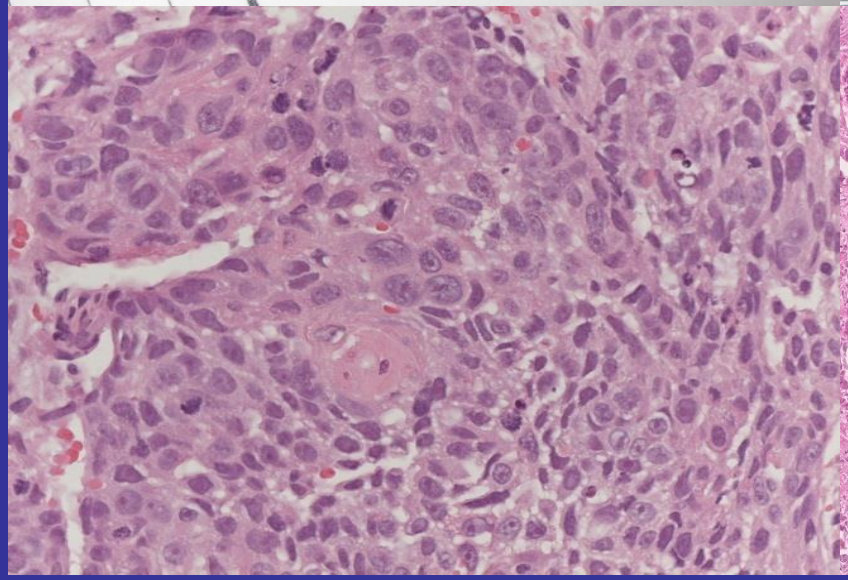
- ChrA
- Syn
- CD56
- CD57

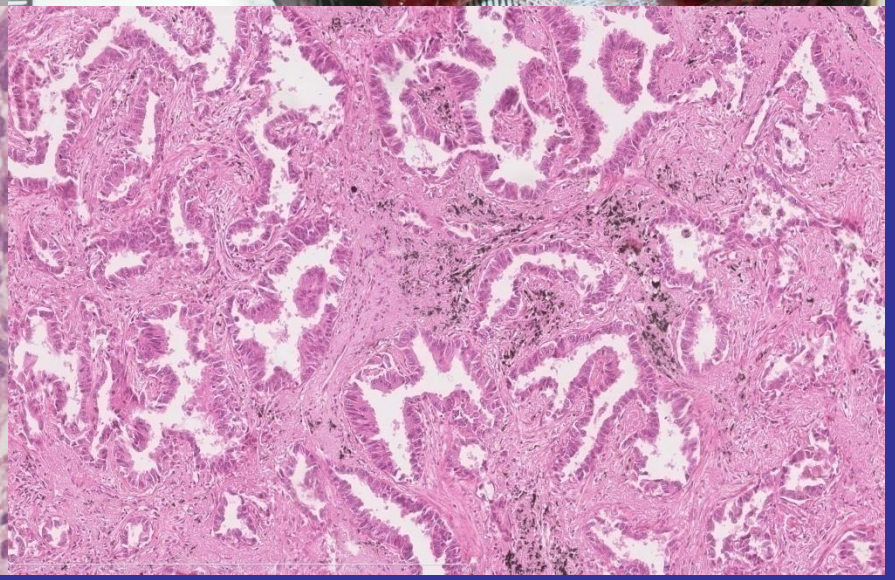
NE carcinoma

Only 25-30% of NSCLC are resectable . . .

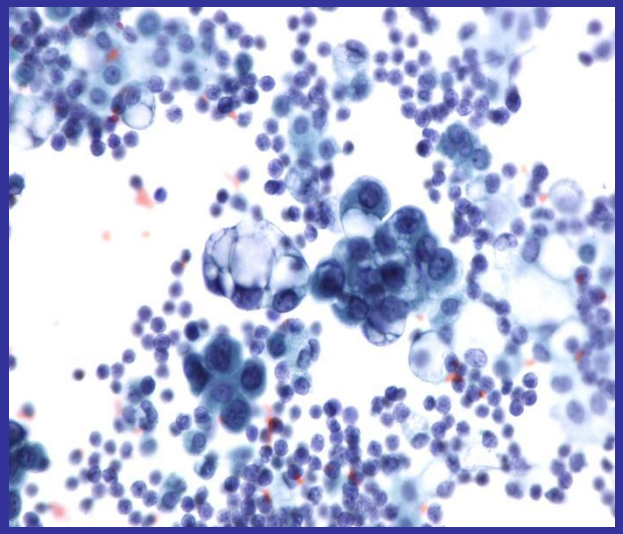
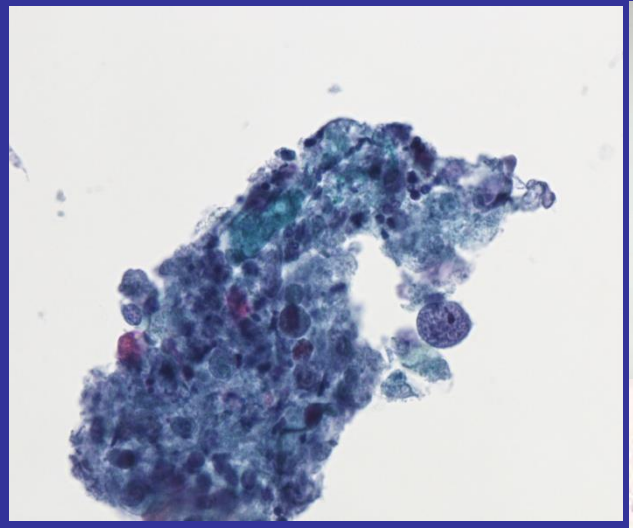
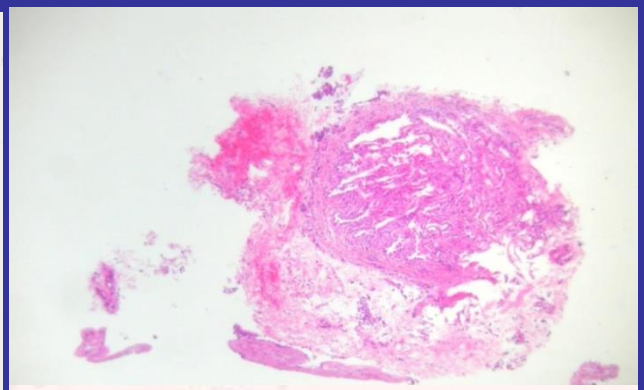
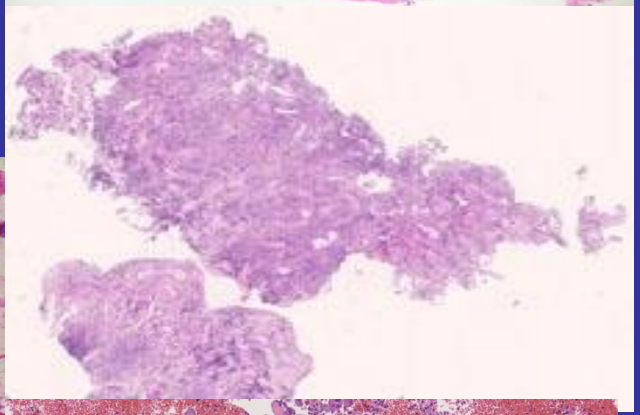
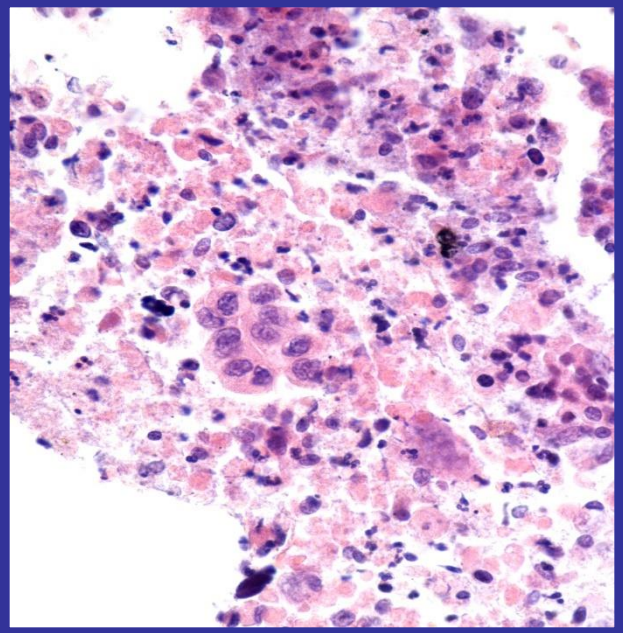
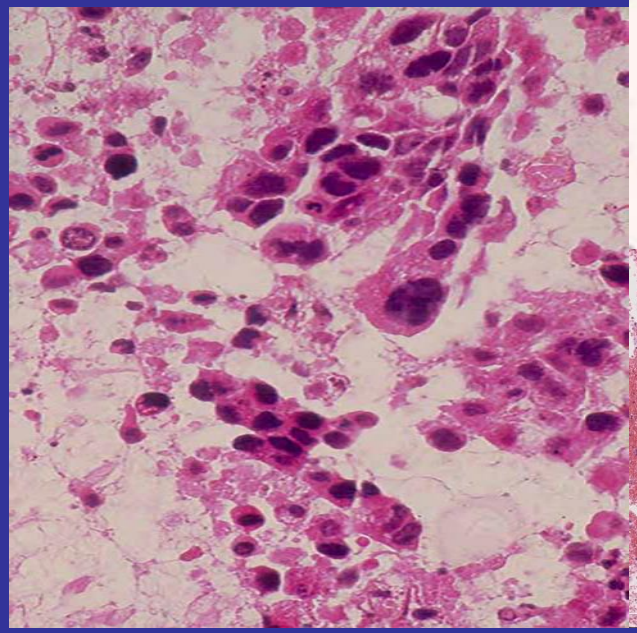
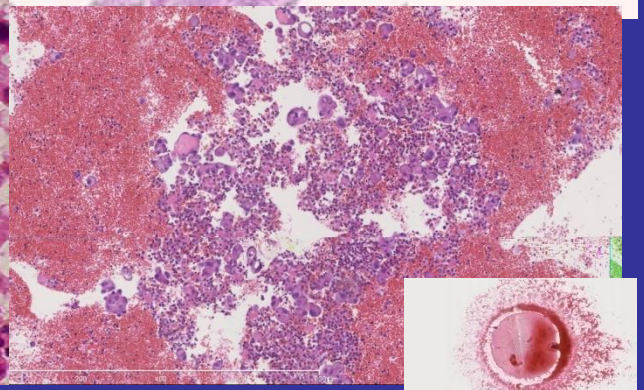








…therefore, diagnosis is mainly based on cytological samples or small biopsies

WHO Classifications

1967 HE

1981 HE & Mucin

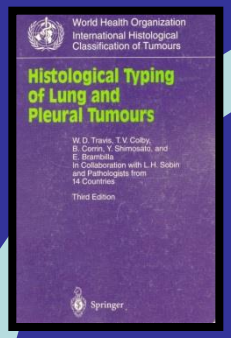
1999 HE, Mucin & IIC

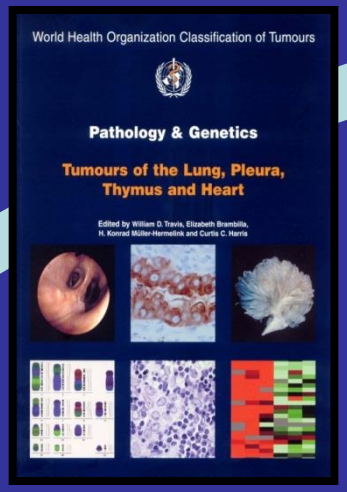
2004 HE, Mucin, IIC & Genetics

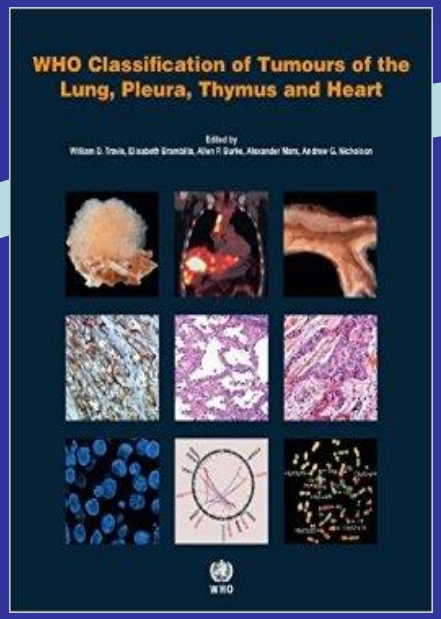
2015 HE, Mucin, IIC & Genetics

for resections

includes small specimens







Use of immunochemistry

- Immunohistochemistry is now recommended, when possible, not only for small biopsies/cytology, but also for resected specimen.
- Whit certain drug approved for specific subgroups of NSCLC patients the requirement for more exact histopathological subtyping is mandatory.

Travis WD et al. *J Thorac Oncol.* 2015;10: 1243–1260

Terminology and criteria in non-resected specimens (1)

Small samples: NSCLC Subtyping

- Established morphological criteria present:

Glandular differentiation and/or mucin → **ADC**
Intercellular bridges and/or keratinization → **SCC**

- Established morphological criteria absent: → **do IHC**

Terminology and criteria in non-resected specimens (2)

Small samples: NSCLC Subtyping

- ADC: TTF1, Napsin
  - Expression may be focal
  - Coexpression with squamous marker possible
- SCC: p40, P63,CK5/6
  - Expression diffuse
  - TTF1 not allowed
- NSCLC,NOS note : possibly ADSC
  - TTF1 and p40 expression in diff. cell populations

Terminology and criteria in non-resected specimens (3)

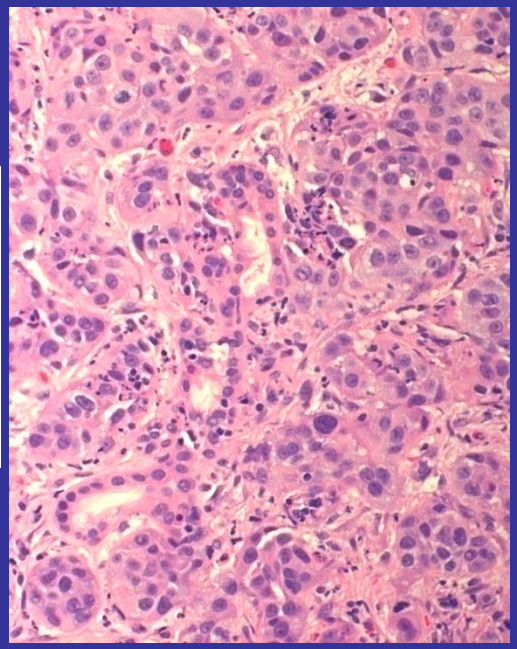
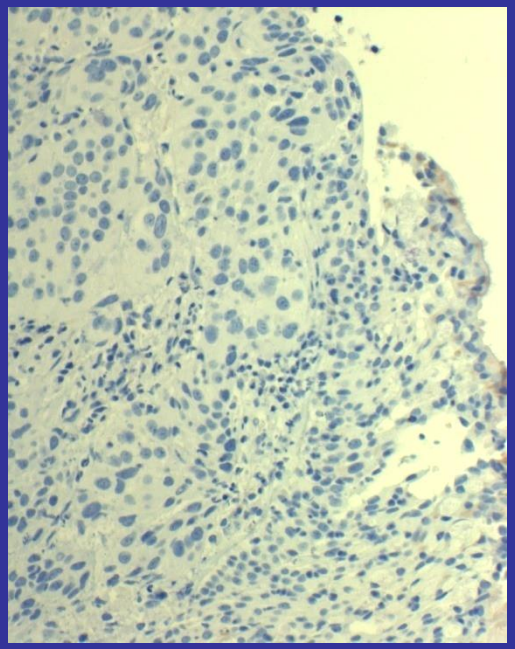
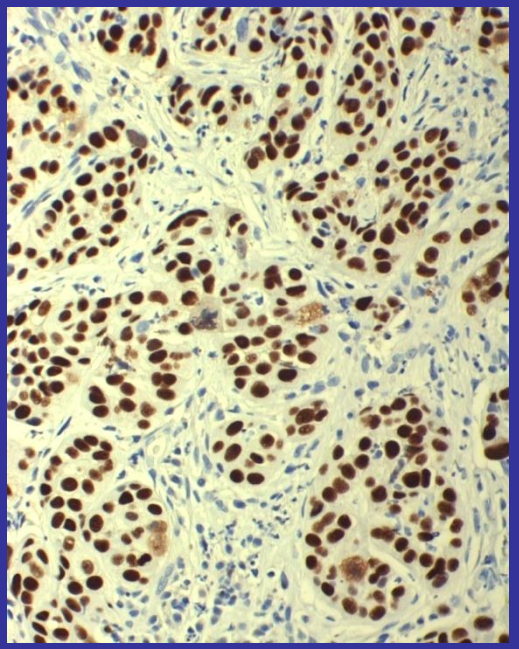
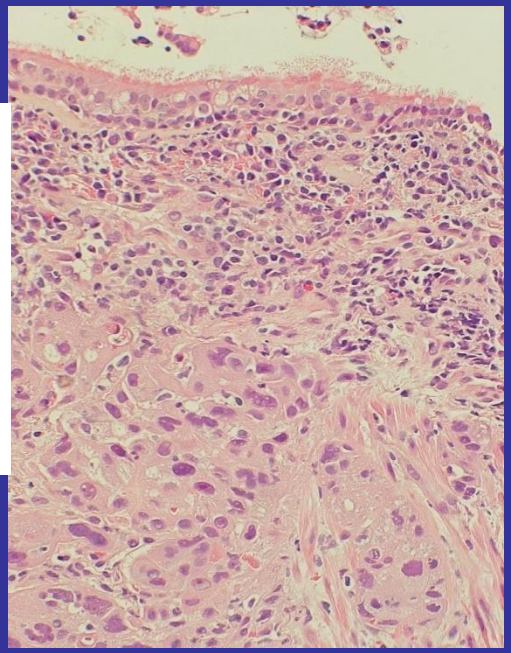
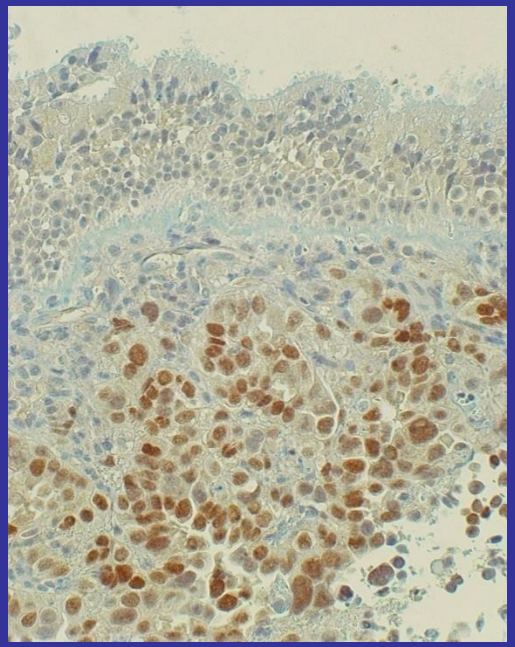
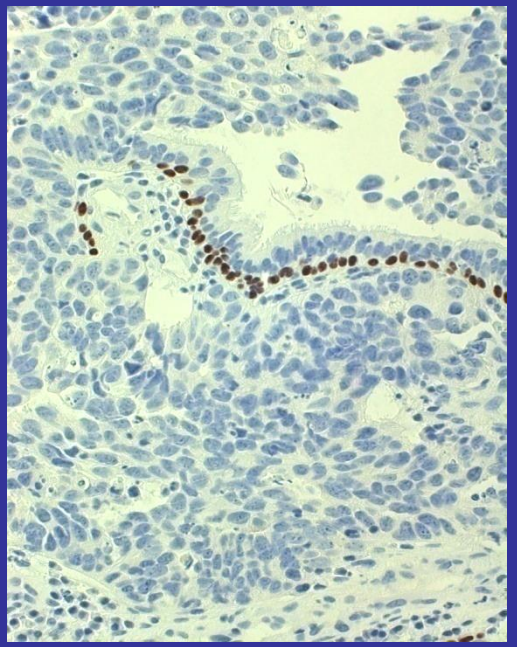
Small samples: NSCLC Subtyping

- Established morphological criteria present:

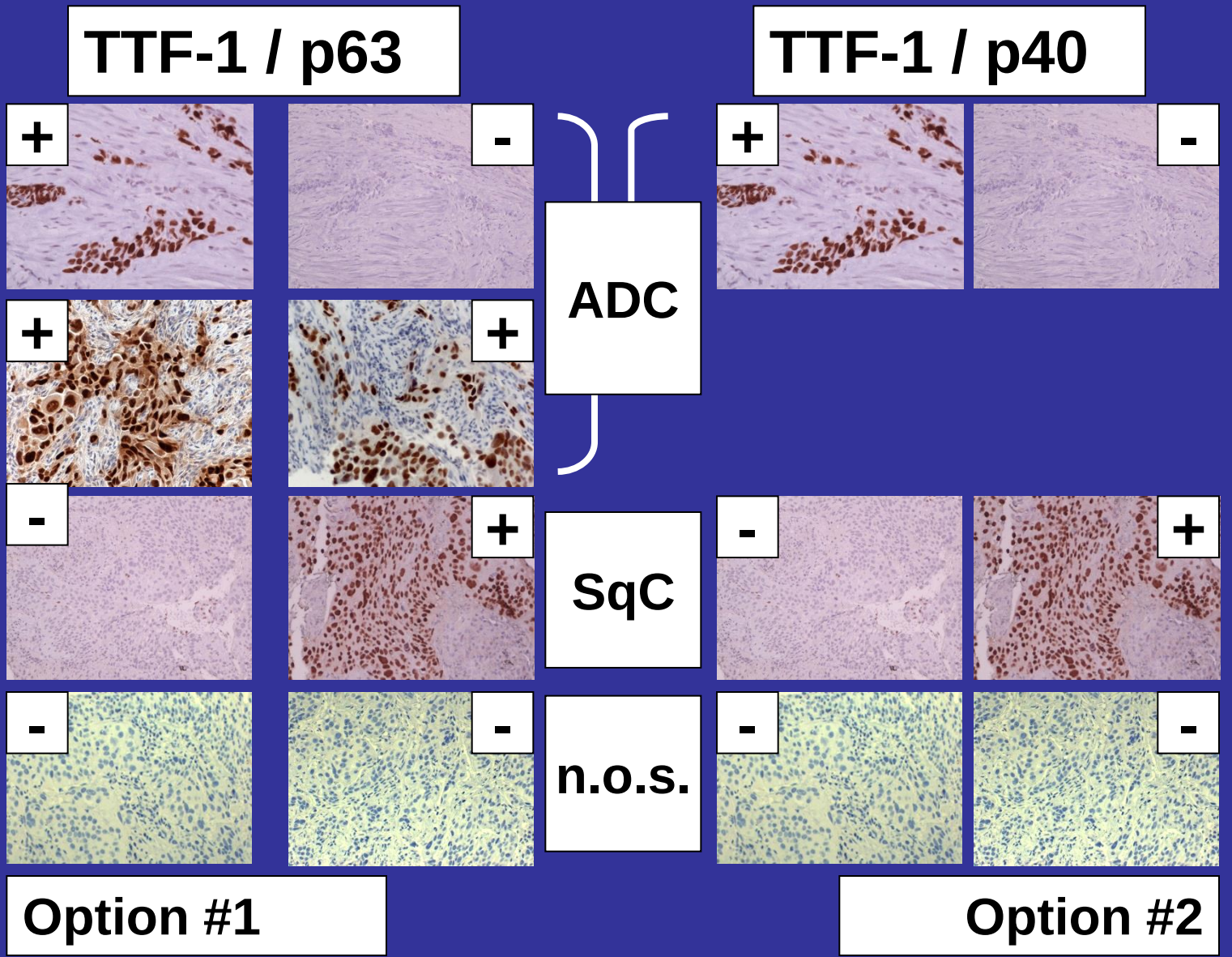
  Glandular differentiation and/or mucin → **ADC**
  Intercellular bridges and/or keratinization → **SCC**

- Established morphological criteria absent → do IHC:

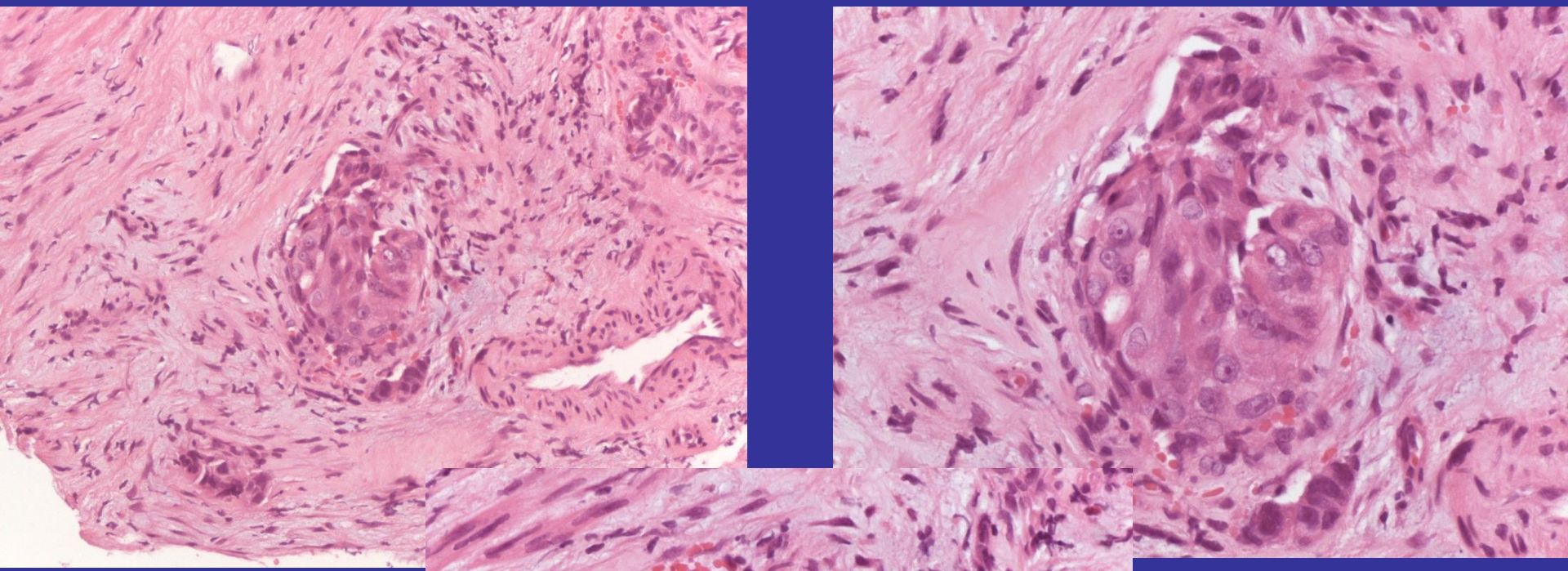
  TTF1+ → **NSCLC, favor ADC**
  p40+ → **NSCLC, favor SCC**
  Inconclusive → **NSCLC, NOS**

	H&E	TTF-1	p63 or p40
NSCLC on H&E SQC at IHC			
NSCLC on H&E ADC at IHC			

Diagnostic algorithms in NSCLC subtyping



Mistakes may happen !!!

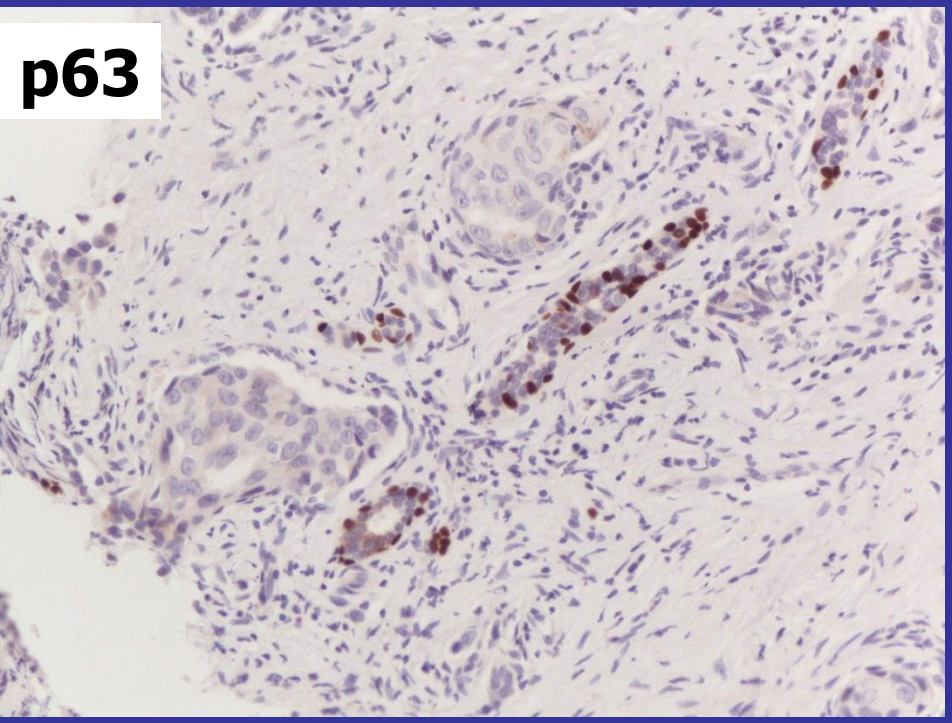


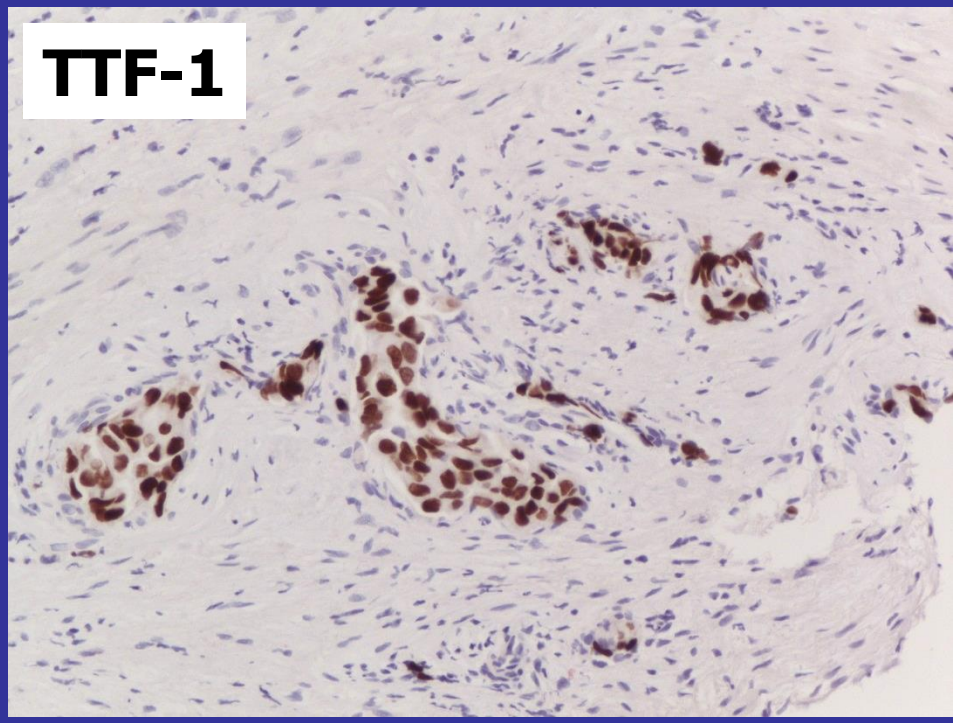
- 65 yr man
- Smoker
- Central mass

(8 cm across)

Squamous cell carcinoma

Mistakes may happen !!!

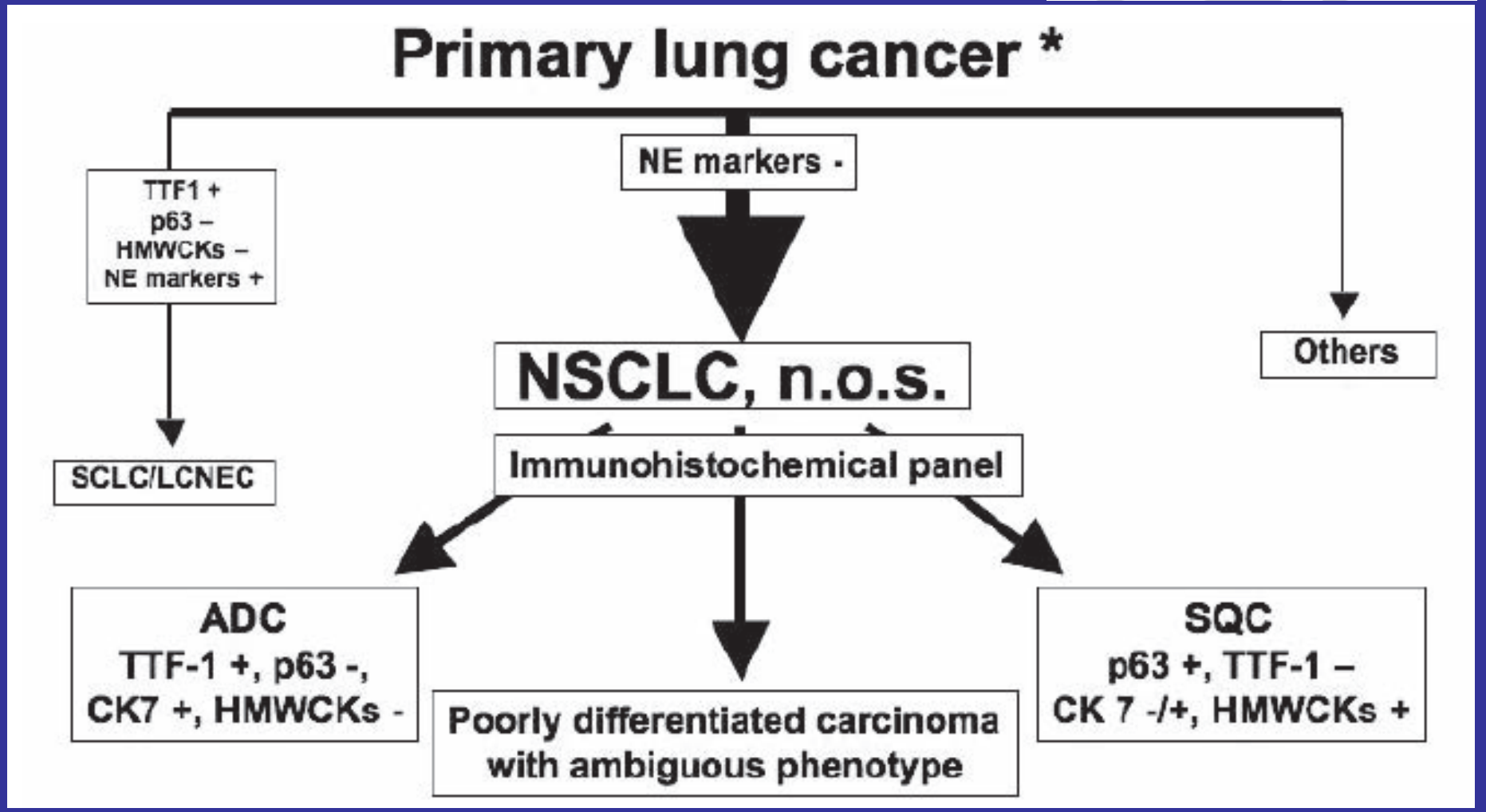




Nowadays, this mistake can preclude some therapeutic strategies in treatment of lung cancer

Diagnostic algorithm of immunohistochemical markers in subtyping primary lung cancer

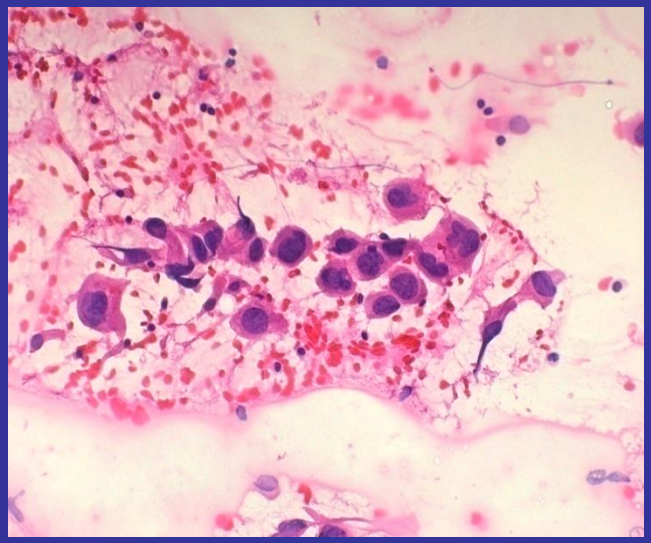
International Journal of Surgical Pathology
Volume 17 Number 3
June 2009 206-218

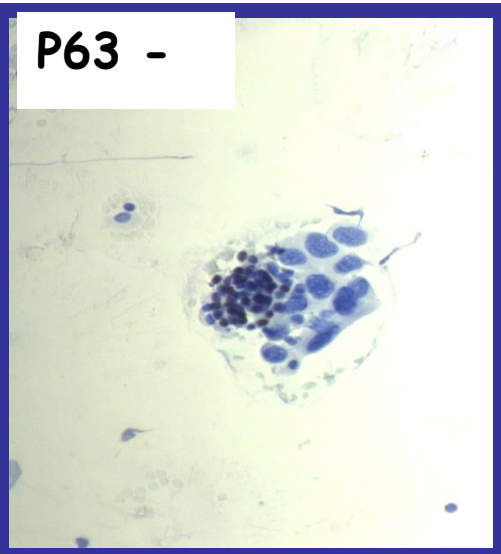


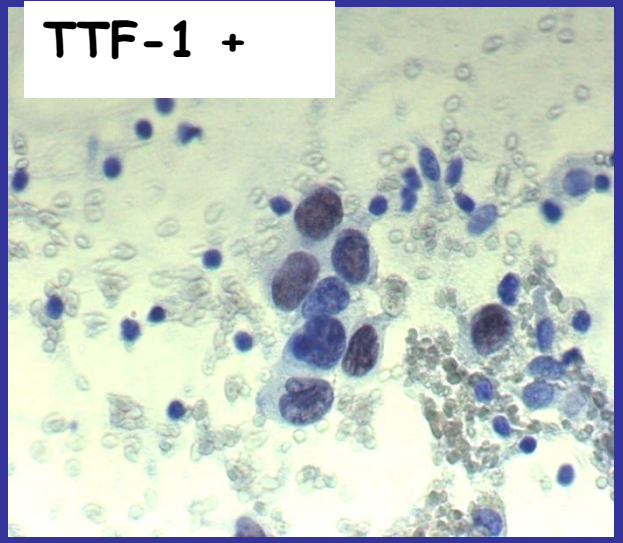
Accuracy of Fine Needle Aspiration Cytology in the Pathological Typing of Non-small Cell Lung Cancer

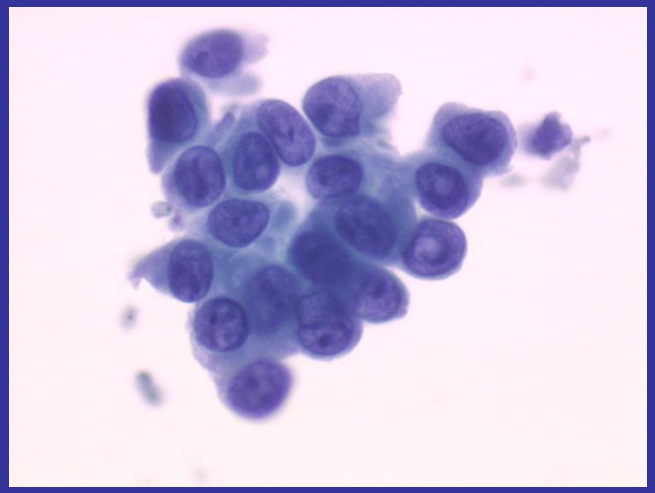
JTO 2011 Mar; 6(3):489-493

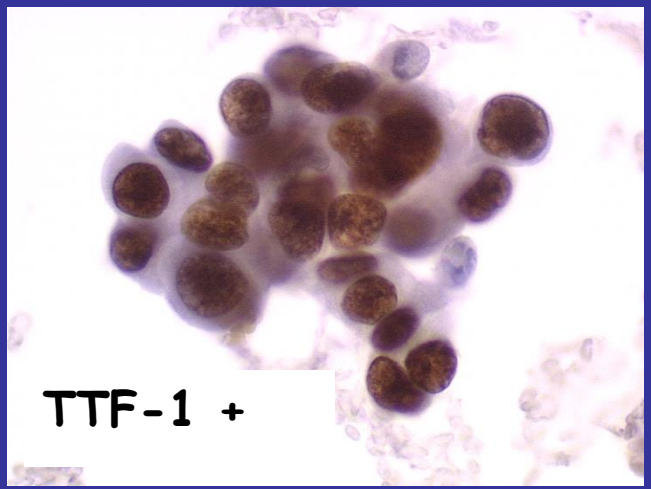
Rita Nizzoli, PhD, Marcello Tiseo, MD,* Francesco Gelsomino, MD,* Marco Bartolotti, MD,* Maria Majori, MD,† Lilia Ferrari, MD,† Massimo De Filippo, MD,‡ Guido Rindi, MD, PhD,§ Enrico Maria Silini, MD, PhD,‖ Annamaria Guazzi, PhD,* and Andrea Ardizzoni, MD**











Terminology and criteria for small biopsies/cytology

TABLE 2. Terminology and Criteria for Adenocarcinoma, Squamous Cell Carcinoma, and NSCC NOS in Small Biopsies and Cytology Compared with Terms in Resection Specimens[a]

New Small Biopsy/Cytology Terminology	Morphology/Stains	2015 WHO Classification in Resection Specimens
Adenocarcinoma (describe identifiable patterns present)	Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma predominant pattern: lepidic, acinar, papillary, solid, and micropapillary
Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)		Minimally invasive adenocarcinoma, adenocarcinoma in situ, or an invasive adenocarcinoma with a lepidic component
Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern)		Invasive mucinous adenocarcinoma
Adenocarcinoma with colloid features		Colloid adenocarcinoma
Adenocarcinoma with fetal features		Fetal adenocarcinoma
Adenocarcinoma with enteric features[b]		Enteric adenocarcinoma
NSCC, favor adenocarcinoma[c]	Morphologic adenocarcinoma patterns not present but supported by special stains (i.e., TTF-1 positive)	Adenocarcinoma (solid pattern may be just one component of the tumor)
Squamous cell carcinoma	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma
NSCC, favor squamous cell carcinoma[c]	Morphologic squamous cell patterns not present but supported by stains (i.e., p40-positive)	Squamous cell carcinoma (nonkeratinizing pattern may be a component of the tumor)
NSCC NOS[d]	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	Large cell carcinoma

Travis WD. et al. *J Thorac Oncol.* 2015;10: 1243–1260

Guidelines for good practice of small biopsies and cytological preparations

- The term NSCLC-NOS should be used as little as possible, and only when a more specific diagnosis is not possible.
- For small biopsies and cytology, NSCC should be further classified into a more specific type, such as adenocarcinoma, or squamous cell carcinoma, whenever possible.
- When a diagnosis is made in conjunction with special studies, it should be clarified.
- The term "non–SQCC" should not be used by pathologist in diagnostic report.

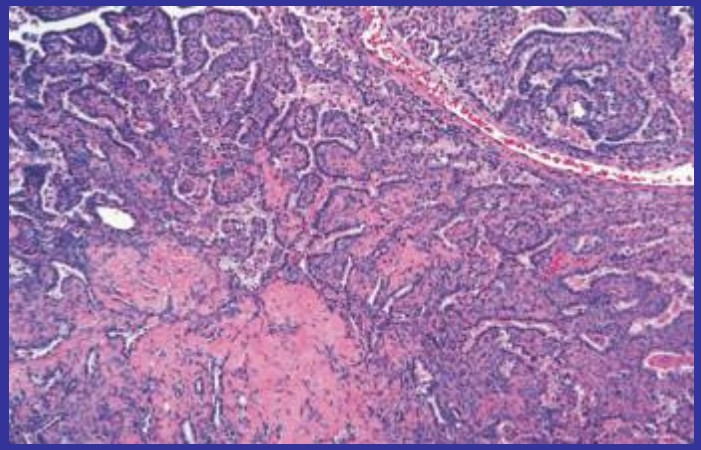
WHO, IARC, 2015

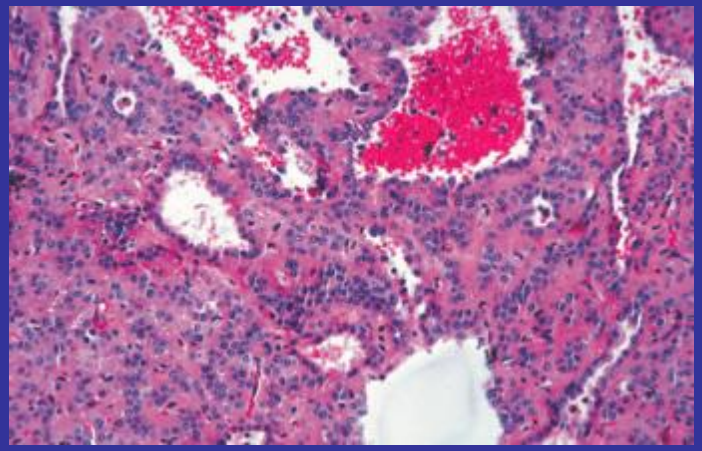
Lung classification in resection specimen

- **Papillomas**
  - **Squamous cell papilloma**
  - **Glandular papilloma**
  - **Mixed squamous cell and glandular papilloma**
- **Adenomas**
  - **Sclerosing pneumocytoma**
  - **Alveolar adenoma**
  - **Papillary adenoma**
  - **Mucinous cystoadenoma**
  - **Mucous gland adenoma**

Sclerosing pneumocytoma

- Two cells type: round stromal cells and surface cells
- Papillary, sclerotic, solid, haemorragic pattern
- Behaves in a clinically benign fashion





- **Adenocarcinoma**

International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma

William D. Travis, MD, Elisabeth Brambilla, MD, Masayuki Noguchi, MD, Andrew G. Nicholson, MD, Kim R. Geisinger, MD, Yasushi Yatabe, MD, David G. Beer, PhD, Charles A. Powell, MD, Gregory J. Riely, MD, Paul E. Van Schil, MD, Kavita Garg, MD, John H. M. Austin, MD, Hisao Asamura, MD, Valerie W. Rusch, MD, Fred R. Hirsch, MD, Giorgio Scagliotti, MD, Tetsuya Mitsudomi, MD, Rudolf M. Huber, MD, Yuichi Ishikawa, MD, James Jett, MD, Montserrat Sanchez-Cespedes, PhD, Jean-Paul Sculier, MD, Takashi Takahashi, MD, Masahiro Tsuboi, MD, Johan Vansteenkiste, MD, Ignacio Wistuba, MD, Pan-Chyr Yang, MD, Denise Aberle, MD, Christian Brambilla, MD, Douglas Flieder, MD, Wilbur Franklin, MD, Adi Gazdar, MD, Michael Gould, MD, MS, Philip Hasleton, MD, Douglas Henderson, MD, Bruce Johnson, MD, David Johnson, MD, Keith Kerr, MD, Keiko Kuriyama, MD, Jin Soo Lee, MD, Vincent A. Miller, MD, Iver Petersen, MD, PhD, Victor Roggli, MD, Rafael Rosell, MD, Nagahiro Saijo, MD, Erik Thunnissen, MD, Ming Tsao, MD, and David Yankelewitz, MD

(*J Thorac Oncol.* 2011;6: 244–285)

• Adenocarcinoma

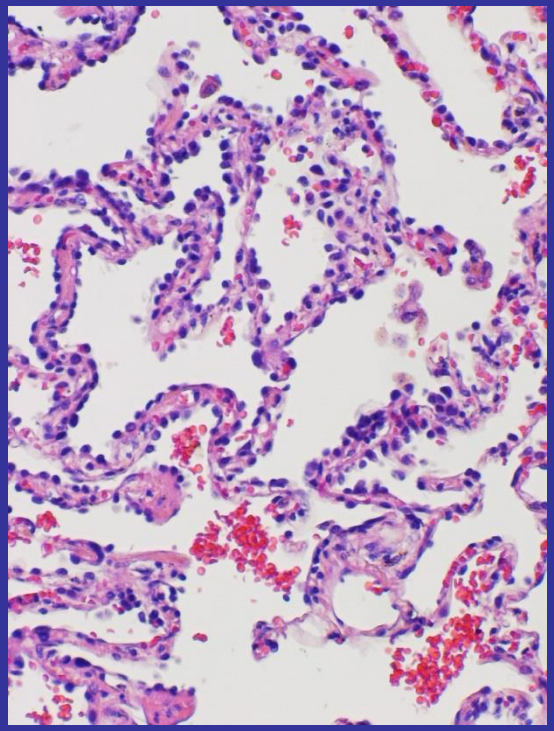
WHO 2004

- Preinvasive lesions
  - AAH
- Invasive adenocarcinoma
- Mixed subtype
- Acinar
- Papillary
- BAC
- Solid
- Variants

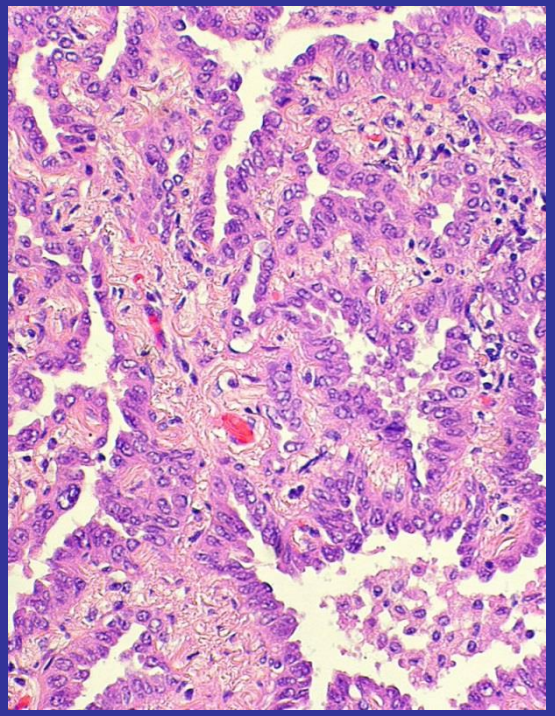
WHO 2015

- Preinvasive lesions
  - AAH
  - AIS (mucinous / non-mucinous)
- Minimally invasive adenocarcinoma (muc /non-muc)
- Invasive adenocarcinoma
  - lepidic (G1)
  - acinar (G2)
  - papillary (G2)
  - micropapillary (G3)
  - solid (G3)
- Variants of invasive adenocarcinoma
  - colloid
  - enteric
  - fetal-type

- **Adenocarcinoma**
- Preinvasive lesions

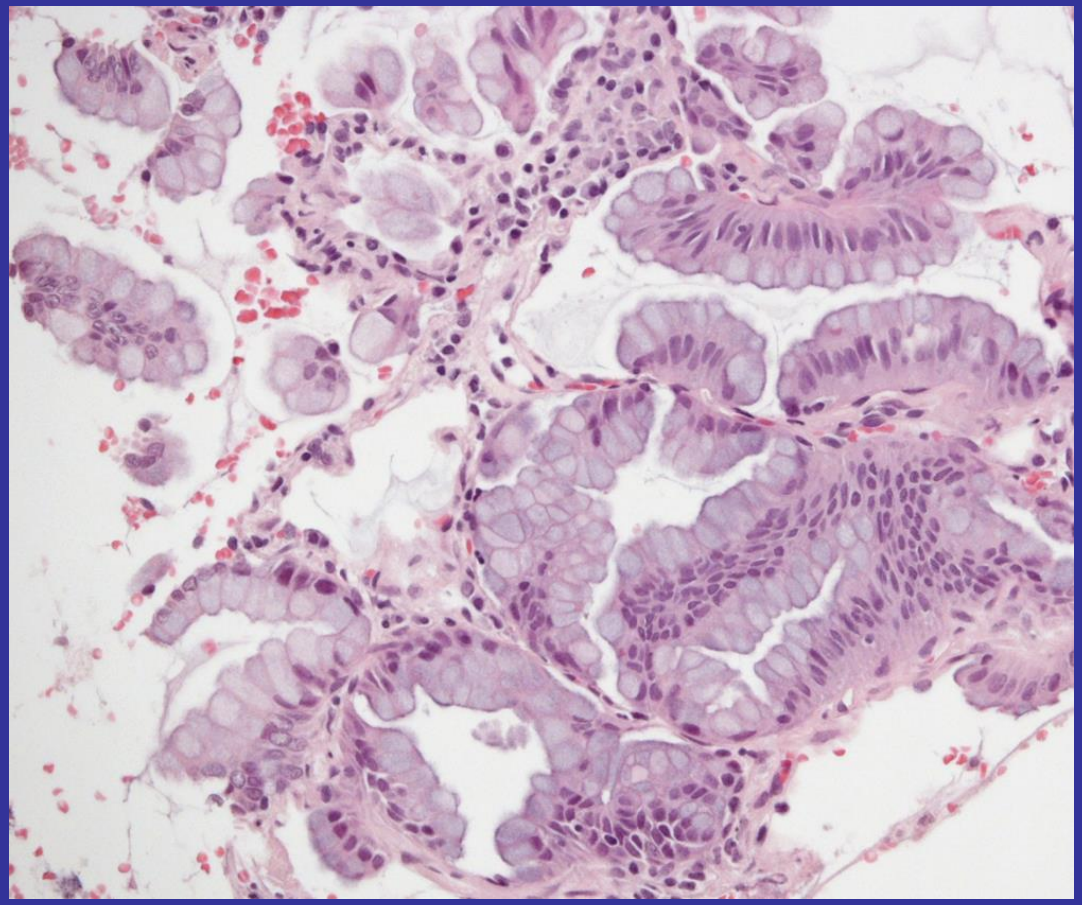


AAH
(≤ 0.5 cm)



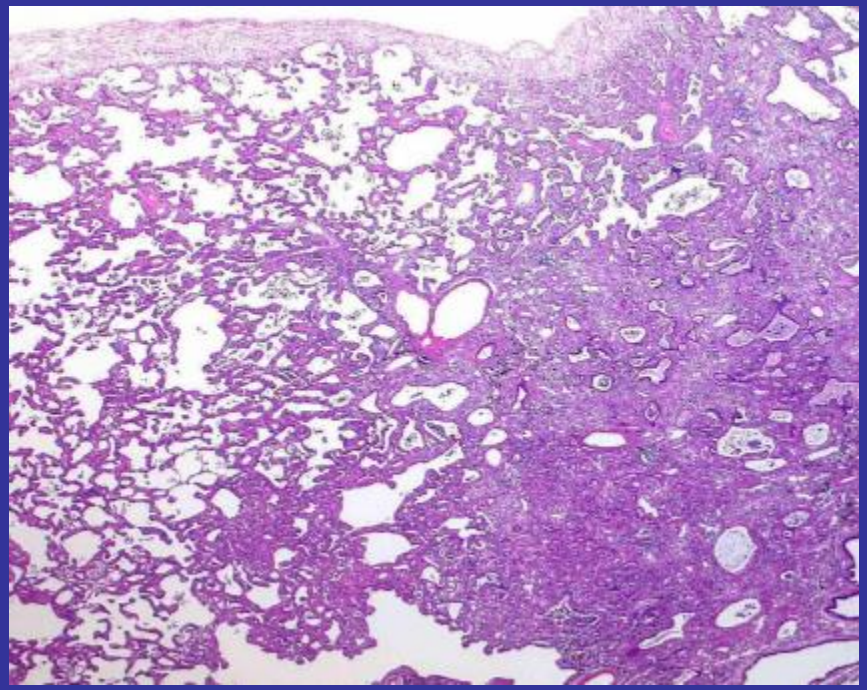
AIS
(≤ 3 cm)

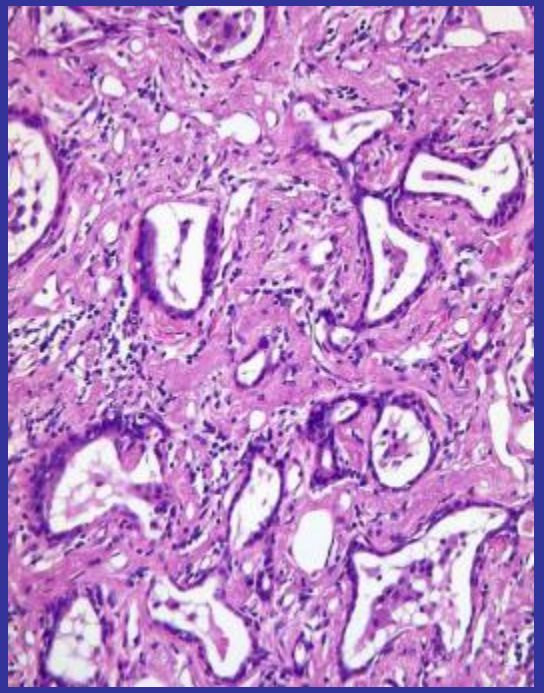
- **Adenocarcinoma**
- Preinvasive lesions



AIS, Mucinous type

- **Adenocarcinoma**
- Minimally invasive adenocarcinoma





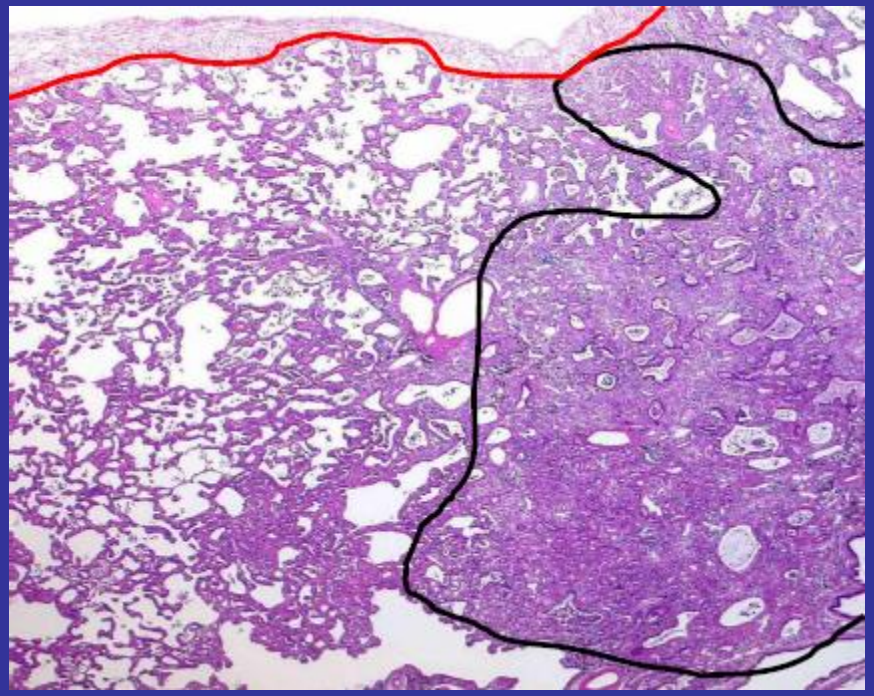
Travis WD et al., JTO 2011; 6 (2)

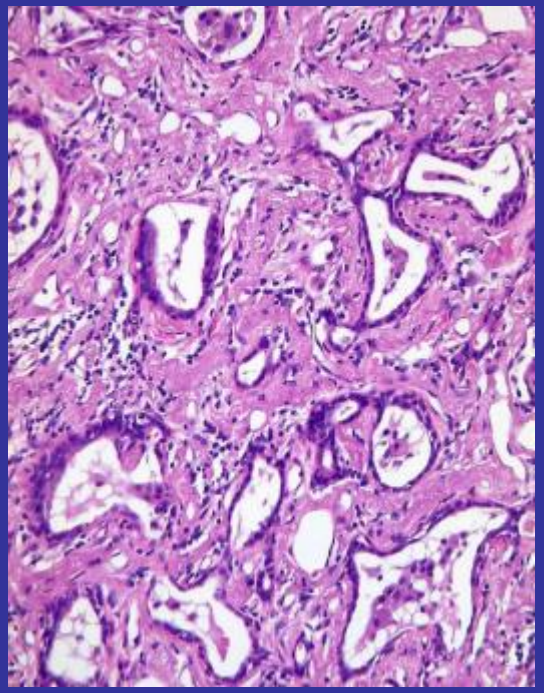
≤ 3 cm
Lepidic predominant

≤ 0.5 cm invasion

~100% diseas-free survival

- **Adenocarcinoma**
- Minimally invasive adenocarcinoma





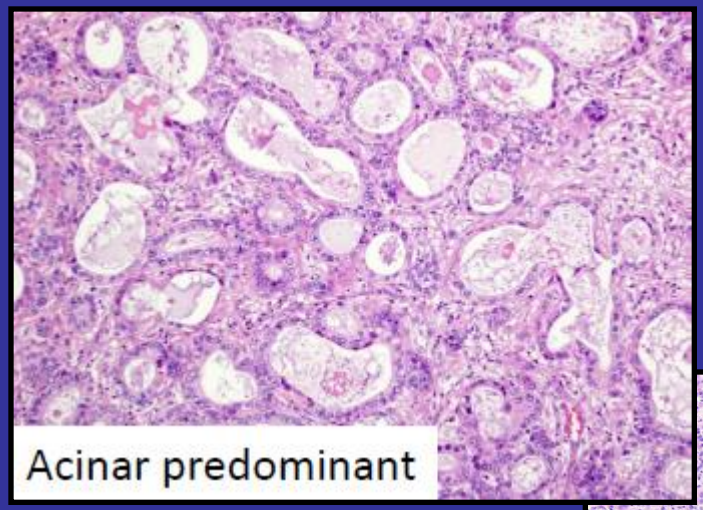
Travis WD et al., JTO 2011; 6 (2)

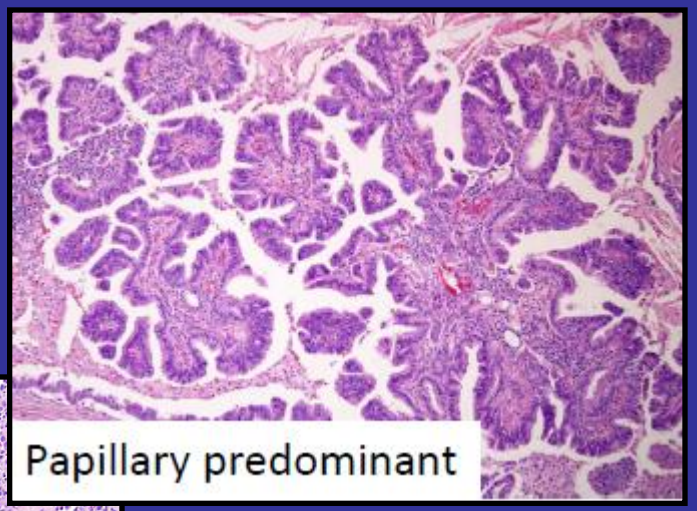
≤ 3 cm
Lepidic predominant

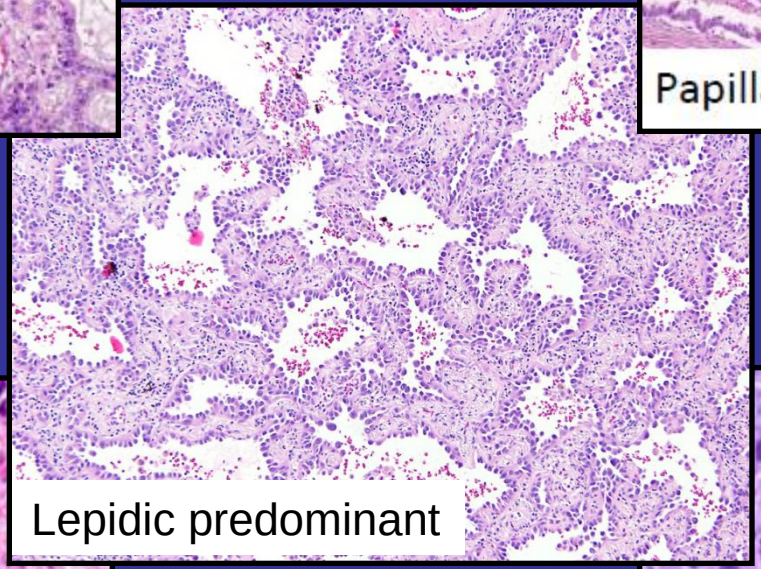
≤ 0.5 cm invasion

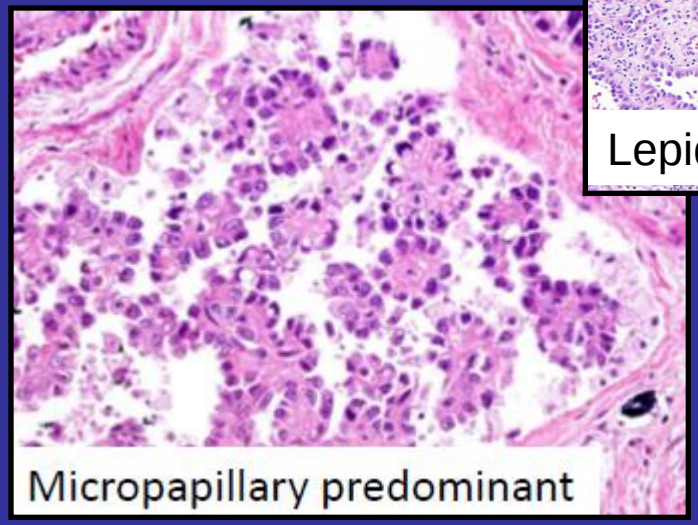
No invasion of lymphatics, blood vessels or pleura, no tumor necrosis

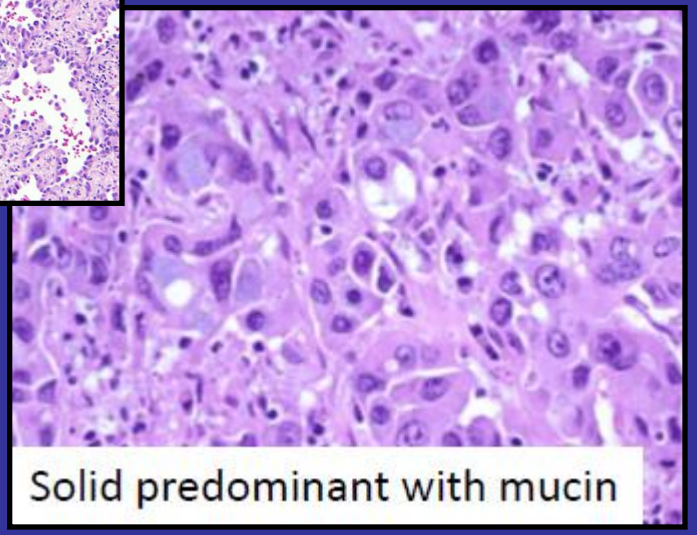
• Adenocarcinoma: patterns


Acinar predominant


Papillary predominant

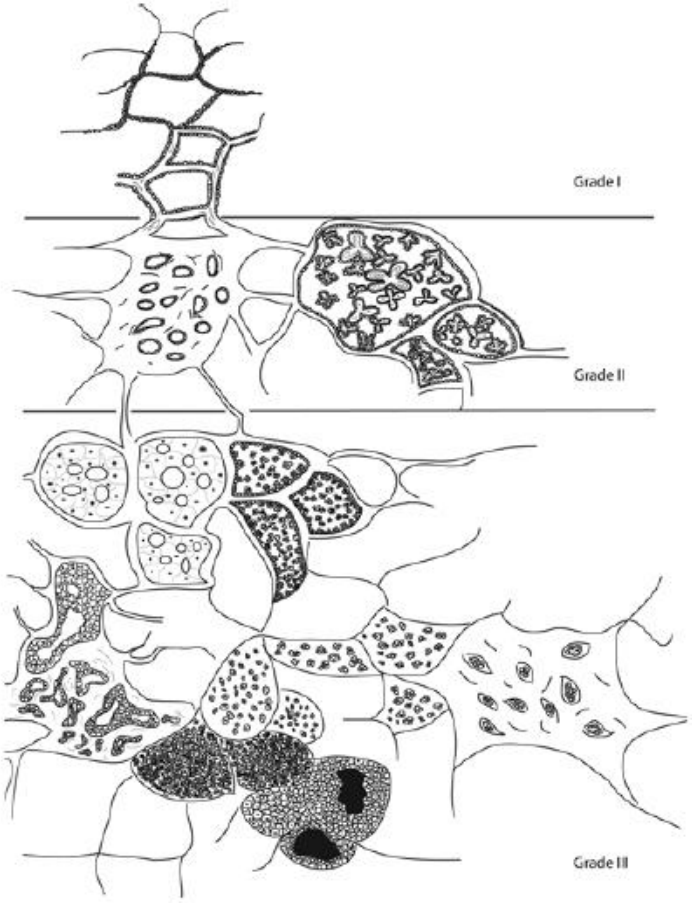

Lepidic predominant


Micropapillary predominant


Solid predominant with mucin

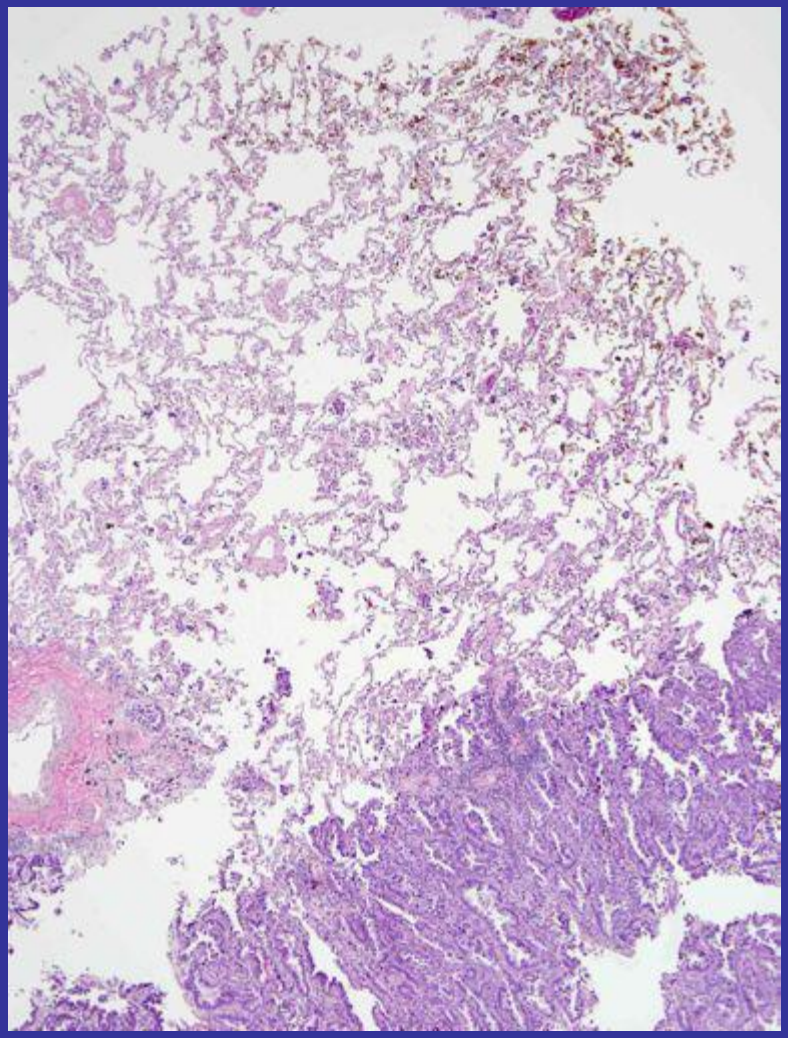
A Grading System of Lung Adenocarcinomas Based on Histologic Pattern is Predictive of Disease Recurrence in Stage I Tumors

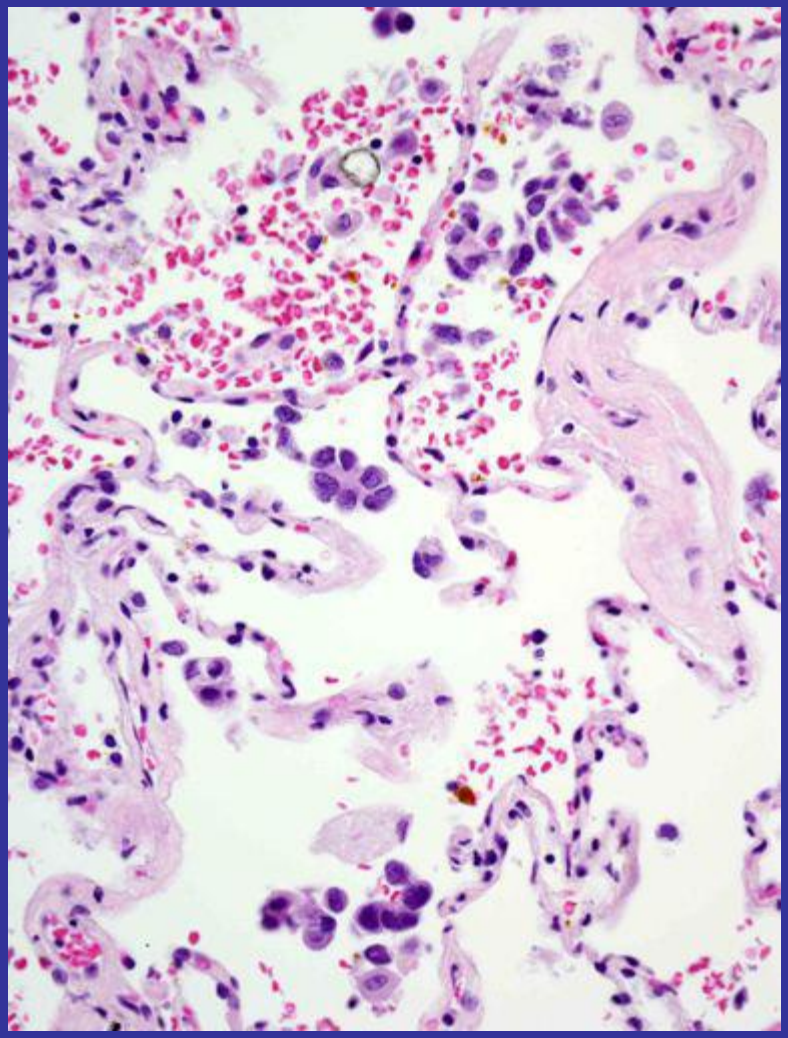
Gabriel Sica, MD, Akihiko Yoshizawa, MD,* Camelia S. Sima, MD, MS,† Christopher G. Azzoli, MD,‡ Robert J. Downey, MD,§ Valerie W. Rusch, MD,† William D. Travis, MD,* and Andre L. Moreira, MD, PhD**



- **Grade I corresponds to WHO 2004 classification of BAC**
- **Grade II corresponds to acinar and papillary patterns**
- **Grade III corresponds to micropapillary, solid, and variants such as cribriform, ragged-anastomosing glands, and dispersed intra-alveolar tumor cells**

Spread Through Alveolar Spaces (STAS)





Travis WD, ECC 2014

Squamous cell carcinoma

WHO 2004

- **Preinvasive lesions**
  - Squamous dysplasia
  - Carcinoma in situ
- **Invasive squamous cell carcinoma**

WHO 2015

- **Preinvasive lesions**
  - Squamous dysplasia
  - Carcinoma in situ
- **Invasive squamous cell carcinoma**
  - keratinizing
  - non-keratinizing
  - basaloid

Neuroendocrine tumors

WHO 2004

- **Preinvasive lesions**
  - DIPNECH
- Carcinoid tumors
  - Tipical carcinoid
  - Atypical Carcinoid
- SCLC
  - Combined SCLC

WHO 2015

- **Preinvasive lesions**
  - DIPNECH
- Carcinoid tumors
  - Atypical Carcinoid
  - Tipical Carcinoid
- SCLC
  - Combined SCLC
- LCNEC
  - Combined LCNEC

Large cell carcinoma

- LCNEC
- Basaloid carcinoma
- Lymphoepithelioma-like carcinoma
- Clear cell carcinoma
- LCC with rhabdoid features
- Undifferentiated

WHO 2004

REVIEW

Large-cell carcinoma of the lung: a diagnostic category redefined by immunohistochemistry and genomics

Lynette M. Sholl[a,b]

Reference	# of cases	Immunohistochemistry panel	Other studies	# reclassified as ADC	# reclassified as SQC	# unclassified
Monica *et al.* [12]	54	DSC3, TTF-1	N/A	24 (44%)	26 (48%)	4 (8%)
Barbareschi *et al.* [51]	56	TTF-1, p63, CK5, CK7, Napsin A, p40, DSC3	miR205 and miR21 profiling	19 (34%) with IHC alone 37 (66%) with IHC and miRNA profile	14 (25%) with IHC alone 19 (34%) with IHC and miRNA profile	23 (41%) with IHC alone 0 with IHC and miRNA profile
Rekhtman *et al.* [11▪▪]	102	TTF-1, p40	N/A	62 (61%)[b]	20 (20%)	20 (20%)
Rossi *et al.* [52▪]	74	TTF-1, p63, CK5/6, CK7, Napsin A, p40, DSC3, chromogranin, synaptophysin, CD56	N/A	40 (80%)	6 (12%)	4 (8%)

ADC 55 %

SCC 26 %

Null 19 %

Curr Opin Pulm Med 2014, 20:324–331

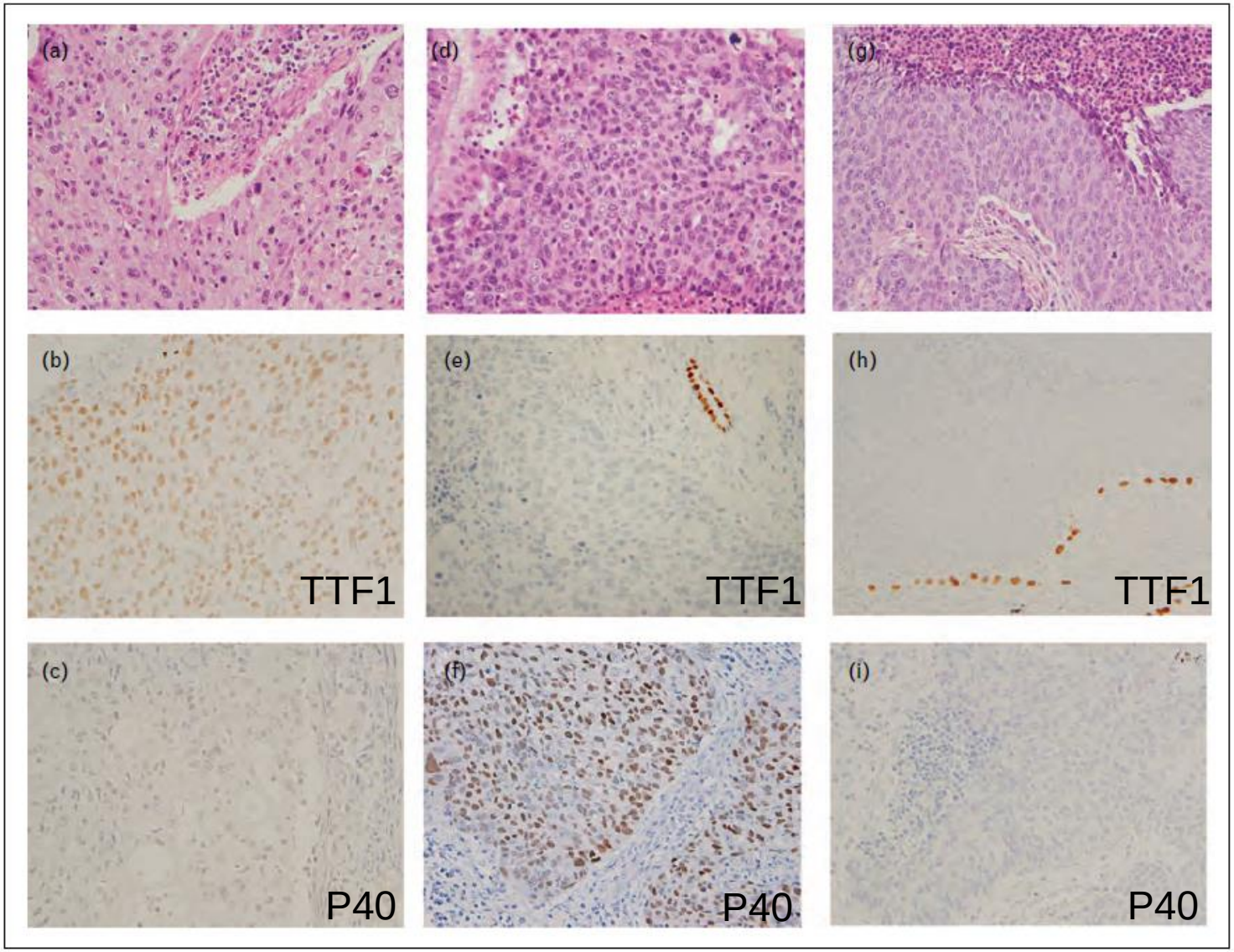


FIGURE 1. The differential immunophenotype of morphologic large-cell carcinomas (LCCs). (a) LCC, adenocarcinoma immunophenotype, with (b) TTF-1 expression and (c) absent P40 expression. (d) LCC, squamous immunophenotype, with (e) absent TTF-1 expression and (f) P40 expression. (g) LCC, null phenotype, with (h) absent TTF-1 and (i) P40 expression. All images at 400×.

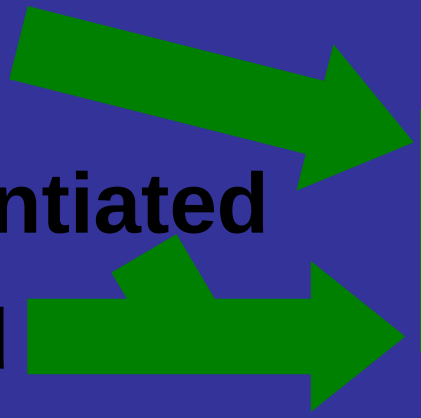
Curr Opin Pulm Med 2014, 20:324–331

- LELC
- Basaloid

Variants of squamous cell carcinoma

- Clear cell
- Undifferentiated

Rhabdoid

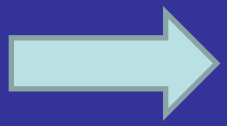


Variants of adenocarcinoma

LCNEC

Variant of neuroendocrine tumor

WHO 2004



WHO 2015

Sarcomatoid carcinoma

- **Plemorphic,spindle cell,giant cell carcinoma**
- **Carcinosarcoma**
- **Pulmonary blastoma**

Pleomorhic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma

Salivary gland type tumors

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Epithelial-myoepithelial carcinoma
- Pleomorphic adenoma

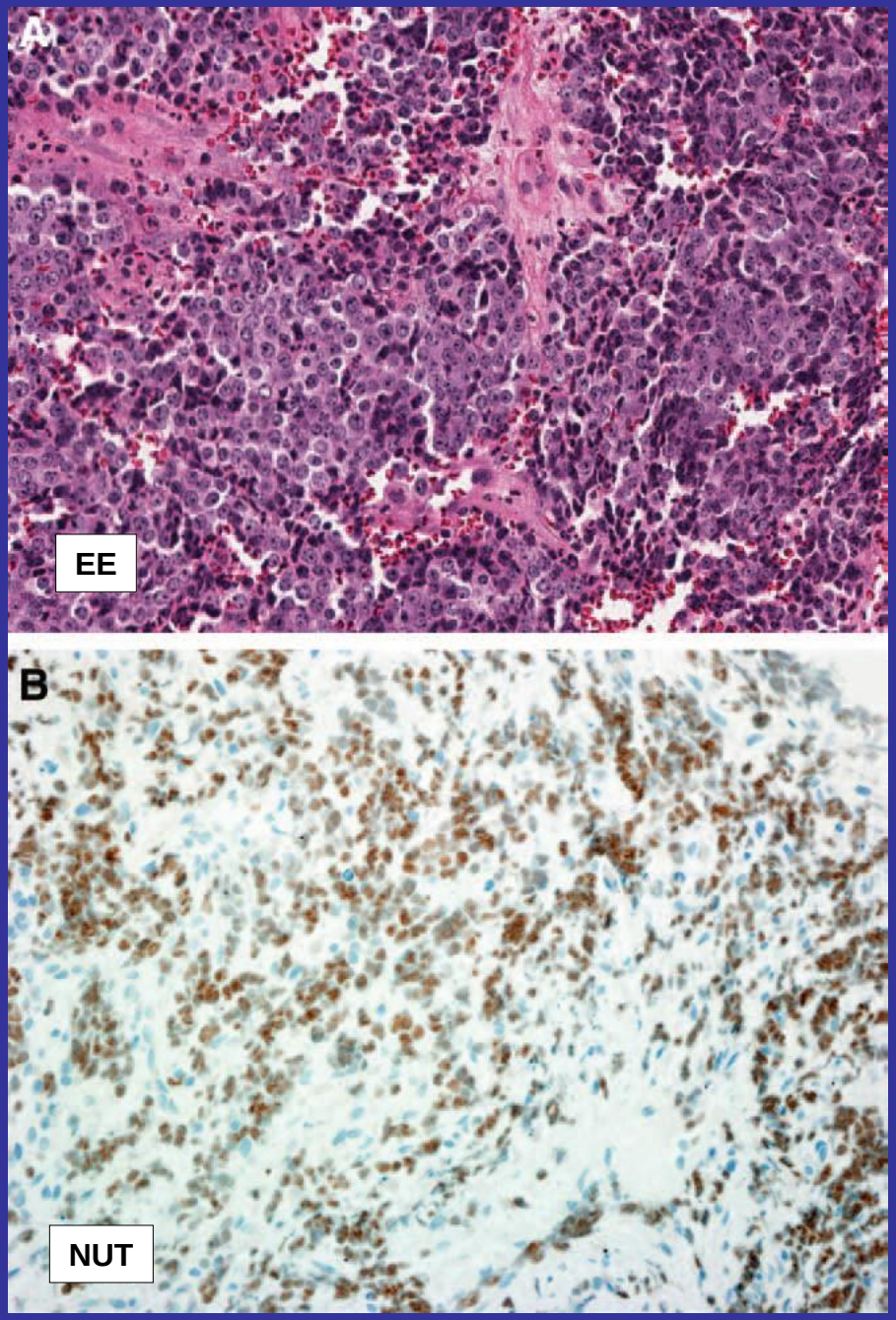
Adenosquamous carcinoma

Other and unclassfied carcinoma

- Lymphoepitelioma-like
- NUT carcinoma

NUT carcinoma

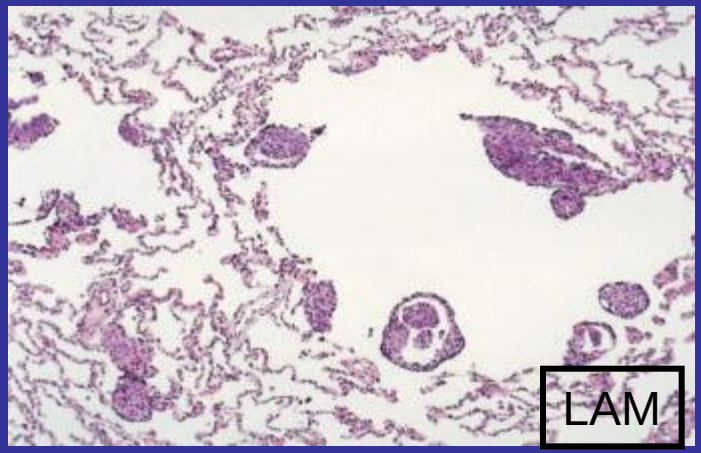
- Chromosomal rearrangement in the NUT gene
- Recognized in the thymus in the WHO 2004 as NUT midline carcinoma
- Very aggressive tumor (median survival of 7 months)

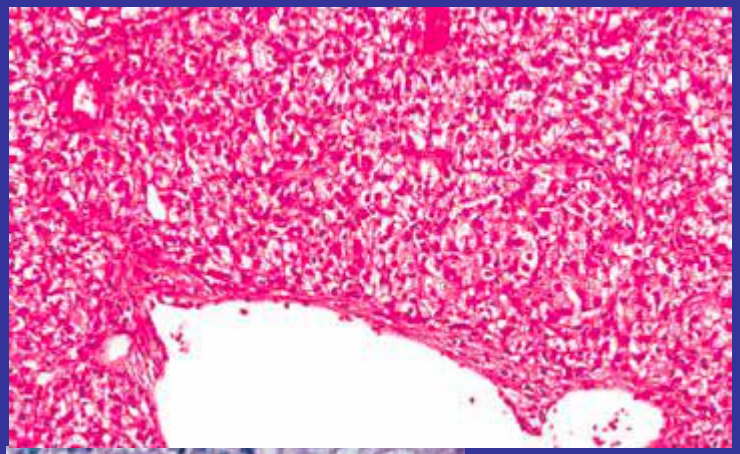


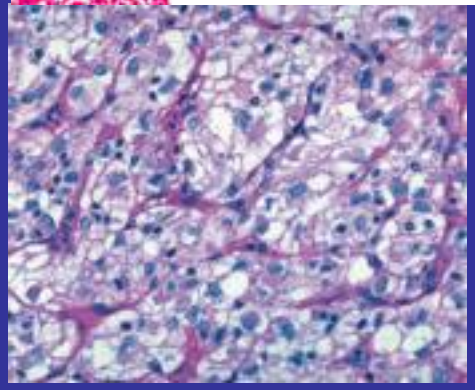
- **Mesenchymal tumors**
  - Pulmonary hamartoma
  - Chondroma
  - PEComatous tumors
  - Congenital peribronchial myofibroblastic tumor
  - Diffuse pulmonary lymphangiomatosis
  - Inflammatory myofibroblastic tumor
  - Epithelioid hemangioendothelioma
  - Pleuropulmonary blastoma
  - Synovial sarcoma
  - Pulmonary artery intimal sarcoma
  - Pulmonary myxoid sarcoma with EWRS1-CREB1 translocation
  - Myoepithelial tumors/myoepithelial carcinoma
  - Others

PEC-omatous tumor

- Arise from perivascular epithelioid cells
- Several form
  - Diffuse multicystic proliferation (LAM)
  - Benign localized mass (clear cell tumor/PEComa)
  - Pecoma, malignant
- Biallelic mutations in the tuberous sclerosis gene TSC2, target of rapamycin pathway (mTOR)



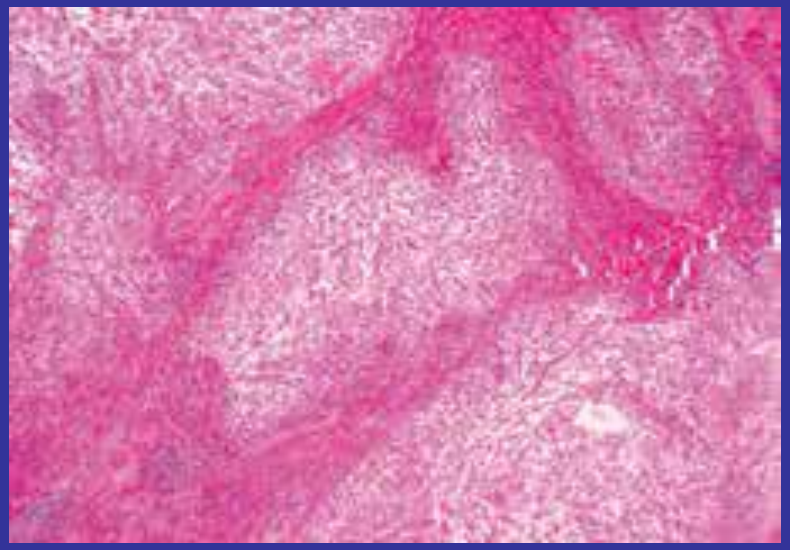


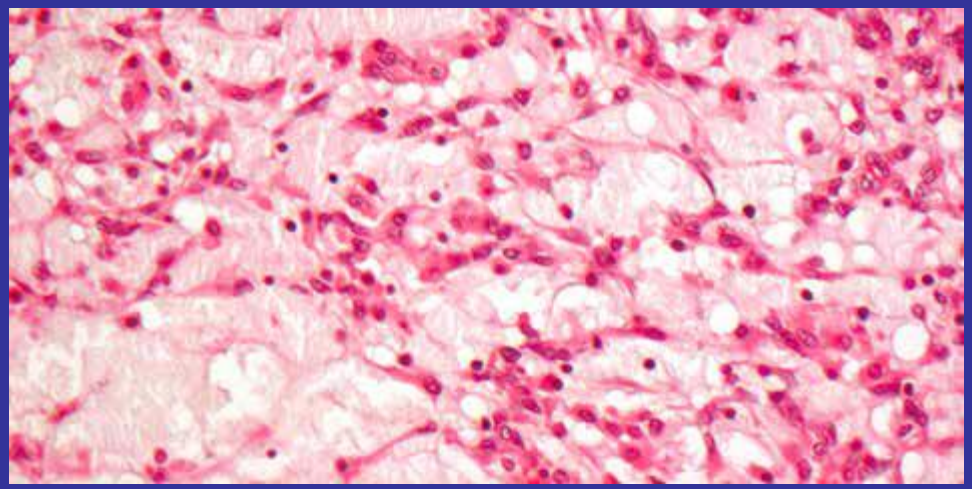


Clear cell

Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation

- Endobronchial
- Lobulated architecture, fibrous pseudocapsule
- Composed of spindle, stellate,poligonal cell in a prominent myxid stroma
- EWSR1-CREB1 fusion gene

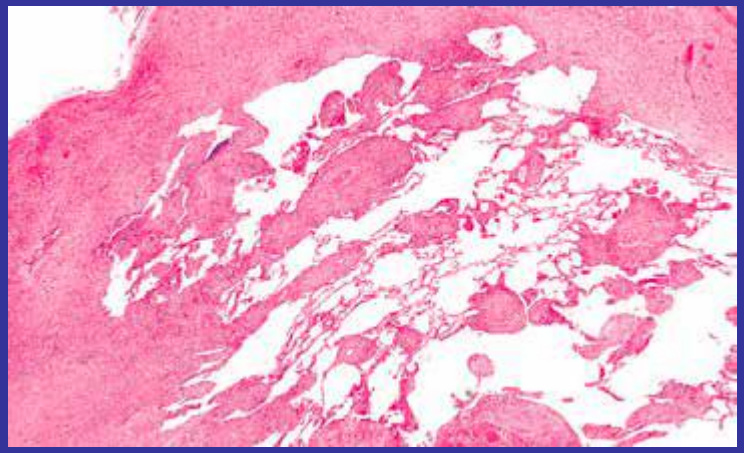


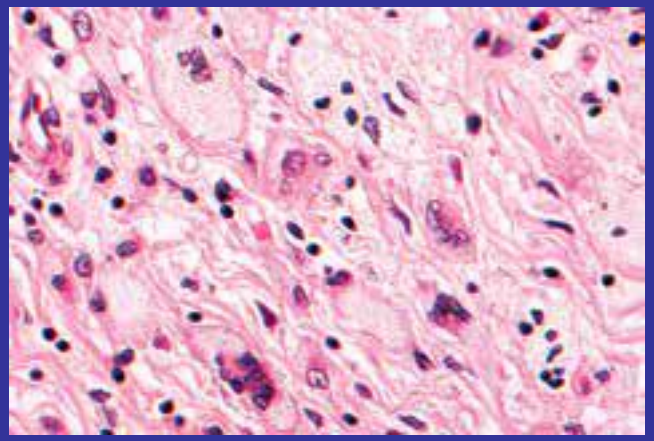


- **Lymphohistiocytic tumors**
  - Marginal zone B-cell lymphoma of MALT origin
  - DLBCL
  - LYG
  - Intravascular lymphoma
  - Langerhans cell histiocytosis
  - Erdheim-Chester disease
- **Tumors of ectopic origin**
  - Germ cell tumors
  - Intrapulmonary thymoma
  - Melanoma
  - Meningioma
- **Metastases to the lung**

Erdheim-Chester disease

- Is a rare xanthogranulomatous istiocytosis
- In the lung leads to intestitial fibrosis with a perilymphatic distribution
- Other extarskeletal manifestations
- BRAF V600e mutations detected in 54% of patients





Conclusions

Small samples:

- Recommended to reduce using the term NSCLC NOS as much as possible and classify tumors according to tier specific histological subtype
- Safe tissue for predictive markers

Immunochemistry:

- Recommendend, not only for small biopsies/cytology, but also for resected specimens

ADC:

- Defined by morphology or expression of pneumocytic markers

SCC:

- Defined by morphology or expression of squamos markers

LLC:

- Only on resections
- No squamos, adeno-or neuroendocrine differentiation by morphology and immunochemistry

Grazie al dott. Giulio Rossi per il materiale…

Grazie a tutti per l'attenzione!