

# Patologia neoplastica del polmone

# A little bit of History

Once upon a time.....

The Pathologist made a diagnosis of Lung Cancer (and probably gave a histological type)

.....but nobody really cared because the patient received radiotherapy (maybe) or 'Best Supportive Care'.

## A little bit of History

Then Chemotherapy for Small Cell Carcinoma was introduced ( 1980 )

If the Pathologist made a diagnosis that was NOT Small Cell Carcinoma

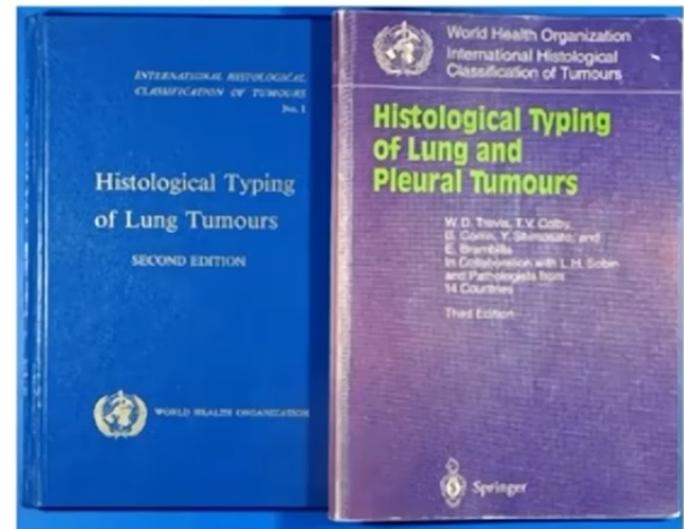
..... nobody really cared because the patient received radiotherapy (maybe) or 'Best Supportive Care'.

# A little bit of History

In the 1990s 'different' chemotherapy was introduced for lung cancer patients who did not have SCLC

The Pathologist made the diagnosis,  
(and probably gave a histological type)

.....but nobody really cared because all patients received the same treatment.



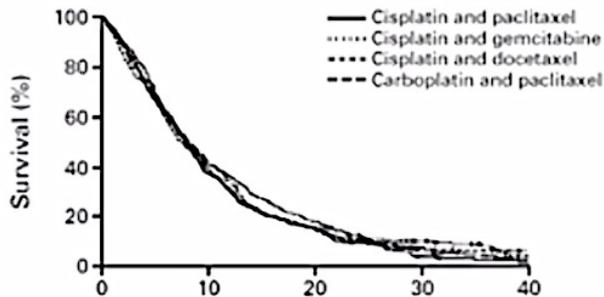
WHO Classification  
1981 & 1999

## Still some History.....

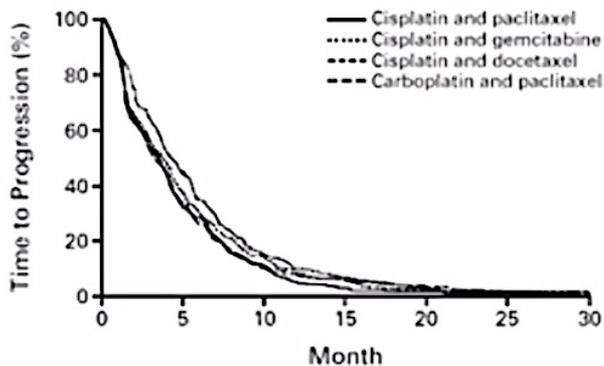
This for patients with Advanced, metastatic lung cancer who did NOT have SCLC

.....which spawned the term 'Non-small cell lung cancer' – NSCLC

So now, in oncologists minds, there were two types of lung cancer  
SCLC and NSCLC



B

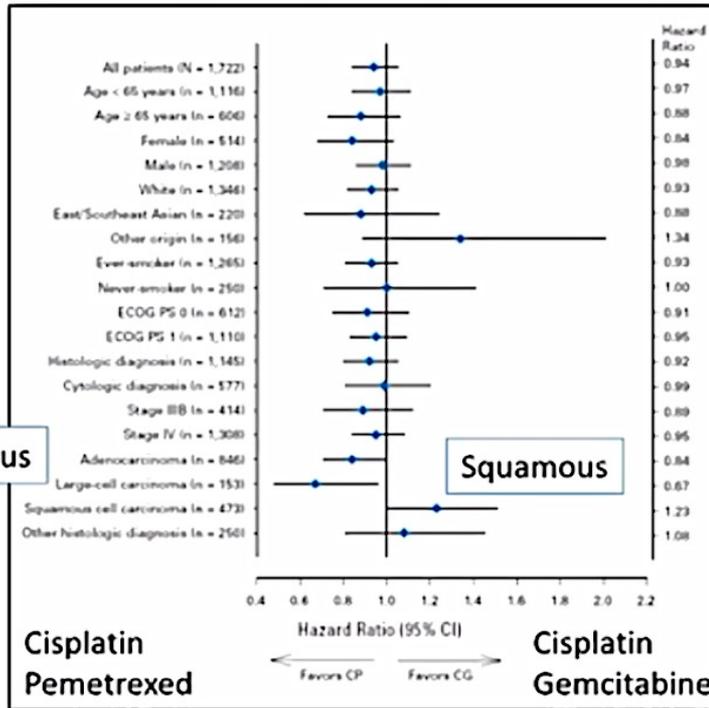


**Figure 2.** Kaplan-Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

CG Cisplatin Gemcitabina  
 CP Cisplatin Pemetrexed

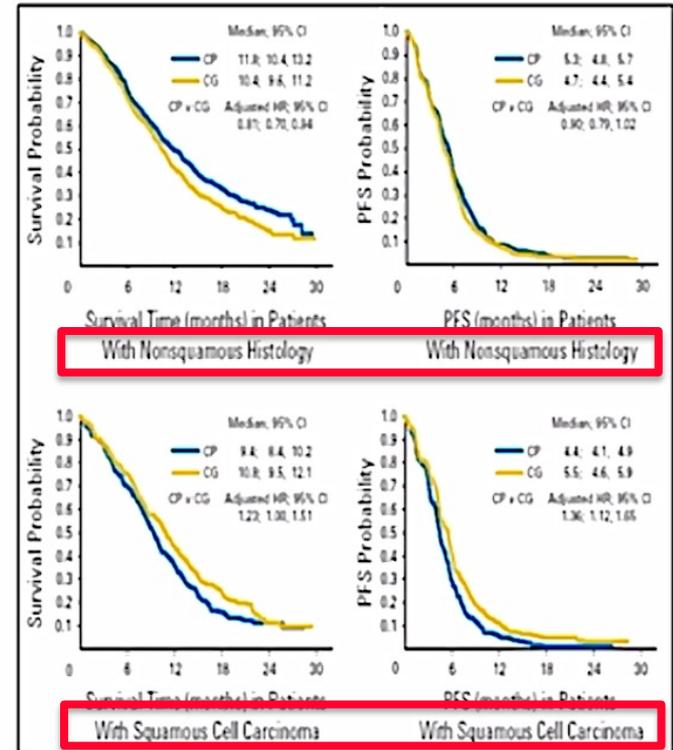
### Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer

Giorgio Vittorio Scagliotti, Purvish Parikh, Joachim von Pawel, Bonne Böesma, Johan Vansteenkiste, Christian Manegold, Piotr Serwatowski, Ulrich Gatzemeier, Raghunadharao Digumarti, Mauro Zukin, Jin S. Lee, Anders Møller, Keunchil Park, Shekhar Patel, Janusz Rolski, Tuncay Gökse, Filippo de Marinis, Lorinda Simms, Katherine P. Sugarman, and David Gandara



NOT Squamous

Squamous



NSCLC-NOS is no longer acceptable!

## Le scelte terapeutiche sono determinate da:

- Tipo istologico  **DIAGNOSI**

## Scelte terapeutiche sono rappresentate da:

- Chirurgia
- Radioterapia
- Terapia medica, con chemioterapici e farmaci a bersaglio molecolare

- Tumori epiteliali

- Tumori mesenchimali

- Tumori linfoidi

- Tumori metastatici

## ORIGINE DEI TUMORI POLMONARI

Il carcinoma polmonare deriva dalla proliferazione di cellule epiteliali o neuroendocrine delle piccole vie aeree o delle vie bronchiali.

# Tumori epiteliali maligni (carcinomi)

Histologic Type and Subtypes	ICDO Code
------------------------------	-----------

## Epithelial tumors

### Adenocarcinoma

Lepidic adenocarcinoma <sup>e</sup>	8140/3
Acinar adenocarcinoma	8250/3 <sup>d</sup>
Papillary adenocarcinoma	8551/3 <sup>d</sup>
Micropapillary adenocarcinoma <sup>e</sup>	8260/3
Solid adenocarcinoma	8265/3
Invasive mucinous adenocarcinoma <sup>e</sup>	8230/3
Mixed invasive mucinous and nonmucinous adenocarcinoma	8253/3 <sup>d</sup>
Colloid adenocarcinoma	8254/3 <sup>d</sup>
Fetal adenocarcinoma	8480/3
Enteric adenocarcinoma <sup>e</sup>	8333/3
Minimally invasive adenocarcinoma <sup>e</sup>	8144/3
Nonmucinous	8256/3 <sup>d</sup>
Mucinous	8257/3 <sup>d</sup>
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0 <sup>d</sup>
Adenocarcinoma in situ <sup>e</sup>	
Nonmucinous	8250/2 <sup>d</sup>
Mucinous	8253/2 <sup>d</sup>

### Squamous cell carcinoma

Keratinizing squamous cell carcinoma <sup>e</sup>	8070/3
Nonkeratinizing squamous cell carcinoma <sup>e</sup>	8071/3
Basaloid squamous cell carcinoma <sup>e</sup>	8072/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8083/3
	8070/2

## Neuroendocrine tumors

Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0 <sup>d</sup>

## Large cell carcinoma

8012/3

## Adenosquamous carcinoma

8560/3

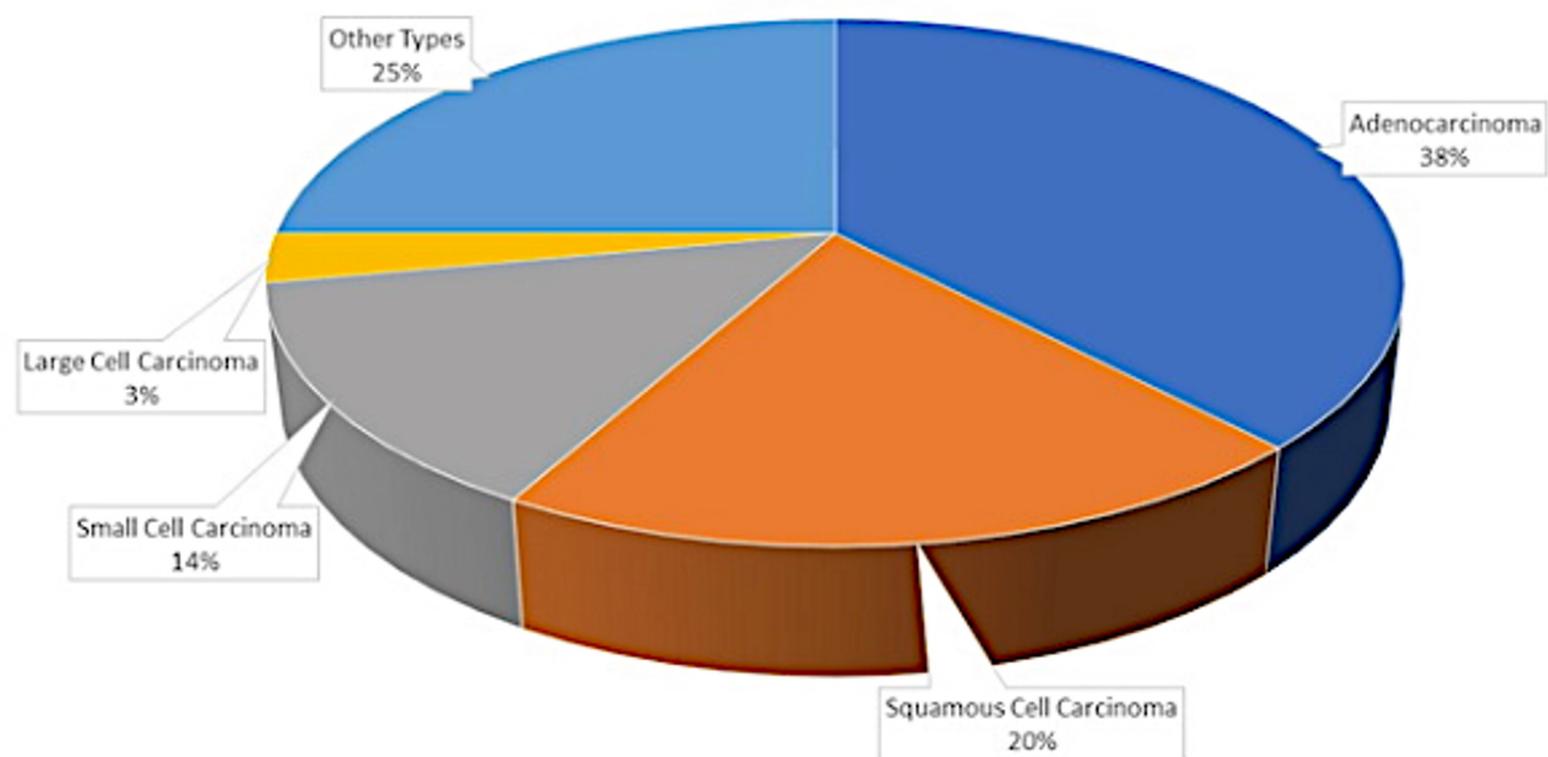
## Sarcomatoid carcinomas

Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma <sup>e</sup>	8023/3 <sup>d</sup>

## Salivary gland-type tumors

Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3

### Lung Cancer : Histologic Types



Il 95% dei carcinomi polmonari appartiene alle seguenti categorie

1. Carcinoma squamoso
  2. Adenocarcinoma
  3. Carcinoma a piccole cellule
  4. Carcinoma a grandi cellule
- NSCLC
- SCLC
- 
- ```
graph LR; 1[1. Carcinoma squamoso] --> NSCLC; 2[2. Adenocarcinoma] --> NSCLC; 3[3. Carcinoma a piccole cellule] --> SCLC; 4[4. Carcinoma a grandi cellule] --> SCLC;
```

Dal punto di vista pratico (terapeutico) è fondamentale la distinzione tra:

- Carcinoma neuroendocrino a piccole cellule (SCLC) (microcitoma)
- Carcinoma non a piccole cellule (NSCLC)  
(adenocarcinoma e carcinoma squamoso)

.....terapia è diversa.....

# Quadri principali di sviluppo del carcinoma polmonare

## Topografia

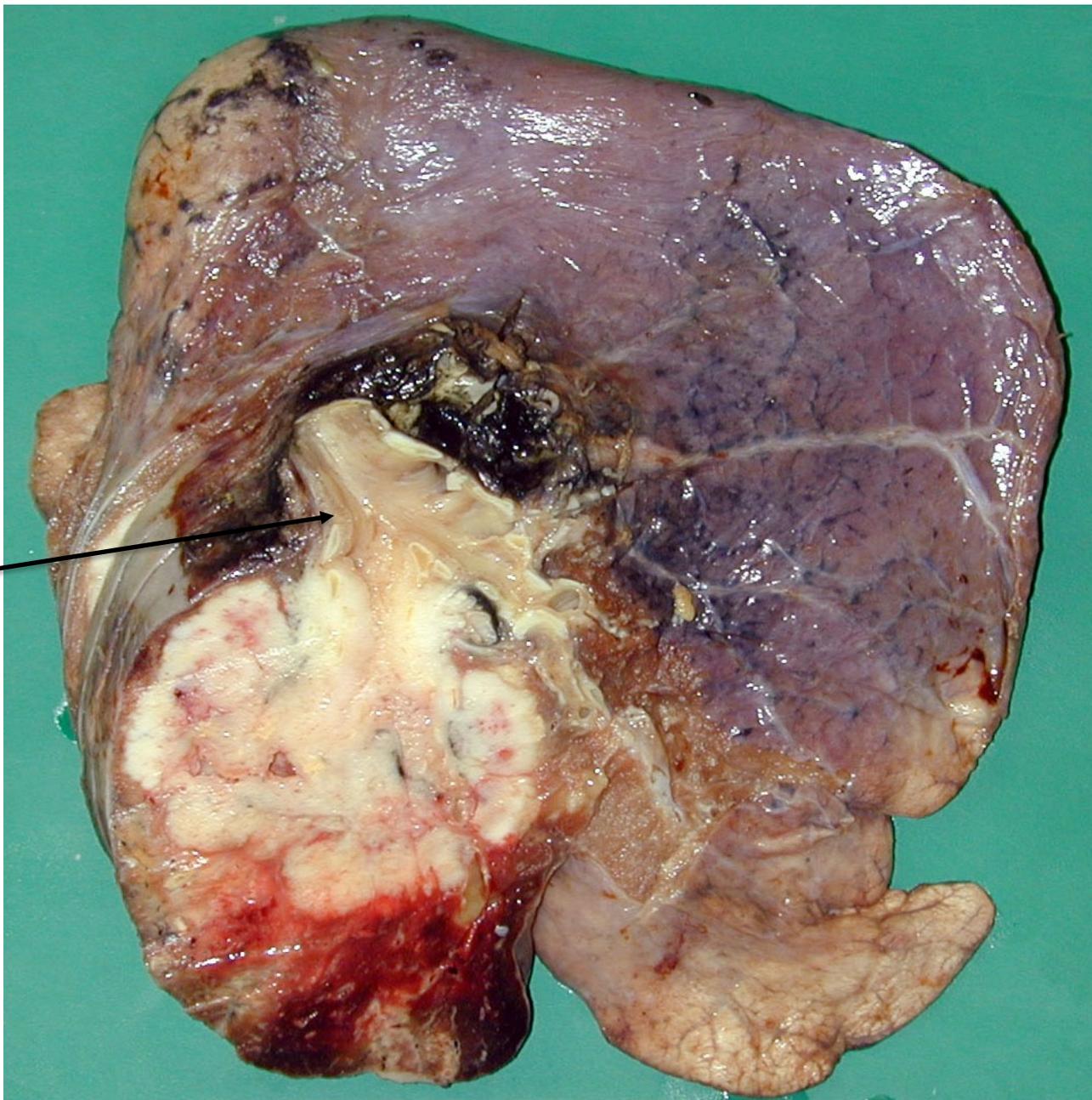
- Forme centrali 70-80% (ca. squamoso e microcitoma): interessano l'ilo e le porzioni mediali del polmone; originano in corrispondenza della biforcazione tracheale o a livello di un bronco principale.
- Forme periferiche 20-30% (adenocarcinoma): origina dalle diramazioni bronchiali periferiche

**Aspetto macroscopico di un  
carcinoma polmonare  
(centrale)**

la neoplasia origina  
da un bronco principale e si  
estende verso il parenchima  
polmonare adiacente

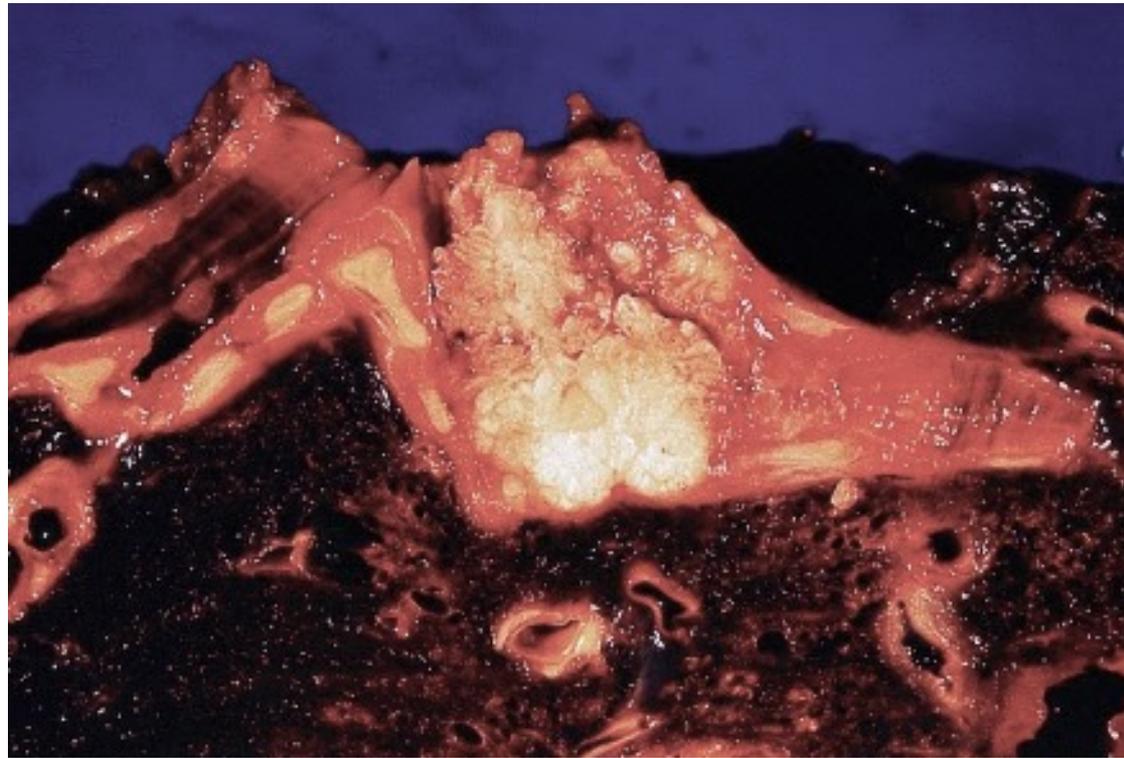


**Diramazione  
bronchiale**



**Aspetto macroscopico di un  
carcinoma polmonare  
(centrale)**

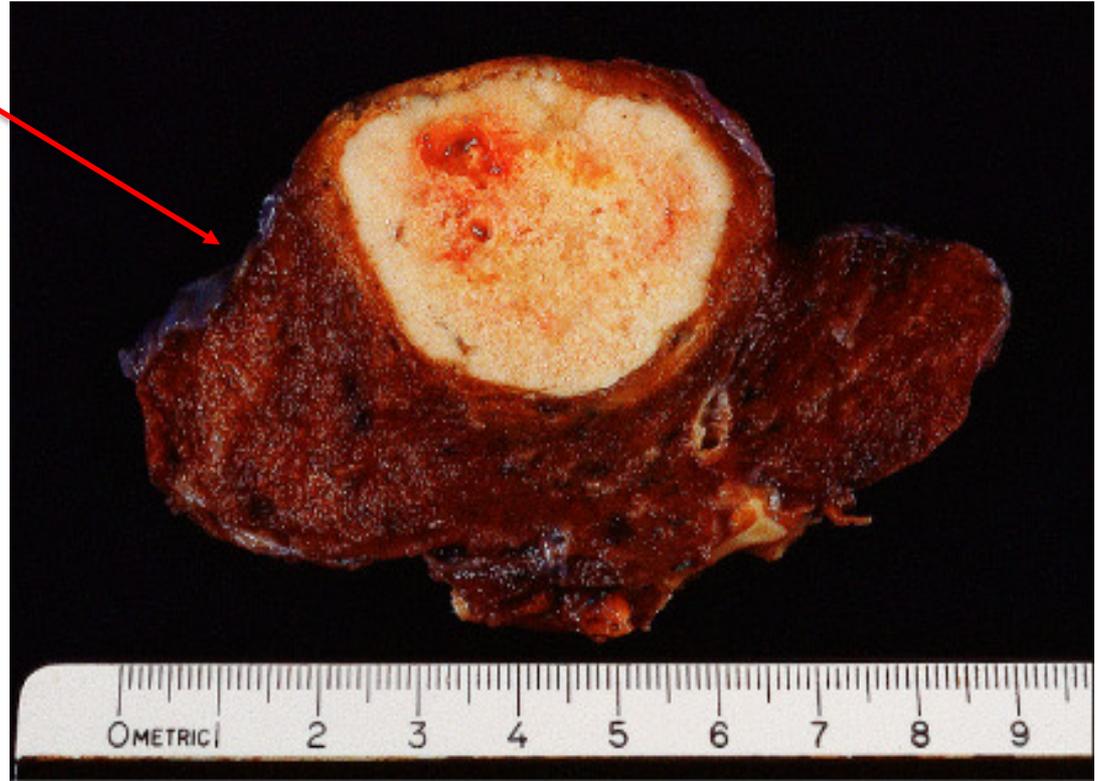
**Carcinoma polmonare  
ostruente il lume bronchiale**



Pleura viscerale

Localizzazione periferica

Adenocarcinoma  
polmonare



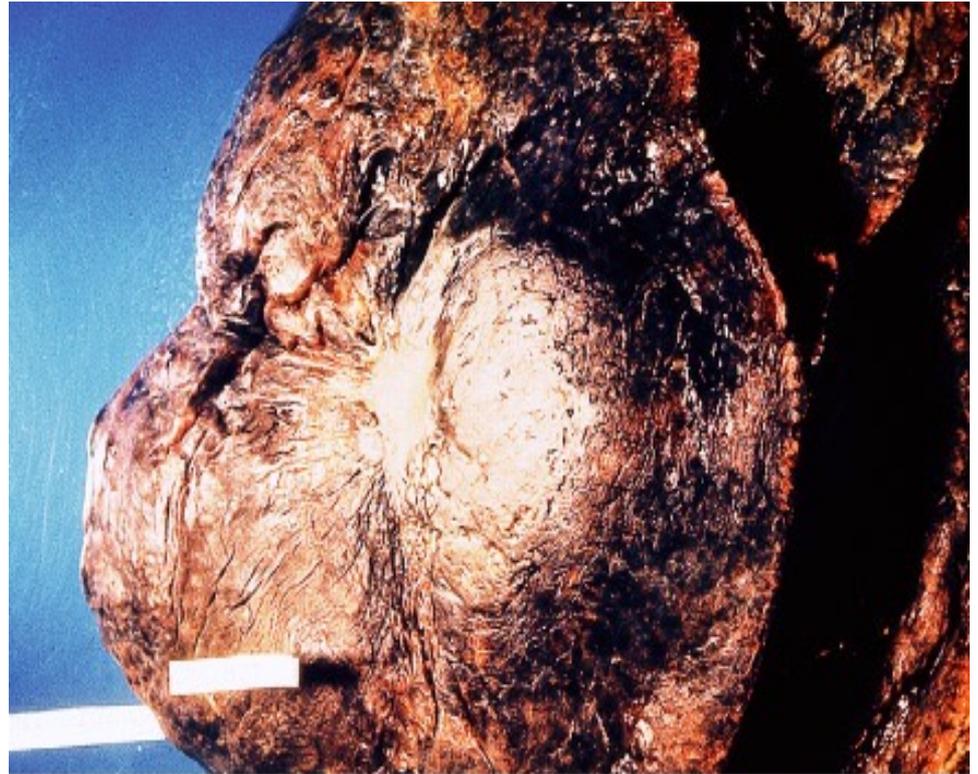
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**Localizzazione periferica**

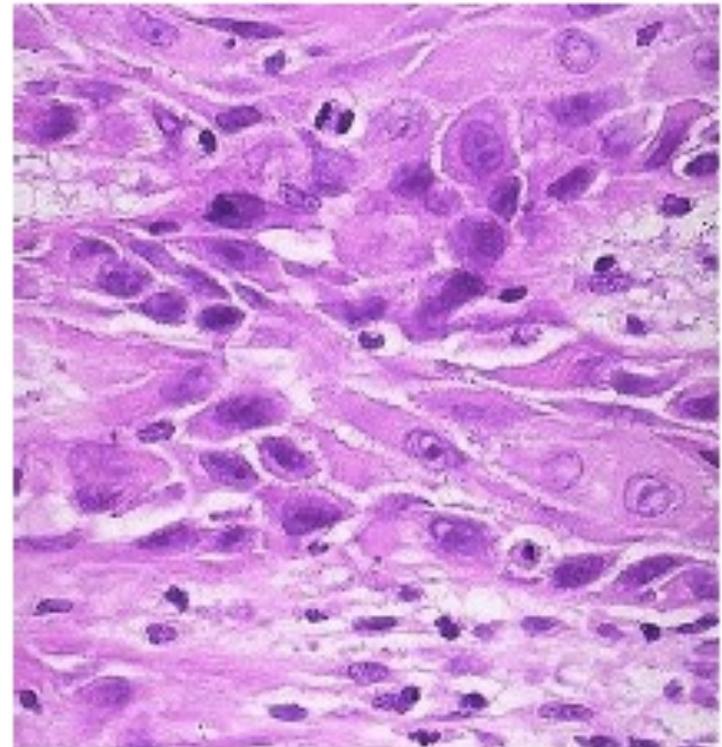
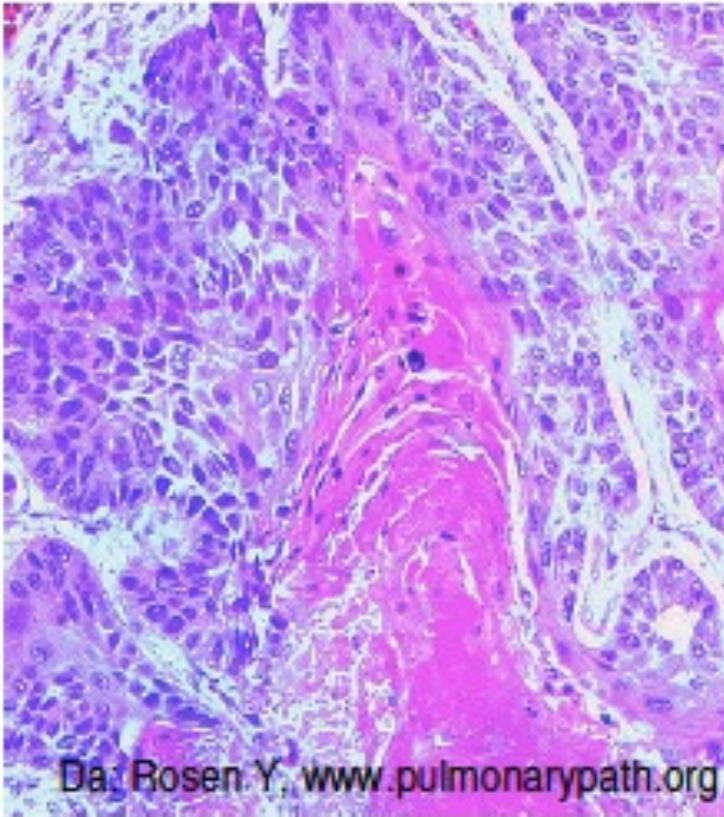
**Adenocarcinoma polmonare  
con infiltrazione della pleura**



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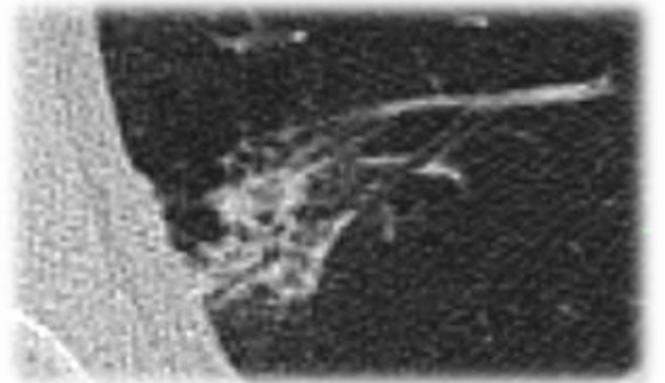
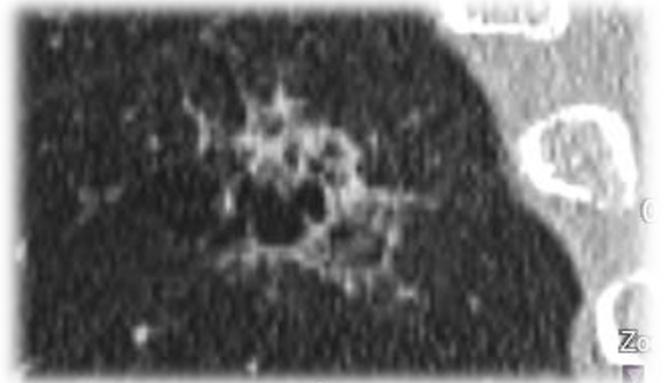
# ISTOLOGIA

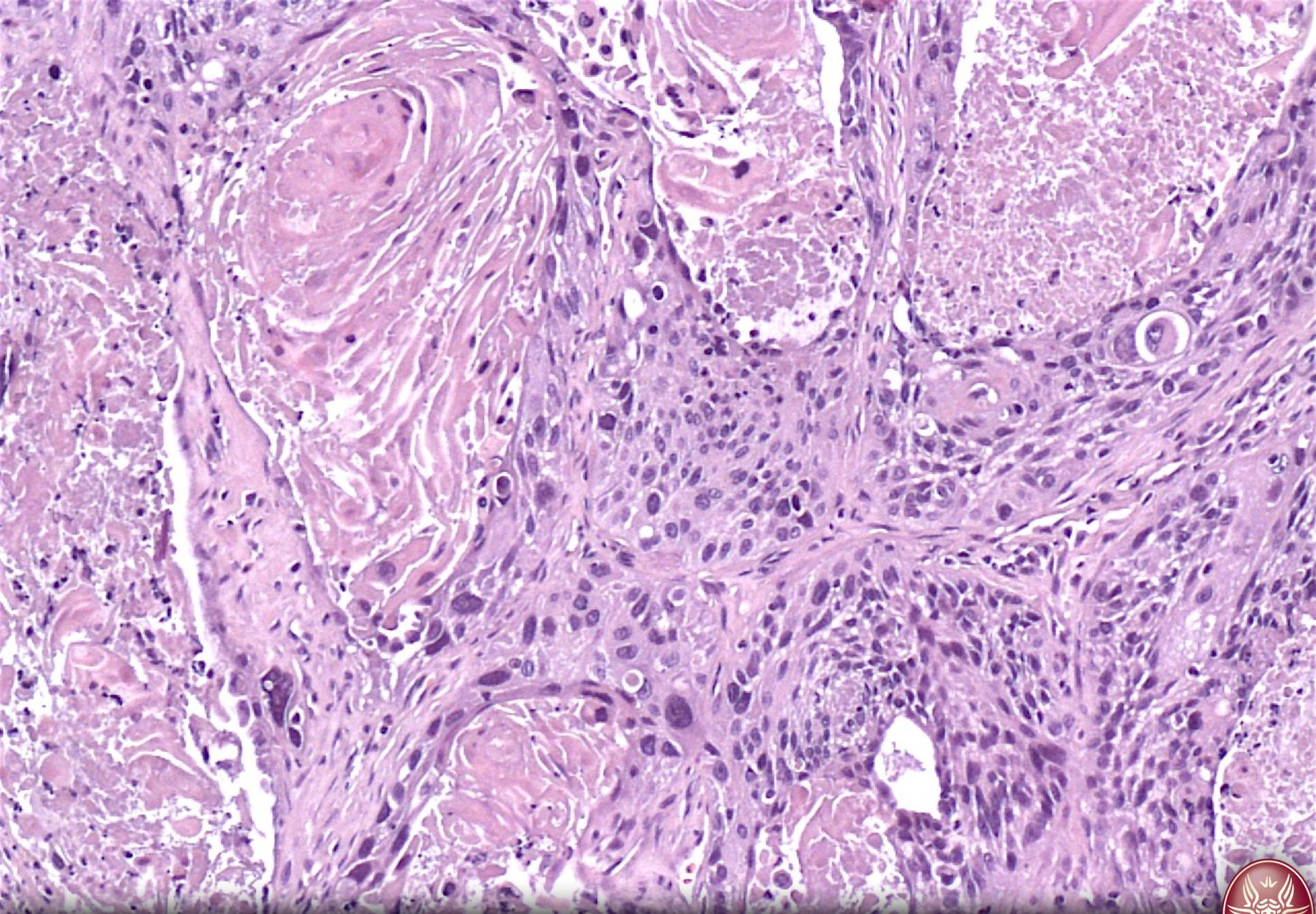
**Carcinoma squamocellulare:**  
neoplasia epiteliale maligna  
presentante cheratinizzazione e/o  
ponti intercellulari

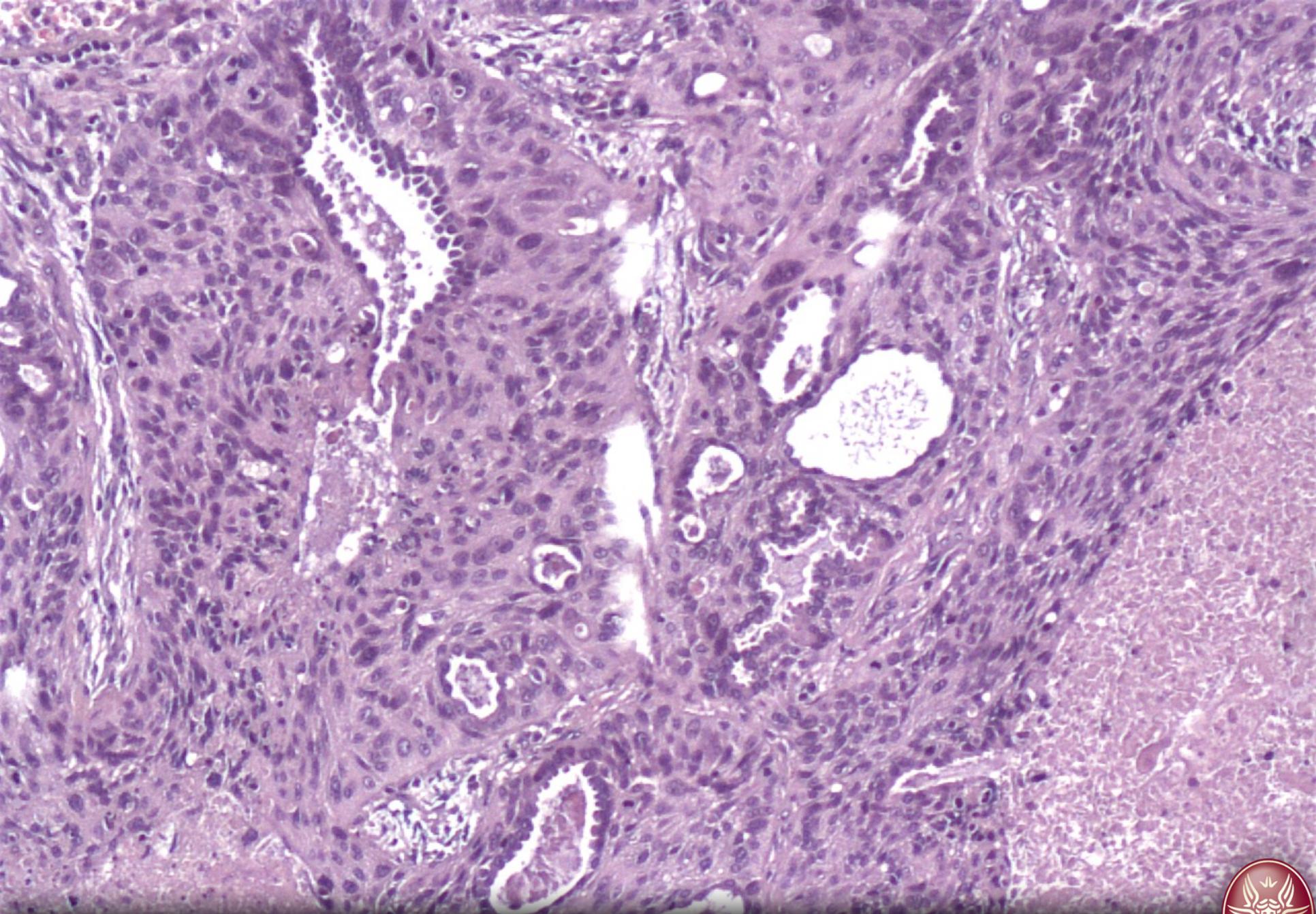


**I carcinomi squamosi** rappresentano il 20% di tutte le neoplasie polmonari e sono più diffusi tra gli uomini.

Si sviluppano come lesioni isolate, nodulari, rotondeggianti nel contesto del parenchima polmonare, o come tumori endoluminali e occludenti all'interno dell'albero bronchiale.



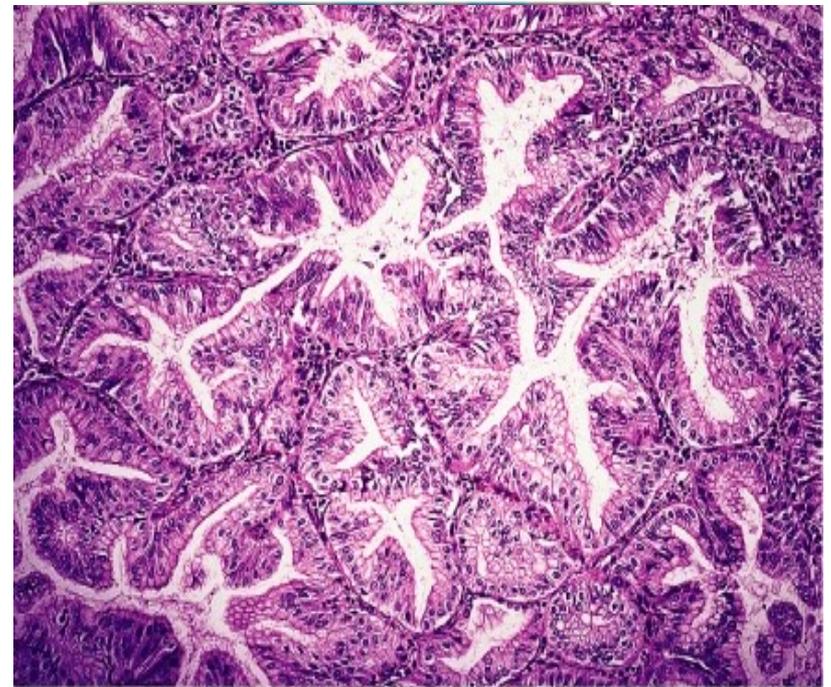
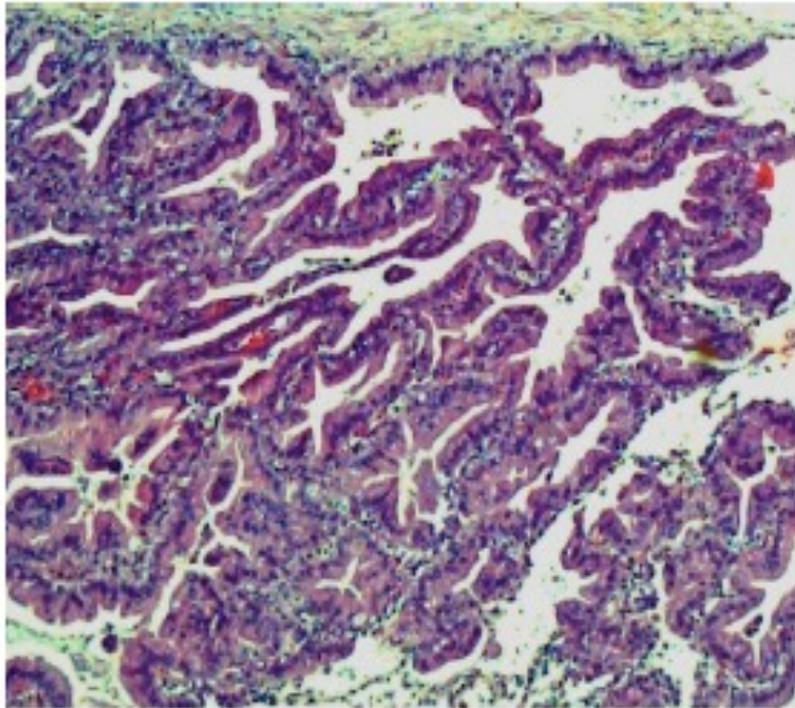




**L'adenocarcinoma** ha una frequenza pari al 40%, è più comune tra chi non abbia mai fumato e tra le donne.

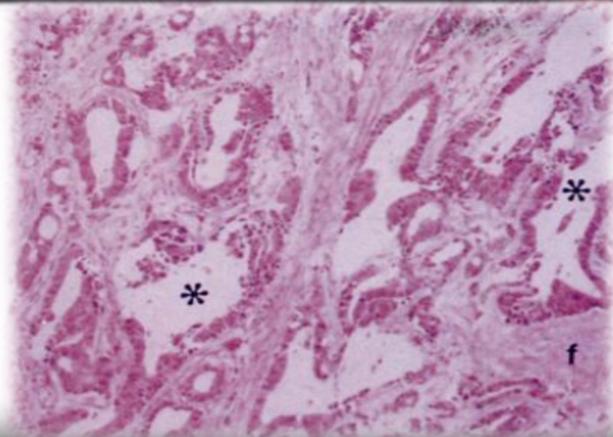
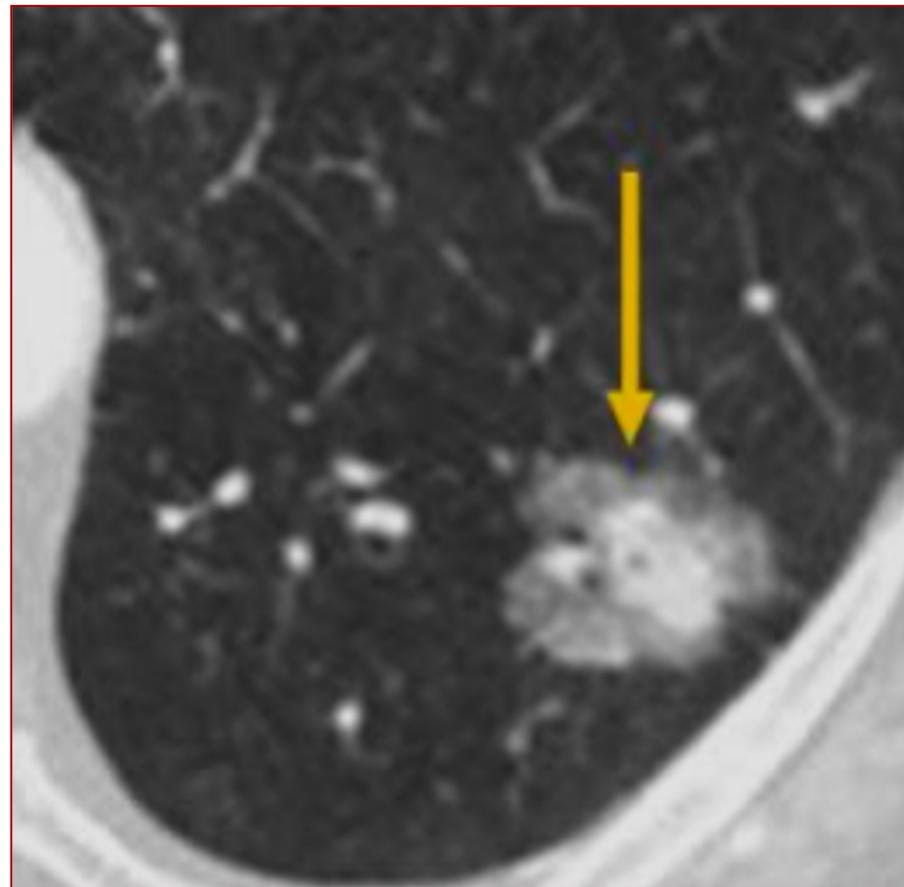
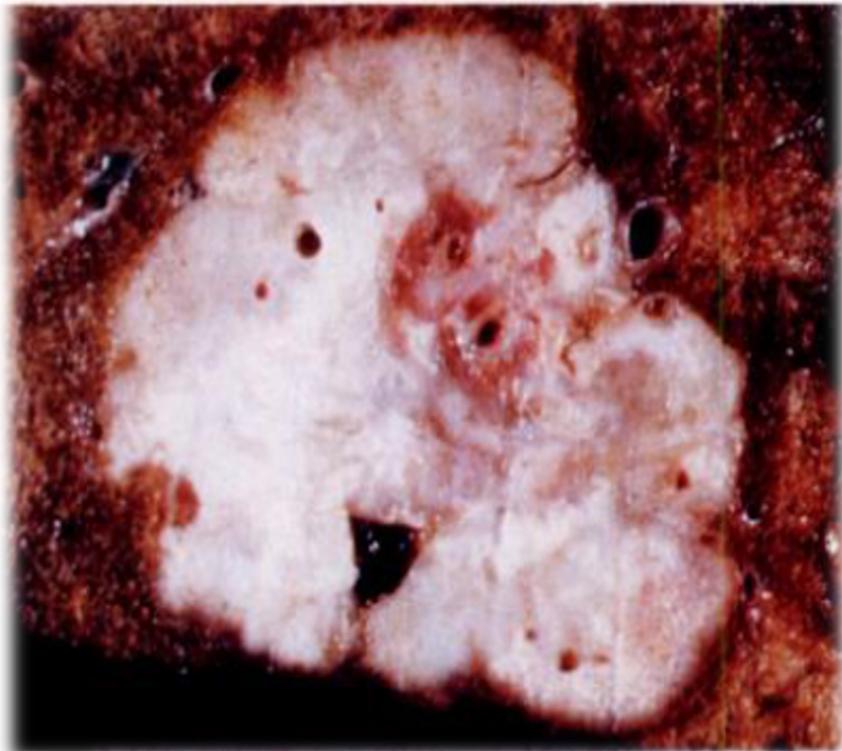
Si sviluppa prevalentemente alla periferia dei polmoni interessando spesso la pleura e si caratterizza per la presenza di strutture ghiandolari

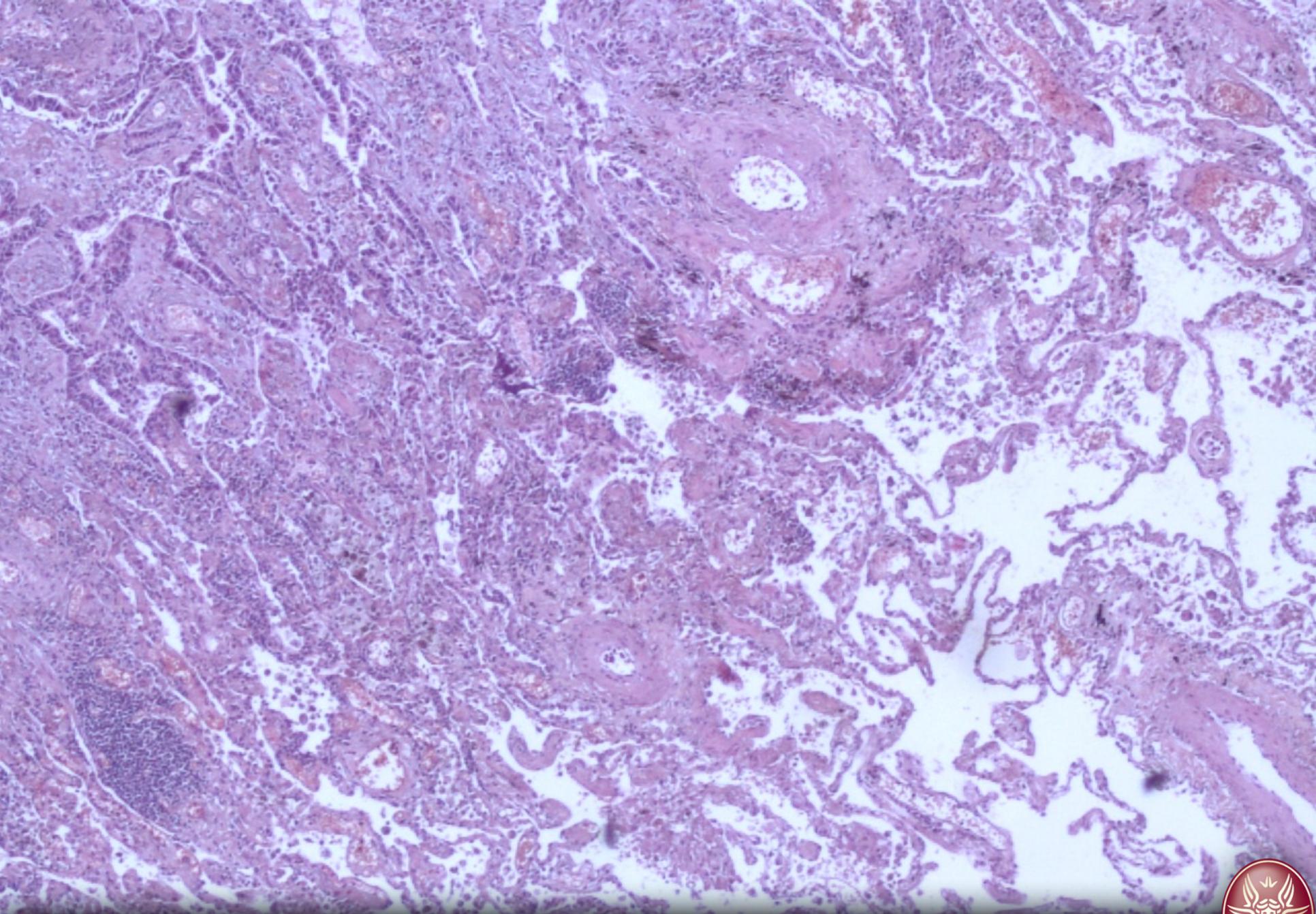
**Adenocarcinoma:** neoplasia epiteliale maligna presentante differenziazione ghiandolare o produzione di muco..

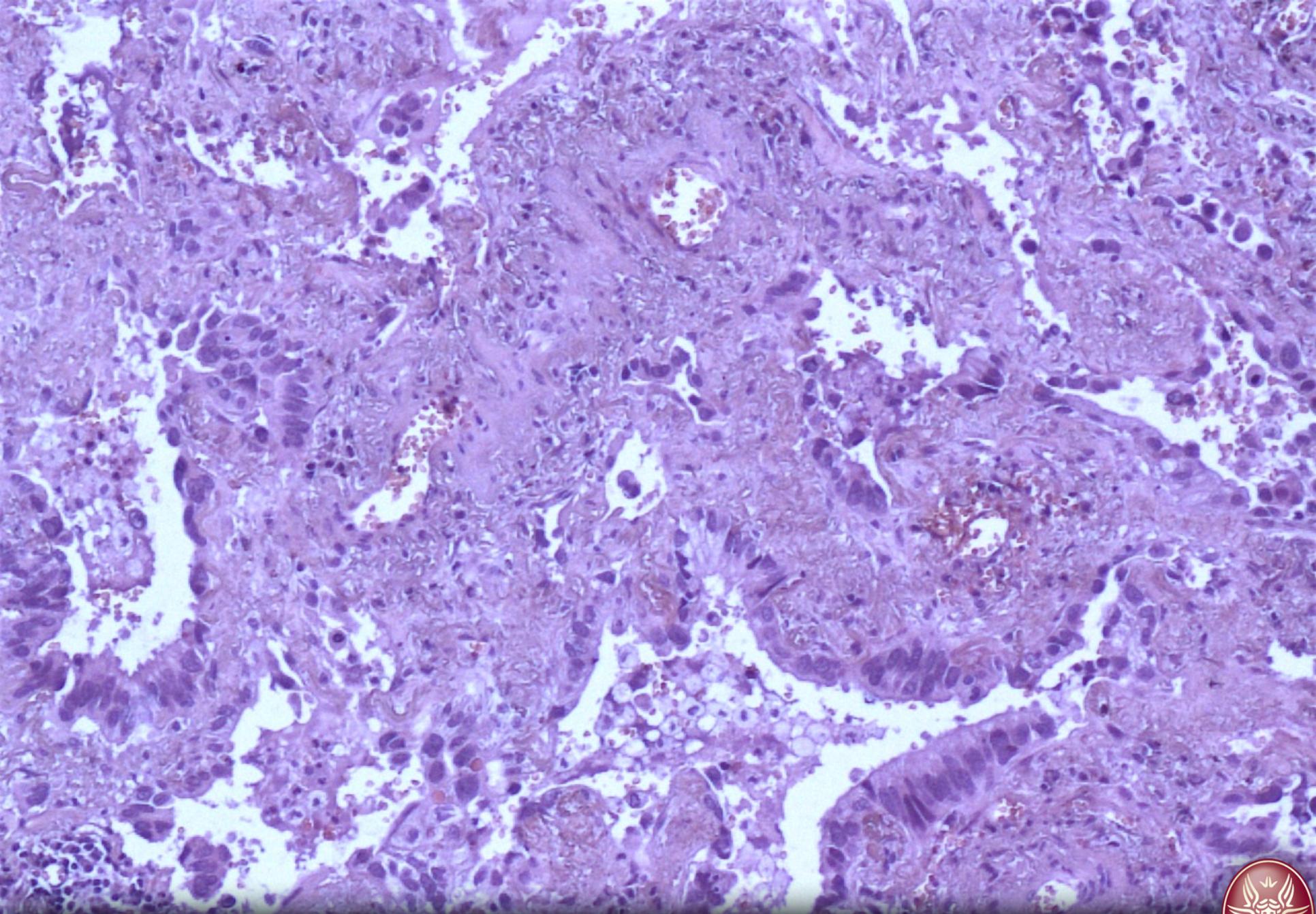


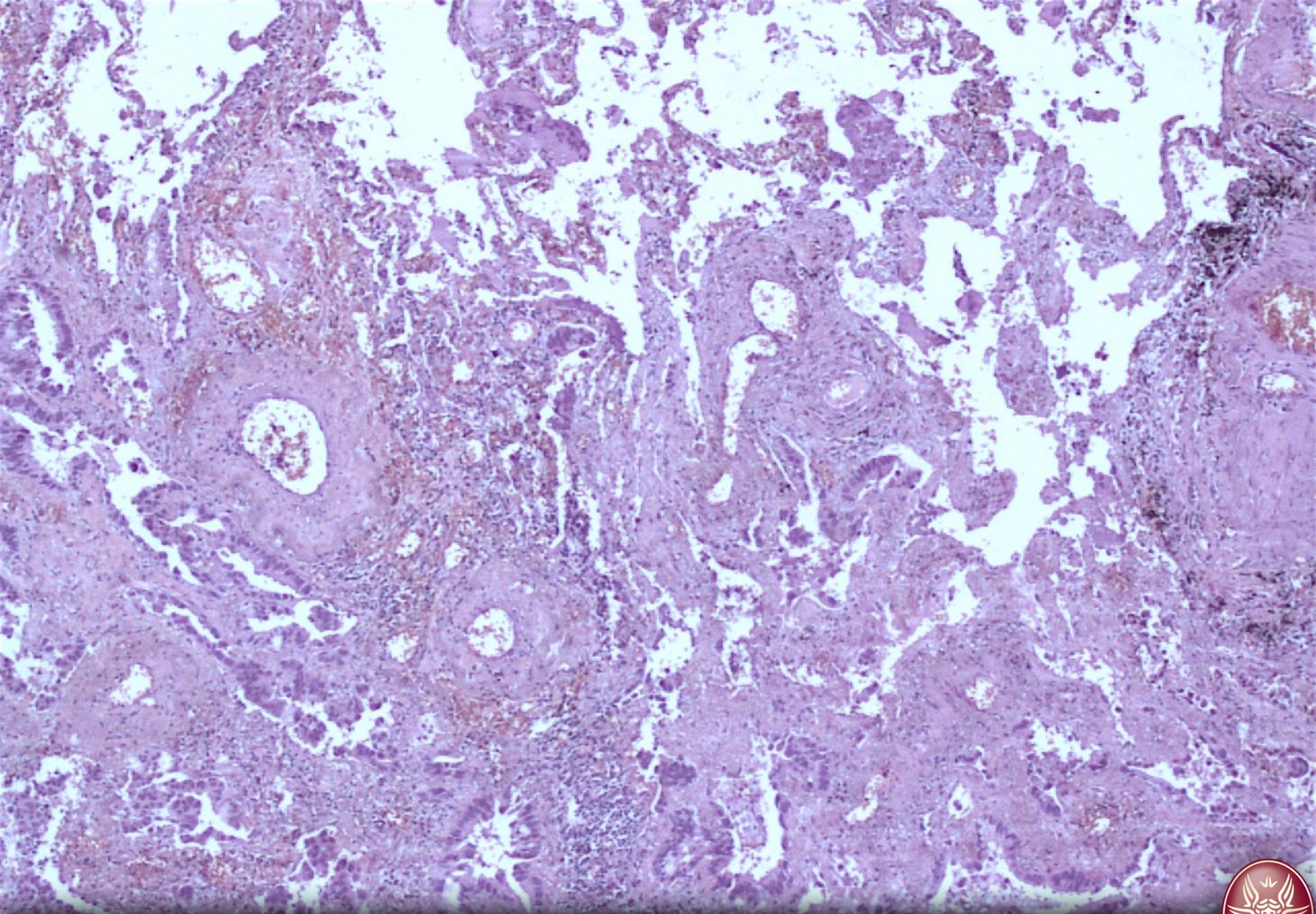


## CORRELAZIONE PATOLOGICA RADIOLOGICA

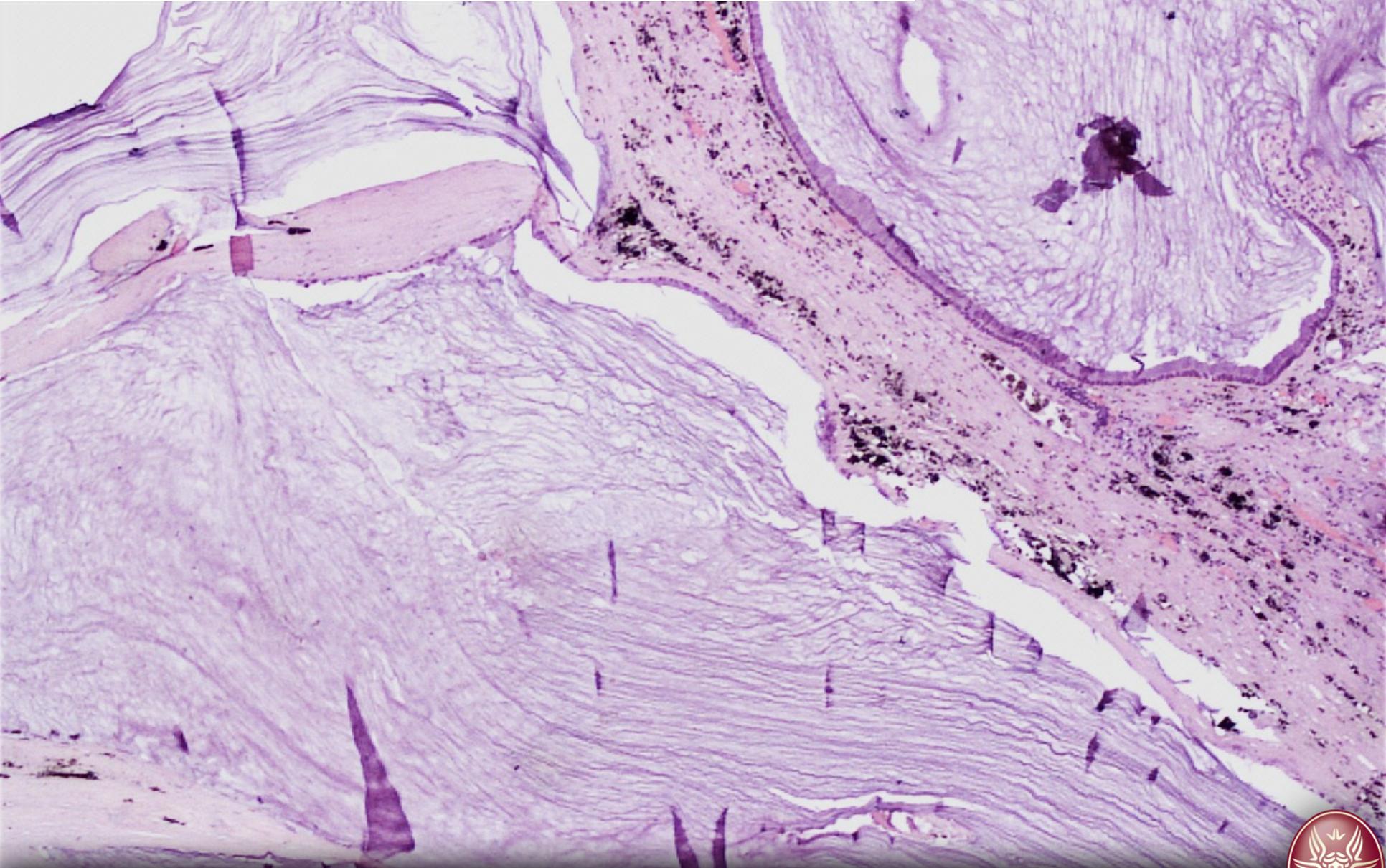


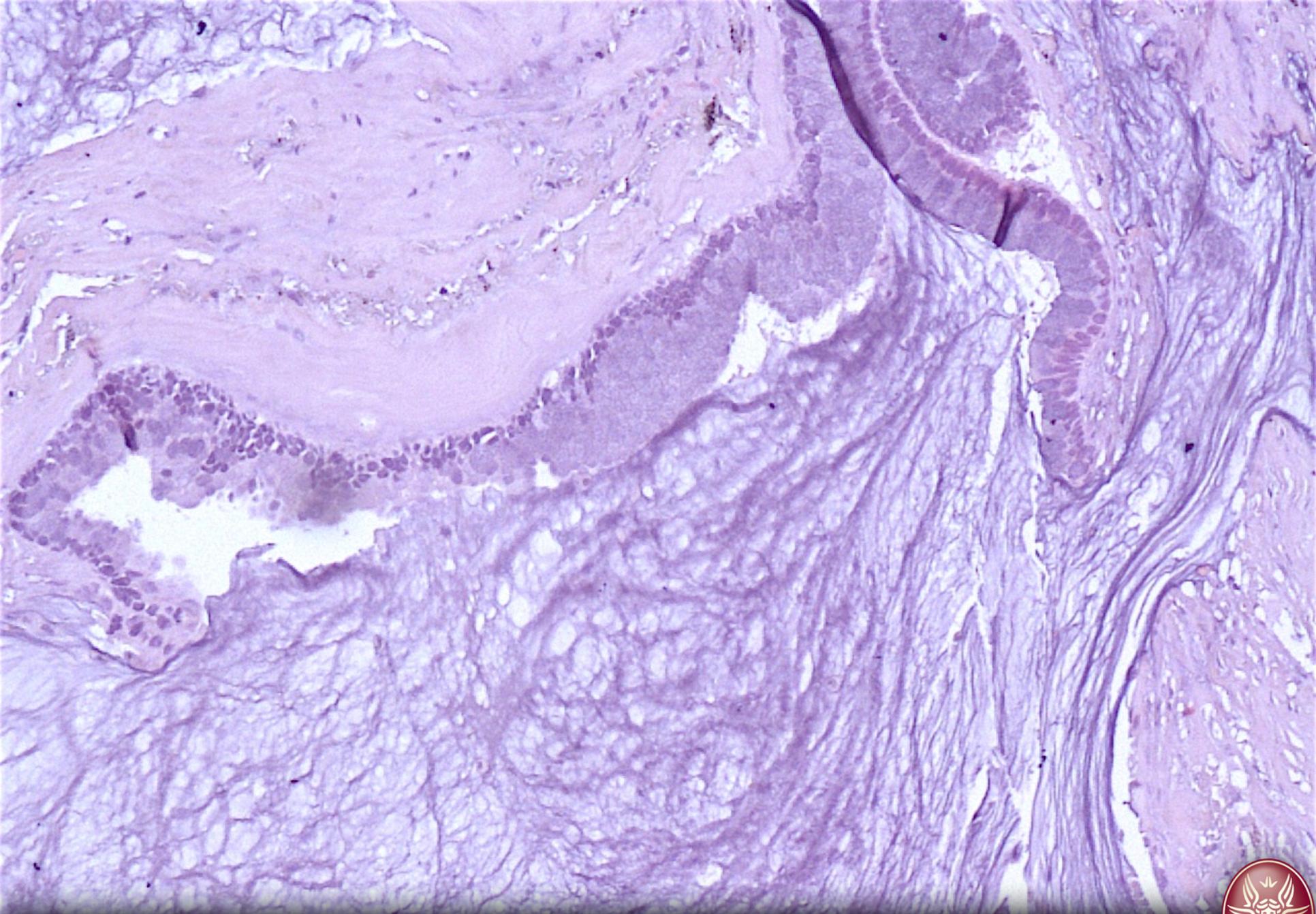






# Adenocarcinoma mucinoso



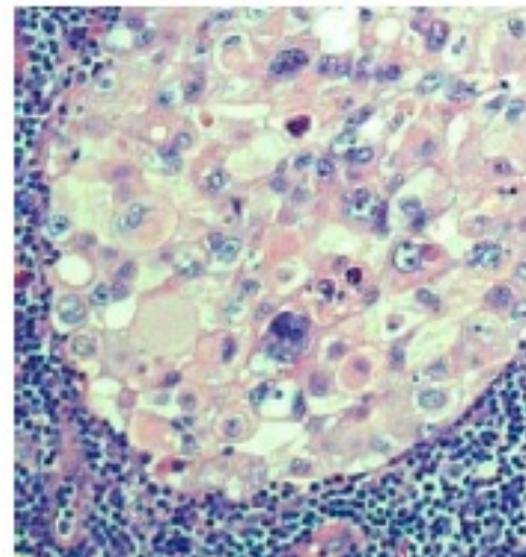
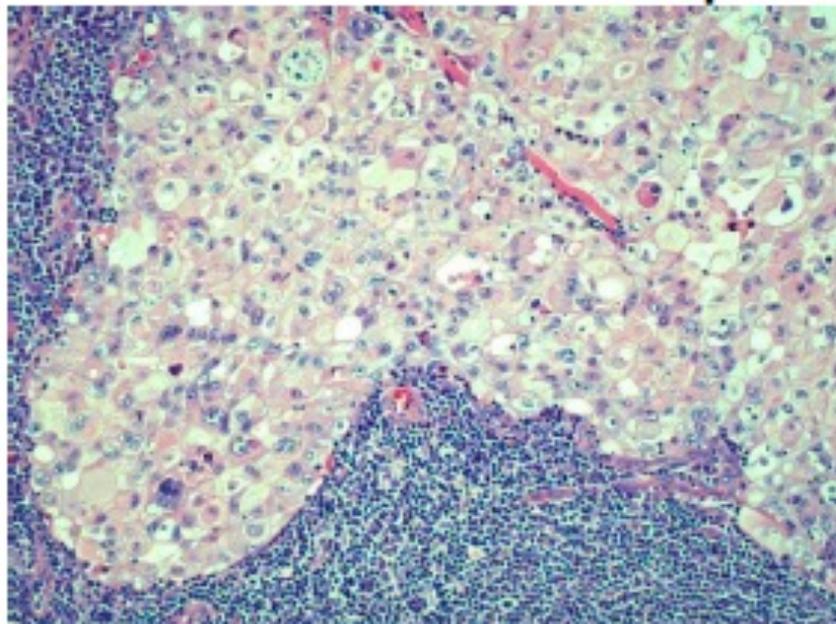


## Carcinoma a grandi cellule

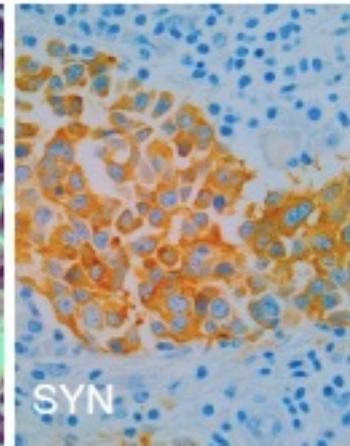
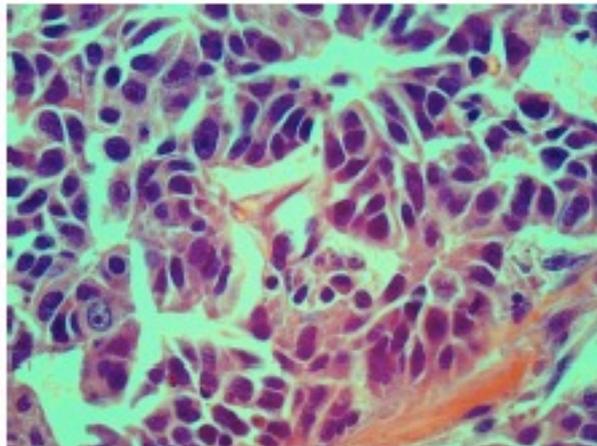
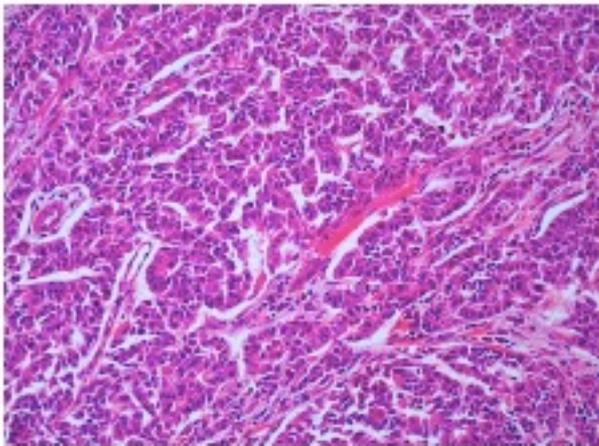
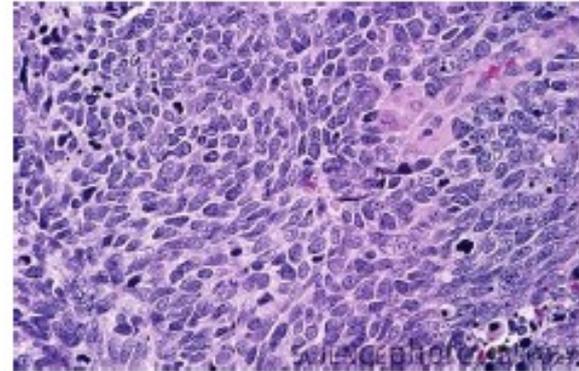
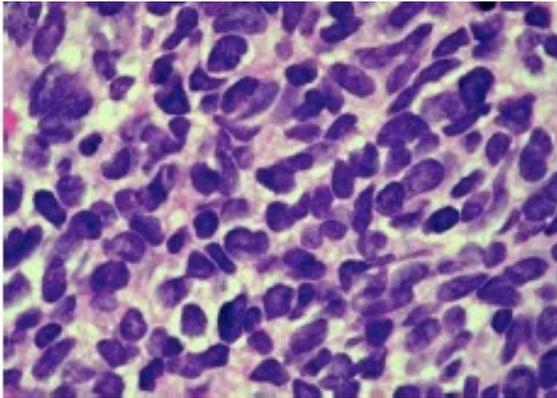
Ha una frequenza del 3% anche se la sua incidenza è in continua diminuzione per l'introduzione nella pratica clinica di tecniche diagnostiche che consentono di differenziarlo dagli adenocarcinomi scarsamente differenziati o squamosi con cui può confondersi.

## **Carcinoma a grandi cellule:**

carcinoma indifferenziato .. in cui mancano gli aspetti citologici .. del carcinoma a piccole cellule e una differenziazione ghiandolare o squamosa



**Carcinoma a piccole cellule:**  
neoplasia epiteliale maligna  
formata da cellule piccole con  
citoplasma scarso.. cromatina  
finemente granulare..nucleoli poco  
appariscenti.. elevata attività  
mitotica



## Carcinoma a piccole cellule (SCLC)

Si sviluppa di solito centralmente, mostrando una crescita a cuffia peribronchiale e perivascolare.

Origina dalle cellule endocrine del Kultschitzky del sistema bronchiale il cosiddetto sistema APUD (sistema neuroendocrino diffuso costituito da cellule nervose che stimolano il rilascio di sostanze ormonali).

## Carcinoma a piccole cellule (SCLC)

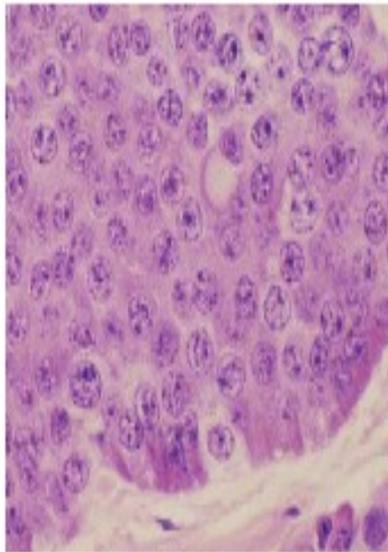
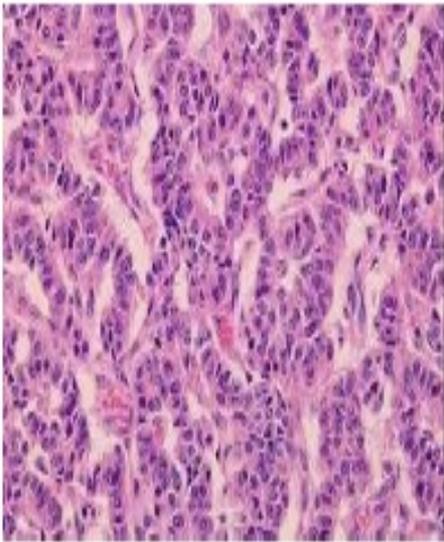
I carcinomi a piccole cellule hanno frazioni di crescita del 50% rispetto al 10% circa degli adenocarcinomi (alta velocità di crescita e metastatizzazione ad altri organi)

A causa di tale aggressività non è in genere indicata la resezione chirurgica.

Il tumore polmonare a piccole cellule risponde bene alla chemioterapia e alla radioterapia.

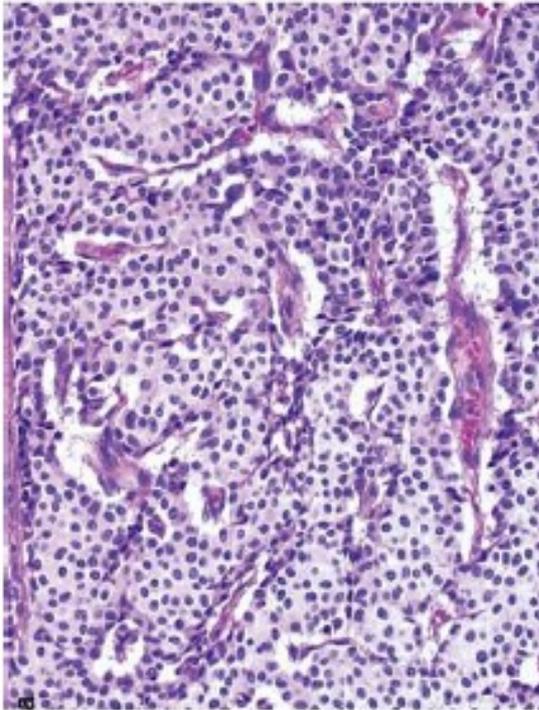
**Tumore carcinoide** è un tumore a basso grado di malignità, raro (1-2% di tutti i tumori polmonari).

Distinto in tipico e atipico.

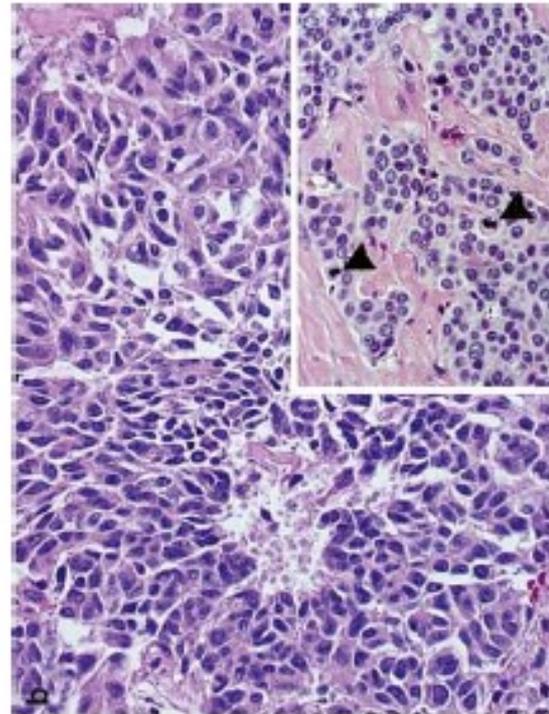


**Tumori carcinoidi:** neoplasie caratterizzate da pattern di crescita suggestivo di differenziazione neuroendocrina.. cellule uniformi con citoplasma moderatamente abbondante, finemente granulare.. cromatina finemente granulare..

- .. con meno di 2 mitosi / 2mmq, senza necrosi (**Carcinoide tipico**)



- .. con 2-10 mitosi / 2mmq e/o necrosi focale (**Carcinoide atipico**)



## PROGNOSI

**Carcinoide tipico:** tumori benigni, di dimensioni inferiori a 3 cm, con un coinvolgimento linfonodale nel 5-15% dei casi.

La sopravvivenza a 5 anni è stimata attorno al 90-98% dei casi.

**Carcinoidi atipici:** presentano invece un decorso clinico più aggressivo, con dimensioni generalmente superiori ai 3 cm di diametro e riscontro di coinvolgimento linfonodale nel 40-48% dei casi.

Le metastasi a distanza sono presenti nel 20% dei casi.

La sopravvivenza a 5 anni è pari al 60%.

# Classificazione degli adenocarcinomi polmonari su prodotto di resezione

**TABLE 1. IASLC/ATS/ERS Classification of Lung Adenocarcinoma in Resection Specimens**

Preinvasive lesions

- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ ( $\leq 3$  cm formerly BAC)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous

Minimally invasive adenocarcinoma ( $\leq 3$  cm lepidic predominant tumor with  $\leq 5$  mm invasion)

- Nonmucinous
- Mucinous
- Mixed mucinous/nonmucinous

Invasive adenocarcinoma

- Lepidic predominant (formerly nonmucinous BAC pattern, with  $>5$  mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin production

Variants of invasive adenocarcinoma

- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
  - Colloid
  - Fetal (low and high grade)
  - Enteric

# Adenocarcinoma polmonare

- Adenocarcinoma in situ  $\leq 3$  cm  
non mucinoso, mucinoso, misto
- Adenocarcinoma minimamente invasivo  $\leq 3$  cm e  $\leq 5$  mm invasione
- Adenocarcinoma invasivo  $\geq 5$  mm invasione
  - predominanza lepidica
  - predominanza acinare
  - predom. papillare
  - predom. micropapillare
  - predom. solida con muco

- **Gruppi prognostici**

- Basso grado

- Adenoca. in situ

- Adenoca. minim. inv.

- Grado intermedio

- Predomin. lepidica.

- Predom. acin.

- Predom. papillare

- Alto grado

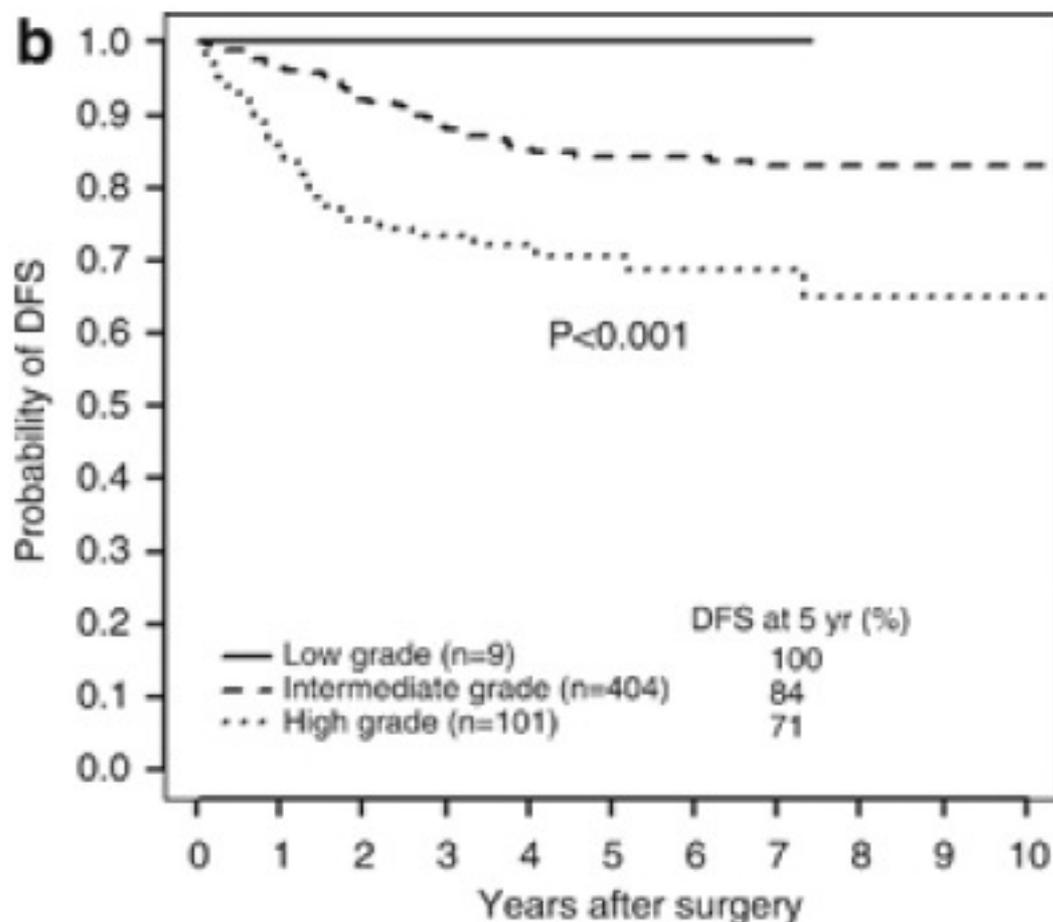
- Predom. micropap.

- Predom. solida

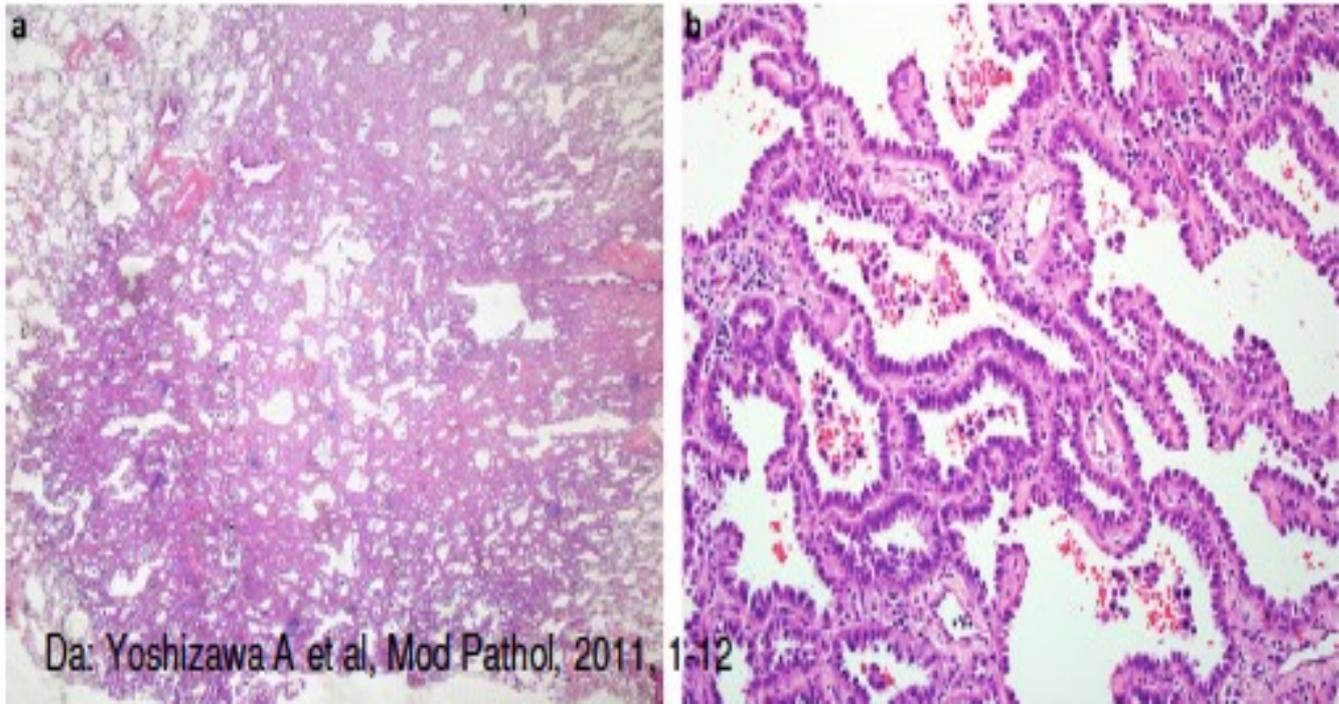
- Predom. colloidea

- Mucinoso invasivo

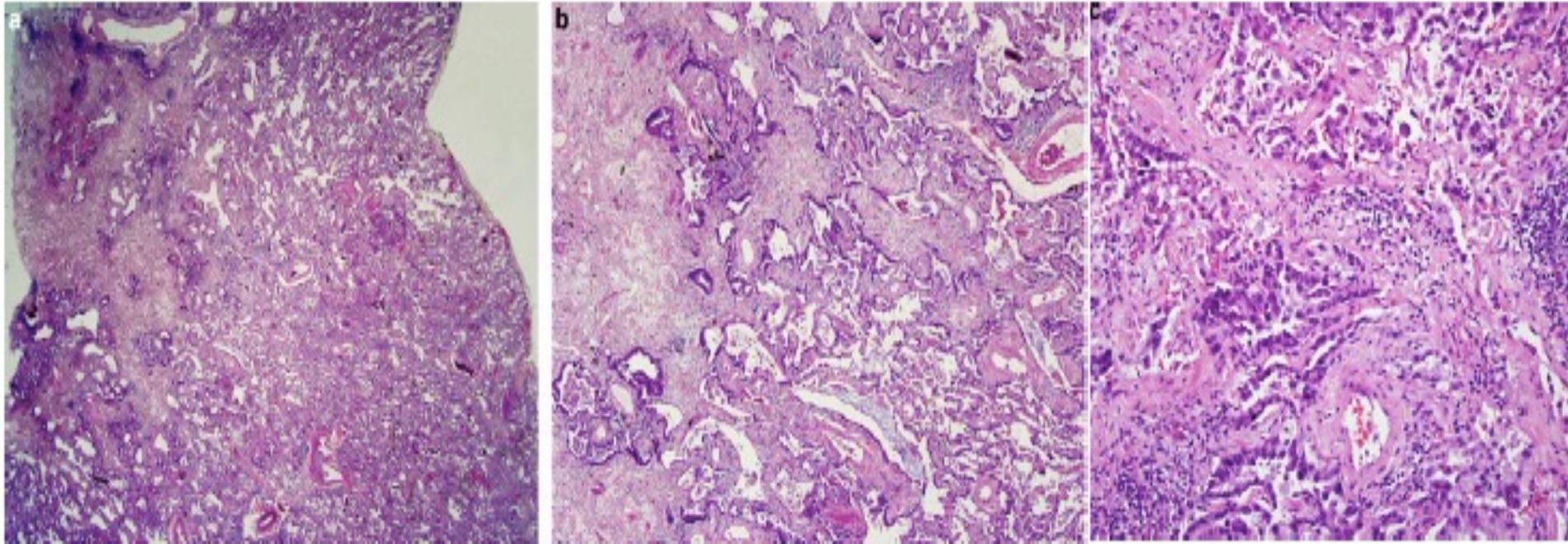
*(da Yoshizawa et al., Mod Pathol, 2011, 1-12)*



Adenocarcinoma in situ: piccolo (<3cm) adenocarcinoma ben circoscritto con crescita “lepidica”, senza invasione (e senza aspetti papillari, micropapillari o cellule tumorali intraalveolari). Quasi tutti sono non-mucinosi



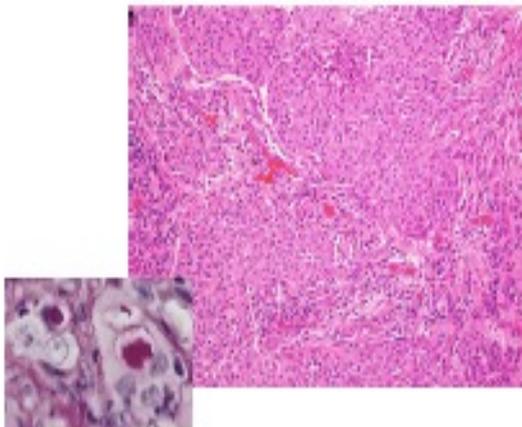
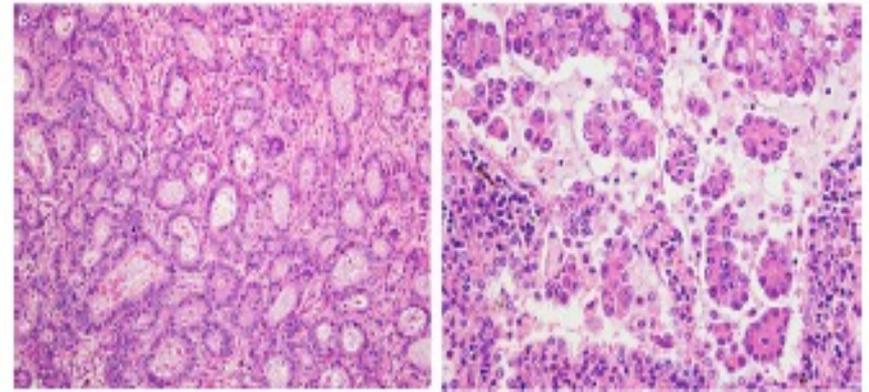
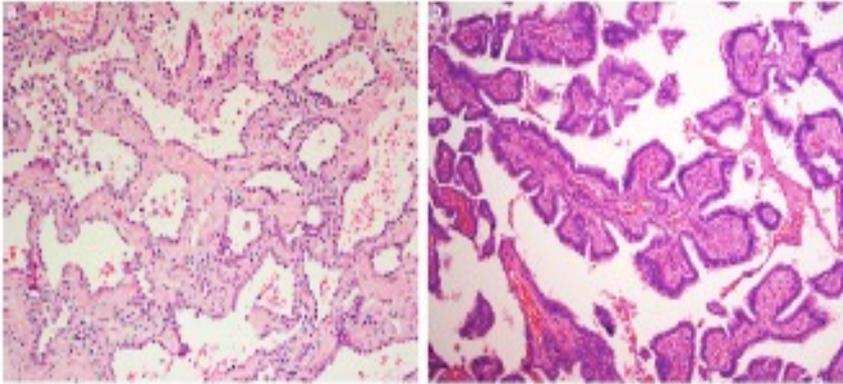
**Adenocarcinoma minimamente invasivo:** piccolo adenocarcinoma (<3cm) solitario, ben circoscritto, con crescita prevalentemente lepidica e focolai d'invasione <5mm di diametro



Da: Yoshizawa A et al, Mod Pathol, 2011, 1-12

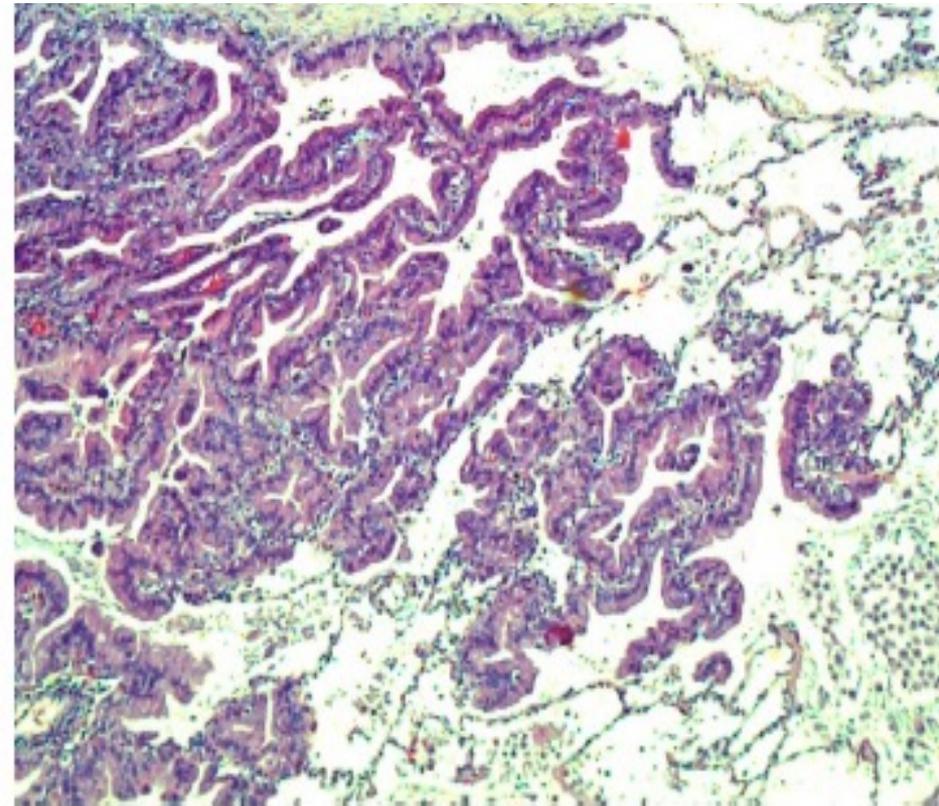
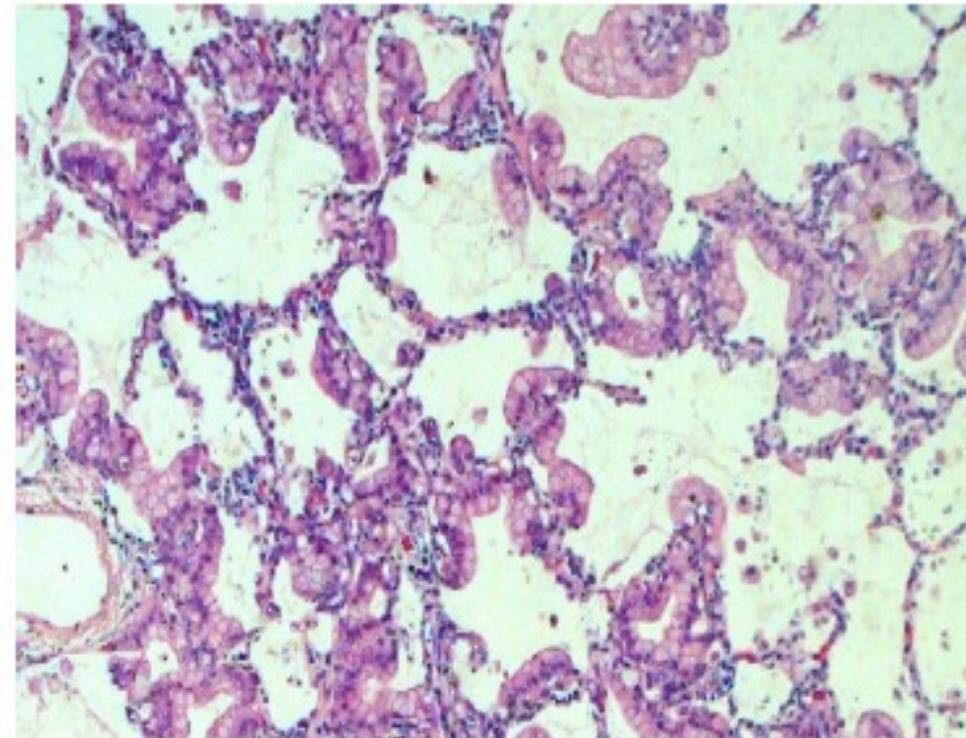
## **Adenocarcinoma invasivo:**

classificato in base alla modalità di crescita predominante – lepidica, acinare, papillare, micropapillare, solida con muco.



Immagini da: Yoshizawa A et al, Mod Pathol, 2011, 1-12

**Adenocarcinoma invasivo mucinoso:**  
costituito da cellule tumorali cilindriche o  
caliciformi con abbondante muco  
intracitoplasmatico.



# Diagnosi anatomo-patologica

Citologia

Istologia (Biopsie)

# Diagnosi anatomo-patologica

## Citologia

Metodica semplice che consente la diagnosi nel 70-80% dei tumori centrali e di circa il 20% di quelli periferici

Il materiale per l'esame citologico può provenire da

- ✓ Espettorato
- ✓ Broncoaspirato
- ✓ Agoaspirato trans-toracico

# Diagnosi anatomico-patologica

## Citologia-accuratezza

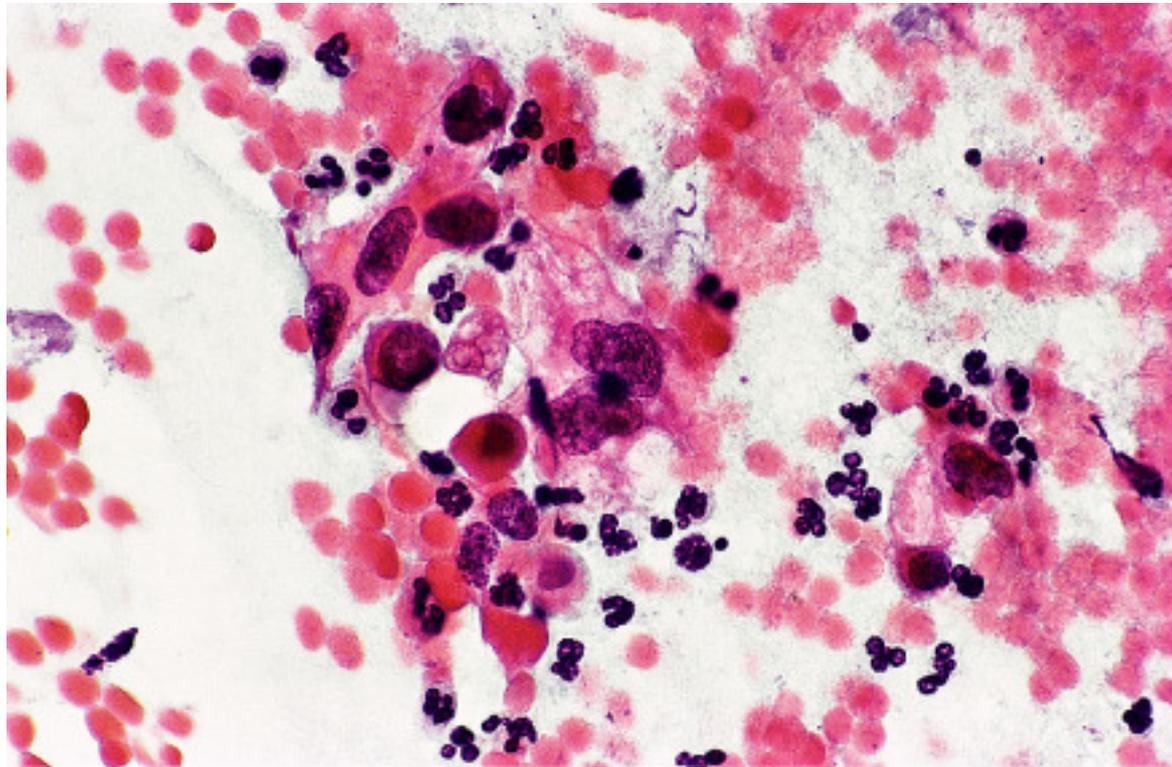
La citologia dell'escreato ha un'accuratezza diagnostica del 60-75%

La citologia dell'agoaspirato trans-parietale ha un'accuratezza diagnostica del 80-90%

In caso di infiltrazione pleurica la diagnosi può essere effettuata sul liquido pleurico opportunamente aspirato

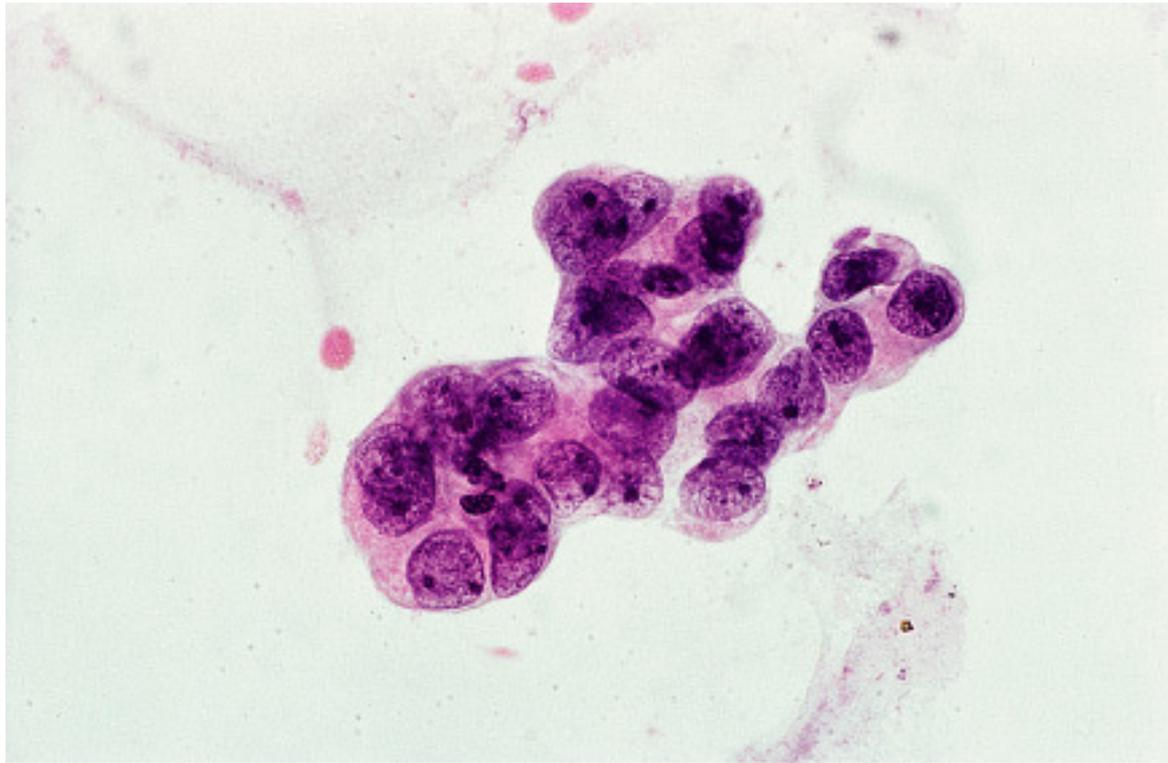
# Espettorato

Campione citologico  
di carcinoma squamoso



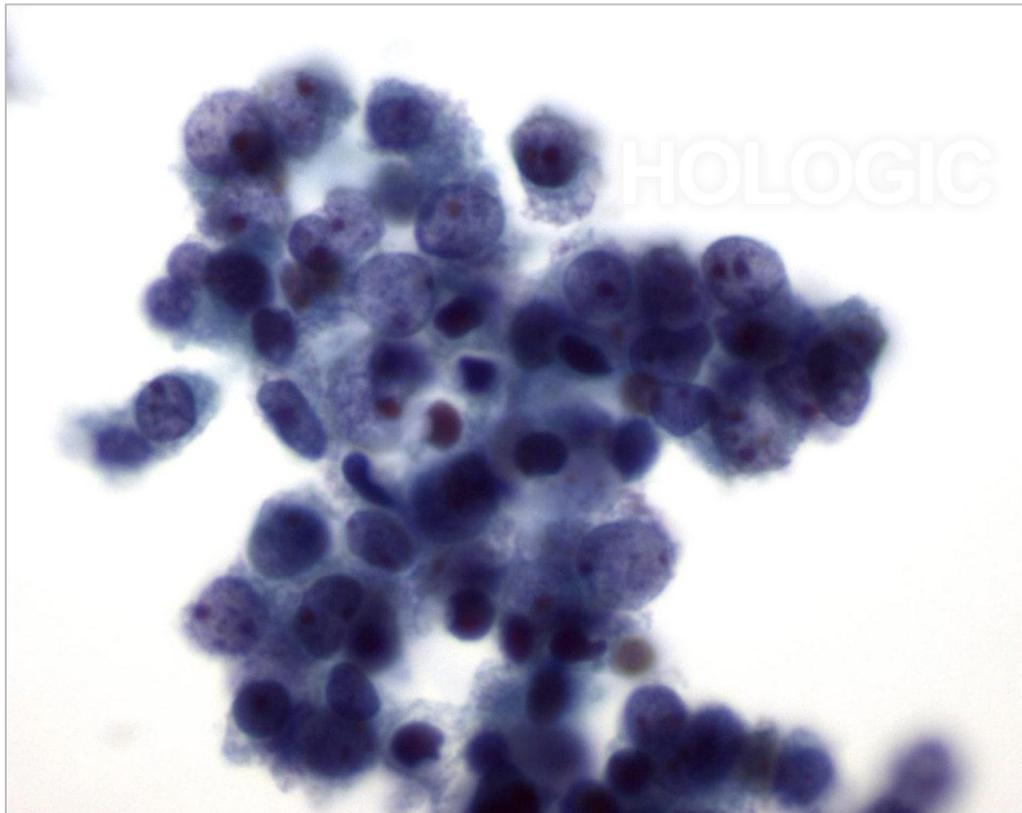
# Espettorato

Campione citologico  
di adenocarcinoma



# Espettorato

Campione citologico  
di carcinoma a piccole cellule



# Diagnosi anatomo-patologica

## Istologia

Il ruolo dell'istologia consiste:

### **BIOPSIA**

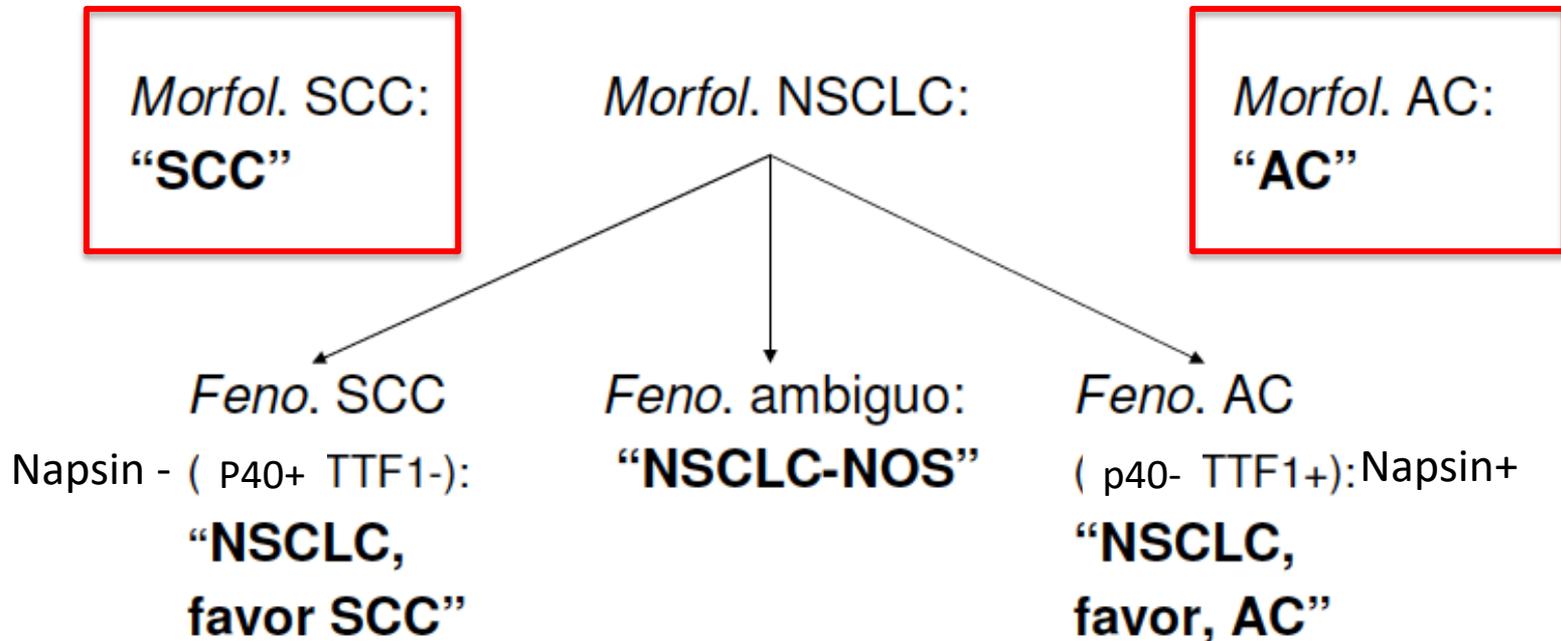
Diagnosi di istotipo su materiale bioptico (broncoscopia o agobiopsia)

### **CAMPIONE OPERATORIO**

Valutazione delle caratteristiche macroscopiche del tumore e dell'**estensione** e dello **stato linfonodale** sul pezzo operatorio.

Valutazione del  **margine bronchiale**  di resezione (giudizio sulla radicalità dell'intervento)

# Classificazione IASLC/ATS/ERS dei NSCLC su piccola biopsia o citologia



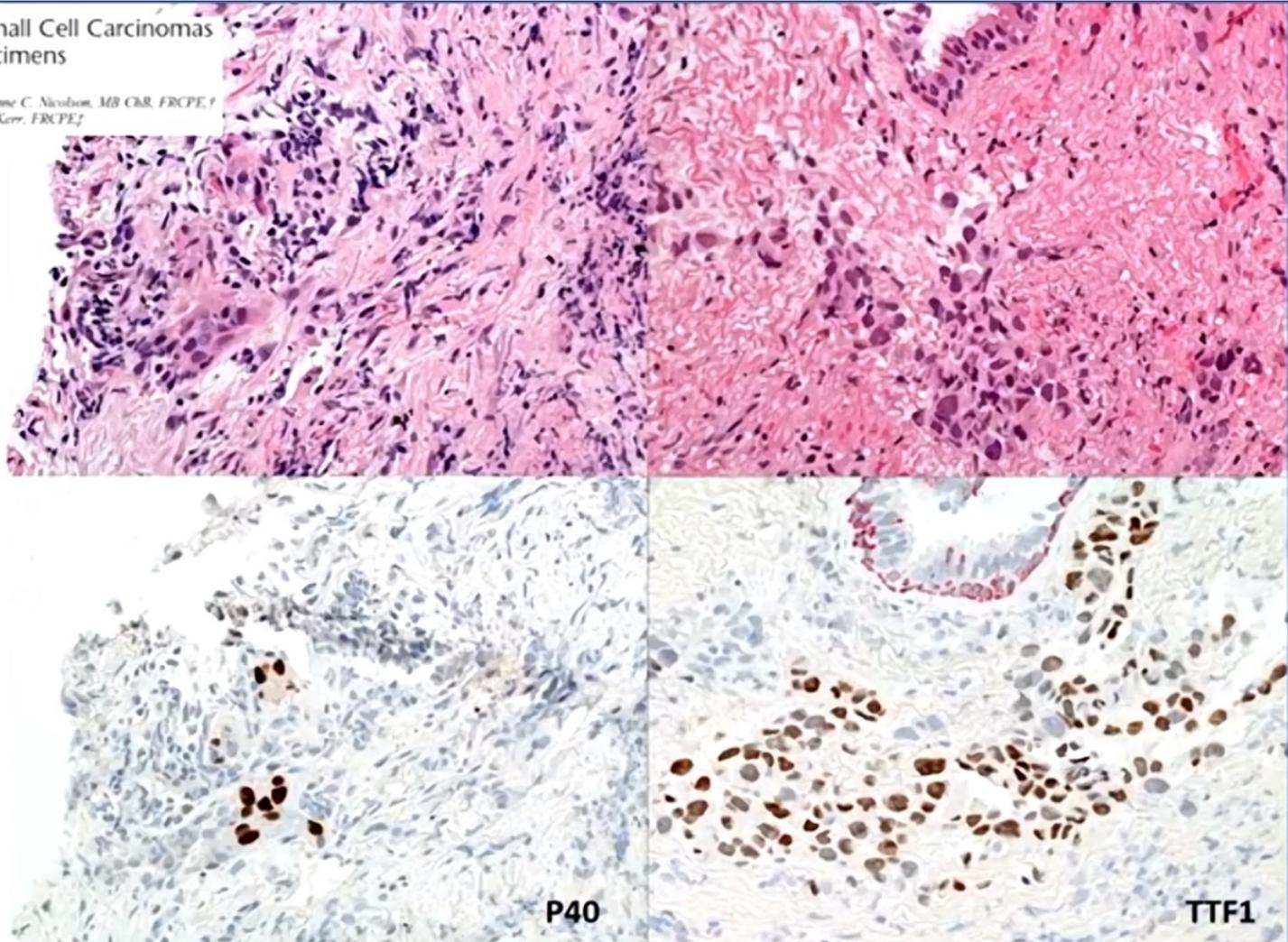
## Subtyping of Undifferentiated Non-small Cell Carcinomas in Bronchial Biopsy Specimens

*Pei Sun Lou, MB ChB,\* Stuart C. Thomas, PhD, MB ChB,\* Marianne C. Nicolson, MB ChB, FRCPE,†  
Margaret N. Fyfe, MSc, CSc,\* and Keith M. Kerr, FRCPE,†*

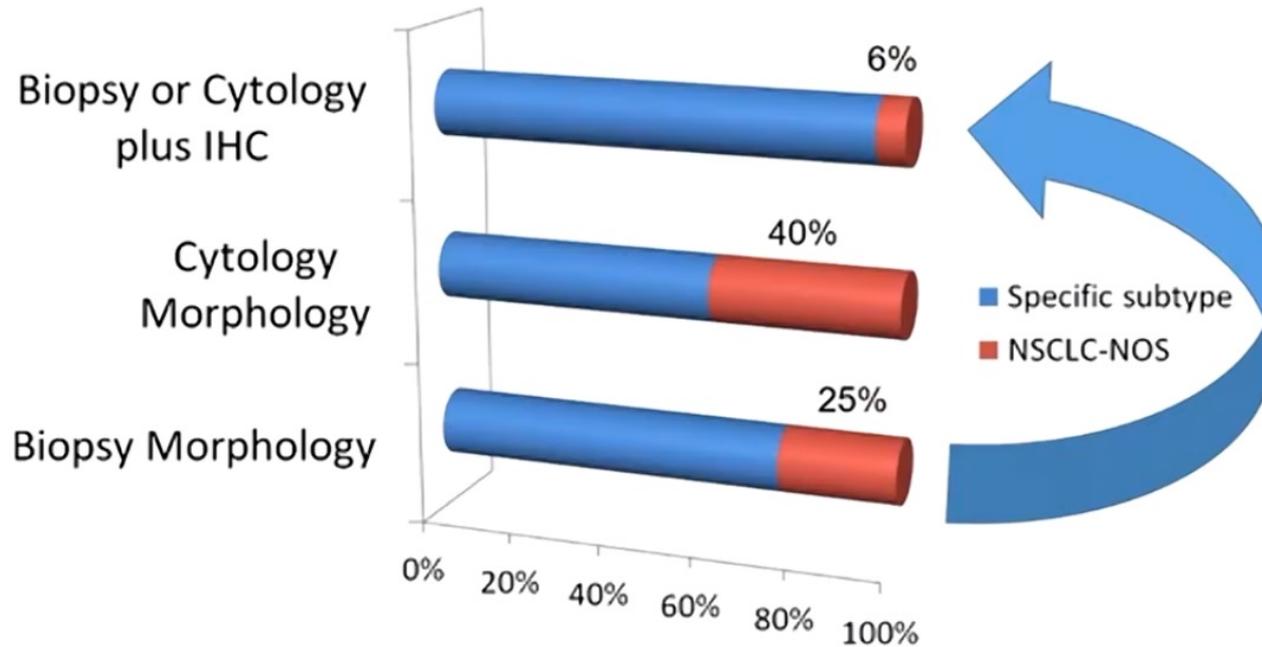
Non-small cell carcinoma  
Not otherwise specified



Diagnosis of Probable  
Squamous or  
Adenocarcinoma  
Favoured

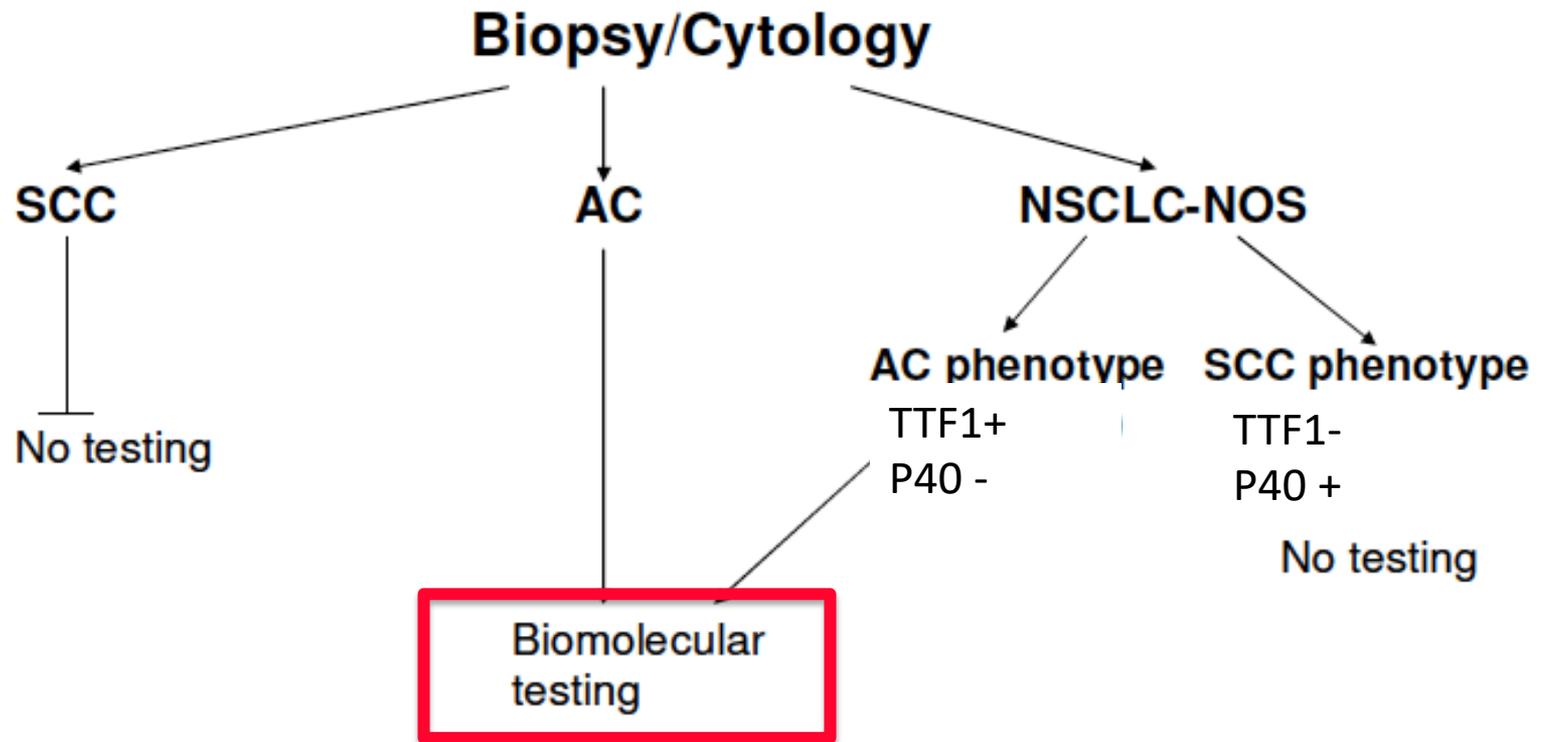


## Subtyping NSCLC: Transformed by Immunohistochemistry



### p40 & TTF1 IHC

- Predictive IHC has 'levelled the playing field'
- Better diagnosis possible on poorer specimens



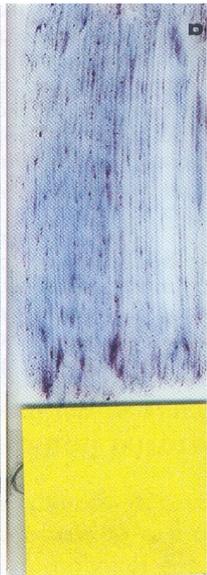
*(from:  
Recommendations for diagnostic workup...of lung biopsies,  
SSPath, Jan. 2011)*

# Il campione

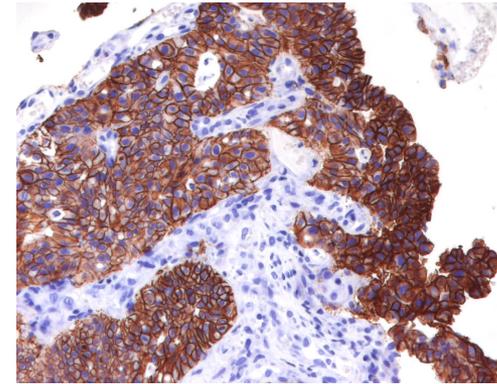


- Copy Number Variations
- Somatic Mutations
- Rearrangements
- Fusion genes
- SNPs
- Methylation
- Gene Expression

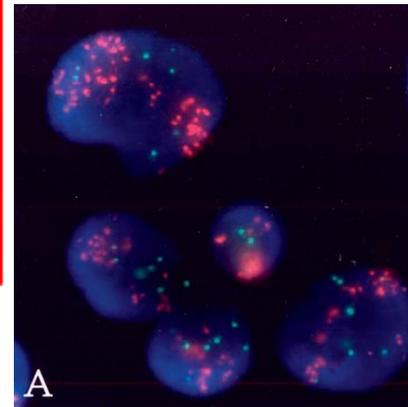
Preparato istologico



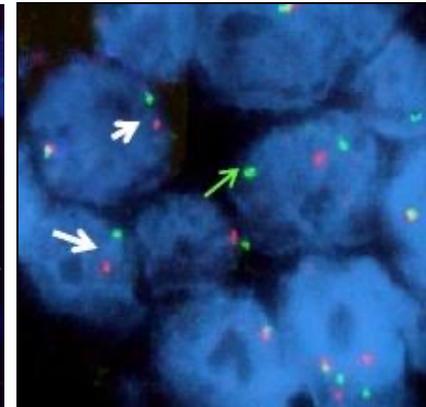
citologico



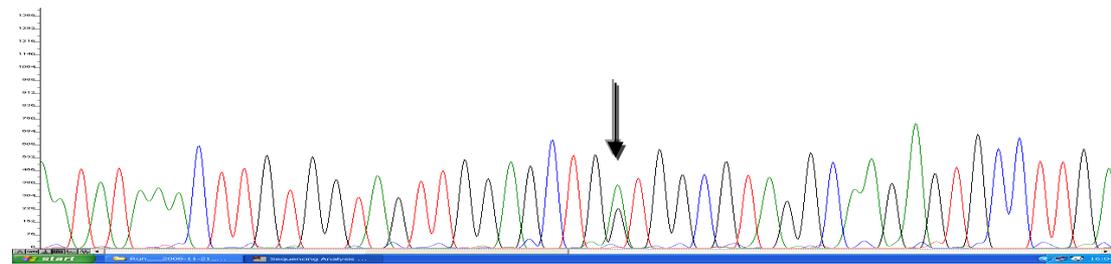
Iperespressione della proteina (IIC)



amplificazione



traslocazione



sequenza

Questionari OPIS Valutazione docente

Manila Antonelli

**ANATOMIA PATOLOGICA E CORRELAZIONI ANATOMO-CLINICHE**

CODICE CORSO

1026108

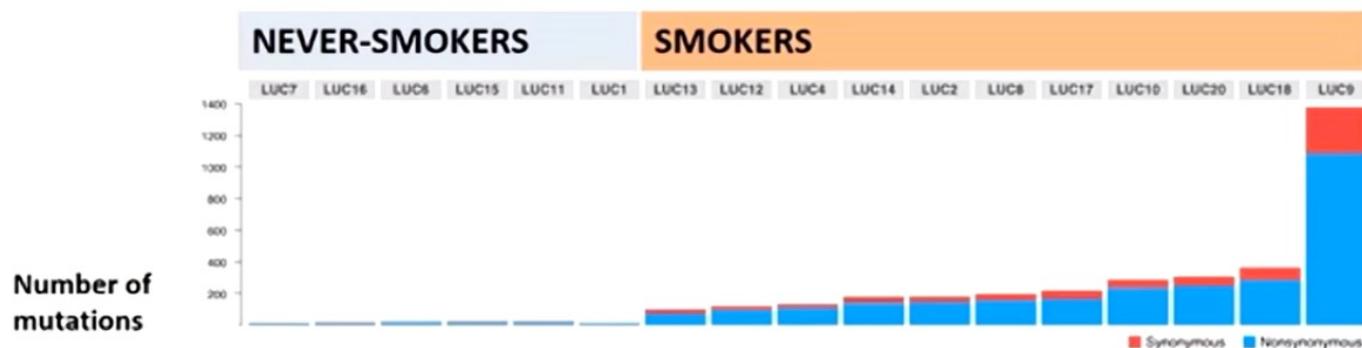
**CODICE OPIS**

N7T9DAGE

# Genomic Landscape of Non-Small Cell Lung Cancer in Smokers and Never-Smokers

Ramaswamy Govindan,<sup>1,2,9</sup> Li Ding,<sup>1,3,4,9</sup> Malachi Griffith,<sup>3,4</sup> Janakiraman Subramanian,<sup>1,2</sup> Nathan D. Dees,<sup>3</sup> Krishna L. Kanchi,<sup>3</sup> Christopher A. Maher,<sup>1,2,3</sup> Robert Fulton,<sup>3,4</sup> Lucinda Fulton,<sup>3,4</sup> John Wallis,<sup>3,4</sup> Ken Chen,<sup>8</sup> Jason Walker,<sup>3</sup> Sandra McDonald,<sup>2,6</sup> Ron Bose,<sup>1,2</sup> David Omritz,<sup>5</sup> Donghai Xiong,<sup>7</sup> Ming You,<sup>7</sup> David J. Dooling,<sup>3,4</sup> Mark Watson,<sup>2,6</sup> Elaine R. Mardis,<sup>2,3,4</sup> and Richard K. Wilson<sup>2,3,4,\*</sup>

Cell. 2012 Sep 14;150:1121-34



Molte neoplasie dipendono da un singolo oncogene per la loro crescita e sopravvivenza - “**oncogene addiction**” o “oncogene driver”

Altre dipendono dall’alterazione di più geni inclusi TSG - «**oncogene expedience**»

## ‘Driver’ mutations and lung adenocarcinoma biology



### Oncogene ‘Addiction’

Genetically simple tumours  
NO tobacco carcinogenesis  
Mutually exclusive drivers  
Almost exclusively adenocarcinomas



### Oncogene ‘Expedience’

Genetically complex tumours  
Tobacco carcinogenesis  
Multiple drivers incl loss of TSG  
Many adenocarcinomas, vast majority  
of squamous and SCLC

# EGFR mutations

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

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

Science 2004

## **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. Hasserlat, 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.

New Engl J Med 2004

## **Gefitinib-Sensitizing EGFR Mutations in Lung Cancer Activate Anti-Apoptotic Pathways Raffaella Sordella, Daphne W. Bell, Daniel A. Haber, Jeffrey Settleman\***

See all authors and affiliations

Science 20 Aug 2004:

Vol. 305, Issue 5687, pp. 1163-1167

DOI: 10.1126/science.1101637

Science 2004

## REVIEW ARTICLE

### The pivotal role of pathology in the management of lung cancer

Morgan R. Davidson<sup>1,2</sup>, Adi F. Gazdar<sup>3,4</sup>, Belinda E. Clarke<sup>1,5</sup>

## Revolution in Lung Cancer

### New Challenges for the Surgical Pathologist

Philip T. Cagle, MD; Timothy C. Allen, MD, JD; Sanja Dacic, MD, PhD; Mary Beth Beasley, MD; Alain C. Borczuk, MD; Lucian R. Chirieac, MD; Rodolfo Laucirica, MD; Jae Y. Ro, MD, PhD; Keith M. Kerr, MD

Targ Oncol (2013) 8:1–2  
DOI 10.1007/s11523-013-0265-x

## EDITORIAL

### Lung cancer: how to face the revolution?

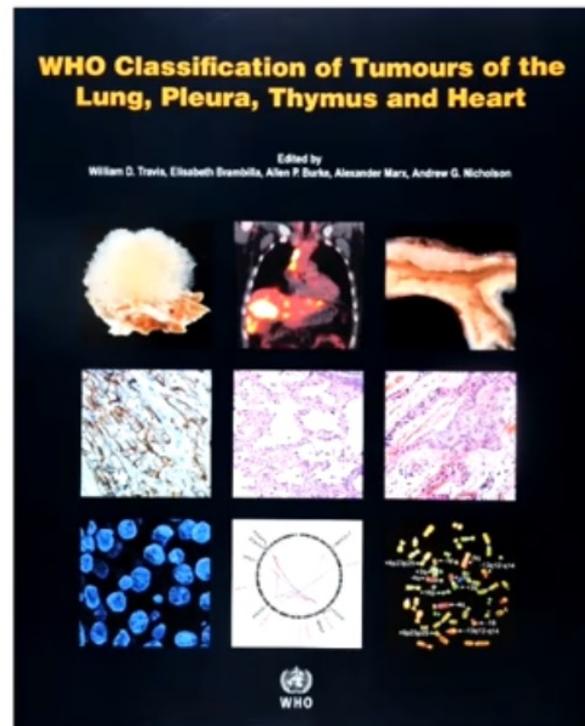
Jean-François Morère • Frédérique Penault-Llorca

*Histopathology* 2012, 60, 531–546. DOI: 10.1111/j.1365-2559.2011.03854.x

## REVIEW

### Personalized medicine for lung cancer: new challenges for pathology

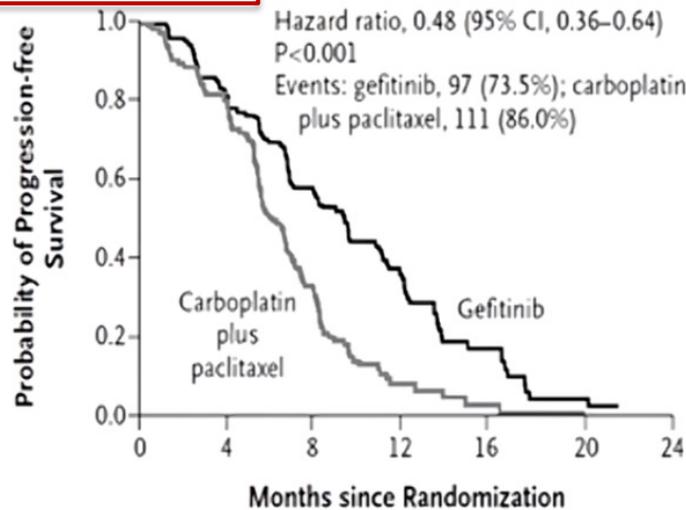
Keith M Kerr



WHO 2015

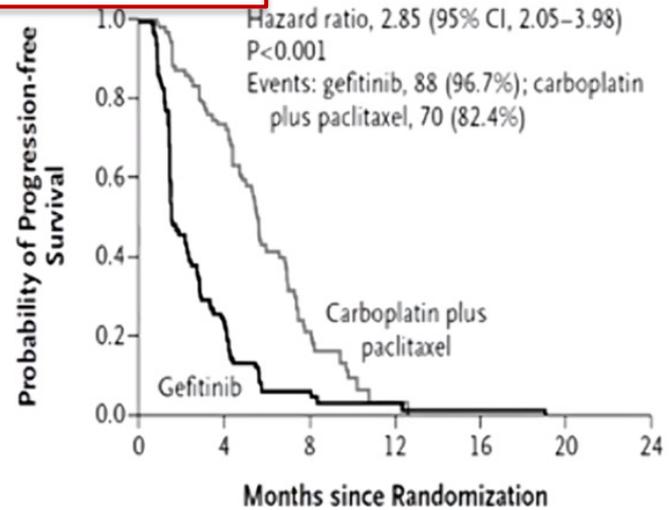
# PASS trial: Results by mutational status

**B EGFR-Mutation-Positive**



| No. at Risk                 |     | 0   | 4  | 8  | 12 | 16 | 20 | 24 |
|-----------------------------|-----|-----|----|----|----|----|----|----|
| Gefitinib                   | 132 | 108 | 71 | 31 | 11 | 3  | 0  |    |
| Carboplatin plus paclitaxel | 129 | 103 | 37 | 7  | 2  | 1  | 0  |    |

**C EGFR-Mutation-Negative**



| No. at Risk                 |    | 0  | 4  | 8 | 12 | 16 | 20 | 24 |
|-----------------------------|----|----|----|---|----|----|----|----|
| Gefitinib                   | 91 | 21 | 4  | 2 | 1  | 0  | 0  |    |
| Carboplatin plus paclitaxel | 85 | 58 | 14 | 1 | 0  | 0  | 0  |    |

**Major Impact!!!**

Mok T et al 2009, 361:947-957 NEJM

Frequency 10-15%

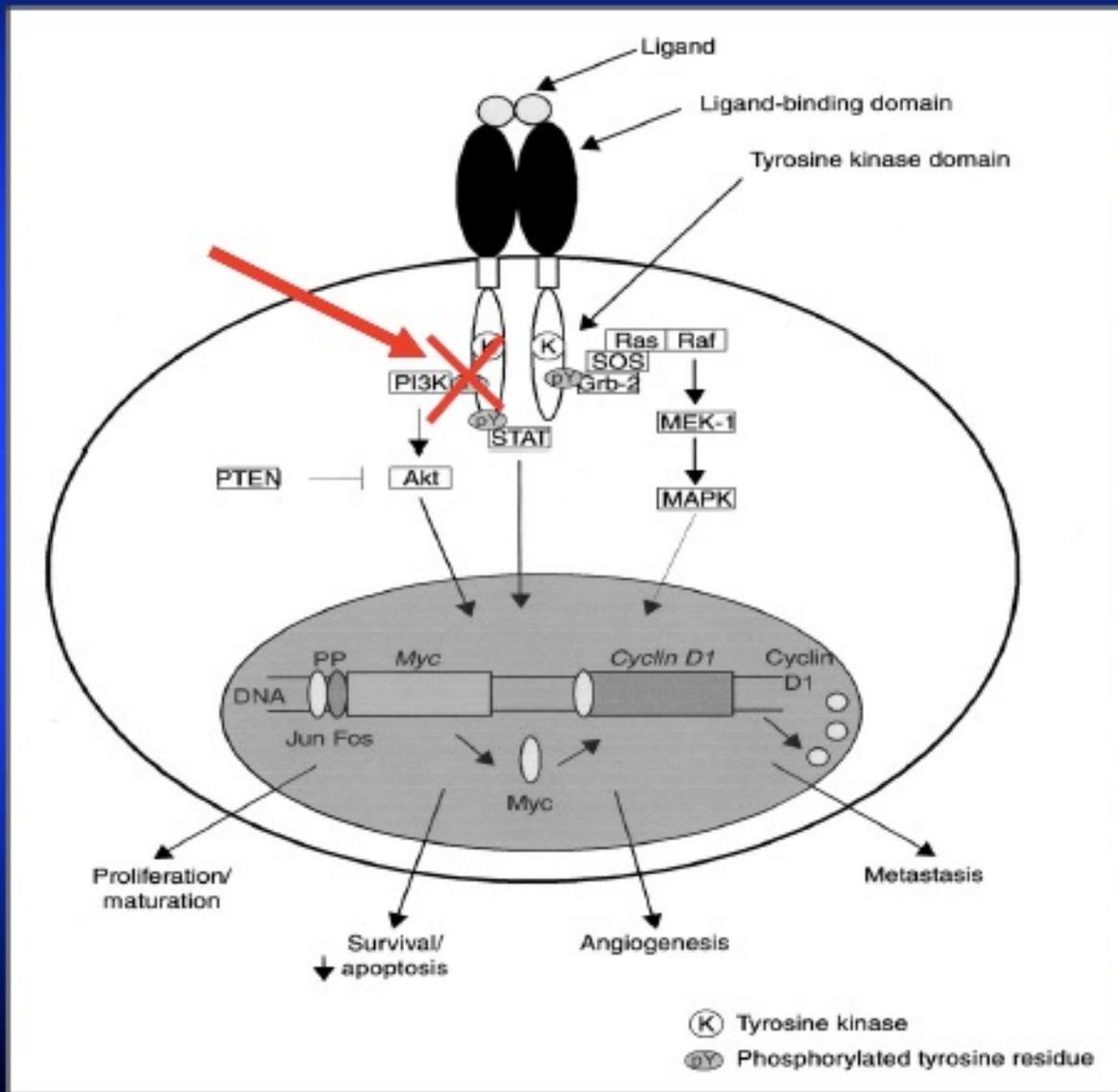
# Terapia con farmaci biologici : Inibitori EGFR TK : Micromolecole



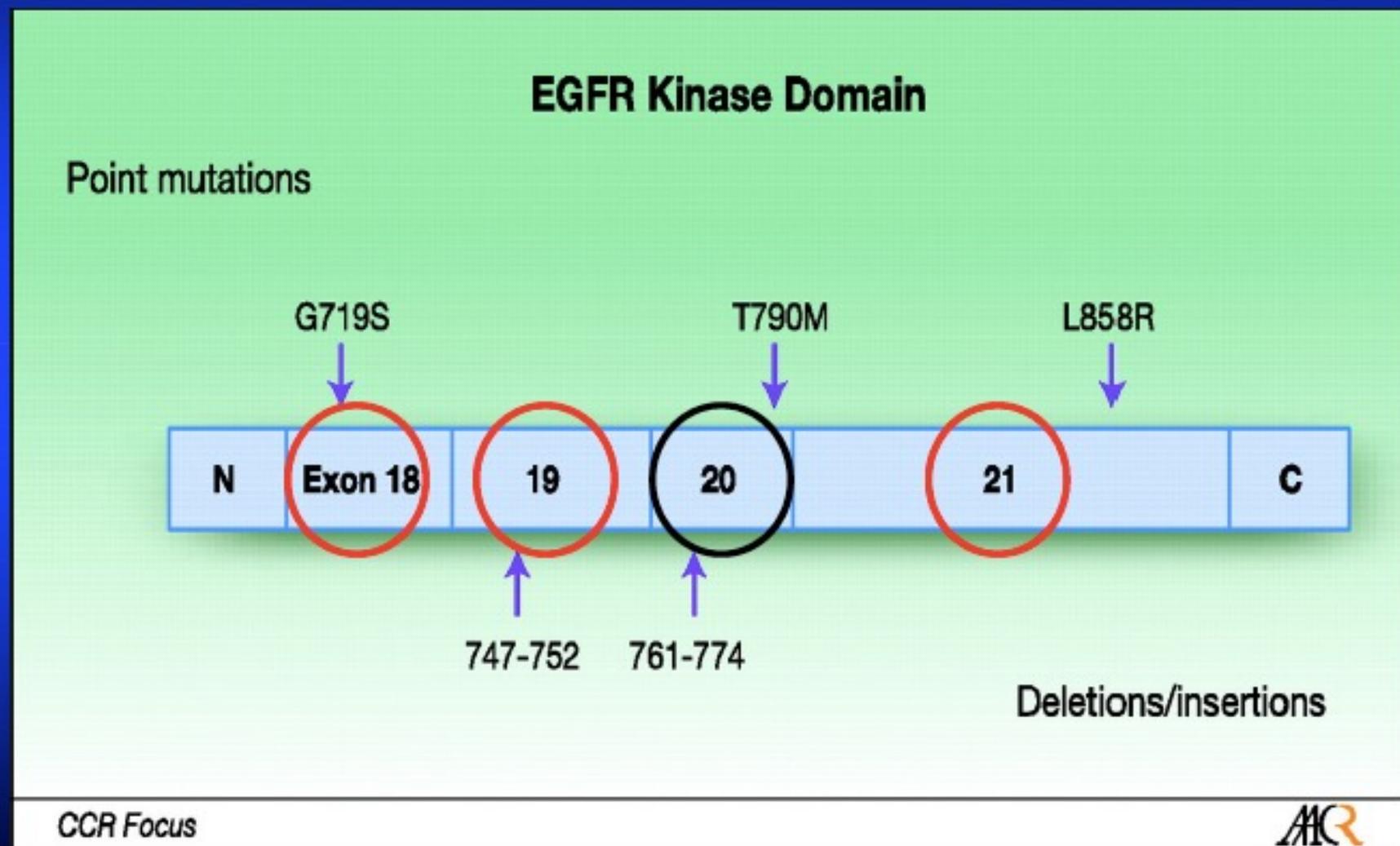
**Blocco reversibile  
autofosforilazione  
tirosino-kinasica (TK)**

Interazione con ATP con  
meccanismo competitivo

blocco interazione tra  
enzima e substrato  
(TYR)



# Mutazioni del dominio Tirosino-kinasico dell' EGFR nel carcinoma polmonare



2007

ARTICLES

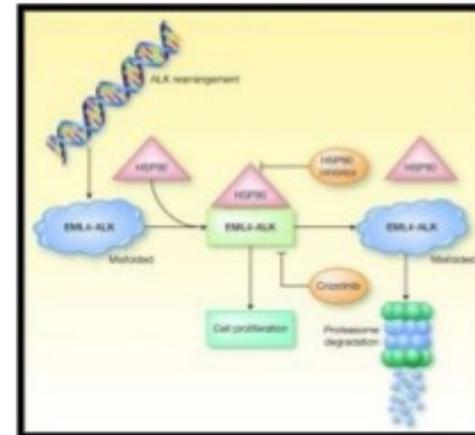
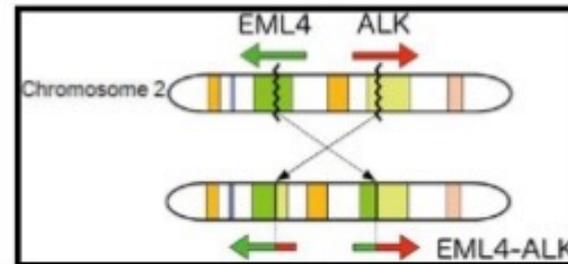
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## Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer

Manabu Soda<sup>1,2</sup>, Young Lim Choi<sup>1</sup>, Munehiro Enomoto<sup>1,2</sup>, Shuji Takada<sup>1</sup>, Yoshihiro Yamashita<sup>1</sup>, Shunpei Ishikawa<sup>5</sup>, Shin-ichiro Fujiwara<sup>1</sup>, Hideki Watanabe<sup>1</sup>, Kentaro Kurashina<sup>1</sup>, Hisashi Hatanaka<sup>1</sup>, Masashi Bando<sup>2</sup>, Shoji Ohno<sup>2</sup>, Yuichi Ishikawa<sup>6</sup>, Hiroyuki Aburatani<sup>5,7</sup>, Toshiro Niki<sup>3</sup>, Yasunori Sohara<sup>4</sup>, Yukihiko Sugiyama<sup>2</sup> & Hiroyuki Mano<sup>1,7</sup>

# EML4-ALK

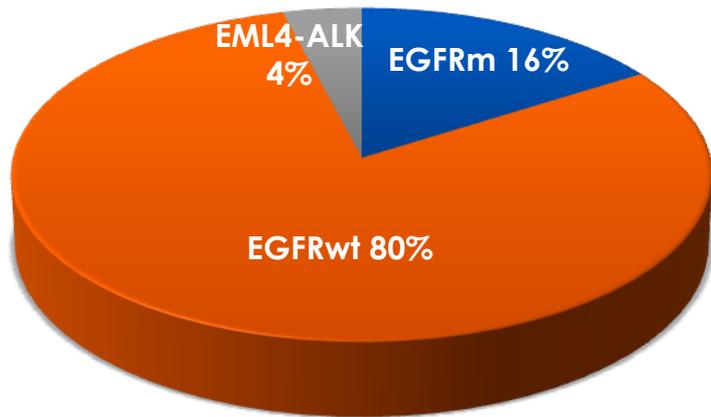
- Estimates **2-7%** of patients with NSCLC and common in **young men** (median: 52 years)
- Due to inversion in chromosome 2 that links EML4 to ALK → **cancer cell proliferation**
- Does not occur concurrently with EGFR
- Sensitive to TKI, **Crizotinib**



Non-Small Cell Lung Cancer, NCCN Guidelines Version 7. 2015

[https://sangakukan.jp/journal/journal\\_contents/2013/01/articles/1301-02-1/1301-02-1\\_article.html](https://sangakukan.jp/journal/journal_contents/2013/01/articles/1301-02-1/1301-02-1_article.html)

# Terapia dei tumori solidi “personalizzata” biomarker-dipendente – EML4-ALK polmone



2010

*The* **NEW ENGLAND**  
**JOURNAL** of *MEDICINE*

ESTABLISHED IN 1812

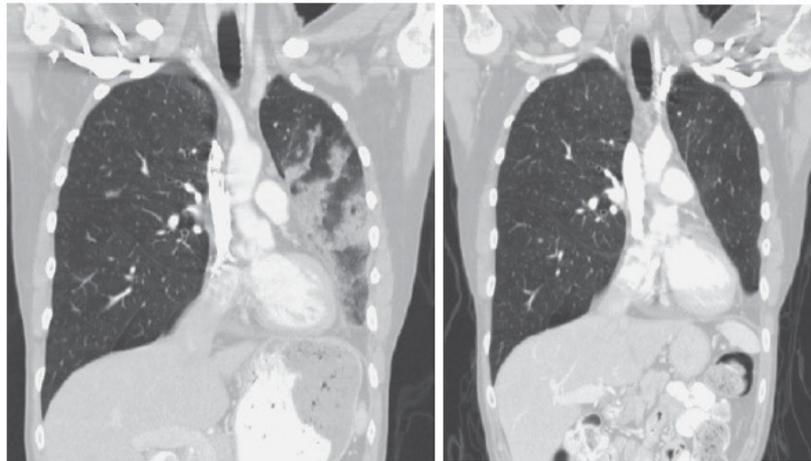
OCTOBER 28, 2010

VOL. 363 NO. 18

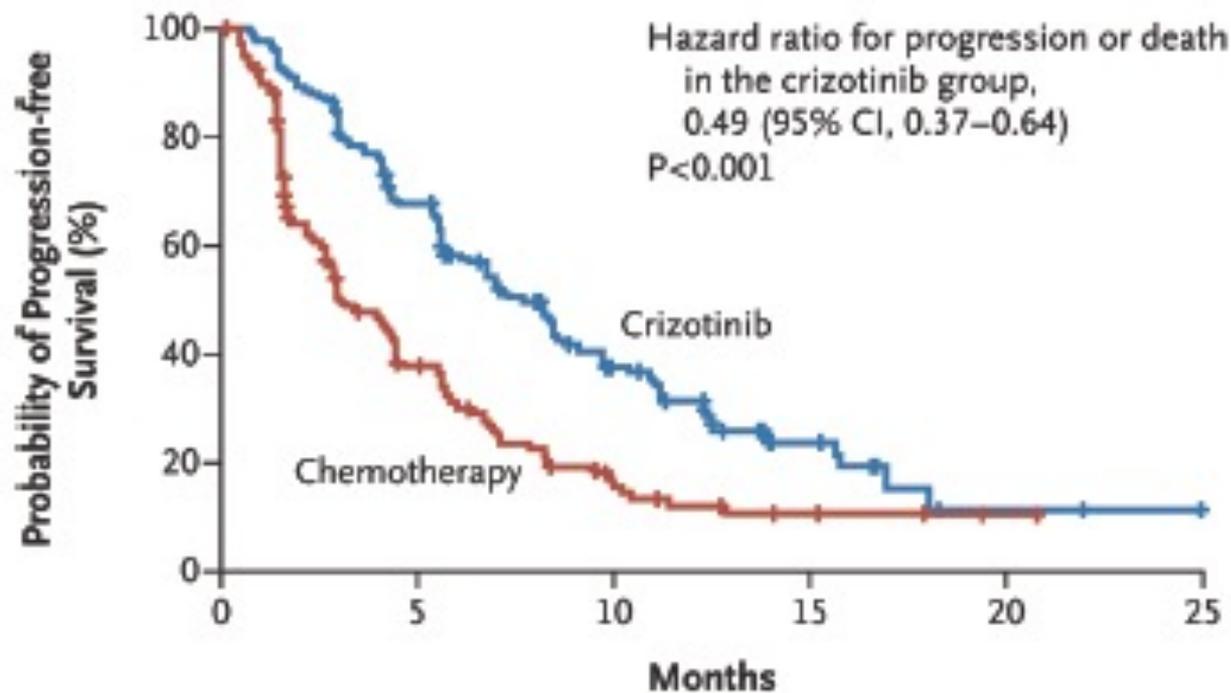
## Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidas, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

**B** CT before and after Crizotinib



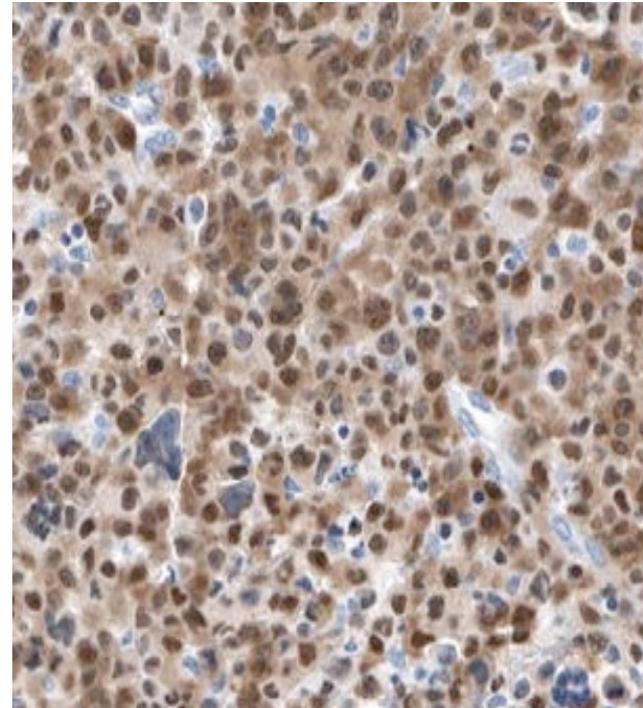
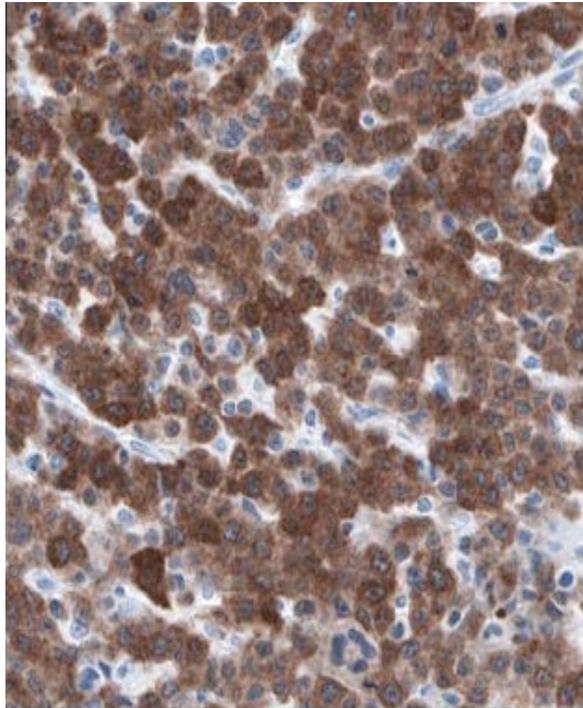
### A Progression-free Survival



#### No. at Risk

|              |     |    |    |    |   |   |
|--------------|-----|----|----|----|---|---|
| Crizotinib   | 173 | 93 | 38 | 11 | 2 | 0 |
| Chemotherapy | 174 | 49 | 15 | 4  | 1 | 0 |

## Fusione EML4-ALK : FISH



### Immunoistochimica per ALK

Svantaggi:

Non può distinguere tra le varianti delle fusioni EML4-ALK.



NIH Public Access

Author Manuscript

*N Engl J Med.* Author manuscript; available in PMC 2015 May 20.

2014

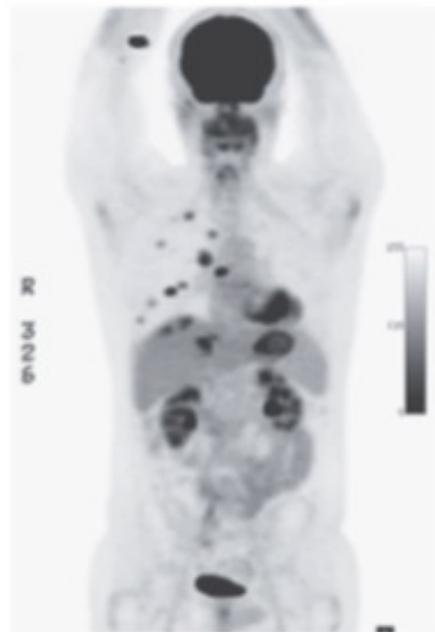
Published in final edited form as:

*N Engl J Med.* 2014 November 20; 371(21): 1963–1971. doi:10.1056/NEJMoa1406766.

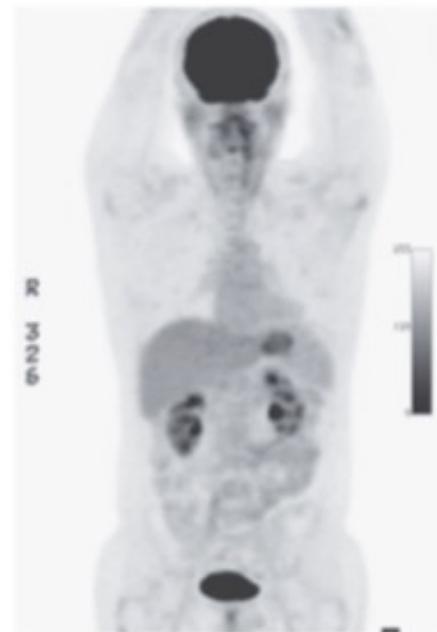
## Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

ROS1 belongs to the human receptor tyrosine kinase (RTK) family and is evolutionarily close to the ALK family, forming part of the scientific basis for using inhibitors of ALK as inhibitors of ROS1.

**B Effect of Crizotinib Therapy**



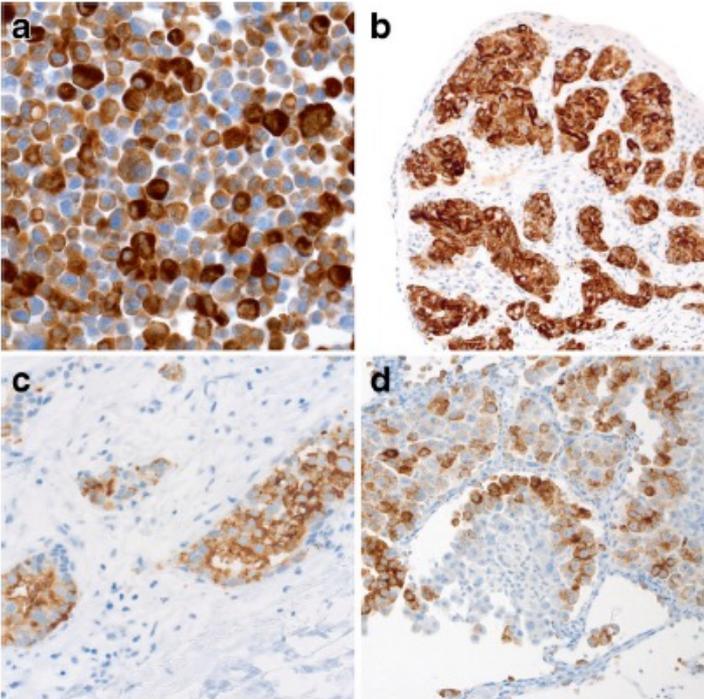
**Baseline**



**After 7 Weeks**

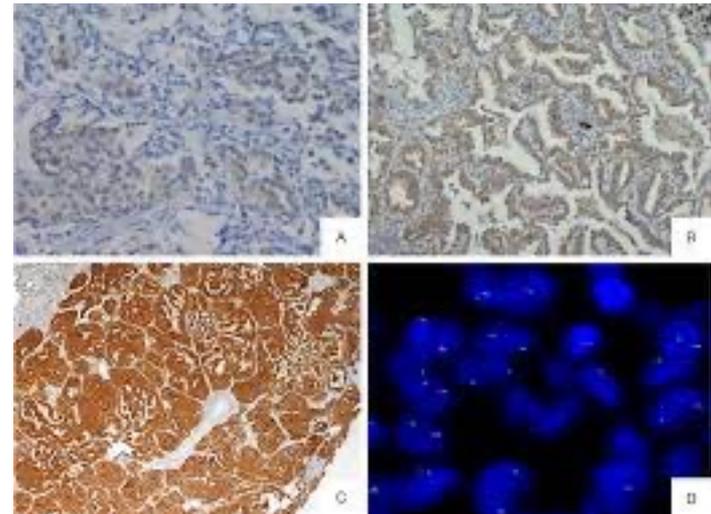
**Quali categorie di pazienti hanno maggiori probabilità di risultare ROS1 positive?**

**Adenocarcinoma.** Il riarrangiamento è mutuamente esclusivo alle mutazioni di **EGFR** o al riarrangiamento **ALK**.

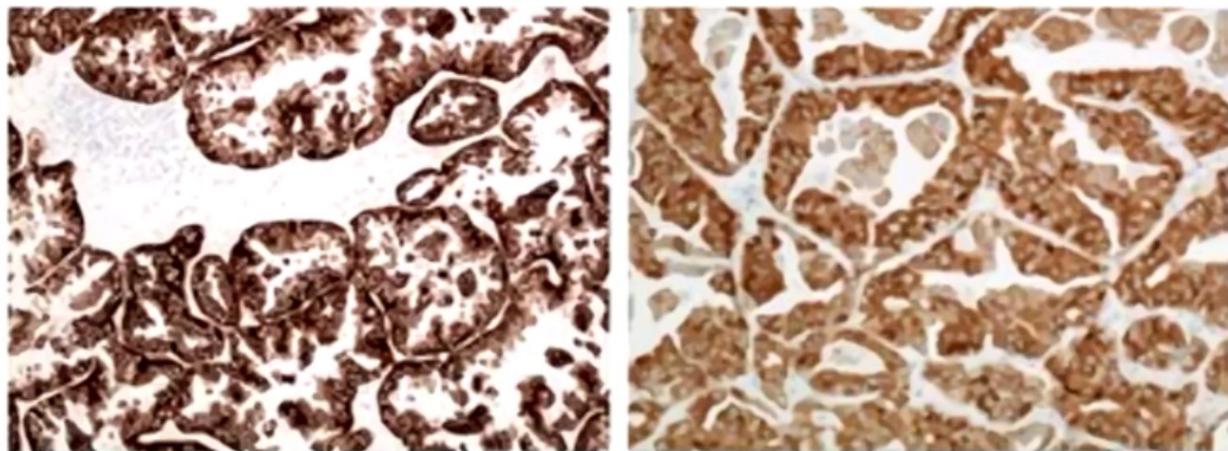


## ROS1

La metodologia del test prevede l'immunoistochimica e la fluorescenza con ibridazione in situ (FISH).



## IHC for fusion gene products in NSCLC

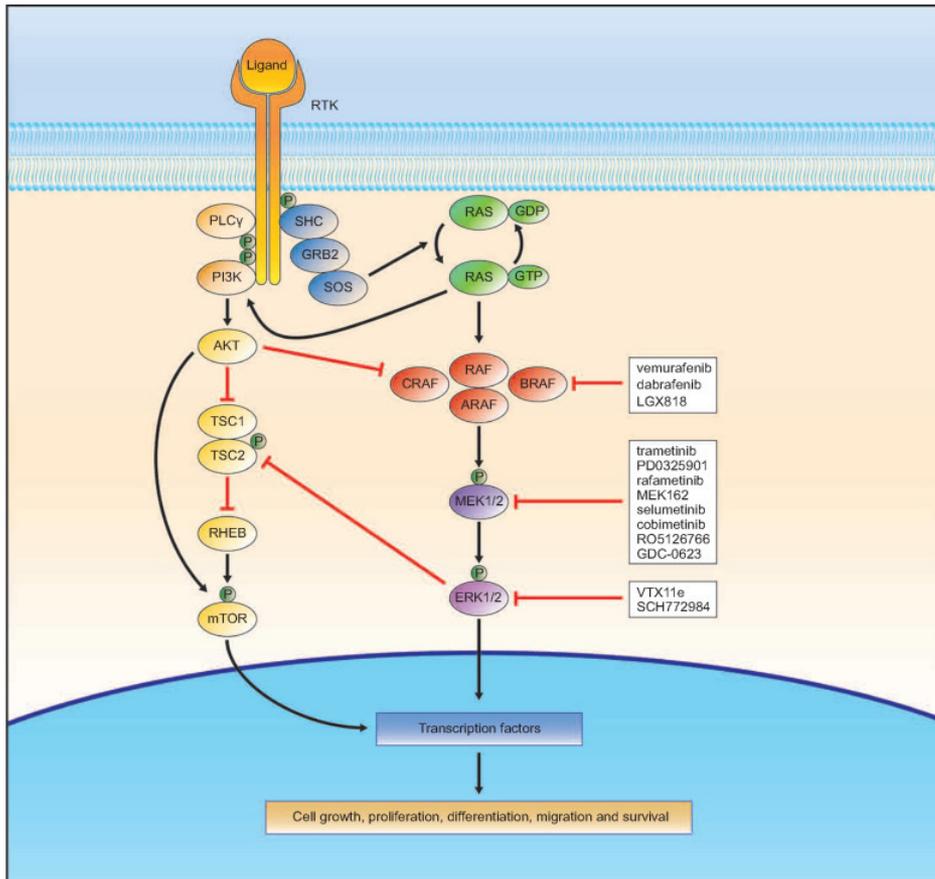


ALK: D5F3 assay

ROS1: SP384 assay

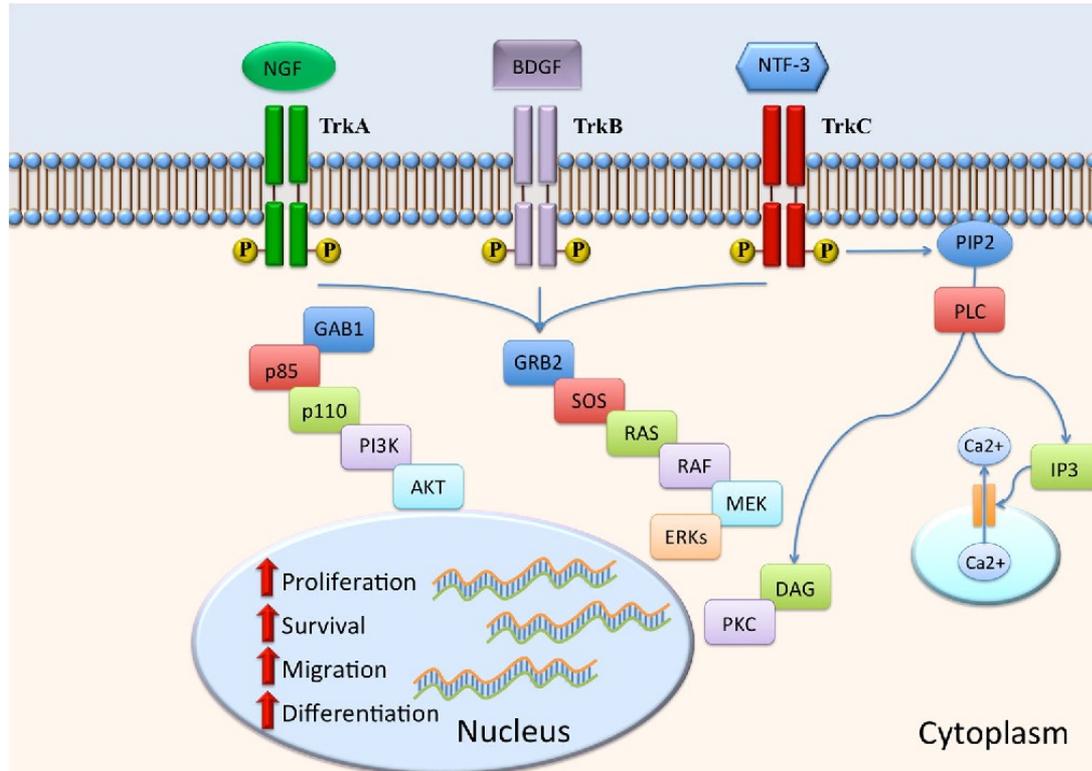
- Screening tool to select cases for molecular confirmation
- Therapy-determining Companion diagnostic test (ALK D5F3 assay)
- Validation tool to confirm molecular test results: translation has occurred
- Rapid turn-around: early warning to the molecular laboratory

The *BRAF* V600E mutation results in constitutive activation of its serine/threonine kinase, with a high dependency on downstream MEK signaling, and represents an actionable component of this pathway



*BRAF* mutations are detected in approximately 2% to 4% of lung cancer, hence occurring at a lower frequency than *EGFR* mutations (10–15%) and probably in a slightly smaller subpopulation than *ALK* rearrangements (3–5%).

# NTRK rearrangement



Only 5 of these targets have agents through approval by the FDA and EMA

- **EGFR mutation**
- **ALK rearrangement**
- **ROS1 rearrangement**
- **BRAF mutation**
- **NTRK rearrangement**

## Addictive oncogenic drivers make excellent drug targets and excellent biomarkers

EMA, European Medicines Agency; FDA, Food and Drug Administration.

1. Data from Tsao, et al. *J Thorac Oncol* 2016;11:613; 2. Sun et al. *J Clin Oncol* 2010;28:4616; 3. Odogwu, et al. *Oncologist* 2018;23:740; FDA website: <https://bit.ly/2TDORX1>. Accessed September 2020.

### 'Driver' mutations and lung adenocarcinoma biology



Oncogene  
'Addiction'

Genetically simple tumours  
NO tobacco carcinogenesis  
Mutually exclusive drivers  
Almost exclusively adenocarcinomas



Oncogene  
'Expeditious'

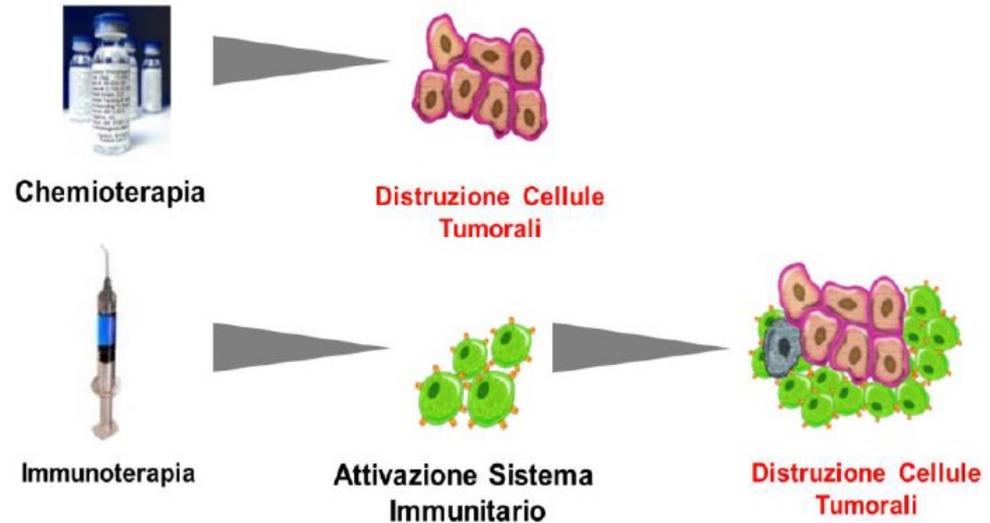
Genetically complex tumours  
Tobacco carcinogenesis  
Multiple drivers incl loss of TSG  
Many adenocarcinomas, vast majority of squamous and SCLC

# Oltre alle terapie a bersaglio molecolare..... ...approccio innovativo nel campo della ricerca oncologica

## Immunoterapia

Sfrutta l'attività del sistema immunitario per aggredire le cellule tumorali.

Immunoterapia rappresenta una nuova opzione di trattamento, accanto ai più tradizionali trattamenti, come la chirurgia, la radioterapia, la chemioterapia e le terapie a bersaglio molecolare.



## **Sistema immunitario e le cellule maligne**

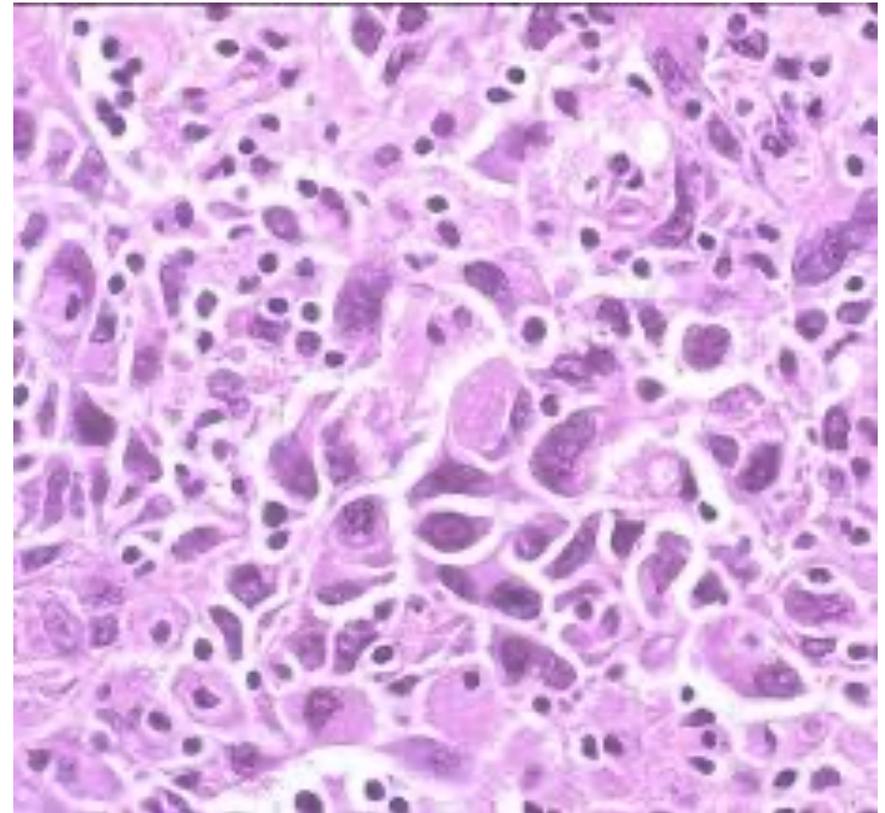
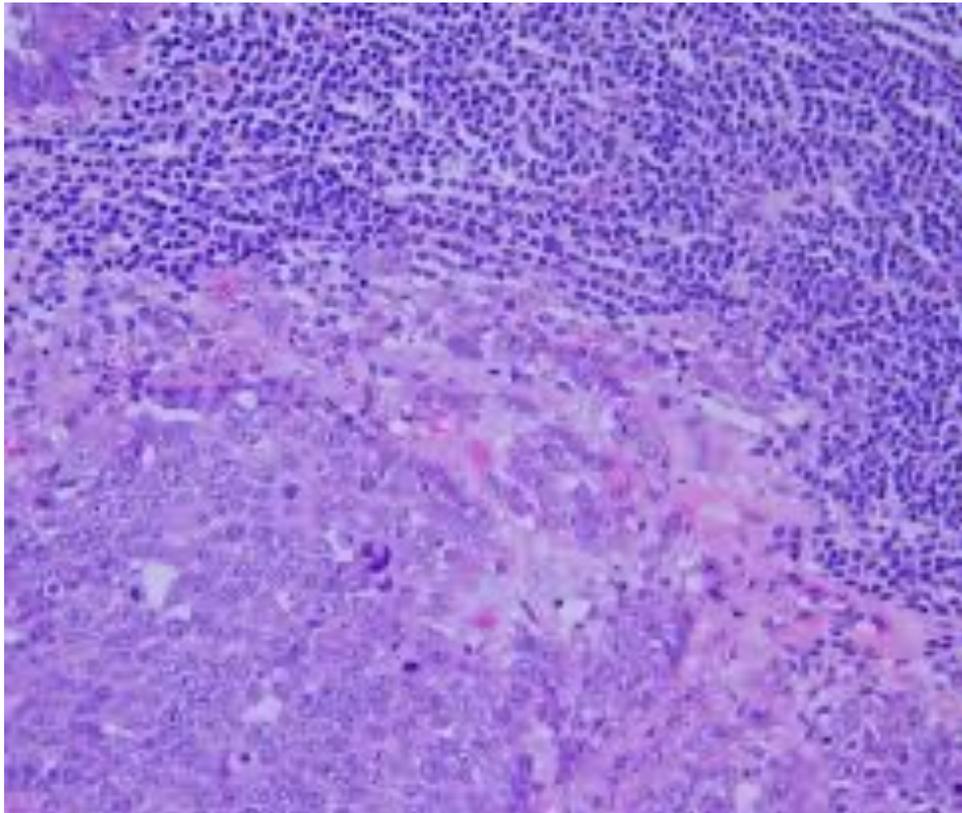
**coesistono spesso in un equilibrio dinamico,**

**e**

**la complessa interazione  
tra tumore in crescita e sistema immunitario  
può determinare il decorso della malattia**

### **La risposta immunitaria adattativa**

è in grado di controllare la crescita di alcuni tumori, come evidenziato dall'osservazione che la presenza di linfociti infiltranti il tumore (TIL) spesso è associata a una sopravvivenza maggiore (OS).



Tuttavia, il sistema immunitario è reso meno efficace con la crescita dei tumori.

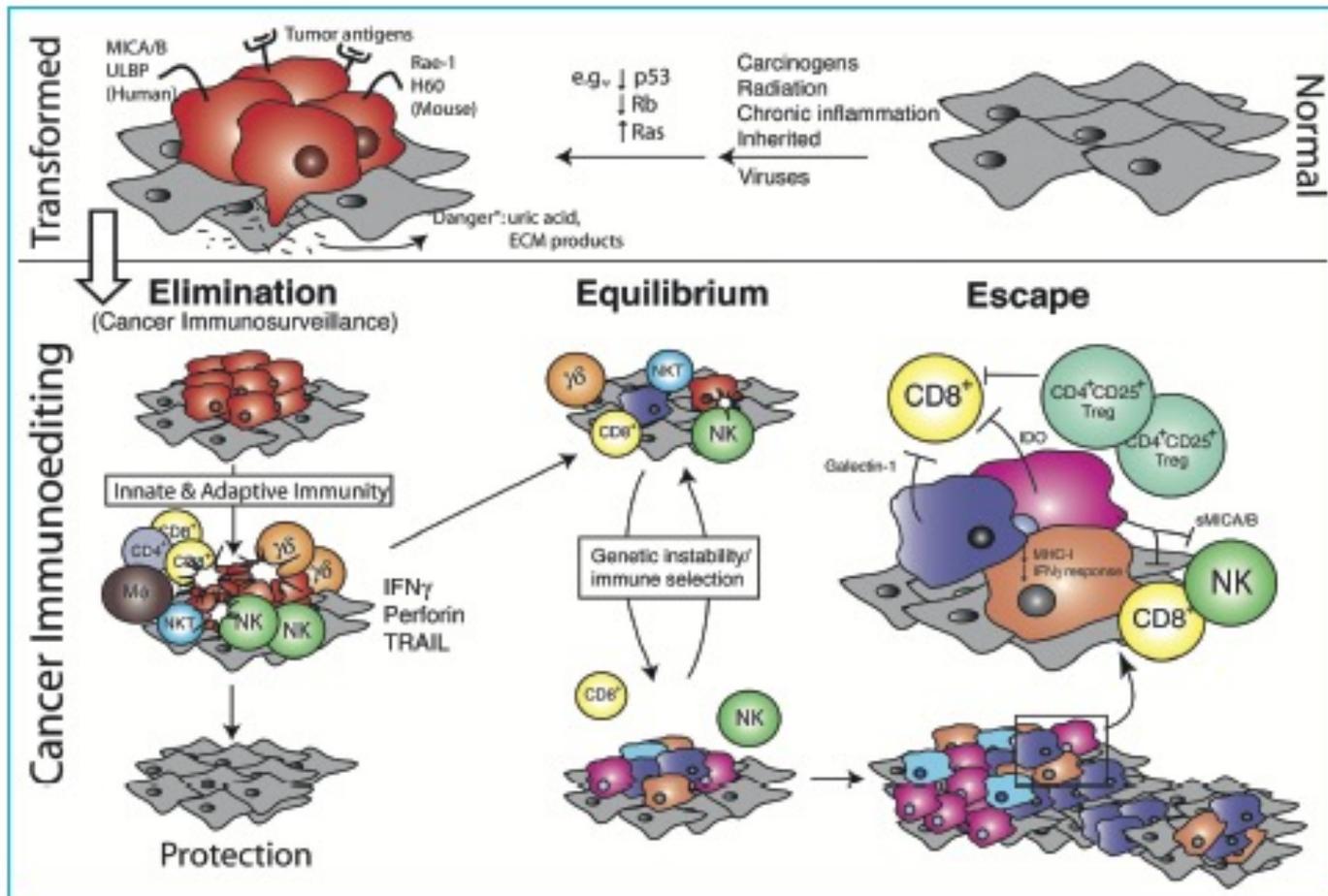
Il **processo di immunoediting** del cancro è un processo dinamico avviato dalle cellule tumorali in risposta all'immunosorveglianza del sistema immunitario;



Esso può essere concettualizzato da un movimento alternato che bilancia la protezione immunitaria con l'evasione immunitaria

# Processo di immunoediting del cancro è un processo dinamico

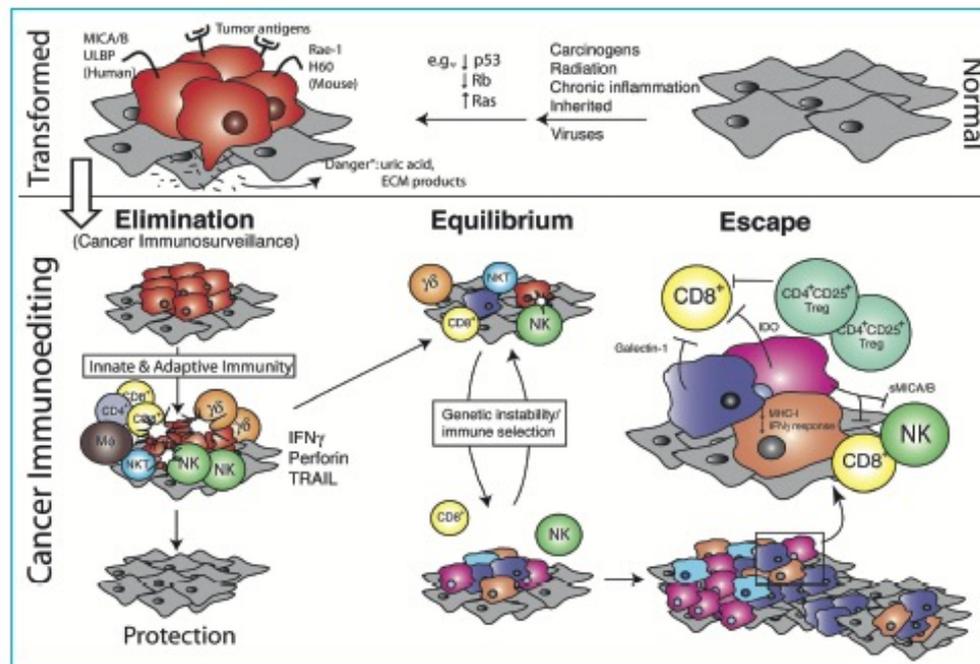
L'immunoediting del cancro comprende tre fasi: eliminazione, equilibrio e fuga.



# Obiettivo dell'immunoterapia

Potenziare o ripristinare la capacità del sistema immunitario di rilevare e distruggere le cellule tumorali superando i meccanismi con cui i tumori eludono e sopprimono la risposta immunitaria;

l'immunoterapia sposta l'equilibrio in favore della protezione immunitaria.



## Immunoterapia passiva

MAbs  
tumore specifici

Citochine

Trasferimento  
adottivo di cellule

## Immunoterapia attiva

Vaccini  
peptidici

Vaccini  
di cellule  
dendritiche

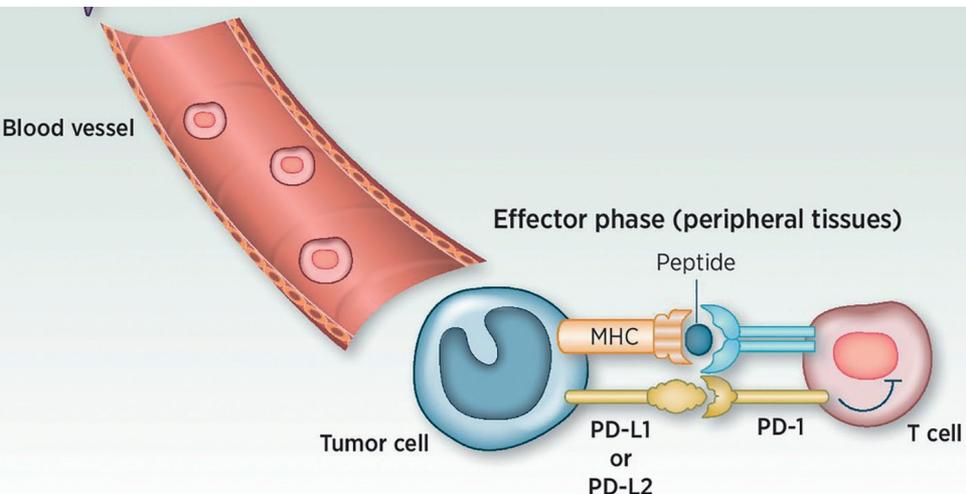
Vaccini  
allogeni di  
cellule intere

Inibitori del  
checkpoint

Virus  
oncolitici

# Ligando di morte cellulare programmata 1 (PDL-1),

## Inibitori di checkpoint immunitario



Recettore di morte programmata 1 (PD1) e i suoi ligandi, il ligando di morte cellulare programmato 1 (PD-L1) e il ligando di morte cellulare programmato 2 (PD-L2)

PD-1 gioca un ruolo chiave nel regolare e mantenere l'equilibrio tra l'attivazione delle cellule T e la tolleranza immunitaria.

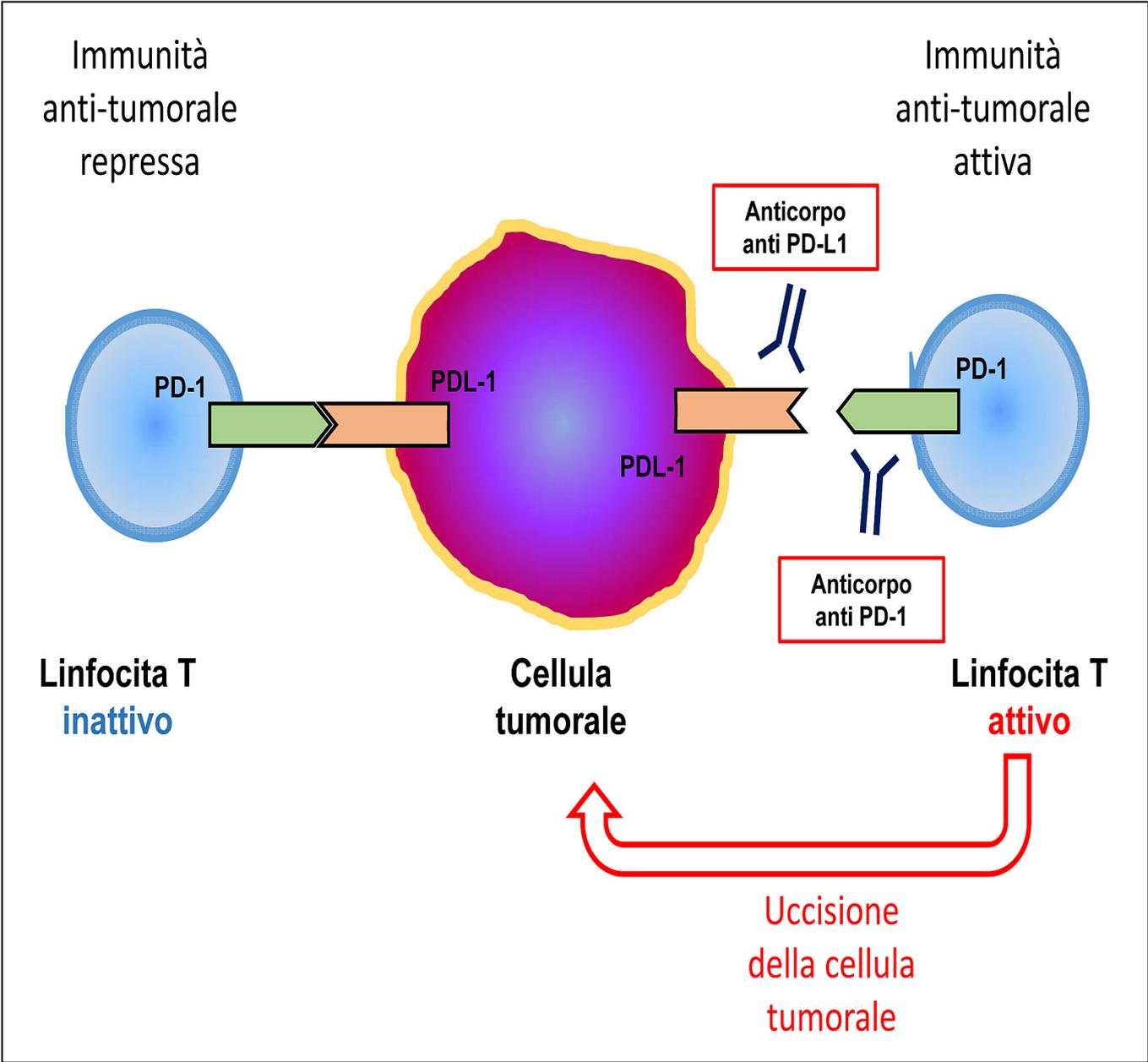
PD-1 è ampiamente espresso e può essere trovato, oltre che sulla superficie delle cellule T, anche su quella delle cellule B e NK

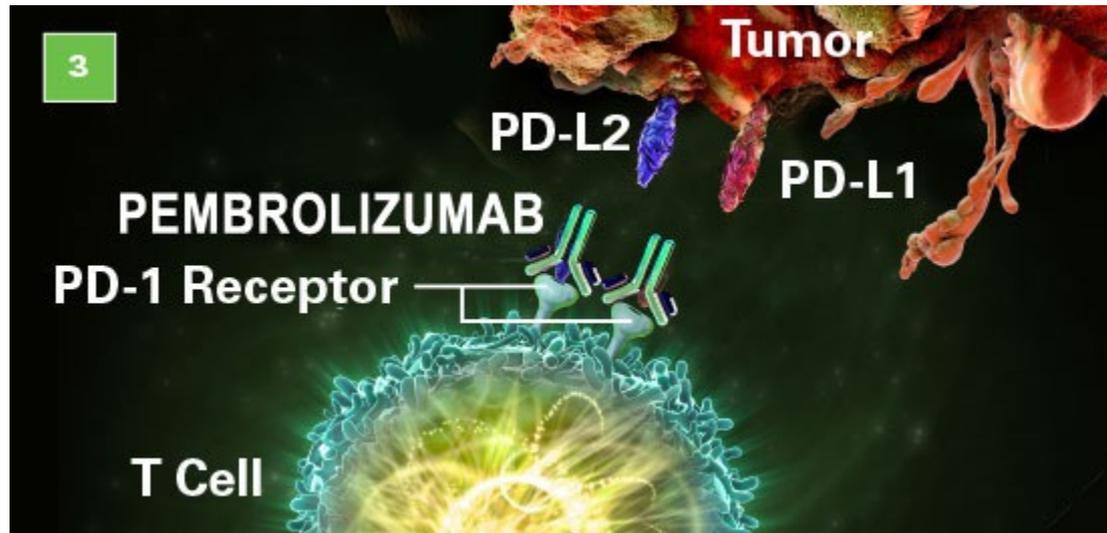
## SISTEMA DI DOWNREGOLAZIONE DELLA RISPOSTA INFIAMMATORIA

I tessuti normali raramente esprimono le proteine PD-L1 sulla propria superficie cellulare, ad eccezione delle tonsille, placenta, al fine di limitare la propagazione dell'area infiammata ed evitare danni ai tessuti circostanti.

I tumori possono sfruttare questo checkpoint e rendere i TIL, in particolare le CTL e le cellule NK, incapaci di uccidere.

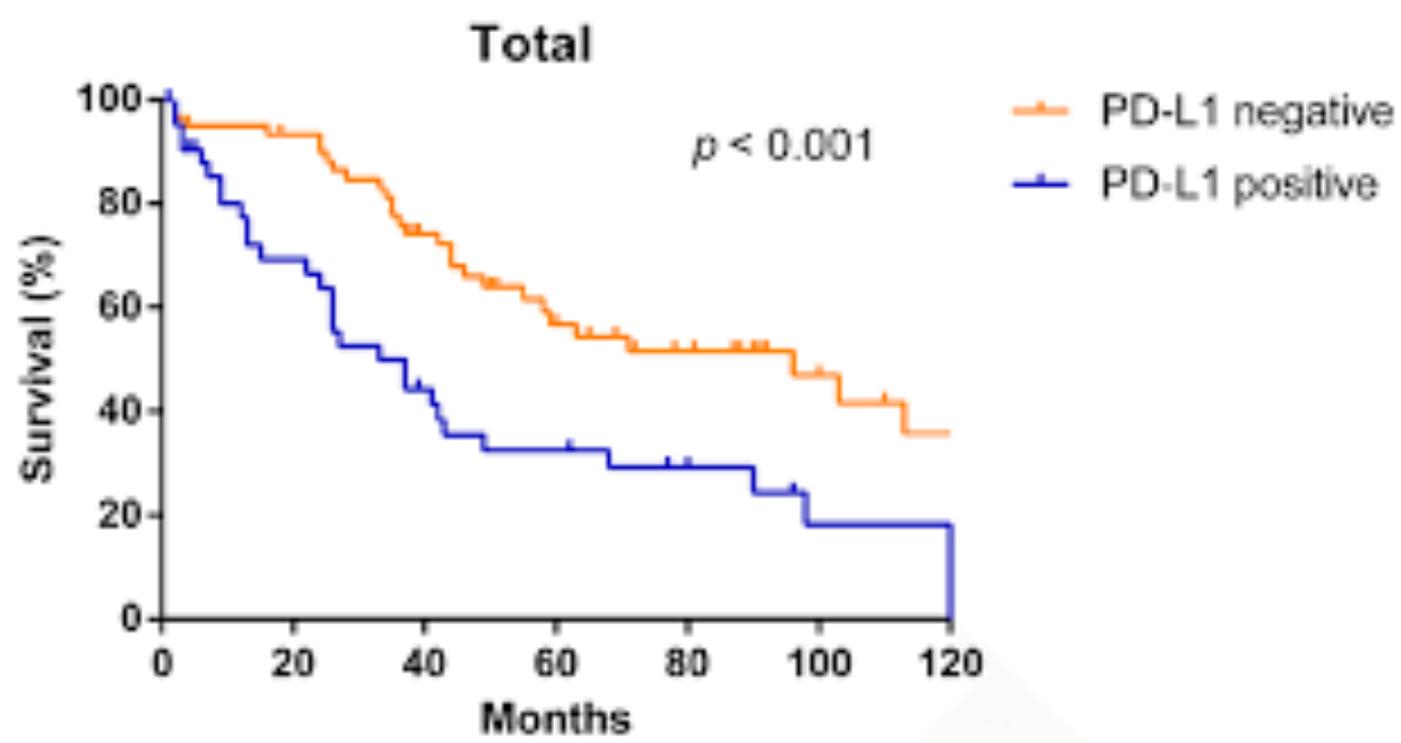
Il ligando PD-L1 è comunemente upregolato in diversi tumori solidi umani, tra cui il melanoma, il polmone, i tumori ovarici e altri.



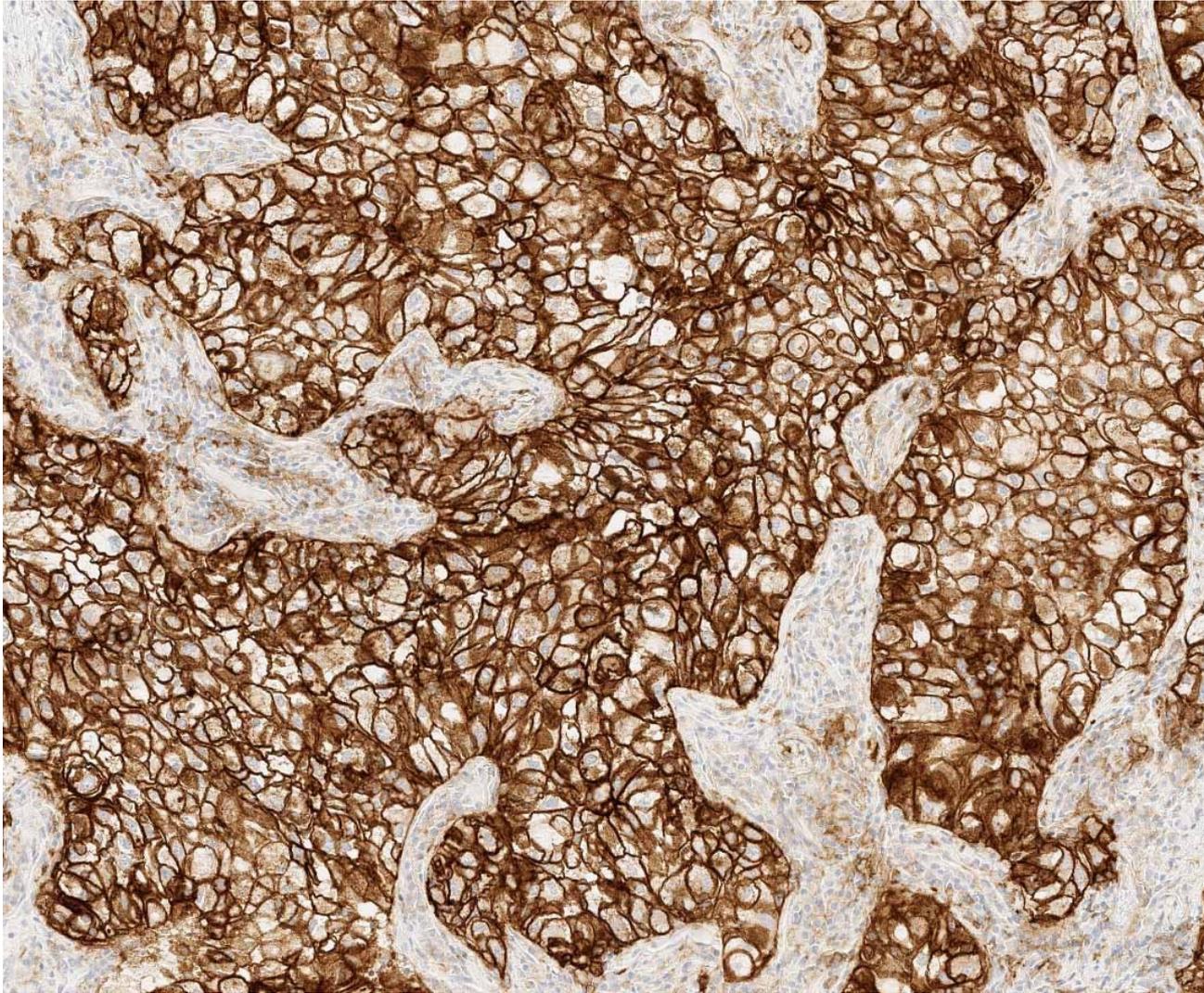


**Pembrolizumab** blocca l'interazione tra il PD-1 e il suo ligando PD-L1, attivando in tal modo i linfociti T che possono colpire sia le cellule tumorali che le cellule sane

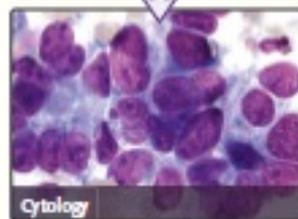
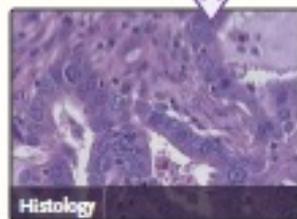
Questi farmaci rappresentano una delle strategie più efficaci nel restituire la funzione ai linfociti T divenuti anergici



# PDL1



# Diagnostic Algorithm in Non-Small-Cell Lung Cancer (NSCLC)

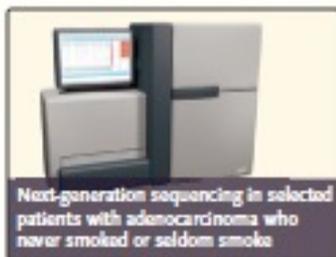
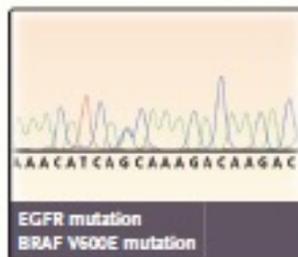


Squamous-cell NSCLC

Non-squamous-cell NSCLC  
Adenocarcinoma  
Large-cell carcinoma  
Other

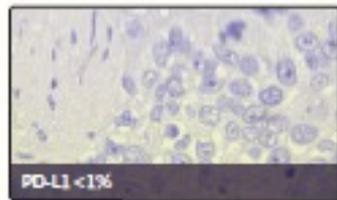
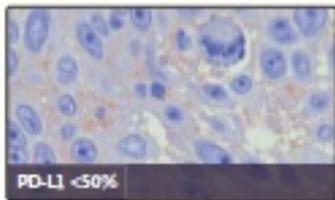
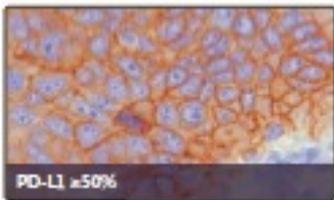
Selected samples evaluable for molecular analysis  
Not yet available for PD-L1 analysis

## MOLECULAR PROFILING



If negative or unknown

## PD-L1 STAINING



Individual treatment

| <b>Histology</b>    | <b>Molecular Pathology</b> | <b>PD-L1 Status (TPS)</b> | <b>First-Line Therapy</b>                                                      | <b>Maintenance Therapy</b> | <b>Second-Line Therapy</b>                                         |
|---------------------|----------------------------|---------------------------|--------------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------|
| Squamous-cell NSCLC | NA                         | <50%                      | Platinum-based chemotherapy<br>Gemcitabine and cisplatin+<br>necitumumab (EMA) | Necitumumab                | Immunotherapy<br>Chemotherapy<br>Docetaxel+ramucirumab<br>Afatinib |
|                     | NA                         | ≥50%                      | Pembrolizumab                                                                  | Pembrolizumab              | Platinum-based chemotherapy                                        |



Associazione Italiana di Oncologia Medica

# Linee guida NEOPLASIE DEL POLMONE

**Edizione 2021**

Aggiornata a ottobre 2021

**Figura 1: Diagnosi e stadiazione**

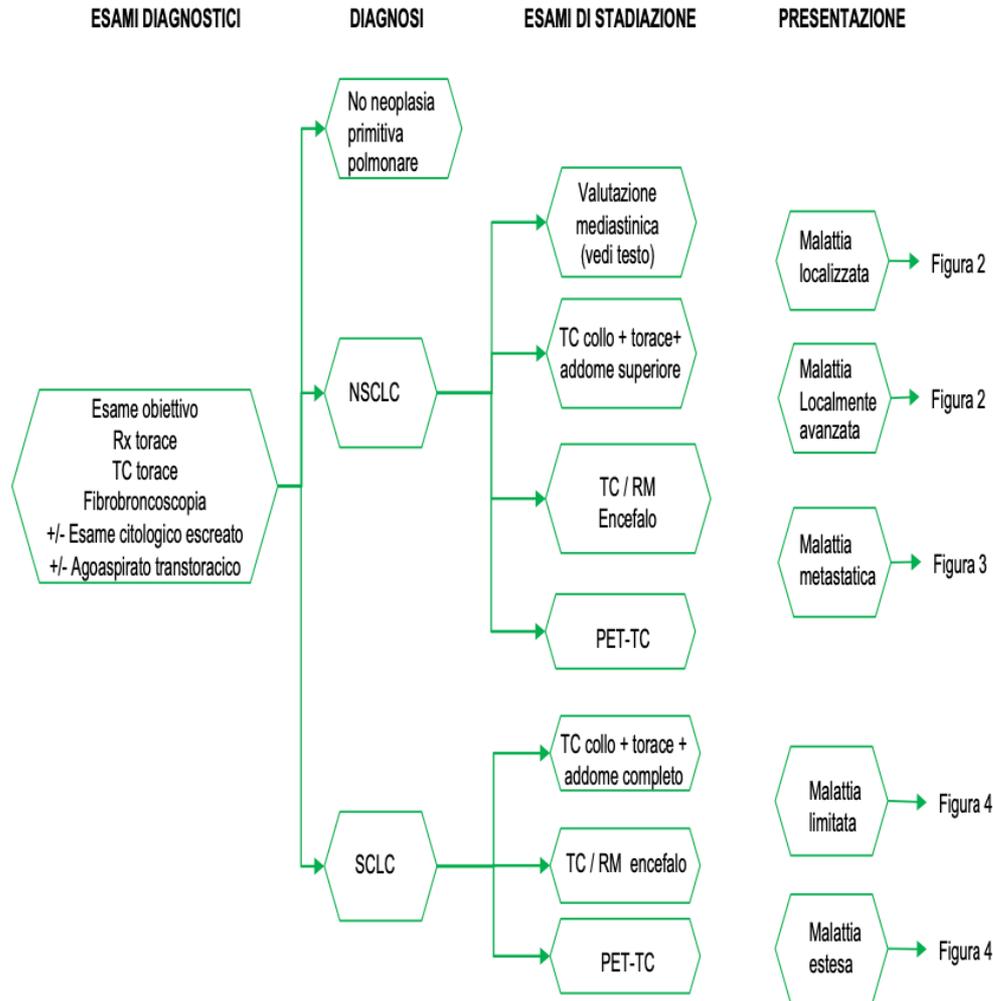
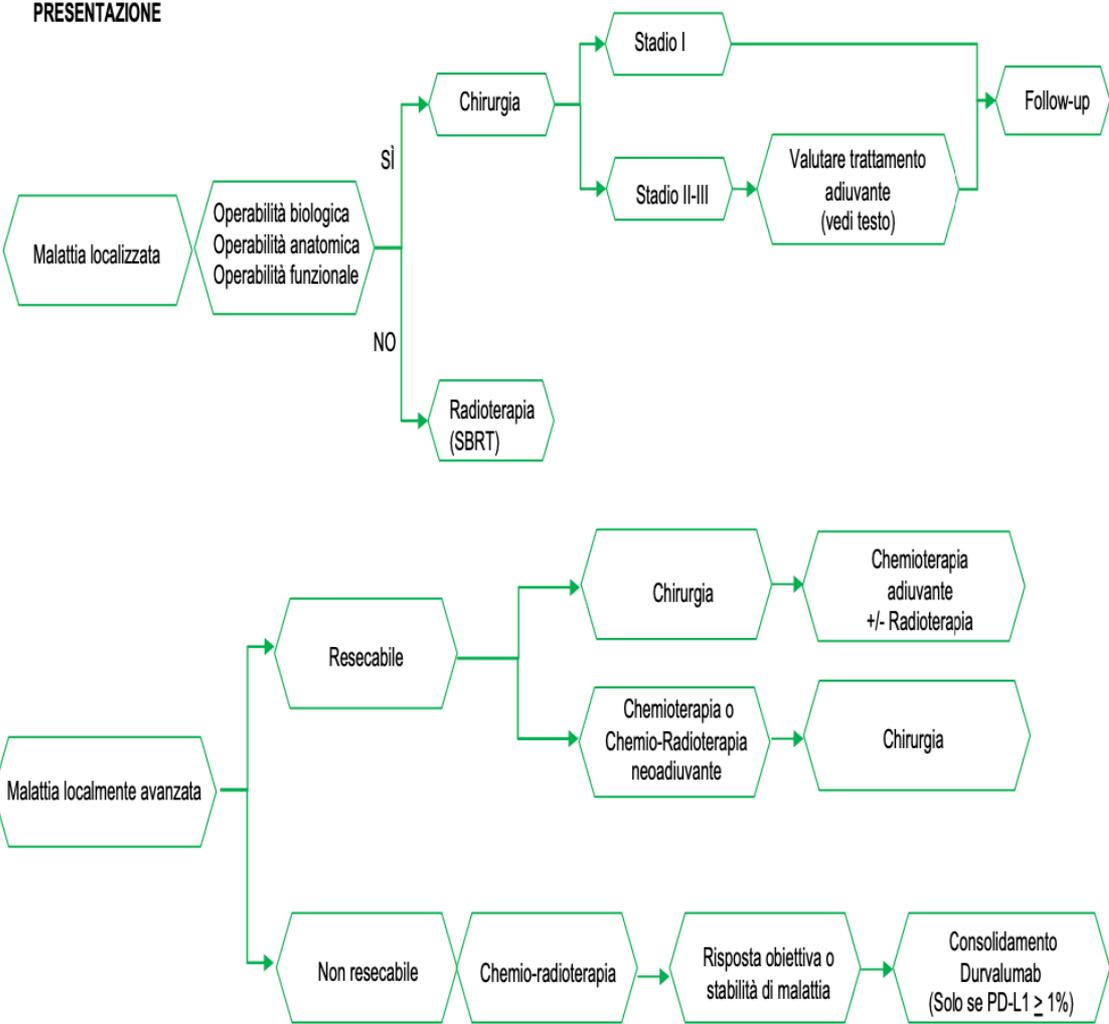


Figura 2: NSCLC: malattia non metastatica

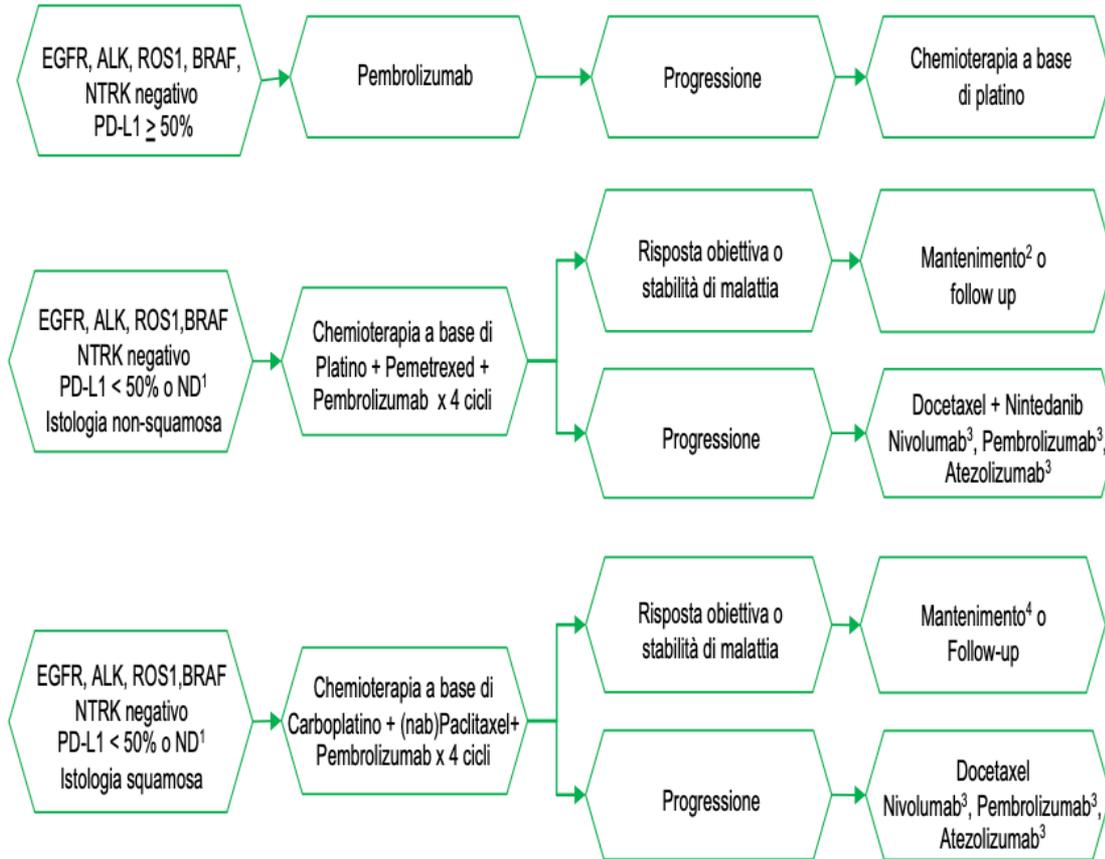


**NSCLC: malattia metastatica non oncogene-addicted**

**NSCLC: malattia metastatica oncogene-addicted**

**Figura 4: NSCLC: malattia metastatica non oncogene-addicted**

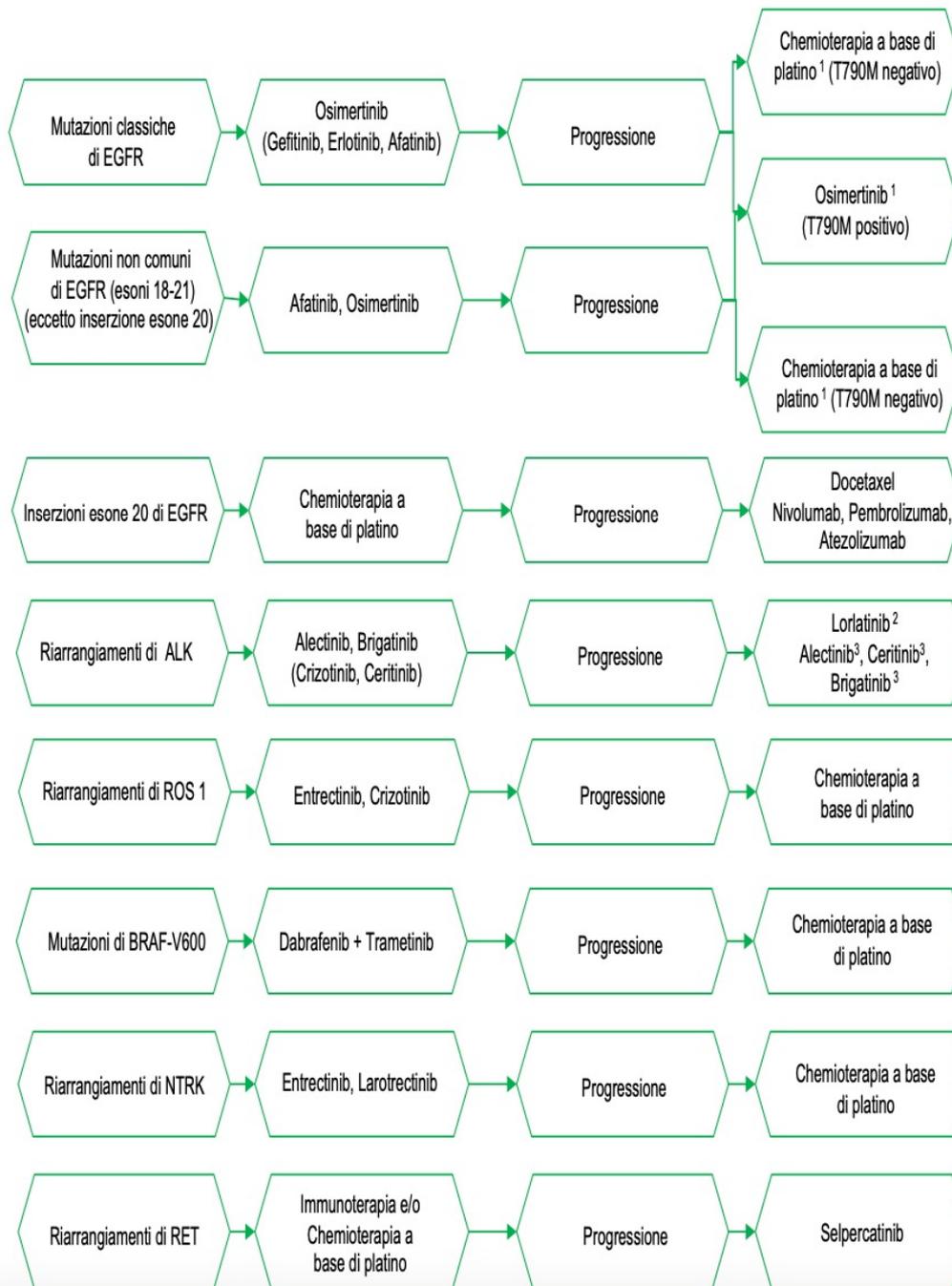
NON ONCOGENE ADDICTED



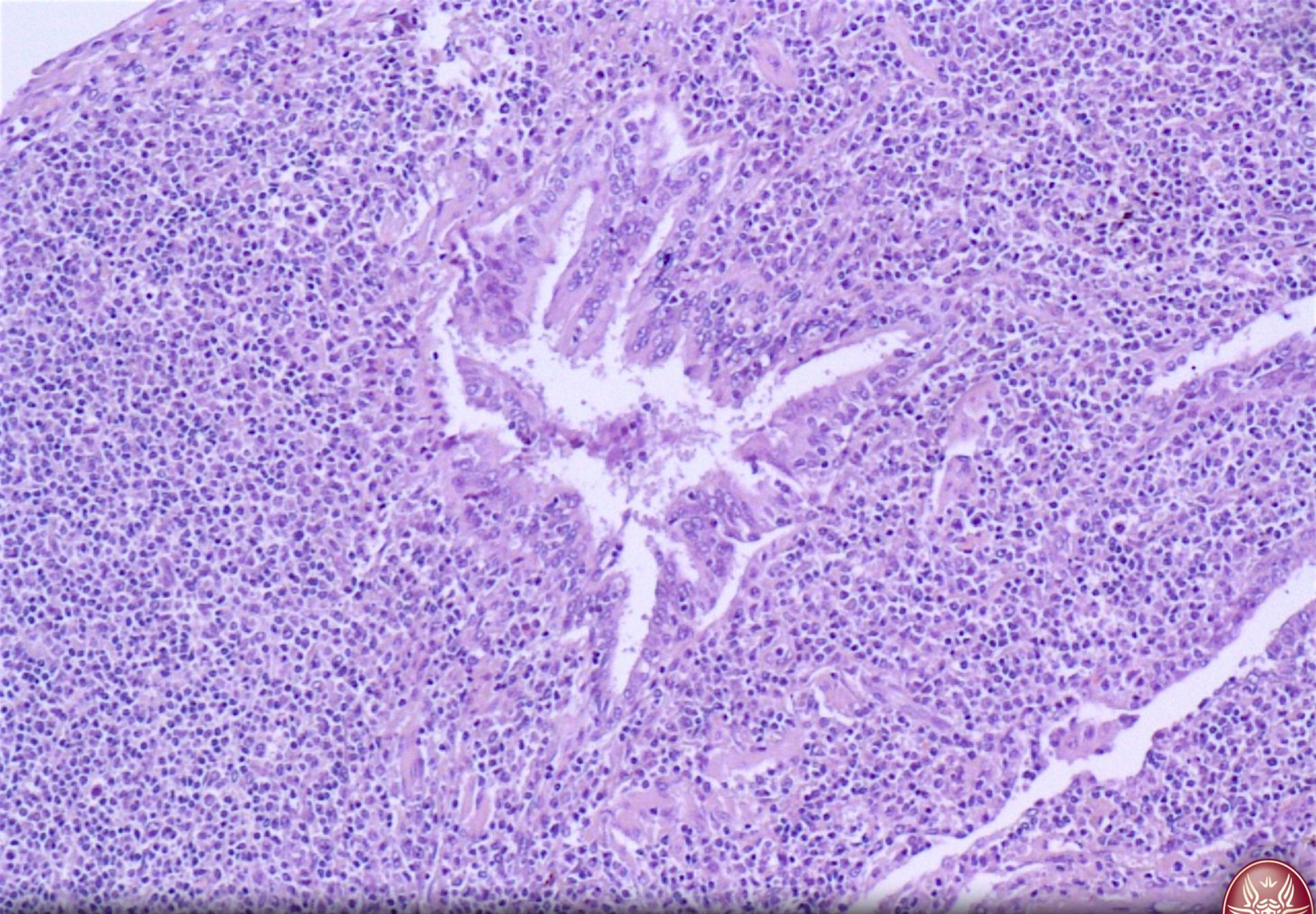
1. Non Determinabile
2. Mantenimento con Pemetredex + Pembrolizumab
3. In pazienti in progressione a chemioterapia (che non hanno ricevuto immunoterapia in I linea)
4. Mantenimento con Pembrolizumab

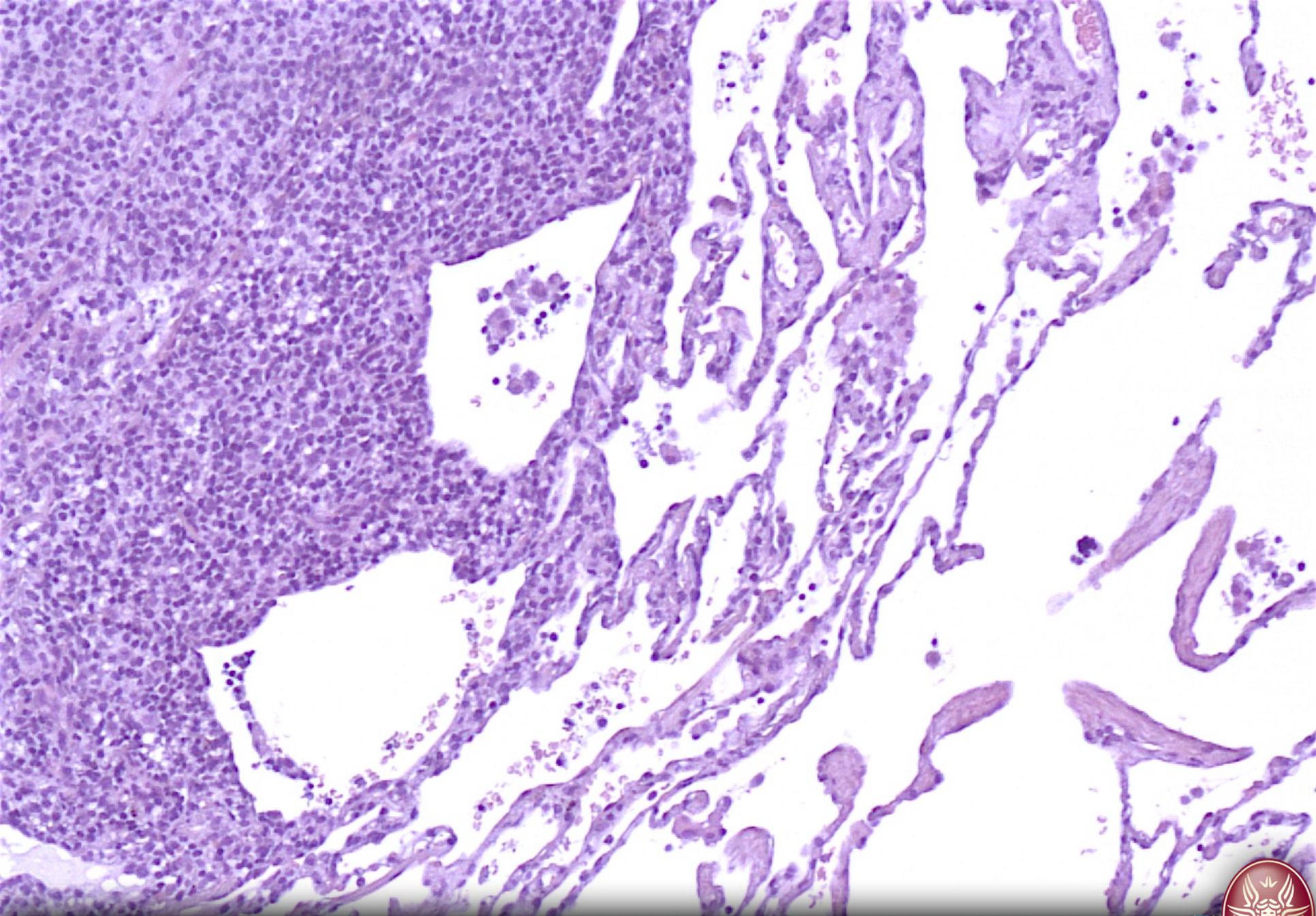
Figura 3: NSCLC: malattia metastatica oncogene-addicted

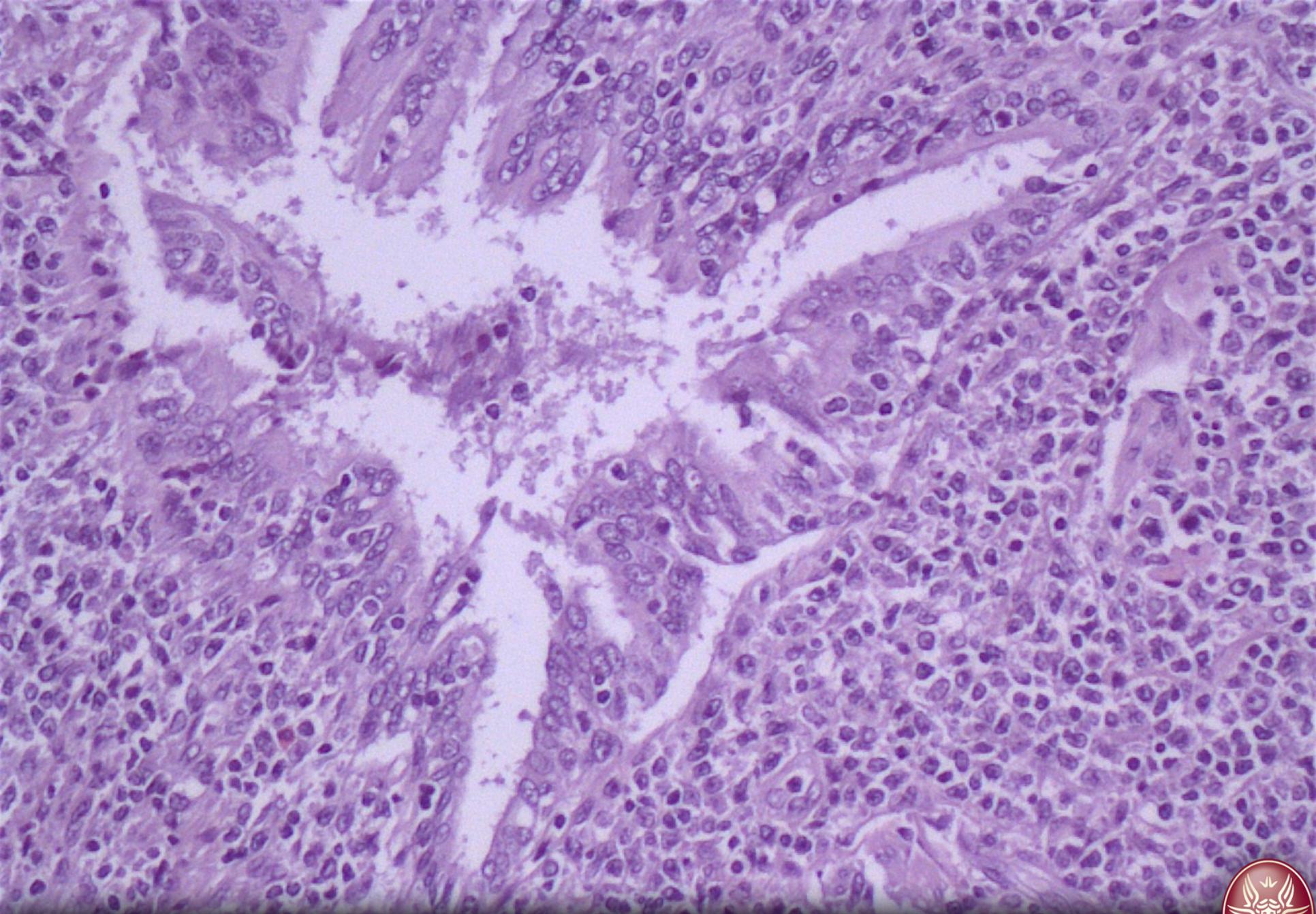
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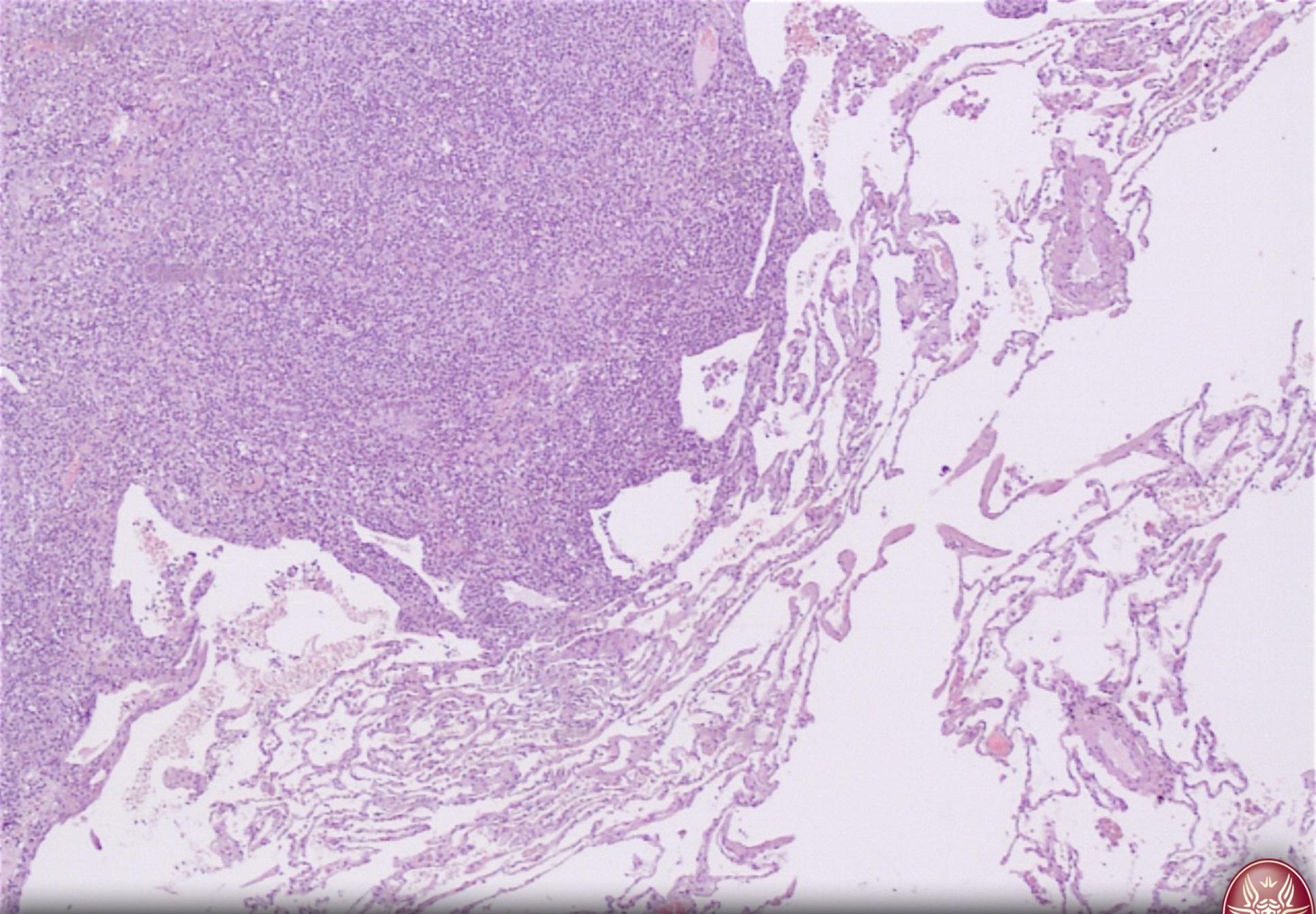


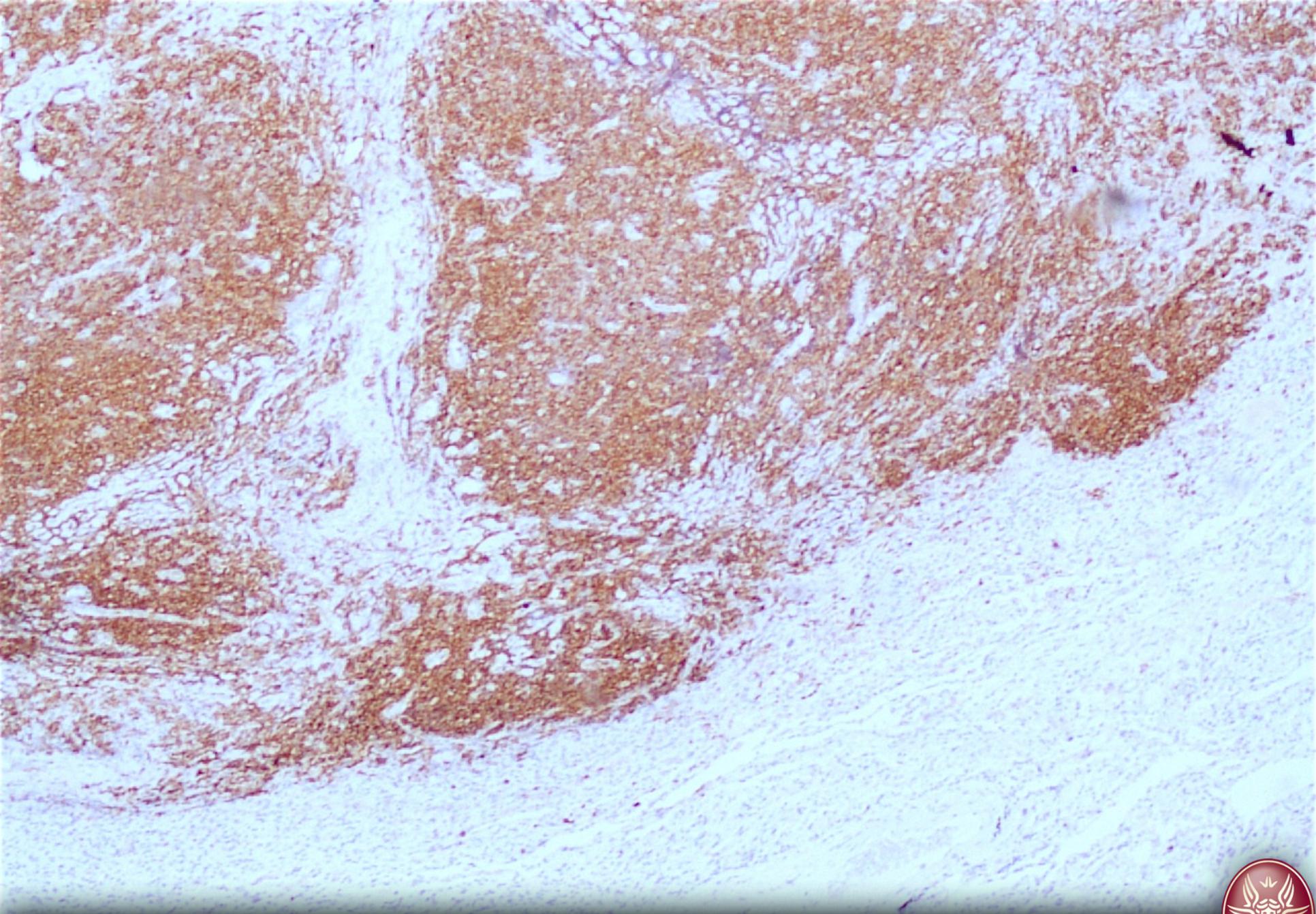
?











# Mesotelioma

# *Principi generali - Definizione*

---

Tumore maligno primitivo delle sierose con origine dalle cellule di derivazione mesodermica

Rivestimento delle superfici delle cavità sierose

- Pleura
- Peritoneo
- Pericardio

# Principi generali - Definizione

---

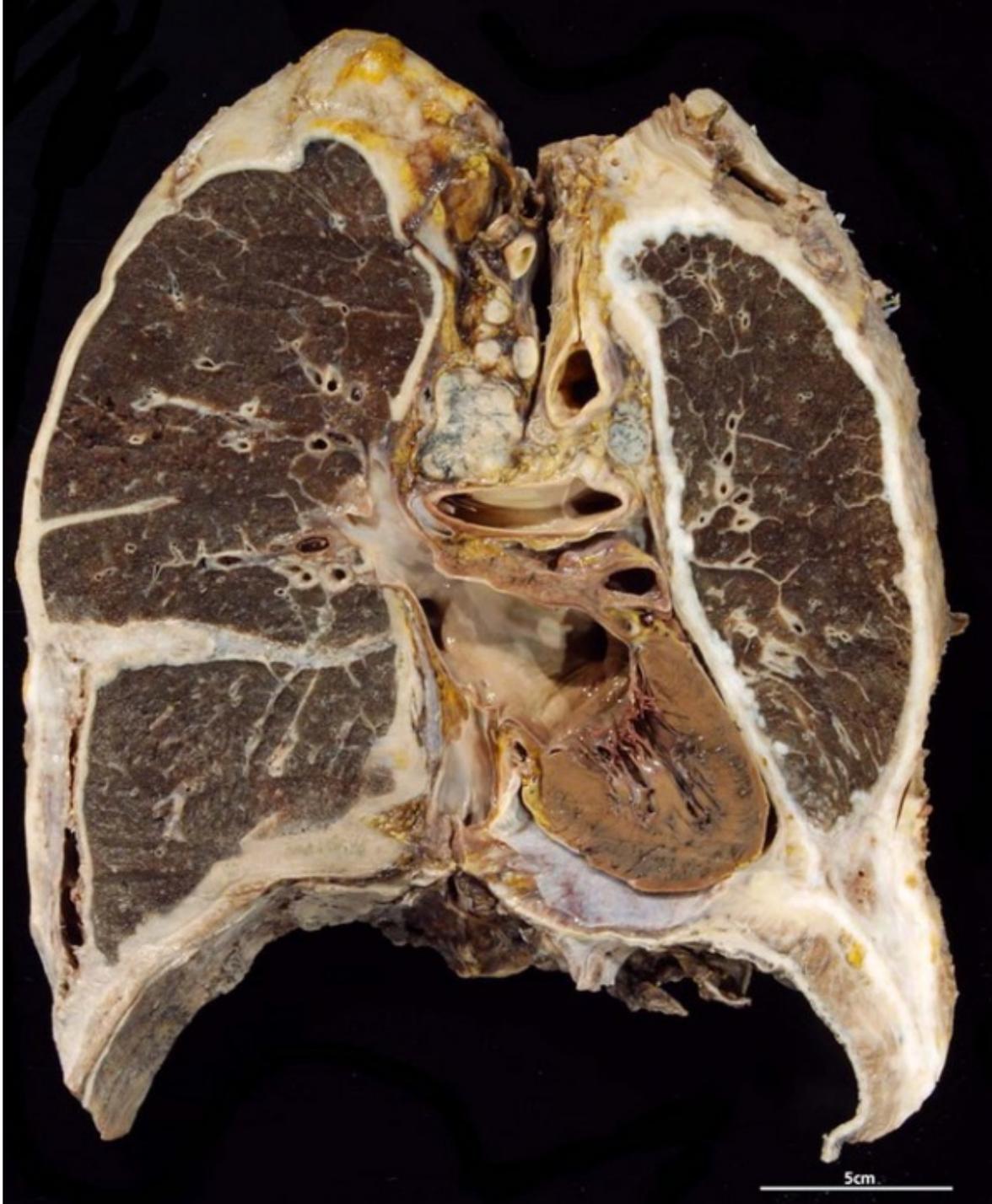
Il mesotelioma maligno è un tumore raro, gravato da una sopravvivenza minore di 1 anno, la cui incidenza è in costante aumento in tutto il mondo in seguito all'esposizione prolungata al suo principale fattore di rischio: **l'asbesto**

L'appartenenza al gruppo delle "**malattie professionali**", fa del mesotelioma un tumore associato a importanti aspetti medico-legali, gravati da enormi oneri di risarcimento da parte delle Istituzioni, tali da rappresentare un considerevole problema per le industrie e per i Governi

**sopravvivenza mediana:**

- 12 - 15 mesi dall'inizio dei sintomi
- 8 - 10 mesi dalla diagnosi

**Attualmente più del 75% dei pazienti muore entro l'anno**

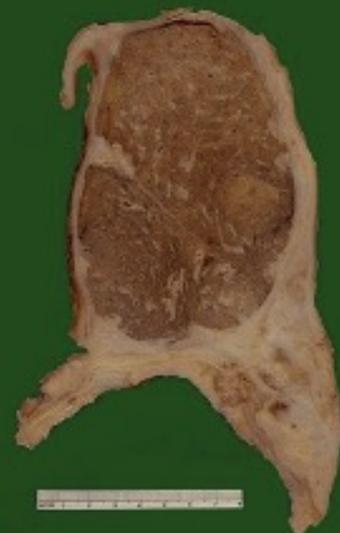


5cm

# *Anatomia patologica*

Macroscopicamente

Stadio precoce



Inizialmente la pleura parietale appare ricoperta da noduli, masse, foci multipli di colorito variabile da bianco rosaceo a rosso vivo

Le masse tendono a confluire estendendosi a tutta la superficie pleurica fino a formare una cotenna che dall'apice polmonare raggiunge la base (aspetto a colata)

Possono essere interessati entrambi i foglietti pleurici: il polmone si trova racchiuso in una cotenna dura di aspetto fibroso (tumore a corazza)

# Anatomia patologica

---

Macroscopicamente

Stadio avanzato

Estensione alla parete toracica, al mediastino ed invasione superficiale del polmone ipsilaterale

Metastasi linfonodali: mediastino, ascella, collo, addome

Metastasi ematogene (forma sarcomatosa): polmone, fegato, rene, surrene, ossa

# Anatomia patologica

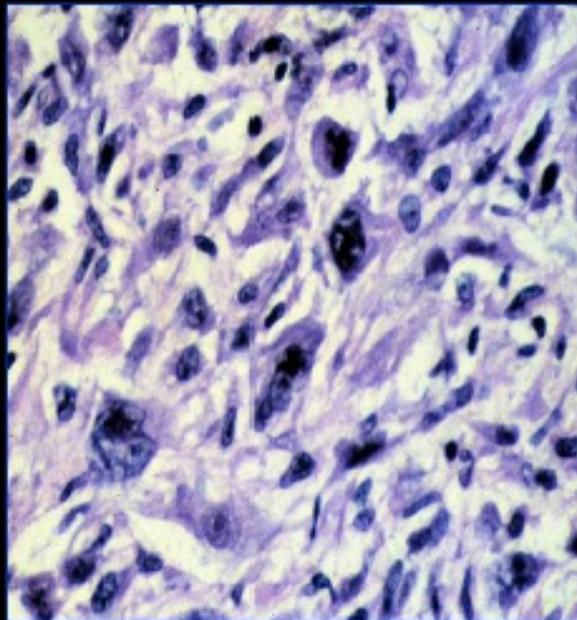
## Macroscopicamente:

- Solitarie
- Diffuse

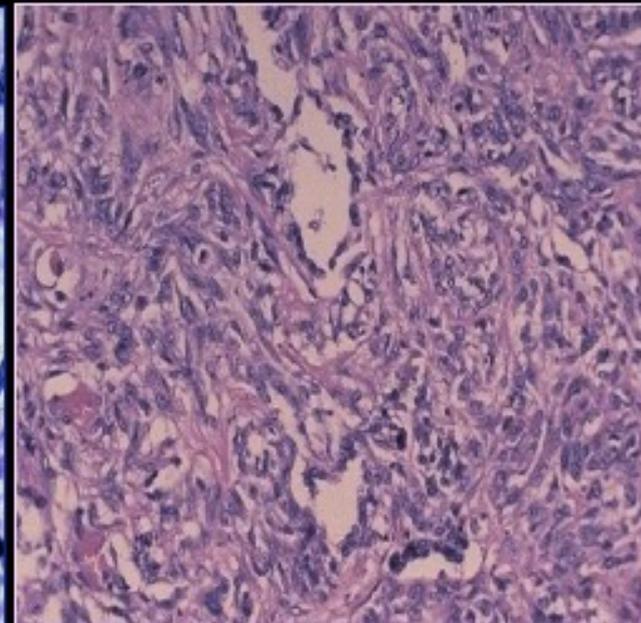


## Microscopicamente:

- Epiteliale (80%)
- Sarcomatoide (15%)
- Miste (5%)



Epiteliale



Sarcomatoide

# *Anatomia patologica: classificazione*

---

Epitelioide

- Tubulopapillare
- Scarsamente differenziato

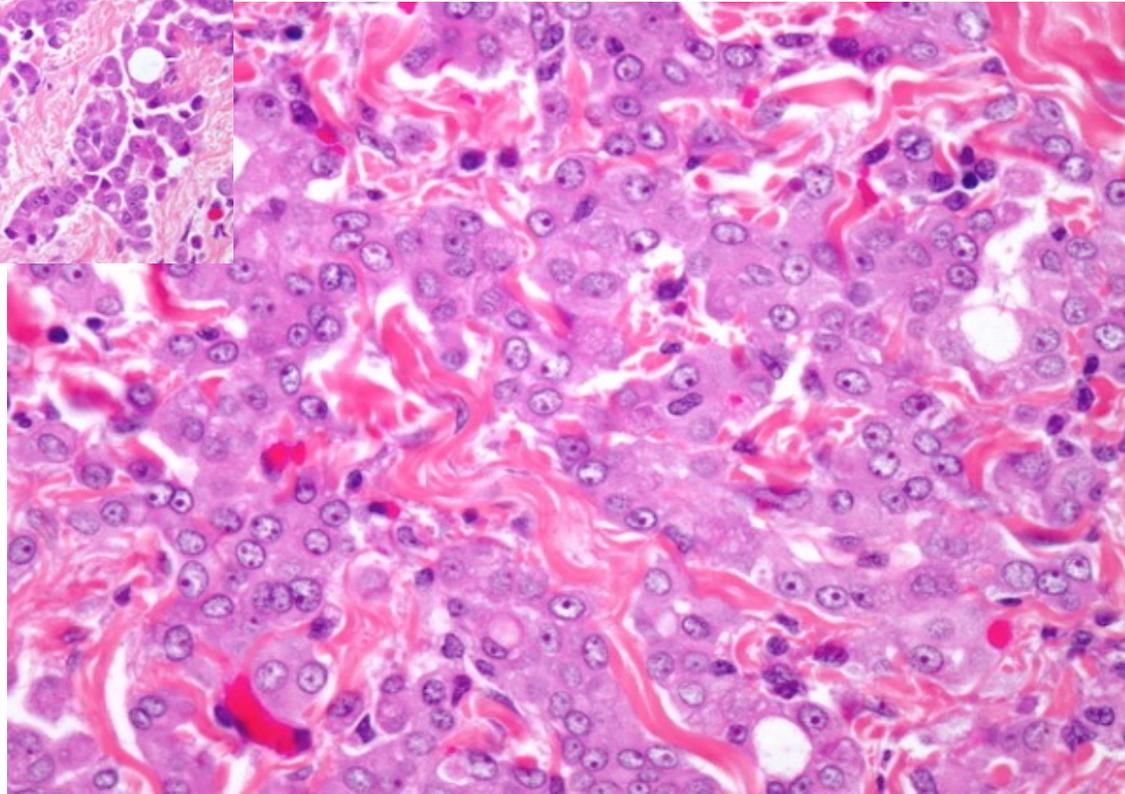
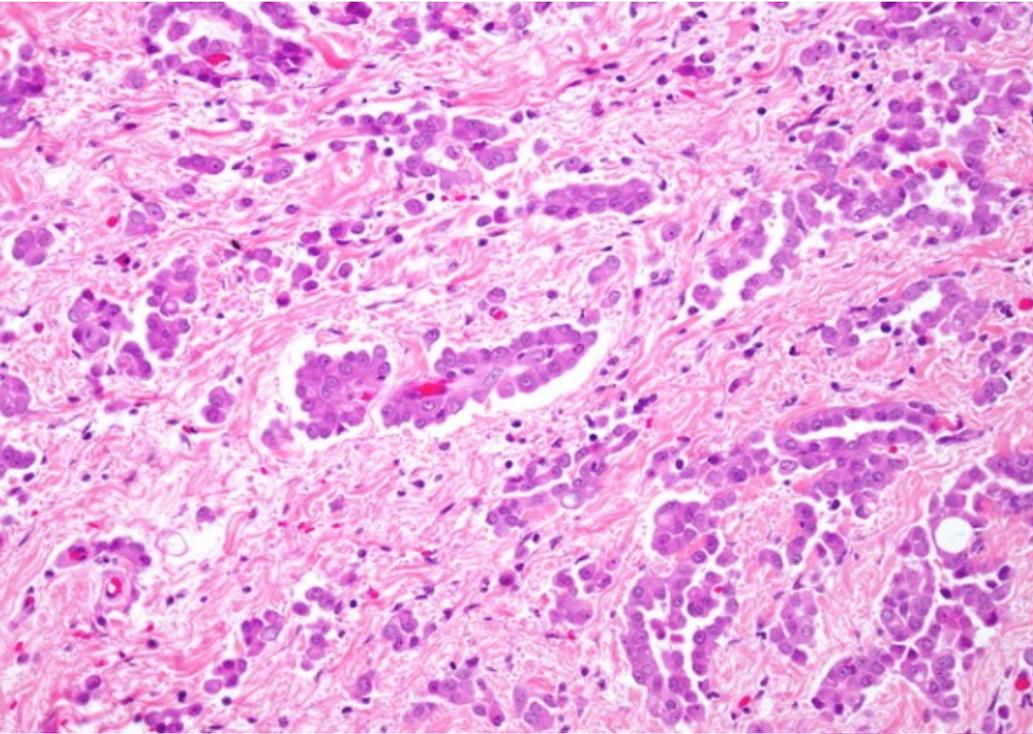
Sarcomatoide

- A cellule fusate
- Anaplastico

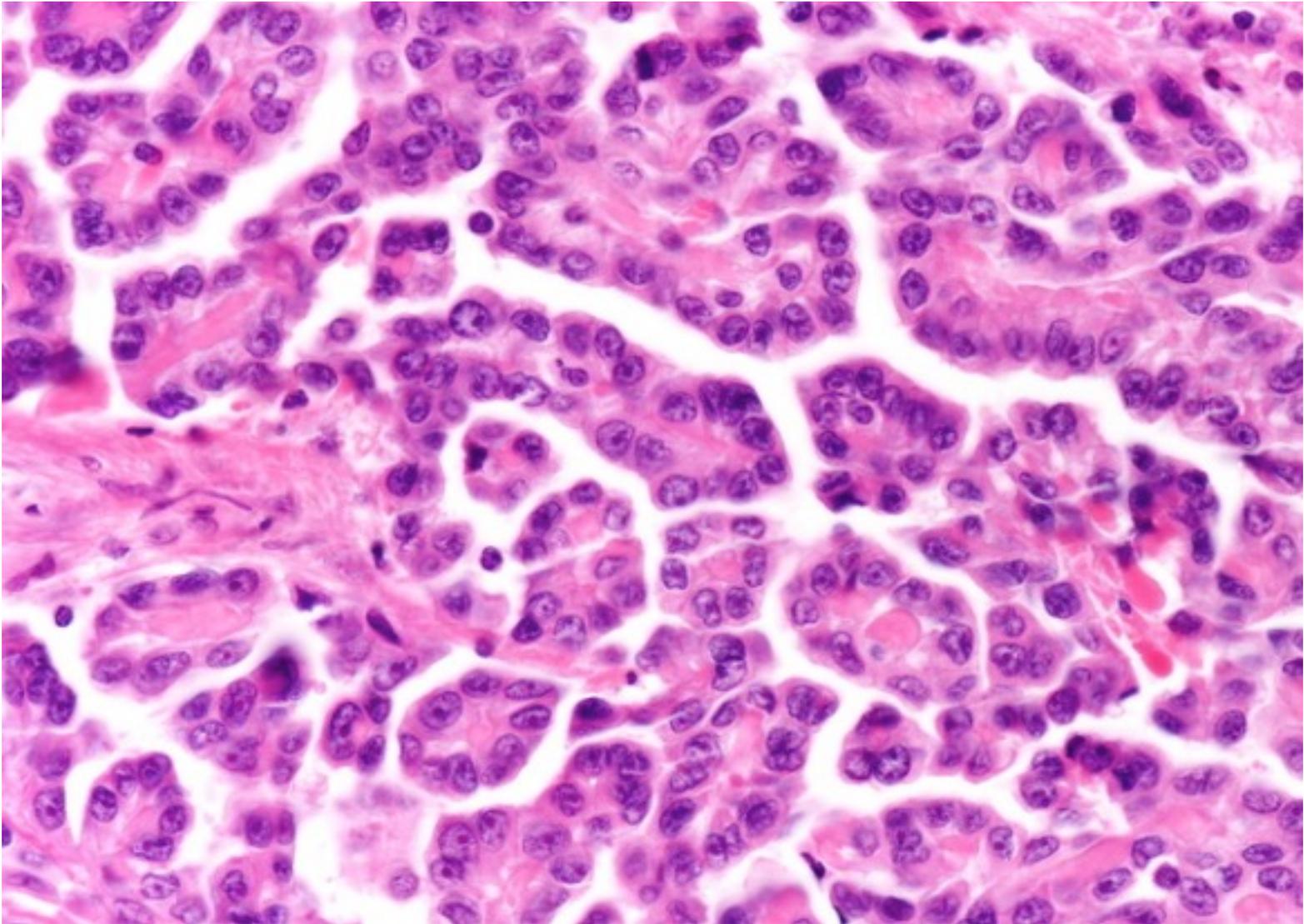
Bifasico

- Misto, epiteliale,  
sarcomatoso

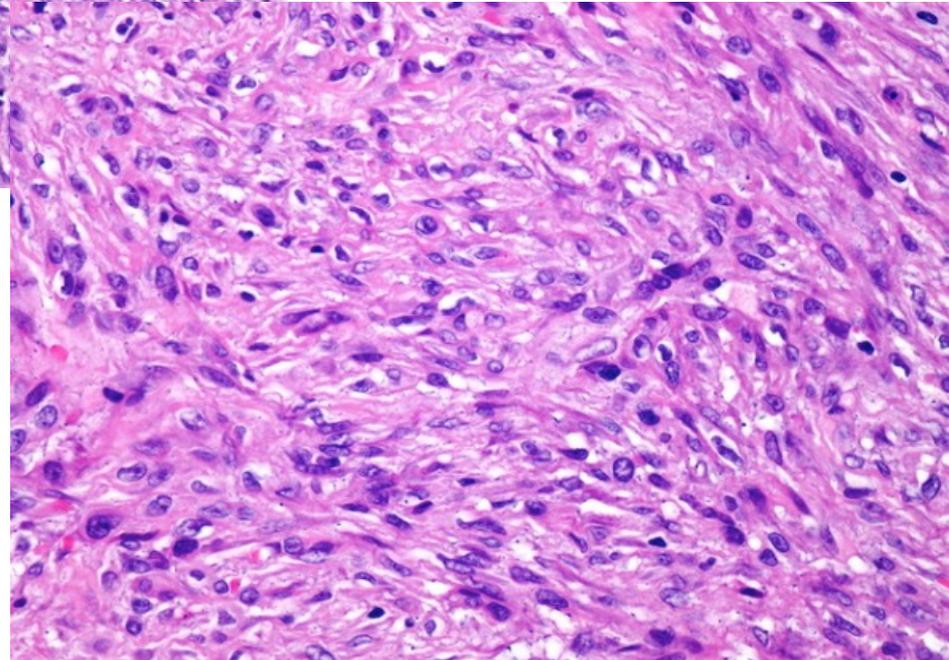
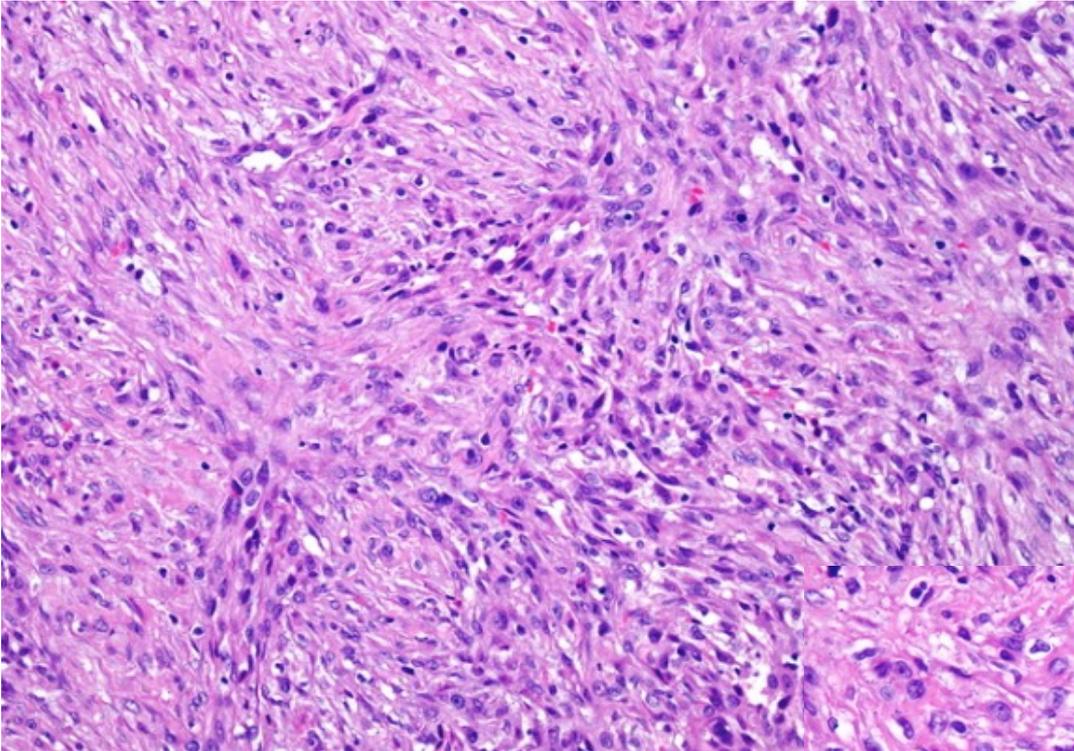
Mesotelioma epitelioido (tubulo-papillare) (50-70%)



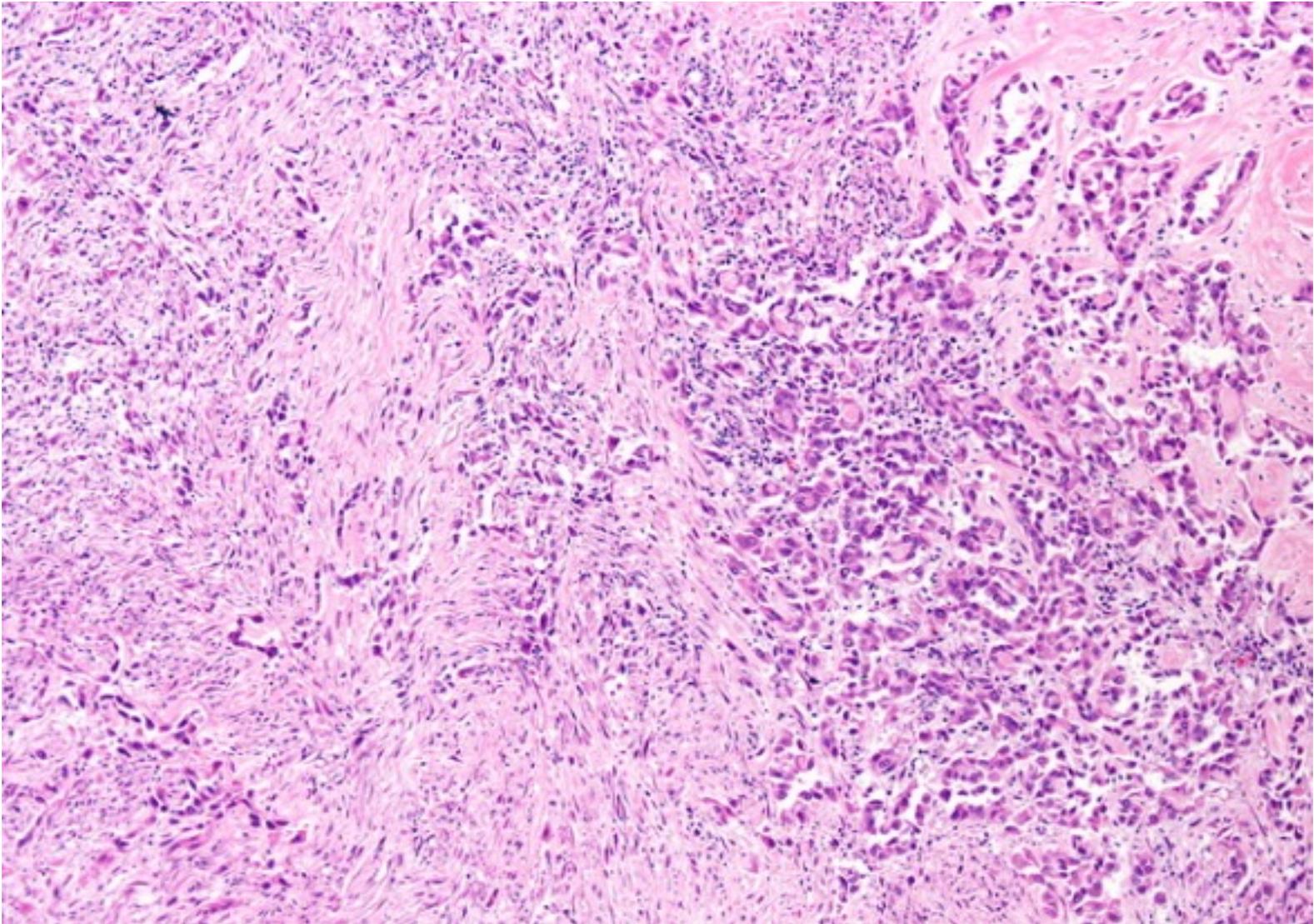
## Mesotelioma epitelioido (papillare)



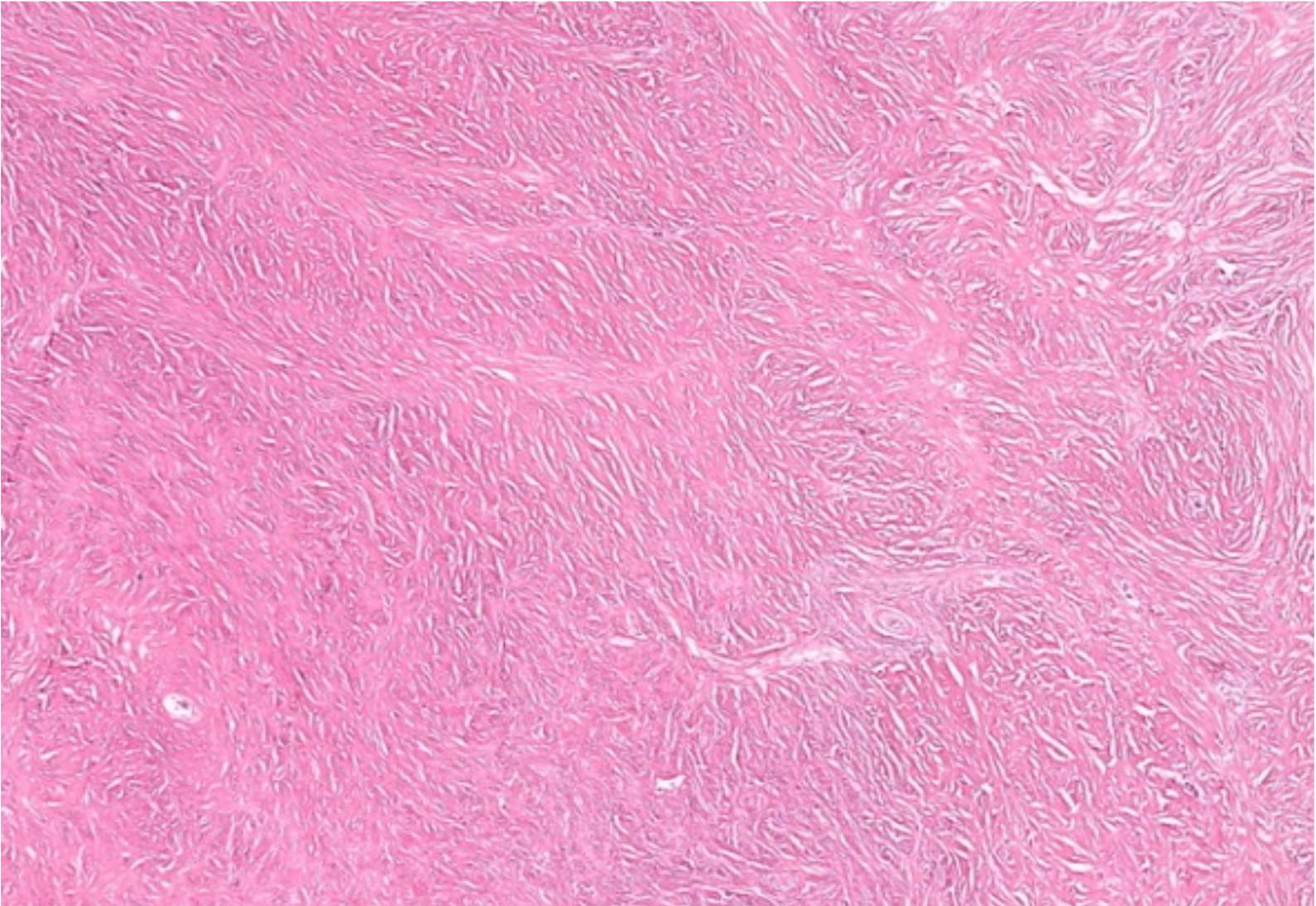
## Mesotelioma sarcomatoide (15%)



## Mesotelioma bifasico



## Mesotelioma desmoplastico



La **diagnosi** è generalmente basata su materiale bioptico, ma in alcuni casi selezionati (ad esempio nelle forme epitelioidi con molte cellule nel campione e quando le immagini radiologiche si accordino con l'ipotesi di mesotelioma) essa può essere effettuata anche su campioni citologici.

# **PROCEDURE DI PRELIEVO PER LA DIAGNOSI DI MESOTELIOMA MALIGNO PLEURICO**

- ✓ **Toracentesi**

## **MESOTELIOMA: principali problematiche diagnostiche**

- **Differenziare una popolazione mesoteliale reattiva da una neoplastica (versamenti e biopsie in assenza di invasione)**

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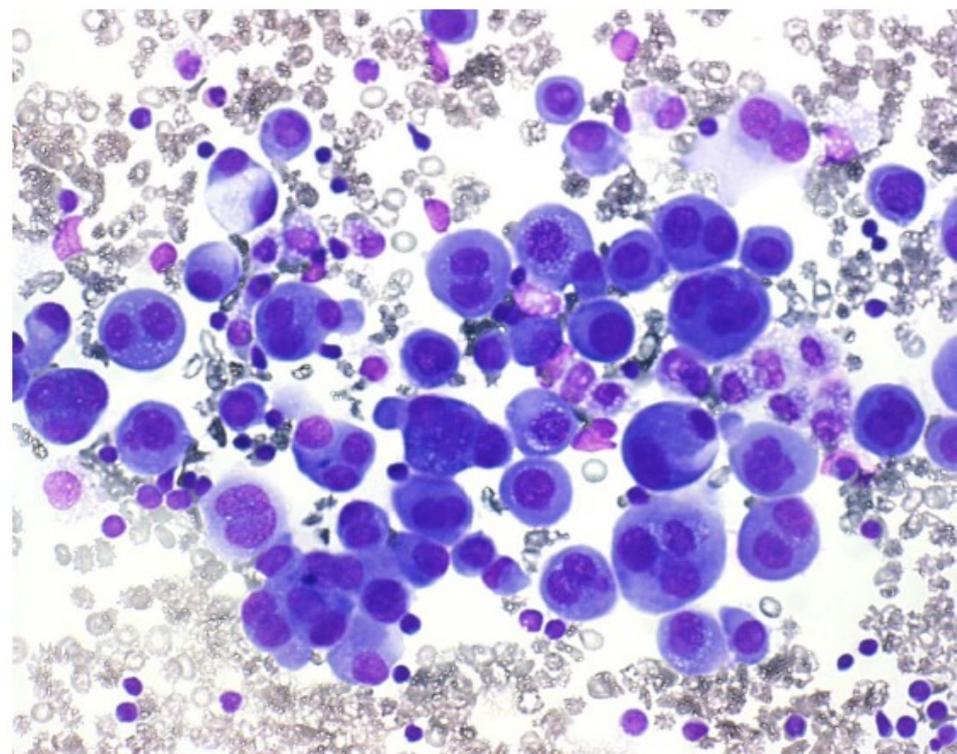
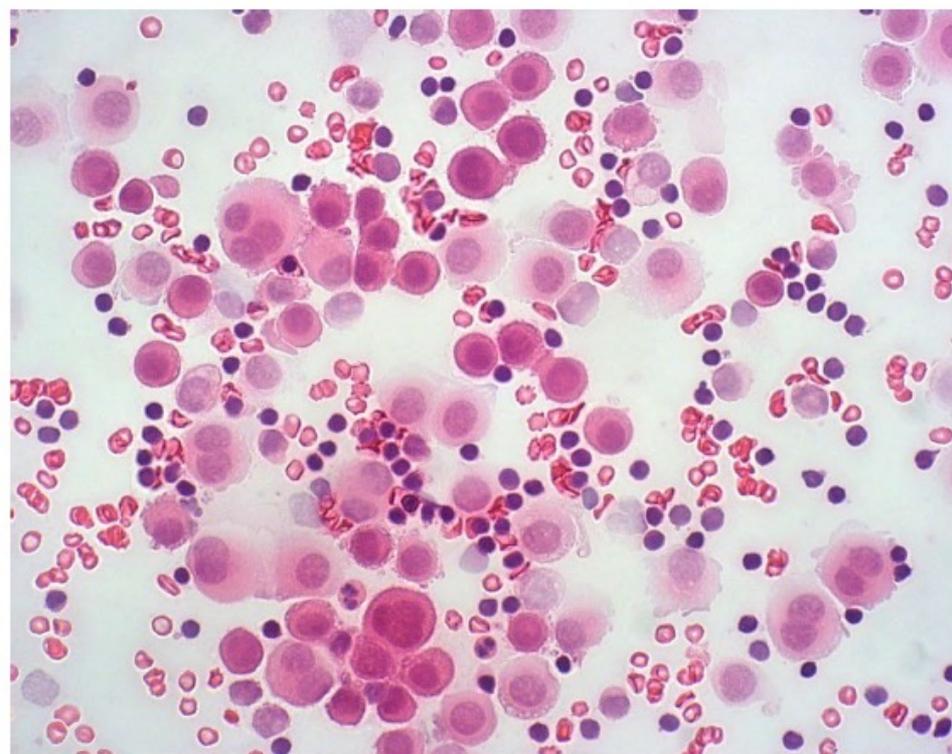
# **Guidelines for the Cytopathologic Diagnosis of Epithelioid and Mixed- Type Malignant Mesothelioma**

**Complementary Statement from the  
International Mesothelioma Interest Group,  
Also Endorsed by the International  
Academy of Cytology and the Papanicolaou  
Society of Cytopathology**

Anders Hjerpe,<sup>1\*</sup> Valeria Ascoli,<sup>2</sup> Carlos W.M. Bedrossian,<sup>3</sup>  
Mathilde E. Boon,<sup>4</sup> Jenette Creaney,<sup>5</sup> Ben Davidson,<sup>6</sup> Annika Dejmek,<sup>7</sup>  
Katalin Dobra,<sup>1</sup> Ambrogio Fassina,<sup>8</sup> Andrew Field,<sup>9</sup> Pinar Firat,<sup>10</sup>  
Toshiaki Kamei,<sup>11</sup> Tadao Kobayashi,<sup>12</sup> Claire W. Michael,<sup>13</sup>  
Sevgen Onder,<sup>14</sup> Amanda Segal,<sup>15</sup> and Philippe Vielh<sup>16</sup>

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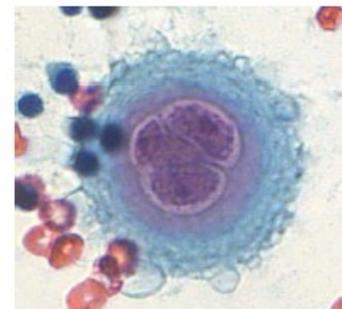
# LE CELLULE MESOTELIALI



Caratteri distintivi principali:

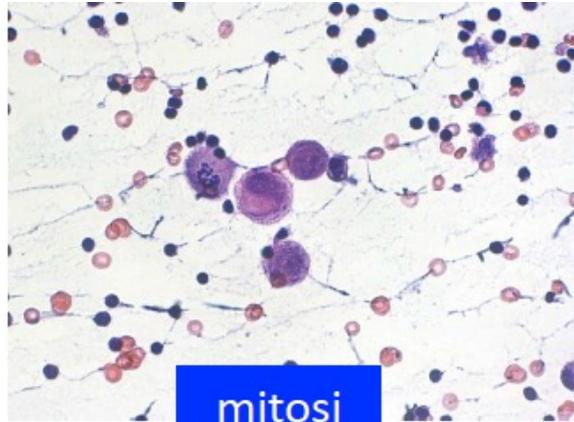
- *nucleo centrale o eccentrico con rima di citoplasma*
- *bicromatismo del citoplasma*
- *microvacuolizzazione della periferia del citoplasma*
- *microvilli*

Altri caratteri: *bi- o plurinucleazione, nucleoli evidenti, vacuoli citoplasmatici, aggregati*

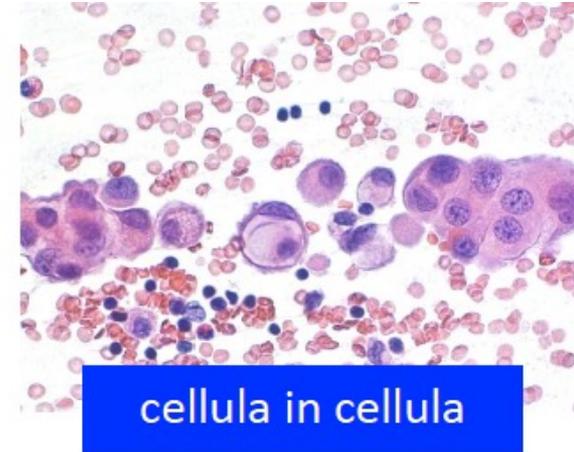




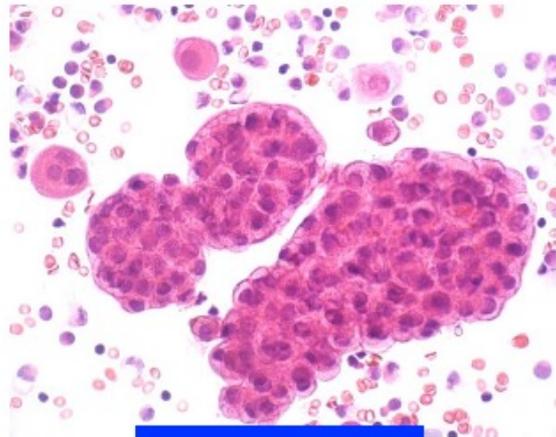
polimorfismo



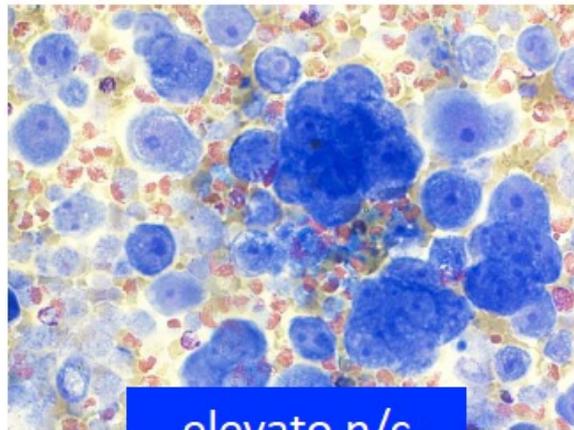
mitosi



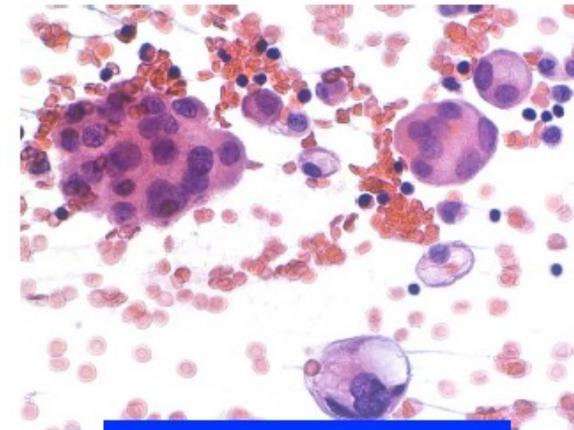
cellula in cellula



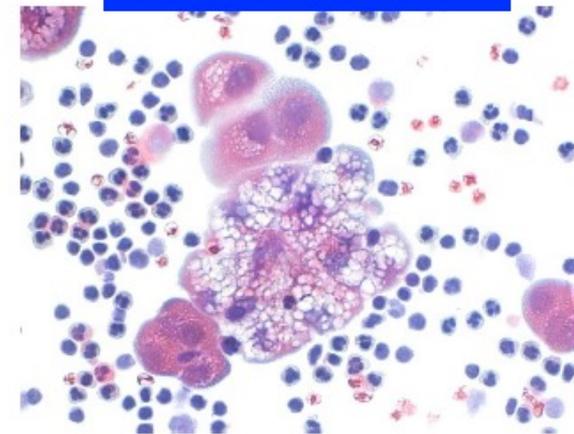
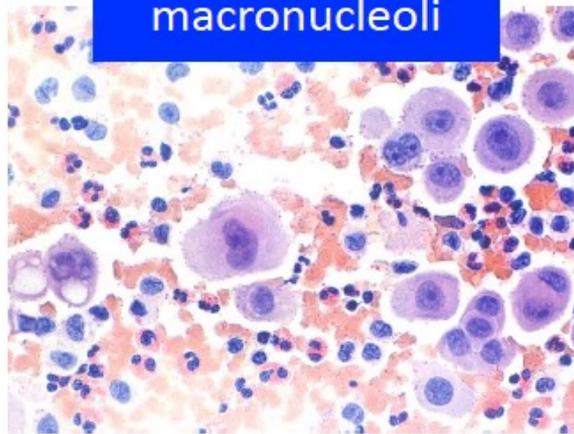
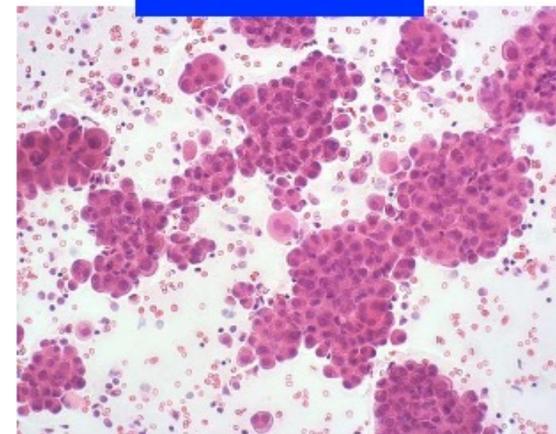
aggregati

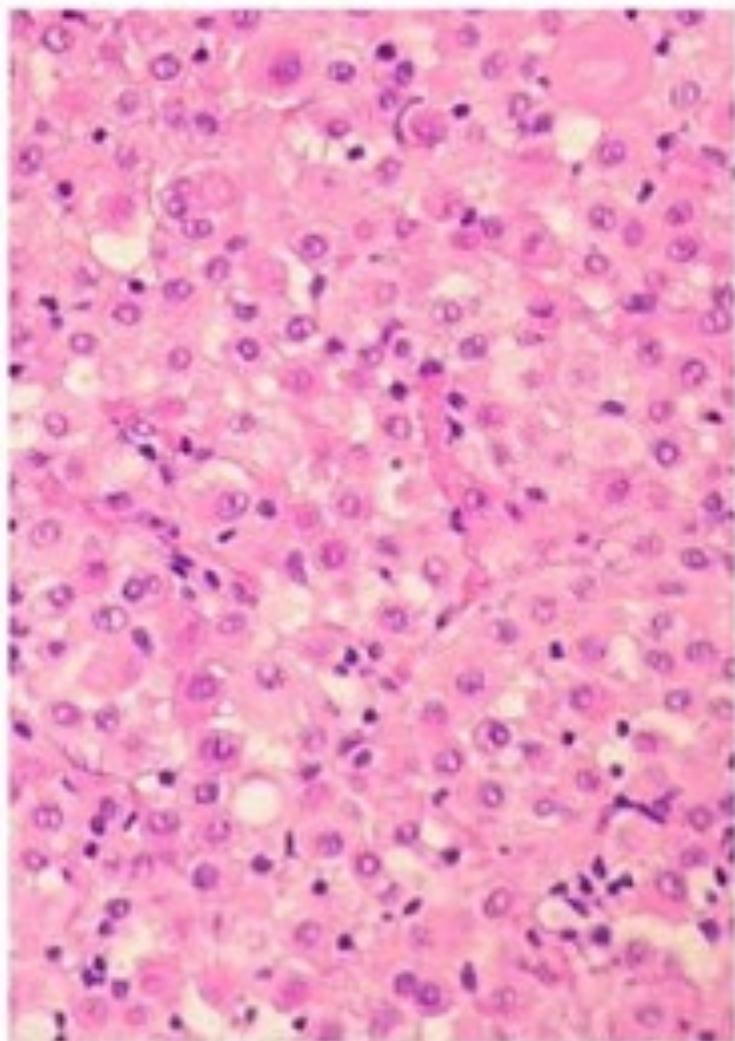


elevato n/c  
macronucleoli

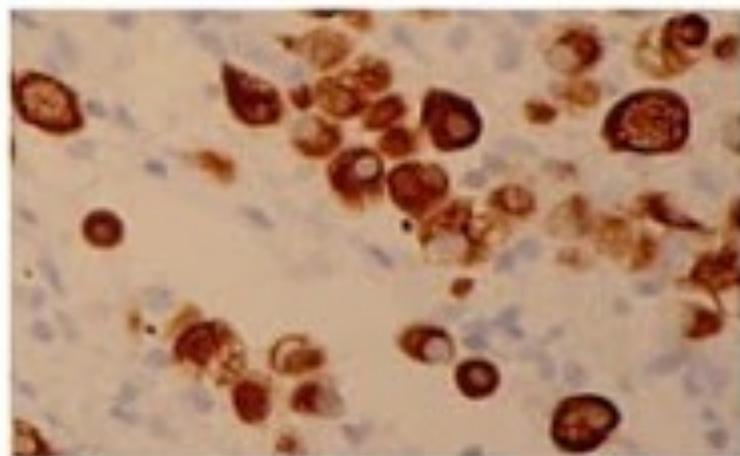


vacuolizzazioni

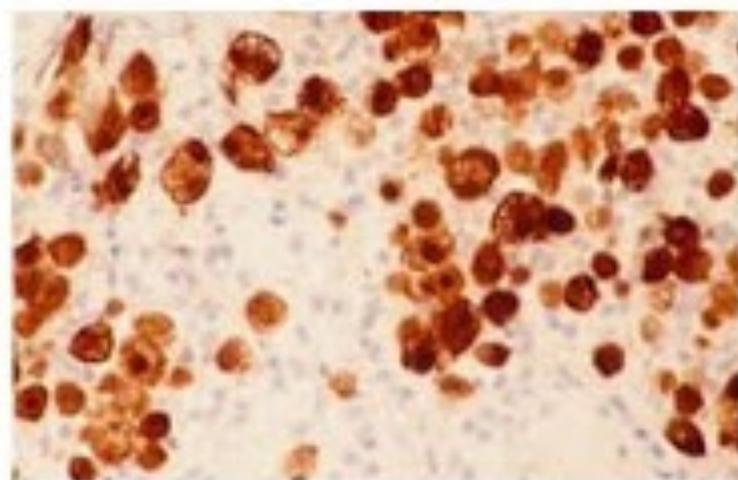




H&E



CK 5/6

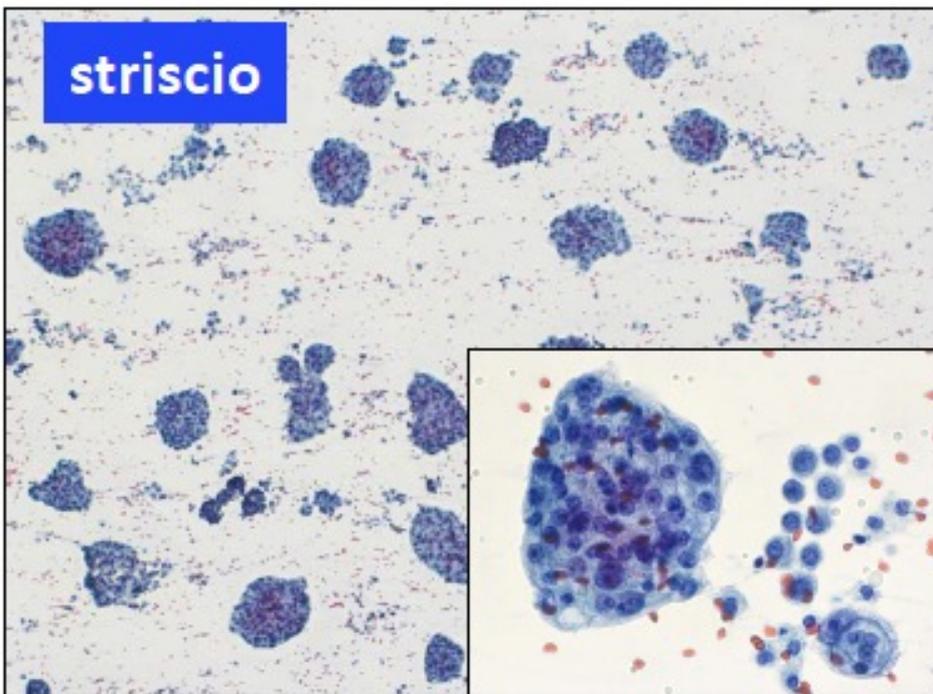


CALRETININA

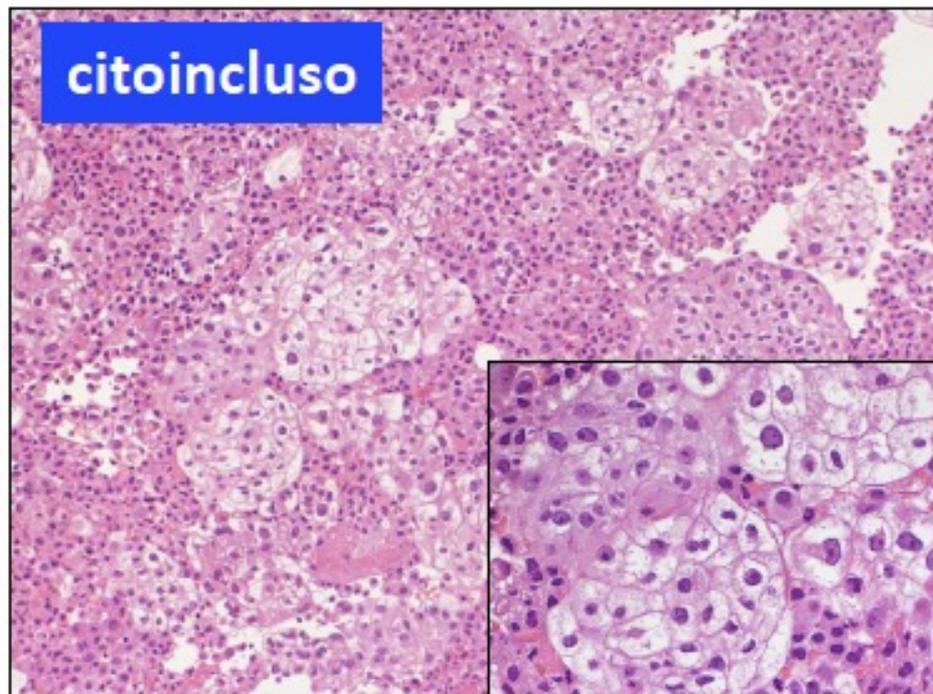
**F, 59 anni**  
**Versamento pleurico**  
**Ricoverata per**  
**volvolo intestinale**

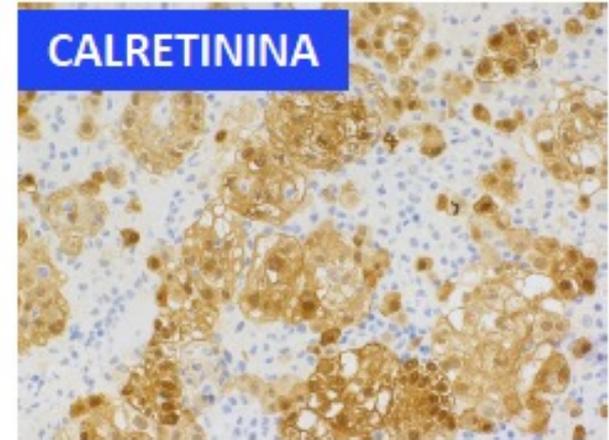
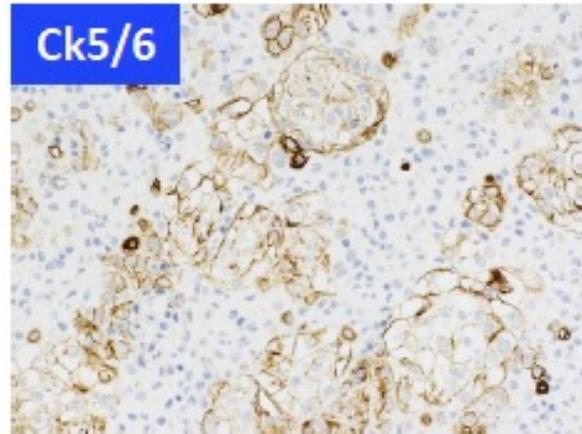
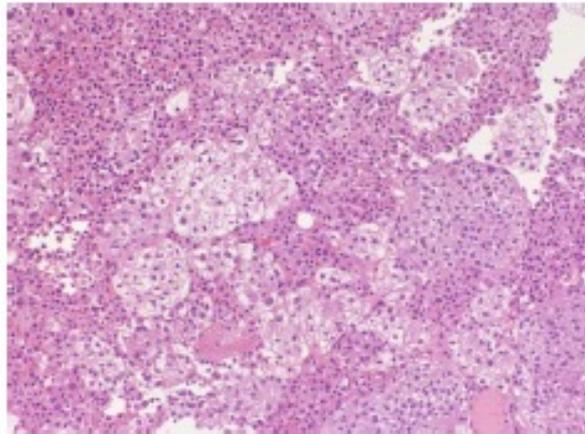


**striscio**



**citoincluso**





**CD10 (-/+)**

**Cl4 (-)**

**TTF1 (-)**

**P63 (-)**

**PAX8 (-)**

**mesotelioma maligno diffuso di tipo  
epiteloide con cellule chiare (confermata da  
biopsia pleurica toracoscopica successiva)**

**Table 5. Immunohistochemical Markers Used in the Differential Diagnosis Between Epithelioid Pleural Mesothelioma and Lung Adenocarcinoma**

| Marker                                                          | Current Value/Comments                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Epithelioid mesothelioma (positive mesothelioma markers)</b> |                                                                                                                                                                                                                                                                                                                |
| Calretinin                                                      | Very useful. It can be demonstrated in nearly all epithelioid mesotheliomas when antibodies to human recombinant calretinin are used. The staining is often strong and diffuse, and both nuclear and cytoplasmic. Five percent to 10% of lung adenocarcinomas are positive, but the staining is usually focal. |
| Cytokeratin 5 or 5/6                                            | Very useful. It is expressed in 75% to 100% of the mesotheliomas. Approximately 2% to 20% of lung                                                                                                                                                                                                              |

**Table 6. Immunohistochemical Markers Used in the Differential Diagnosis Between Epithelioid Pleural Mesothelioma and Squamous Carcinoma of the Lung**

| Marker                         | Current Value/Comments |
|--------------------------------|------------------------|
| WT-1                           |                        |
| D2-40 (podoplanin)             |                        |
| <b>Lung adenocarcinoma</b>     |                        |
| MOC-31                         |                        |
| BG8 (Lewis <sup>y</sup> )      |                        |
| CEA (monoclonal)               |                        |
| B72.3                          |                        |
| Ber-EP4                        |                        |
| TTF-1                          |                        |
| Napsin A                       |                        |
| <b>Lung squamous carcinoma</b> |                        |
| p63 or p40                     |                        |
| MOC-31                         |                        |
| BG8 (Lewis <sup>y</sup> )      |                        |
| Ber-EP4                        |                        |
| Cytokeratin                    |                        |

**Table 7. Immunohistochemical Markers Used in the Differential Diagnosis Between Epithelioid Pleural Mesothelioma and Renal Cell Carcinomas**

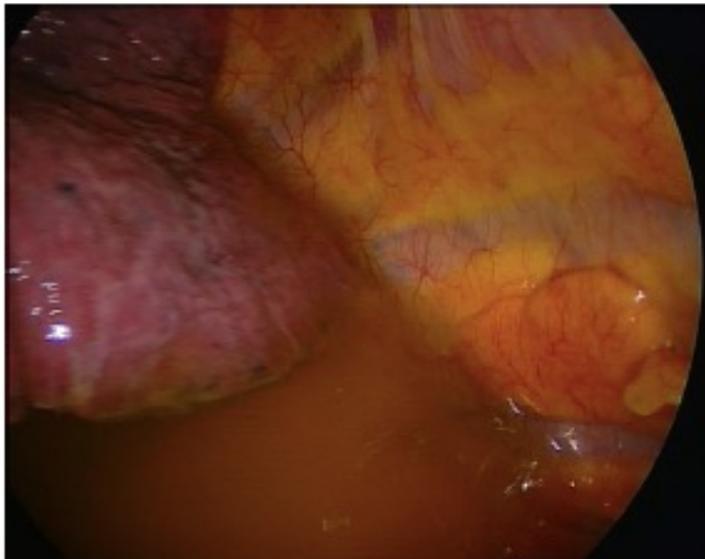
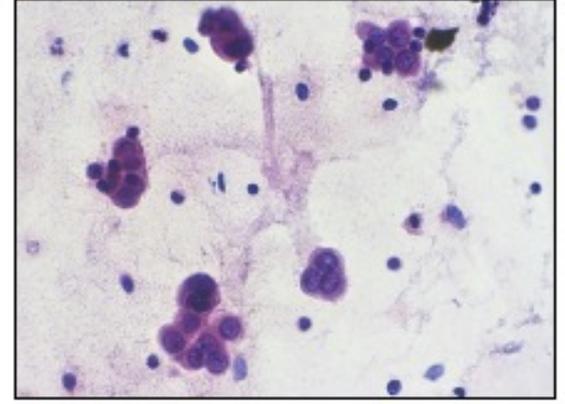
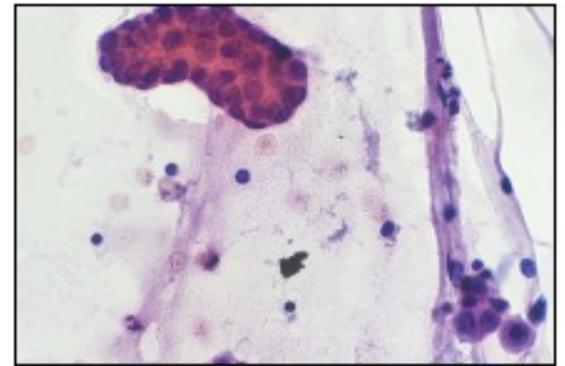
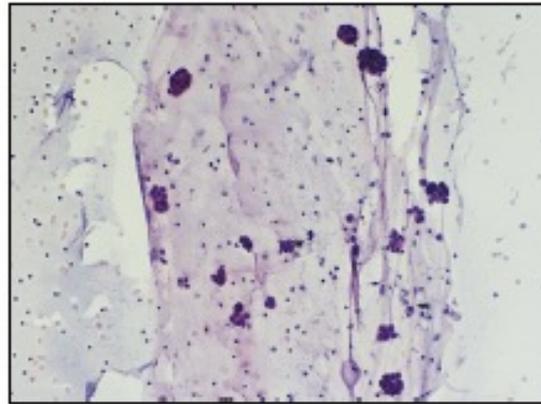
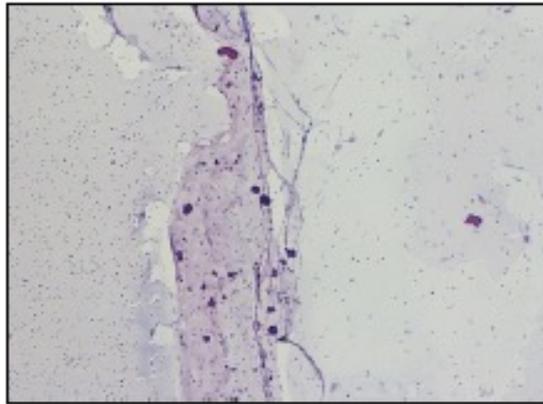
| Marker                          | Current Value/Comments |
|---------------------------------|------------------------|
| <b>Epithelioid mesothelioma</b> |                        |
| WT-1                            |                        |
| Calretinin                      |                        |
| <b>Renal cell carcinoma</b>     |                        |
| PAX8 or PAX2                    |                        |
| CD15 (Leu-M1)                   |                        |
| RCC Ma                          |                        |
| MOC-31                          |                        |
| Ber-EP4                         |                        |
| Cytokeratin                     |                        |
| CD10                            |                        |
| BG8 (Lewis <sup>y</sup> )       |                        |

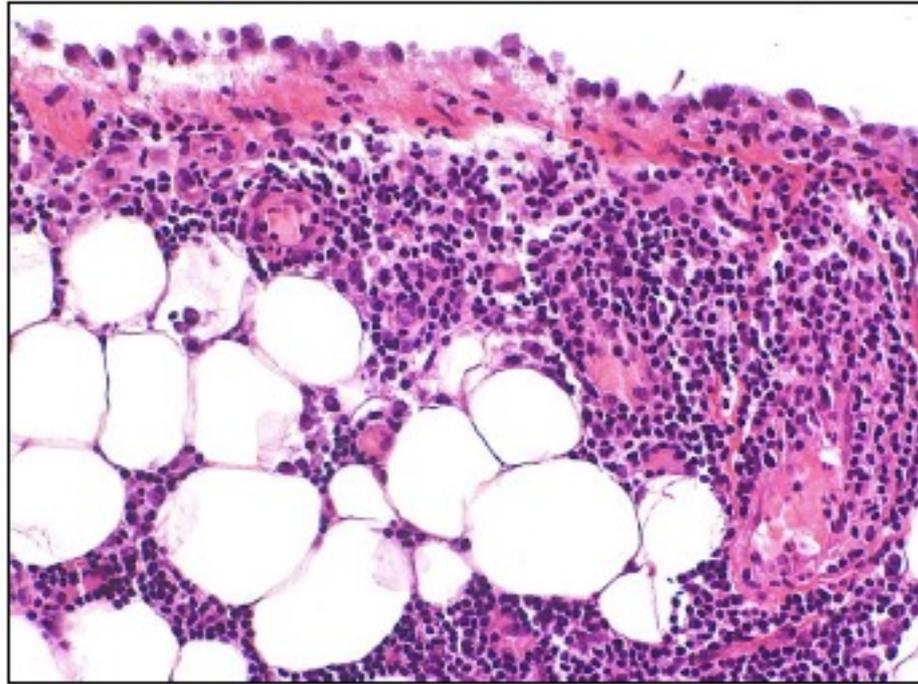
**Table 8. Peritoneal Malignant Mesothelioma (PMM) Versus Papillary Serous Carcinoma (PSC) and Nongynecologic Adenocarcinoma (AdCa)**

| Marker                                                                        | Current Value/Comments                                                                                                                                  |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Positive mesothelioma markers</b>                                          |                                                                                                                                                         |
| Calretinin                                                                    | Useful. Positivity in 85% to 100% of PMM cases, but reactivity in 0% to 38% of PSCs limits its use as a single marker.                                  |
| D2-40                                                                         | Potentially useful. Positivity in 93% to 96% of PMM cases, but wide spectrum of positivity in PSCs from 13% to 65%; requires more data in this context. |
| CK5/6                                                                         | Not useful. Positivity in 53% to 100% of PMM cases, and positivity in 22% to 35% of PSC cases.                                                          |
| WT-1                                                                          | Not useful. Positivity in 43% to 93% of PMM cases, but 89% to 93% of PSCs are positive.                                                                 |
| <b>PSC markers</b>                                                            |                                                                                                                                                         |
| MOC31                                                                         | Very useful. Positivity in 98% of PSCs and 5% of PMM cases.                                                                                             |
| PAX 8                                                                         | Very useful. Positivity in most müllerian carcinomas; negativity in PMM.                                                                                |
| BG8                                                                           | Very useful. Positivity in 73% of PSCs and 3% to 9% of PMM cases.                                                                                       |
| Ber-EP4                                                                       | Useful. Positivity in 83% to 100% of PSCs and 9% to 13% of PMM cases.                                                                                   |
| B72.3                                                                         | Limited utility. Positivity in 65% to 100% of PSCs and 0% to 3% of PMM cases, but many cases show only trace/focal staining.                            |
| CEA                                                                           | Not useful. Zero percent to 45% of PSCs (average, 20%) and 0% of PMM cases, but sensitivity in PSC is too low compared to other choices.                |
| ER                                                                            | Useful. Sixty percent to 93% in PSCs, and negativity or very low positive rate (0%–8%) in PMM cases.                                                    |
| PR                                                                            | Limited utility. Lower sensitivity than ER, but uniformly negative staining in PMM. May be valuable if shows positivity.                                |
| <b>PMM versus nongynecologic AdCa (biliary, pancreatic, gastric, colonic)</b> |                                                                                                                                                         |
| Calretinin                                                                    | Very useful. Positivity in 85% to 100% of PMM cases but also positivity in 10% of pancreatic AdCas, so limited as a single marker.                      |
| WT-1                                                                          | Very useful. Positivity in 43% to 93% of PMM cases, 3% of gastric AdCas, negativity in pancreatic AdCa.                                                 |
| D2-40                                                                         | Potentially useful. Positivity in 93% to 96% of PMM cases, negativity in pancreatic and gastric AdCa (but limited data).                                |
| CEA                                                                           | Very useful. Positivity in 81% of AdCas, negativity in PMM.                                                                                             |
| B72.3                                                                         | Very useful. Positivity in 84% of pancreas, 89% of bile duct, 98% of colon AdCas; 0% to 3% of PMM cases.                                                |
| Ber-EP4                                                                       | Useful. Positivity in >98% of pancreatic and gastric AdCas, 9% to 13% of PMM cases.                                                                     |
| CDX2                                                                          | Useful. Ninety percent to 100% of colon, 80% of small intestine, and 70% of gastric carcinomas are positive; negativity in PMM.                         |

*Arch Pathol Lab Med. 2012;136:1–21; doi: 10.5858/arpa.2012-0214-OA*

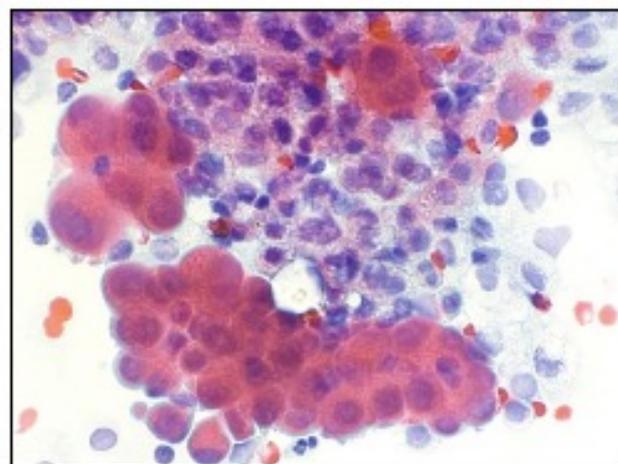
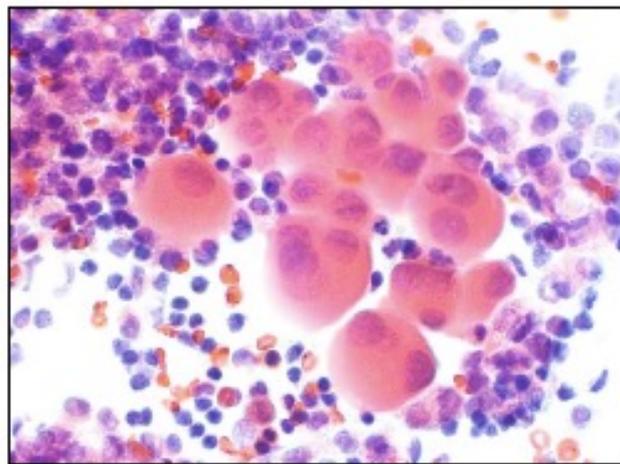
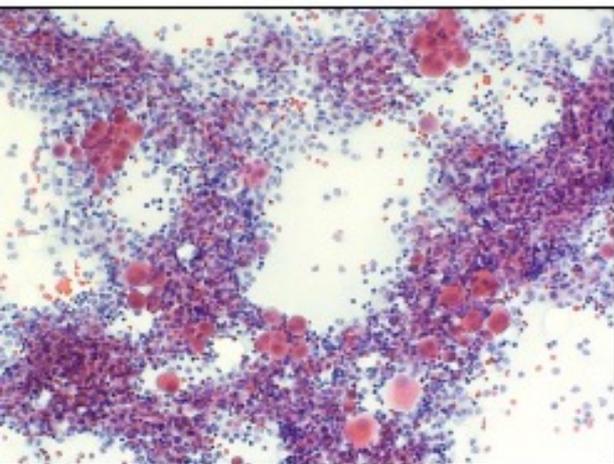
**F, 61 anni con scompenso cardiaco e  
versamento pleurico inizialmente  
bilaterale, persistente a sinistra**





**Biopsia pleurica: *pleurite cronica non specifica***

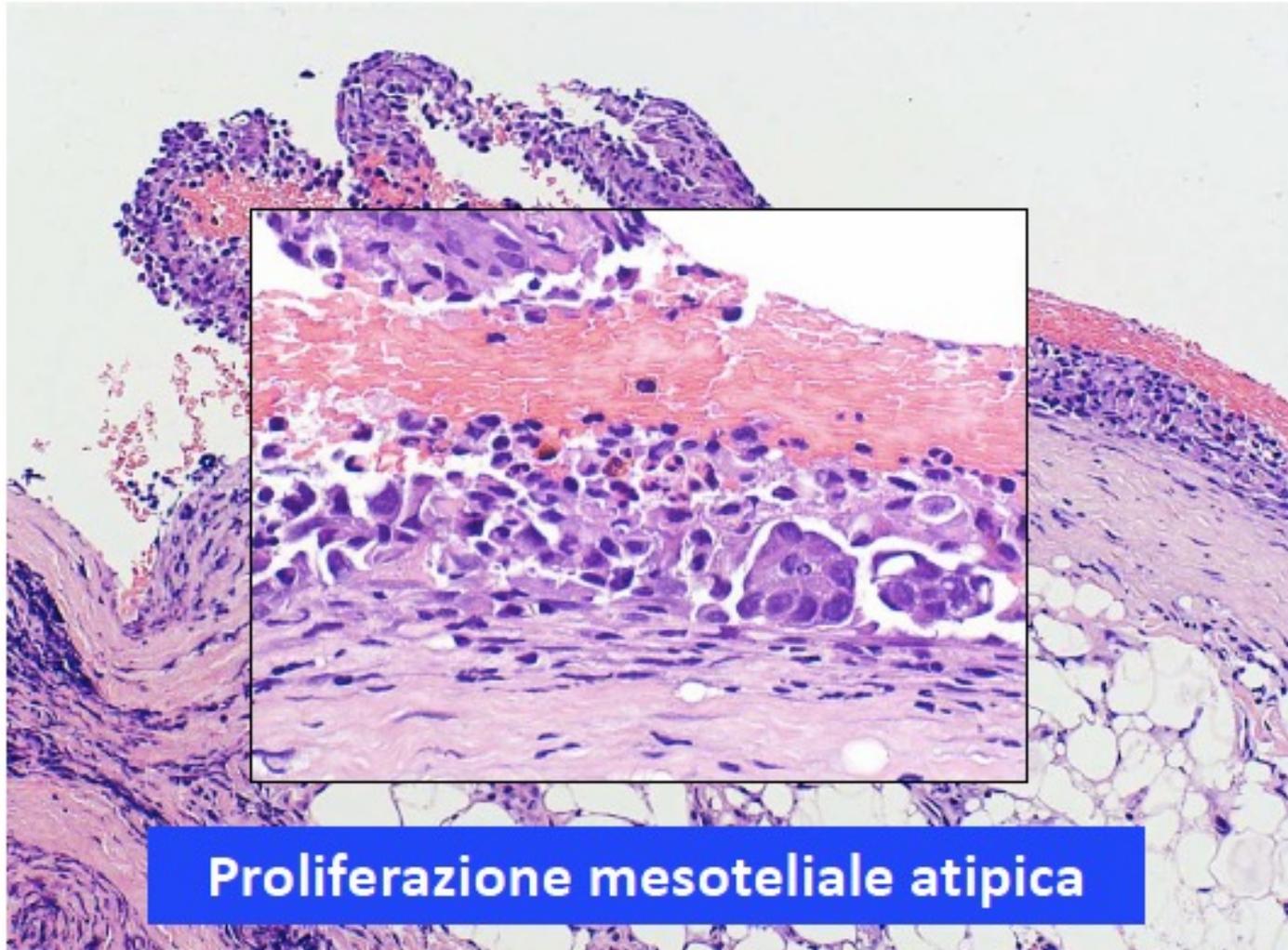
***F, 91 anni, cardiopatica, con versamento pleurico a destra da alcuni mesi, paucisintomatico***



**Proliferazione mesoteliale atipica. Mesotelioma?**



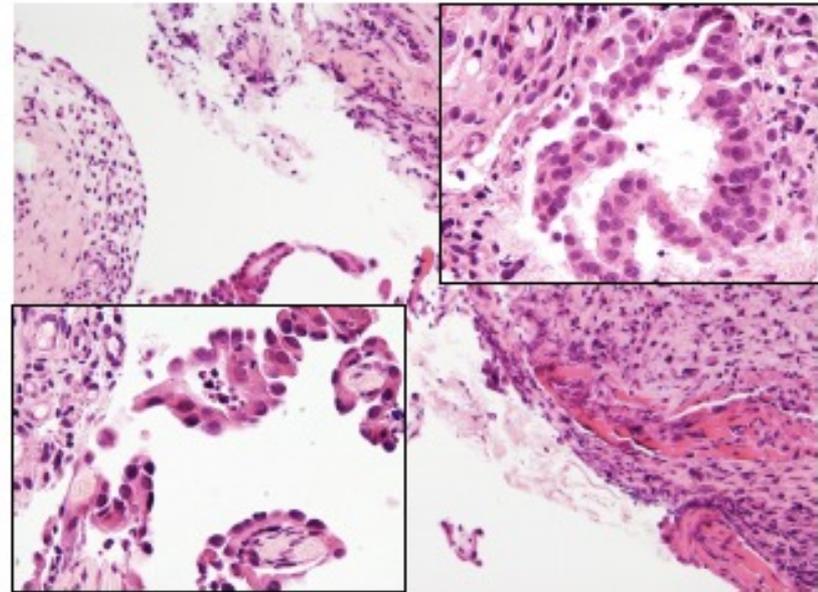
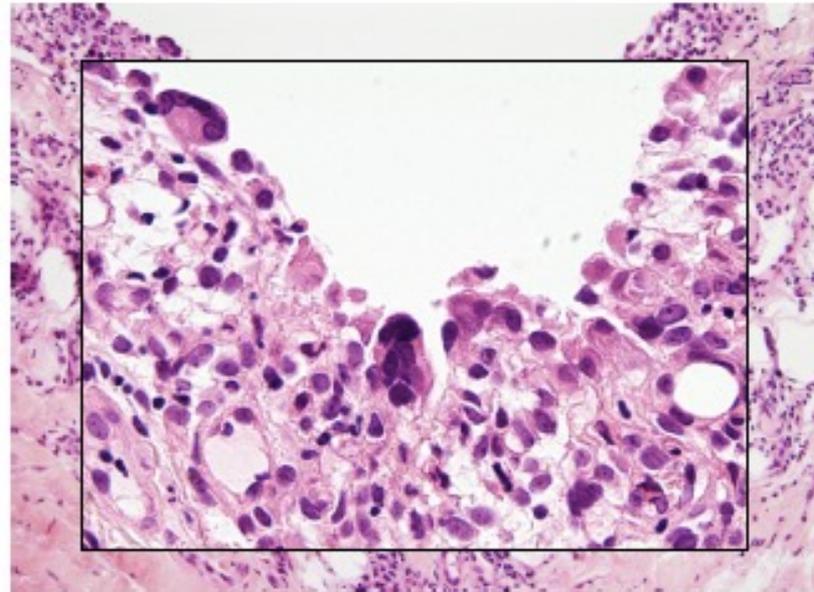
- Uomo di 44 anni con pleuropatia sinistra di n.d.d.
- Non nota esposizione ad asbesto
- Toracoscopia (05.2011): quadro aspecifico
- Biopsia



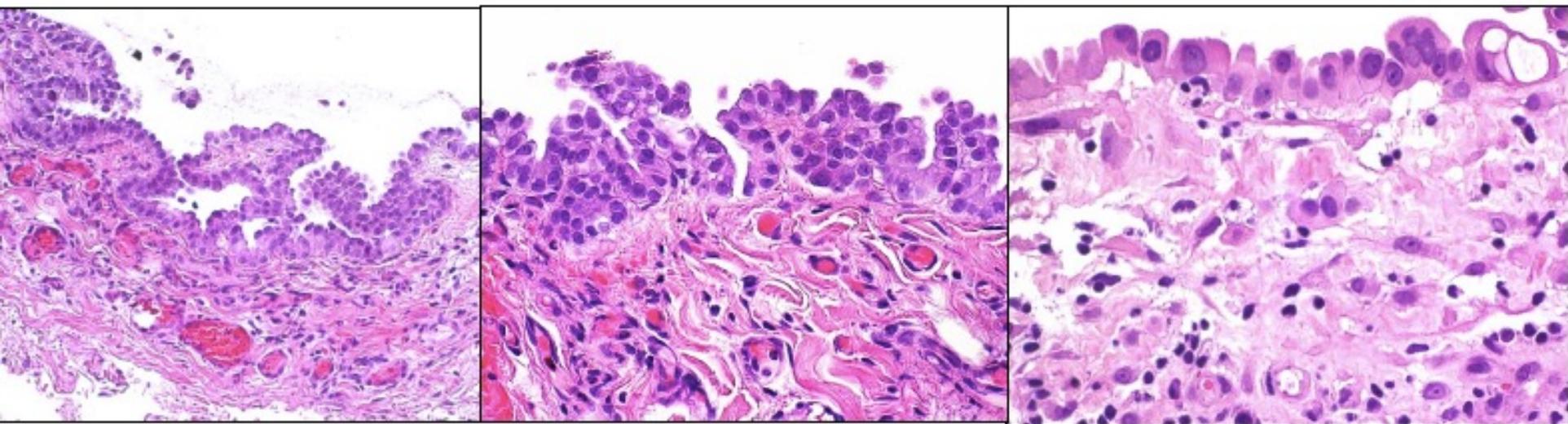
**Proliferazione mesoteliale atipica**

**F 44 aa, pregresso ca mammario operato + RT (1997).  
Versamento pleurico, toracoscopia con biopsia**

**07.2007**



**PROLIFERAZIONE MESOTELIALE ATIPICA**



- In presenza di elementi morfologici che suggeriscono un mesotelioma (papille, stratificazione, proliferazione continua) ma che non sono sufficienti per una diagnosi di certezza (assenza di invasione e/o noduli)
- In assenza di cause o condizioni riconducibili ad una proliferazione mesoteliale reattiva ancorché esuberante

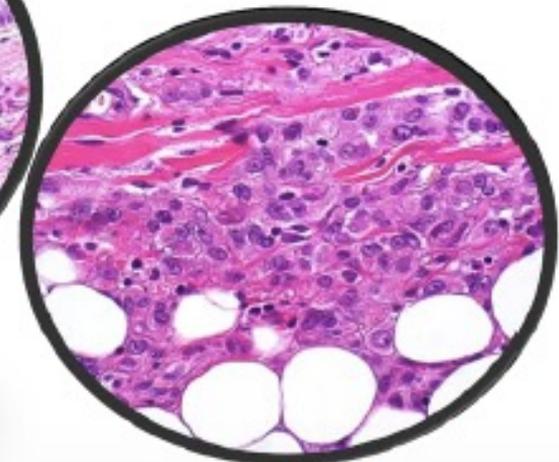
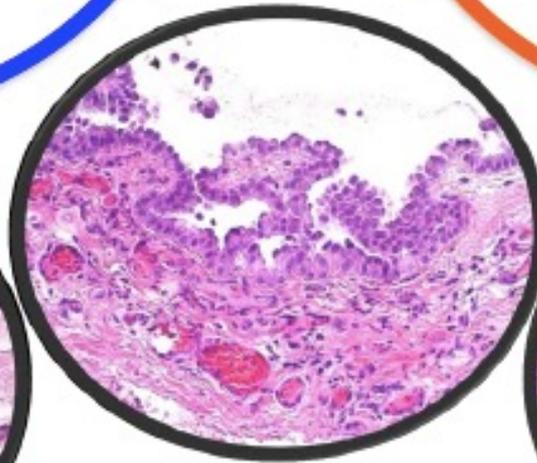
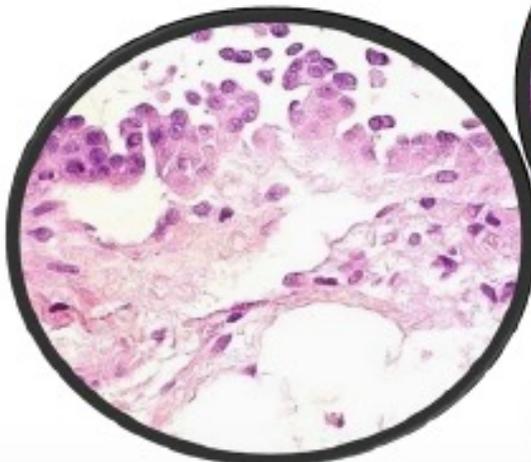


**PROLIFERAZIONE MESOTELIALE ATIPICA**

**PROLIFERAZIONE  
MESOTELIALE  
ATIPICA**

**IPERPLASIA  
MESOTELIALE  
REATTIVA**

**MESOTELIOMA  
MALIGNO**



# PROLIFERAZIONE MESOTELIALE ATIPICA

## CLINICA

- Versamento pleurico recidivante in un lasso di tempo imprevedibile (da mesi ad anni)
- Toracosopia iniziale: alterazioni minime non specifiche
- Toracosopia/e di controllo: non specifica/ispessimento/noduli

**Correlazione clinico-radiologica, follow-up, eventuale ripetizione della biopsia con estensivo campionamento**