Update on Classification and Staging of Pulmonary Tumors

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Disclosures

Relevant financial relationships:

None

Off-label usage:

None

Learning Objectives

At the end of this talk and the accompanying case presentations, the participant should be able to do the following:

- Explain the most important updates to the WHO lung tumor classification in 2015
- Describe the changes to AJCC staging of lung tumors in the new 8th Ed.
- Describe common diagnostic challenges with lung tumor diagnosis and possible solutions

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4 Important Thematic Questions

1. If “tissue is the issue” why is the “sample not ample”?
2. Adenocarcinoma in situ: what, when, and how?
3. Am I staging lung cancers accurately?
4. What other new entities should I know about?

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Musings on the “vanishing biopsy”

- Growing *inverse relationship* between sample size and the data required for patient management

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Musings on the "vanishing biopsy"

- Growing *inverse relationship* between sample size and the data required for patient management
- "Learn to do more with less, or we will find something that can!"

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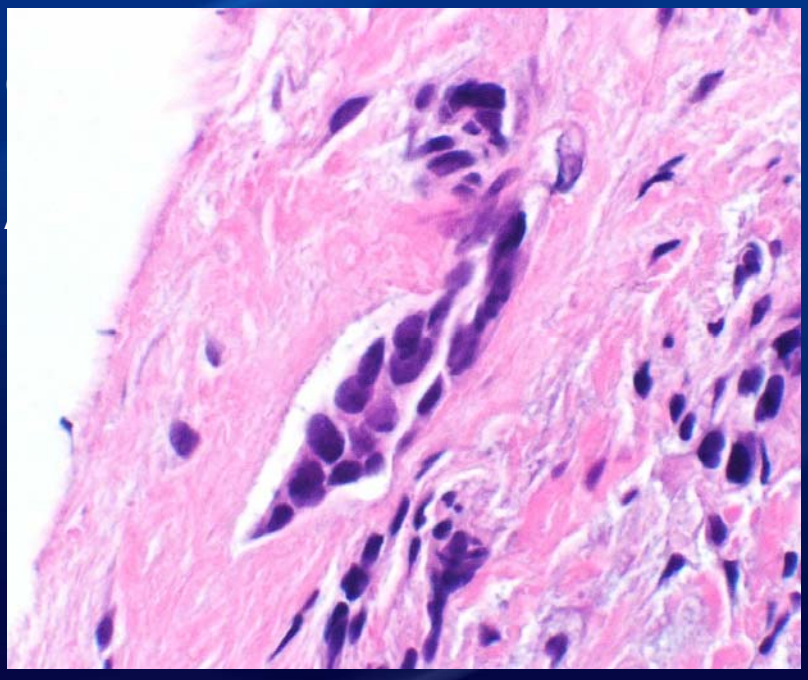

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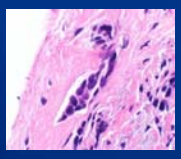
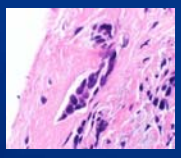


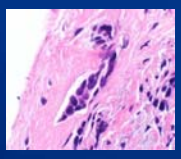
You call the pulmonologist in the Bronchoscopy Suite after you decide the included cell groups are malignant, and “non-small” cell….

…really more like adenocarcinoma on the morphology, if you had to bet.



You comment further that only one TBBx sample has tumor and not much at that.

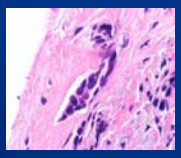
The pulmonologist thanks you for your help and promises to get more samples.



The next day, you attempt IHC to confirm lung origin. No additional biopsies received.

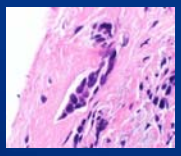
Results: TTF-1 neg, CK7 pos

Napsin A, CK20, synaptophysin, chromogranin, and p40 …insufficient tumor in the recuts.



After signing the case out as “non-small cell carcinoma, NOS”, the oncologist calls to ask if the tumor could be from the patient’s prior breast cancer… “after all, that was the clinical question”.

…and if you think it is, please test for Her2.



…but if you really think this is more like a lung primary, could you send it to Bill Travis for a more accurate classification?

And of course, because of those liver nodules… we will need EGFR, ALK1, ROS1 and a NextGen sequencing panel….ASAP!

If this scenario sounds familiar, you are not alone.

The problem is most often a result of a “failure to communicate”.

However, to the surgeon, pulmonologist, interventional radiologist, oncologist…and even the molecular laboratory, this is a pathologist problem.

To these “upstream clients”, we are judged responsible for making sure that:

a. The sample is ample.
b. The diagnosis is accurate.
c. The immunohistochemistry is thorough.
d. The specimen is appropriately triaged for “all appropriate” special studies.
e. A composite final report goes to all relevant parties.

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Lung Cancer: The Problem

- 2014 estimated 224,210 new cases
- By 2019 only 40,000 of these will be alive
- Approximately 437 people die of lung cancer every day
- Only 25% of lung cancer is surgically removable for intended cure at time of diagnosis

Siegel R, et al., CA Cancer J Clin 2014; 64;9-29

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1970

"Lung cancer offers a challenge for earlier diagnosis and better treatment results.

At present lung cancer is recognized late.

Opportunities to improve survival are through early detection, accurate diagnosis, absolute localization, and curative therapy."

National Institutes for Health Conference
Lung Cancer: Perspectives and Prospects
Carbone, et al. Annals of Internal Medicine 73(6):1006

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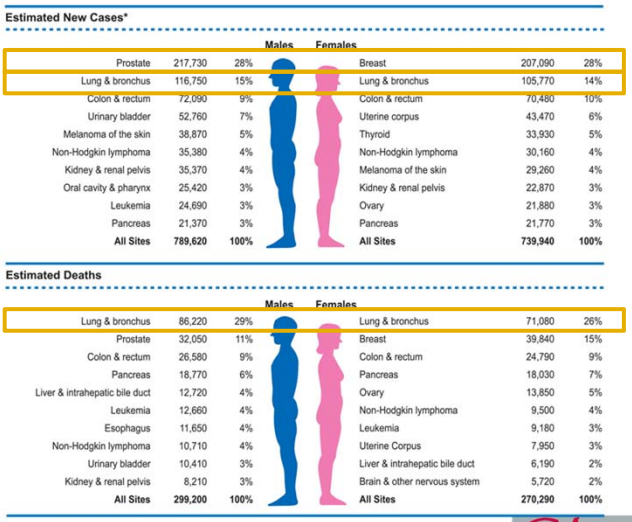
FIGURE 1 Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, 2010



Estimated New Cases*

Males				Females		
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All Sites	**789,620**	**100%**		**All Sites**	**739,940**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**		**All Sites**	**270,290**	**100%**

From Jemal, A. et al.
CA Cancer J Clin 2010;0:caac.20073v1

CA A Cancer Journal for Clinicians

Various Cancers: 5 year Survival (%)

	1960-63	2001-07
Lung	8	16*
Colon	43	64*
Breast	63	89*
Prostate	50	99*

*(P<0.05)

Landis SH, et al., CA Cancer J Clin 1999;49:8-31
Siegel R, et al., CA Cancer J Clin 2012;62:10-29

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Primary Lung Carcinoma: Classification

Non-Small Cell Carcinoma (80%)

Adenocarcinoma	50%
Squamous Cell Carcinoma	20%
Large Cell Carcinoma	10%

Chemoresistant
Surgically treated if possible

Small Cell Carcinoma (20%)

Small cell carcinoma	20%

Chemosensitive
Not treated surgically

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Immunohistochemical Profiles of Lung Cancer

Adenocarcinoma:
CK7, TTF1, Napsin A

Squamous Cell Carcinoma:
PanCK, CK5/6, p40, p63

Small Cell Carcinoma:
PanCK, TTF1, Synaptophysin (+/-), Chromogranin (+/-)

Large Cell Neuroendocrine Ca
PanCK, TTF-1, chromogranin, synaptophysin, Napsin A (+/-)

Large Cell Carcinoma:
PanCK

Mucoepidermoid Carcinoma:
CK5/6, CK7, p63/40, MAML2

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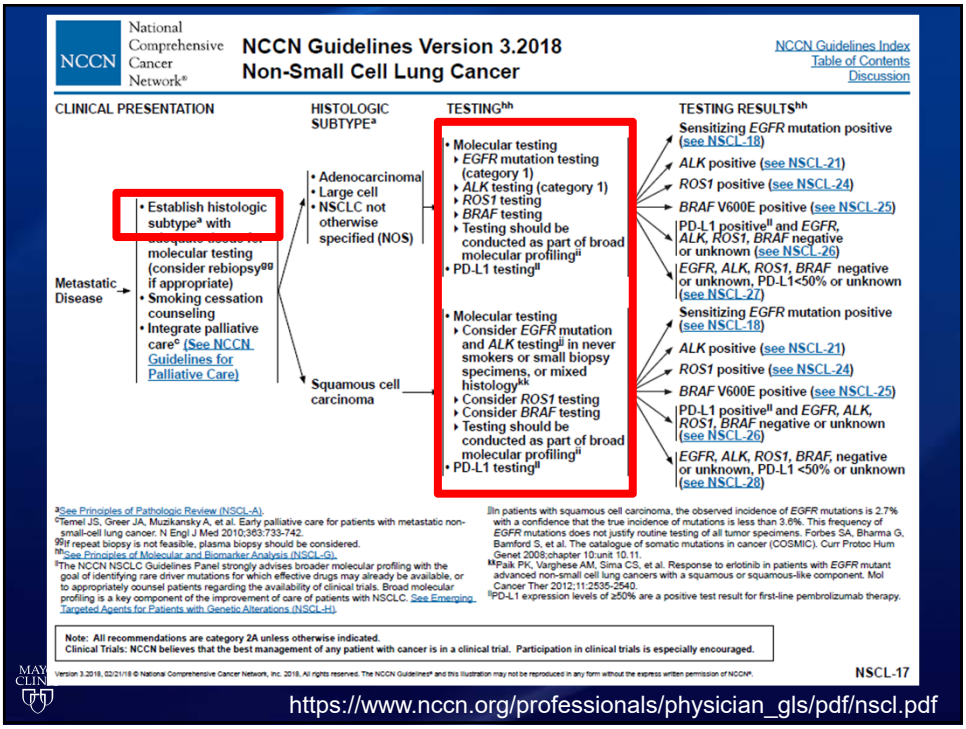

https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

DIAGNOSIS

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Morphological diagnosis superseded by molecular profile?

Molecular profile

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If oncologists were performing biopsies the "samples might be more ample"!

In the current paradigm, we become the oncologist's surrogate at FS and ROSE. Unfortunately, we are rarely privy to the therapeutic options for a given patient at the time of biopsy.

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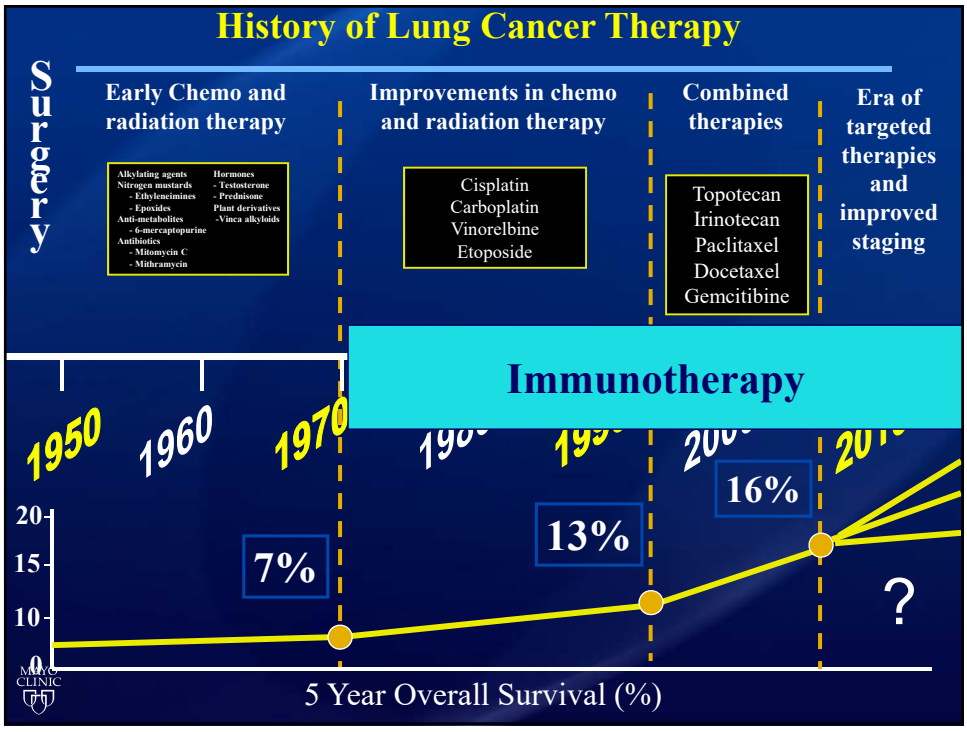
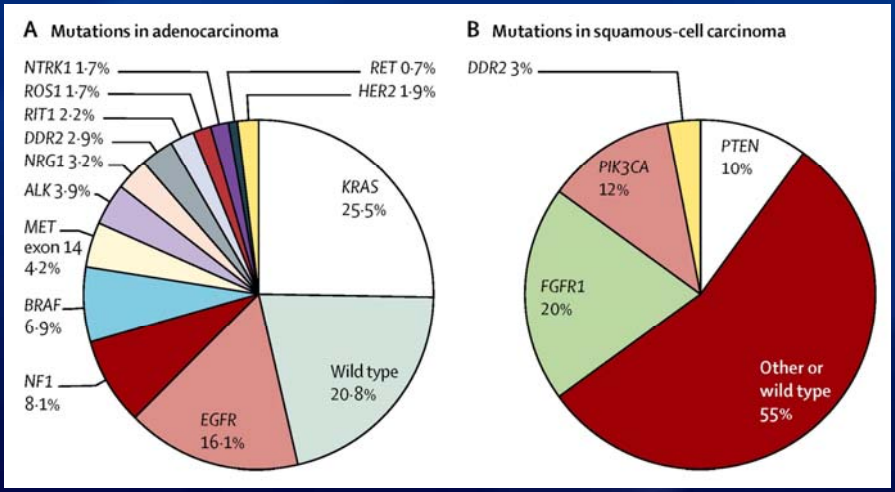


Mutations in NSCLC



Rosell R and Karachaliou N. Large-scale screening for somatic mutations in lung cancer. Lancet. 2016 Apr 2;387(10026):1354-6.

Driver Mutations Define Treatment Options

- Testing for *EGFR* and *BRAF* mutations and *ALK* and *ROS1* rearrangements now standard
  - *KRAS, HER2, RET*, *PIK3CA*, others can define trial eligibility & potential treatments
- Resistance essentially universal due to acquisition of additional mutations
  - Bx at progression can guide next steps
- Tissue bx is invasive, and amount of tissue is often limited
- "Liquid bxs" could overcome limitations

What is a “Liquid Biopsy”?

Biopsy: “An examination of tissue removed from a living body to discover the presence, cause, or extent of a disease”
---Oxford English Dictionary

Liquid biopsy: An examination of liquid removed from a living body to discover the presence, cause, or extent of a disease?

walmart.com

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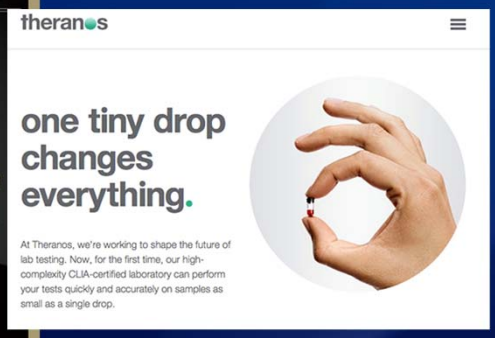
forbes.com



theranos.com

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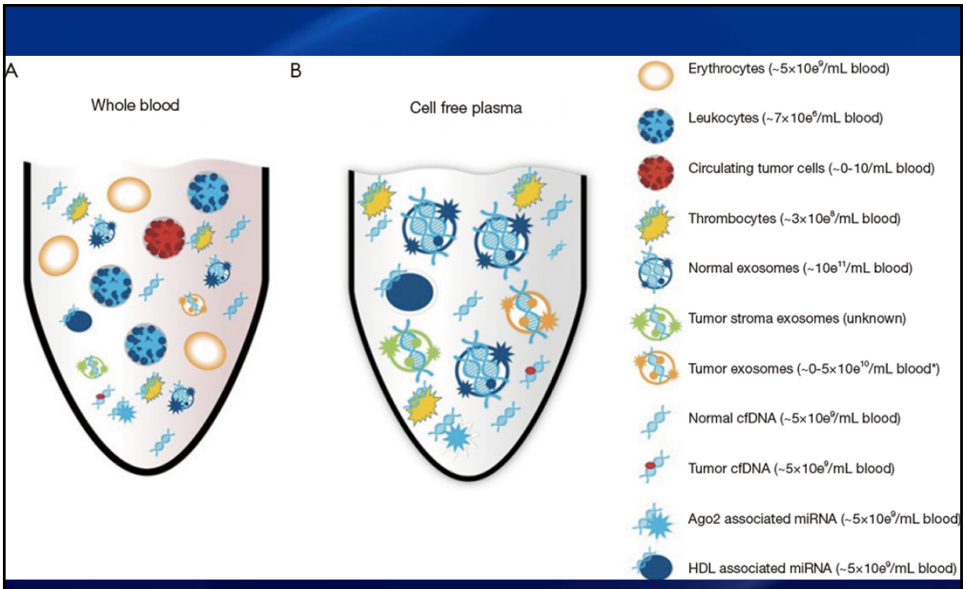
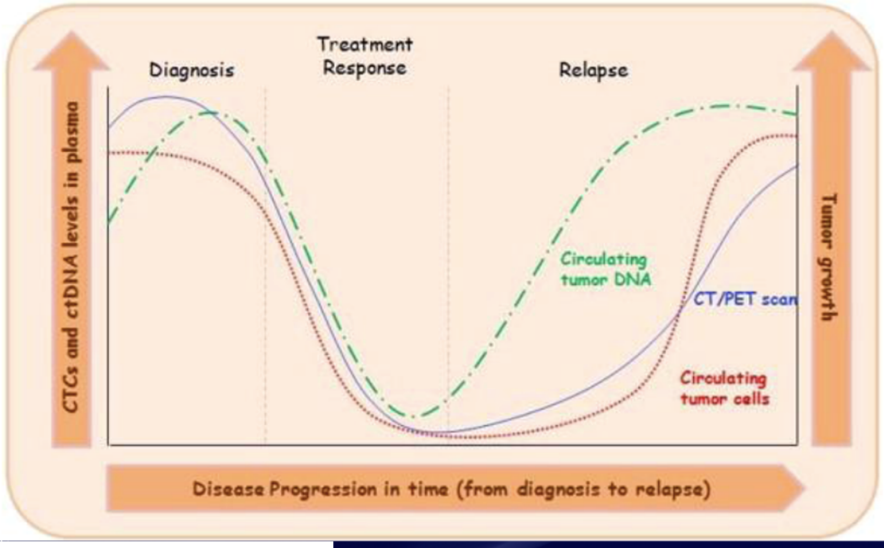
What is a “Liquid Biopsy”?

- Misnomer?
- Sexy marketing term?
- Blood-based assay to capture and analyze:
  - Circulating cell-free DNA (cfDNA)
  - Circulating tumor cells
  - Circulating cell-free RNA and microRNA



Brock G, et al. Liquid biopsy for cancer screening, patient stratification and monitoring. Transl Cancer Res 2015;4(3):280-290. doi: 10.3978/j.issn.2218-676X.2015.06.05

Comparison Between CTC and ctDNA



Ilie et al, Ann Transl Med, 2014

Advantages of "Liquid Biopsy"

- Easier to obtain than tissue bx
- Non-invasive
- Inexpensive

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Potential Applications for “Liquid Bx”

Profiling mutations
Profiling acquired resistance mutations
Monitoring treatment response earlier
Monitoring for acquisition of resistance
Assessing tumor heterogeneity
Prognostic and predictive applications?
Primary diagnosis?
Screening?

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Morphology Still Matters!

By Ryan E. Poplin, public domain, monarch butterfly, commons.wikimedia.org

By Thomas Bresson, public domain, monarch butterfly, commons.wikimedia.org

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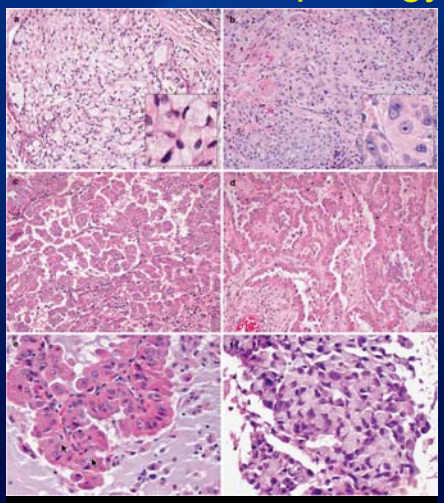
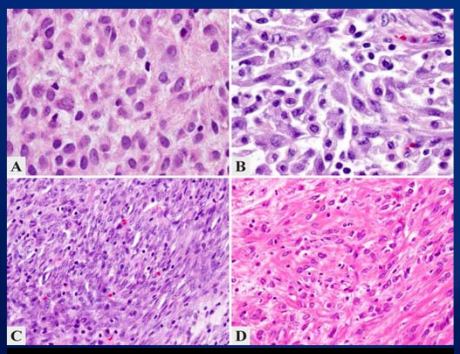
Morphology Still Matters!



Pulmonary adenocarcinoma with EML4-ALK

Nishino M et al., Mod Pathol 2012 Nov;25(11):1462-72.



Inflammatory myofibroblastic tumor of lung with EML4-ALK

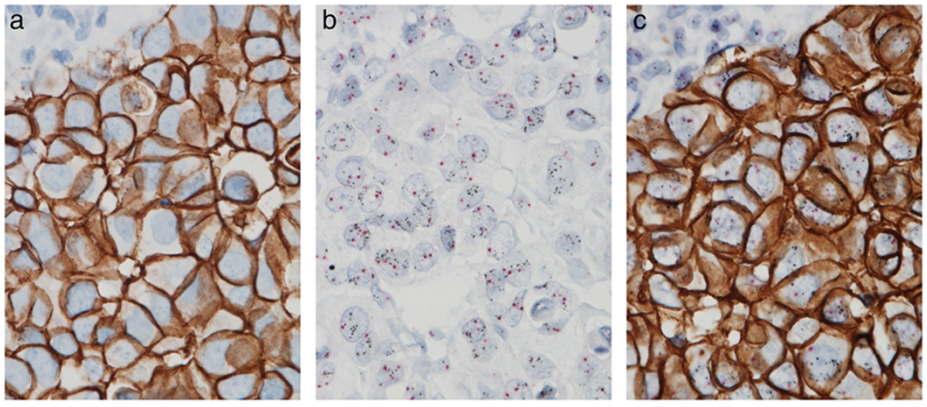
Antonescu CR et al., Am J Surg Pathol 2015 Jul;39(7):957-67.

Morphology Still Matters!

A few neoplasms with *BRAF*^{V600E} mutation:

Lung adenocarcinoma
Papillary thyroid carcinoma
Colorectal adenocarcinoma
Melanoma
Ovarian serous carcinoma
Hairy cell leukemia
Acute lymphoblastic leukemia
Langerhans cell histiocytosis
Erdheim-Chester disease
Papillary craniopharyngioma
Pleomorphic xanthroastrocytoma
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Subependymal giant cell astrocytoma

Morphology Still Matters!



Nitta H et al., Pathol Int 2016 Jun;66(6):313-24.

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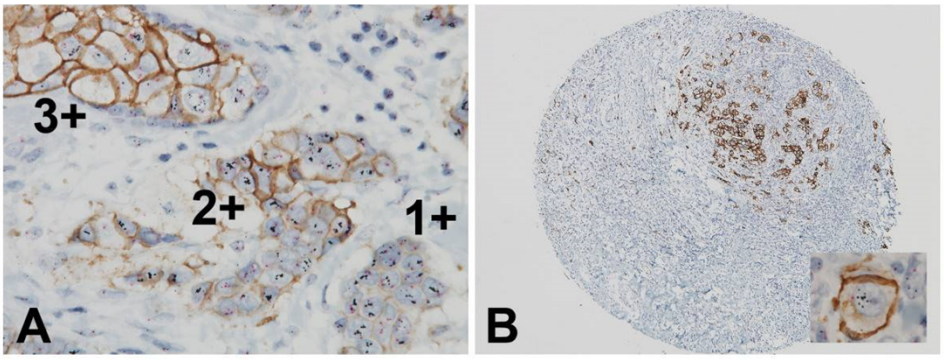
Morphology Still Matters!



Nitta H et al., Diagn Pathol 2012 May 30;7:60

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Will "Liquid Biopsy" Replace Conventional Tissue-Based Sampling?

- Probably not anytime soon, especially in pretreatment setting
- Tissue bx provides morphologic context that liquid bx cannot:
  - Tumor type
  - Tumor behavior (lymphatic invasion, proliferation index, etc.)
  - Tumor heterogeneity
  - Gene-protein correlation
- Assessment of immune cell infiltration / PD-L1 requires tissue bx
- Data on efficacy of treatment is based primarily on tissue assays
- Efficacy data based on liquid bx results alone are limited
- Liquid bx has not been validated in the pretreatment setting
- Liquid bx tends to be less sensitive than tissue bx (could cause delays in diagnosis if negative)
- Many lung cancers do NOT have a tumor-specific mutational profile
- Mutational overlap with some hematolymphoid neoplasms

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Will "Liquid Biopsy" Complement Conventional Tissue-Based Sampling?

- Probably, especially after initial diagnosis is confirmed
- Liquid bx is feasible, inexpensive, non-invasive
- Liquid bx appears reflective of tumor status in trials to date
- Serial assessments / monitoring for relapse
- Assessment for acquisition of resistance mutations
- Alternative if tissue is unavailable?
- Rigorous clinical and laboratory validation must occur before liquid biopsies become part of standard practice
- STAY TUNED!!!

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Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Neal I. Lindeman, MD; Philip T. Cagle, MD; Dara L. Aisner, MD, PhD; Maria E. Arcila, MD; Mary Beth Beasley, MD; Eric Bernicker, MD; Carol Colasacco, MLIS, SCT(ASCP); Sanja Dacic, MD, PhD; Fred R. Hirsch, MD, PhD; Keith Kerr, MB, ChB; David J. Kwiatkowski, MD, PhD; Marc Ladanyi, MD; Jan A. Nowak, MD, PhD; Lynette Sholl, MD; Robyn Temple-Smolkin, PhD; Benjamin Solomon, MBBS, PhD; Lesley H. Souter, PhD; Erik Thunnissen, MD, PhD; Ming S. Tsao, MD; Christina B. Ventura, MPH, MT(ASCP); Murry W. Wynes, PhD; Yasushi Yatabe, MD, PhD

progressed after treatment with an ALK-targeted tyrosine kinase inhibitor.

Key Question 5: What is the role of testing for circulating cell-free DNA for lung cancer patients?

15. There is currently insufficient evidence to support the use of circulating cell-free plasma DNA molecular methods for the diagnosis of primary lung adenocarcinoma.	No recommendation
16. In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA assay to identify *EGFR* mutations.	Recommendation
17. Physicians may use cell-free plasma DNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted tyrosine kinase inhibitors; testing of the tumor sample is recommended if the plasma result is negative.	Expert consensus opinion
18. There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of EGFR or other mutations, or the identification of *EGFR* T790M mutations at the time of EGFR TKI resistance.	No recommendation

- Arch Pathol Lab Med, epub 01/23/2018

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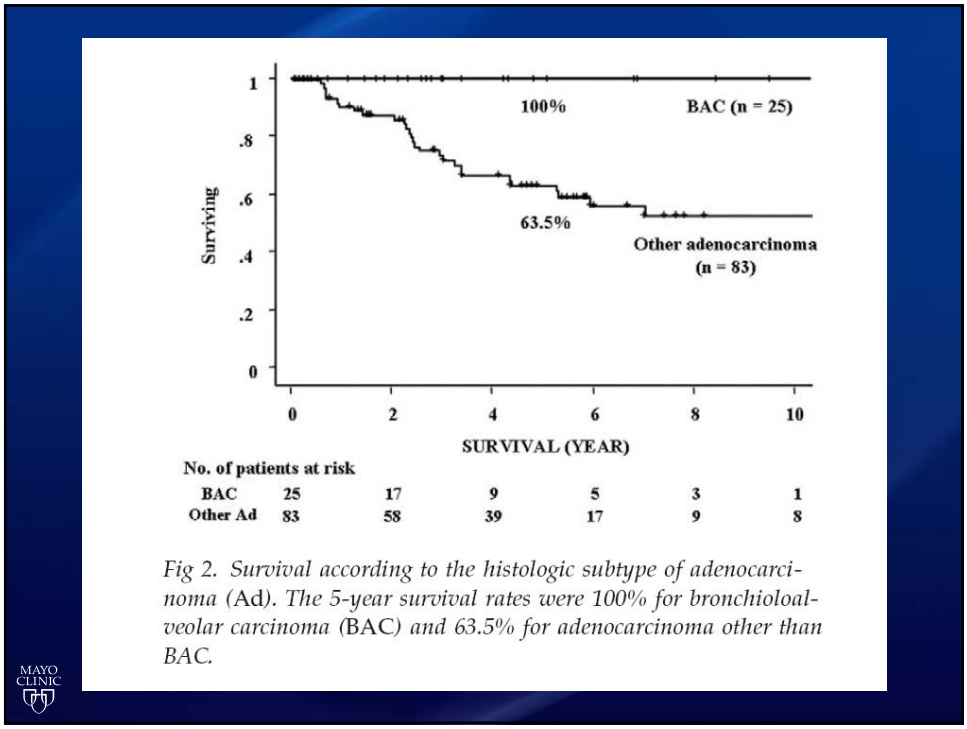

Fig 2. Survival according to the histologic subtype of adenocarcinoma (Ad). The 5-year survival rates were 100% for bronchioloalveolar carcinoma (BAC) and 63.5% for adenocarcinoma other than BAC.

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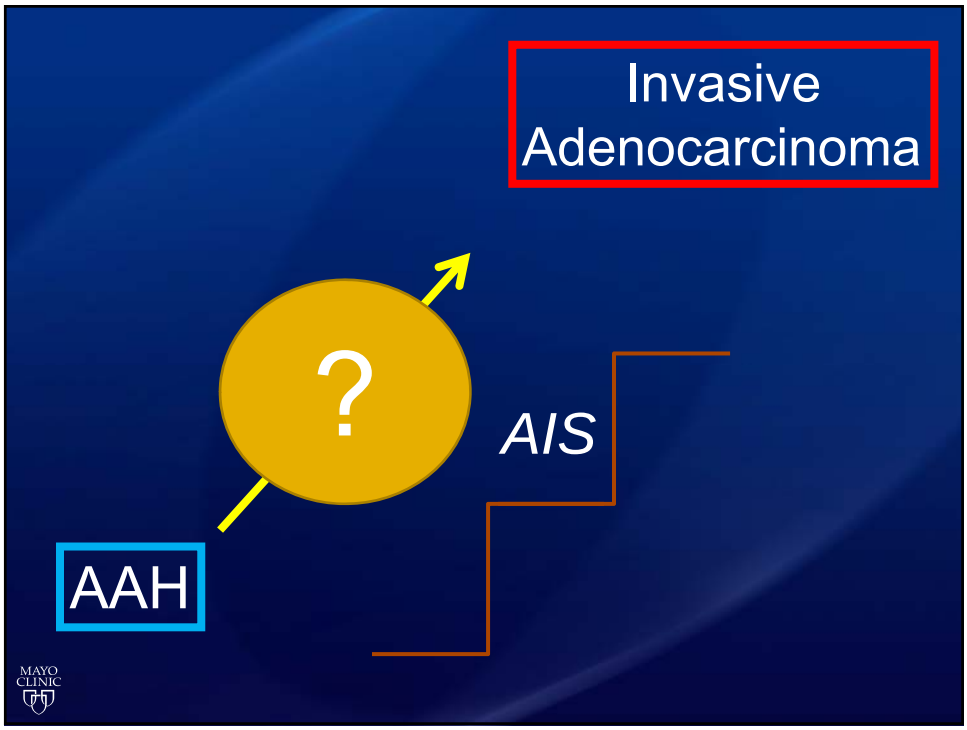

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Rationale for recognizing AIS

- Other cancers have an *in situ* phase
- Might explain why some small singular BACs have better survival
- Lack of consistent relationship between AAH and established invasive adenocarcinomas, suggests a missing link

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IASLC/ATS/ERS INTERNATIONAL MULTIDISCIPLINARY CLASSIFICATION OF LUNG ADENOCARCINOMA

Travis, WD, et al J Thorac Oncol. 2011 Feb;6(2):244-85.

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We recommend discontinuing the use of the term “BAC”. (Strong recommendation, low quality evidence)

For small (≤3.0 cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term

“Adenocarcinoma *in situ*” (AIS)

…that defines patients who should have 100% disease-specific survival, if the lesion is completely resected. (strong recommendation, moderate quality evidence).

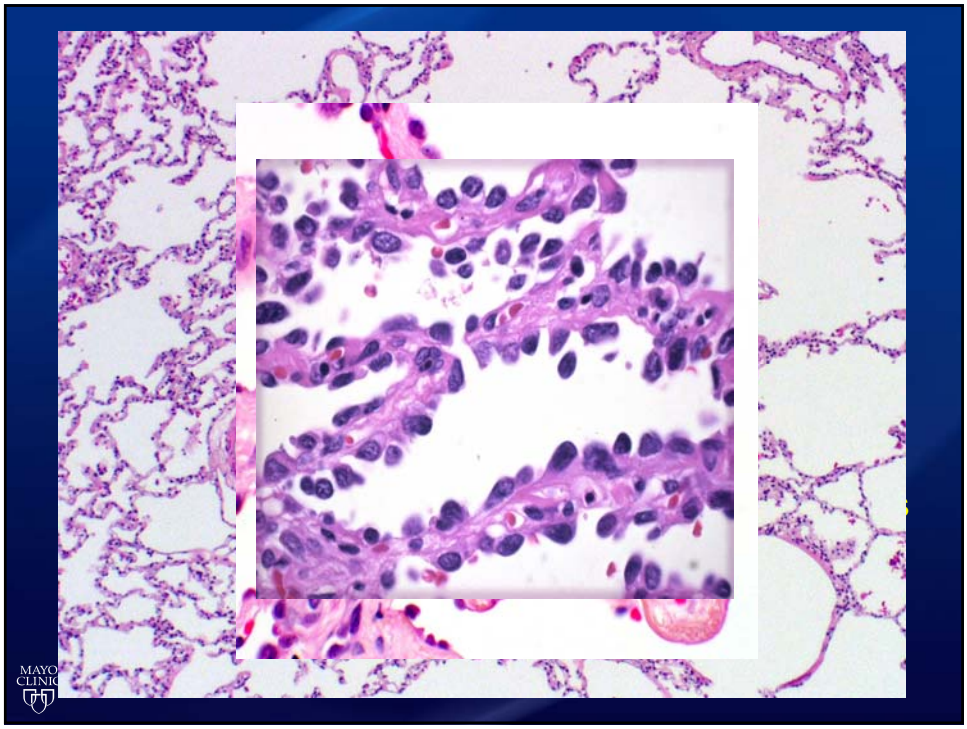
Remark: Most AISs are non-mucinous, rarely are they mucinous.

Adenocarcinomas with predominantly lepidic growth and small foci of invasion measuring 0.5 cm or less, we recommend a new concept of:

“Minimally invasive adenocarcinoma” (MIA)

to define patients who should have near 100% disease specific survival, if completely resected. (strong recommendation, low quality evidence).

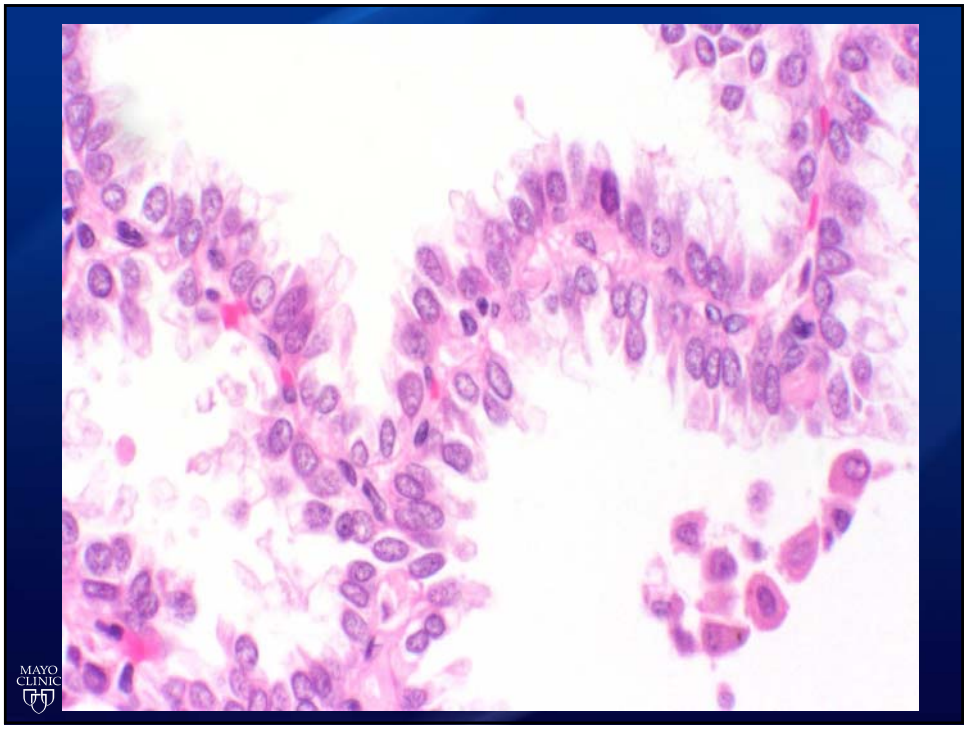
Remark: Most MIAs are non-mucinous, rarely are they mucinous.



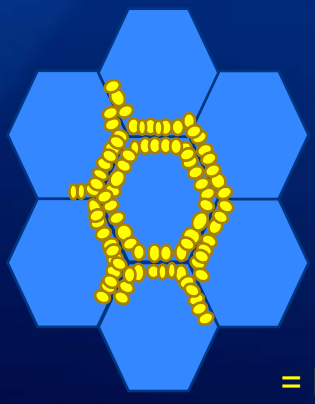
How do we distinguish AAH from AIS?

= lesion 5mm or less

Lung structure intact, minimal atypia, spaces between cells --AAH



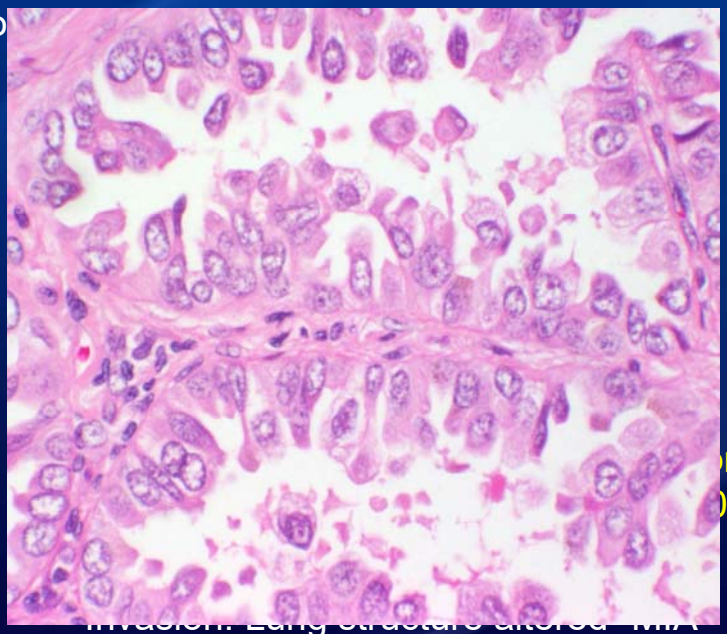
What criteria are required for AIS?



= lesion 3 cm or less

No Invasion. Lung structure intact
larger cells, more overlap -- AIS

Ho



or less
n no
mm

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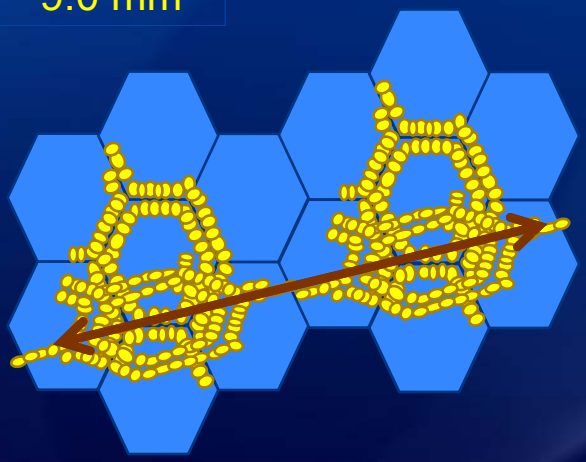
How do we measure “invasion” in MIA?

“9.0 mm”



NO! Do not sum separate foci…

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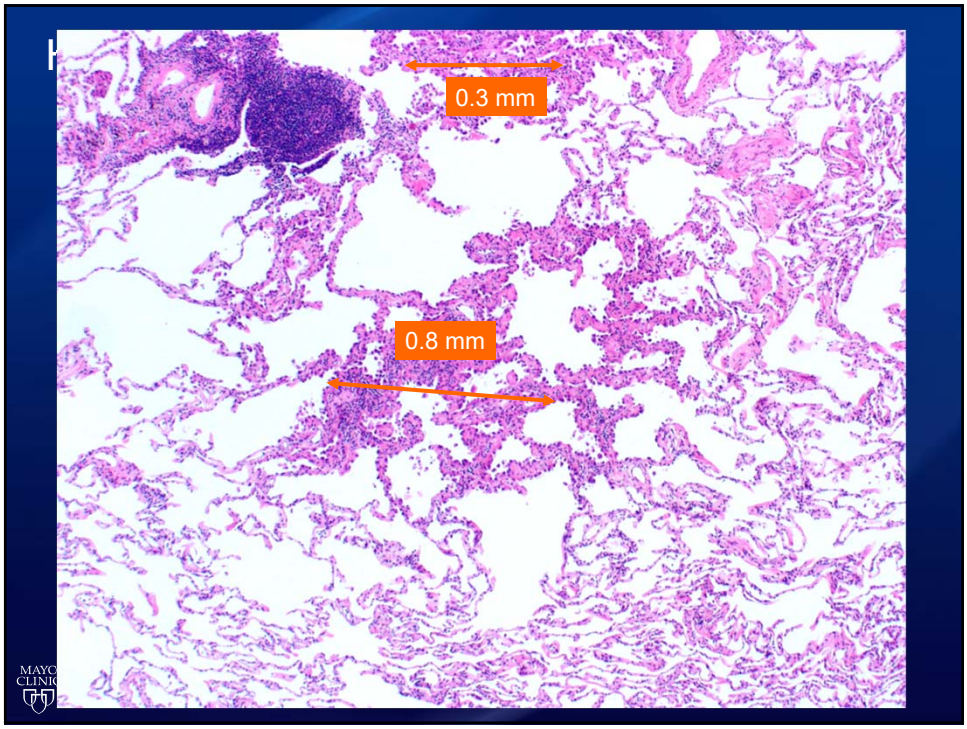
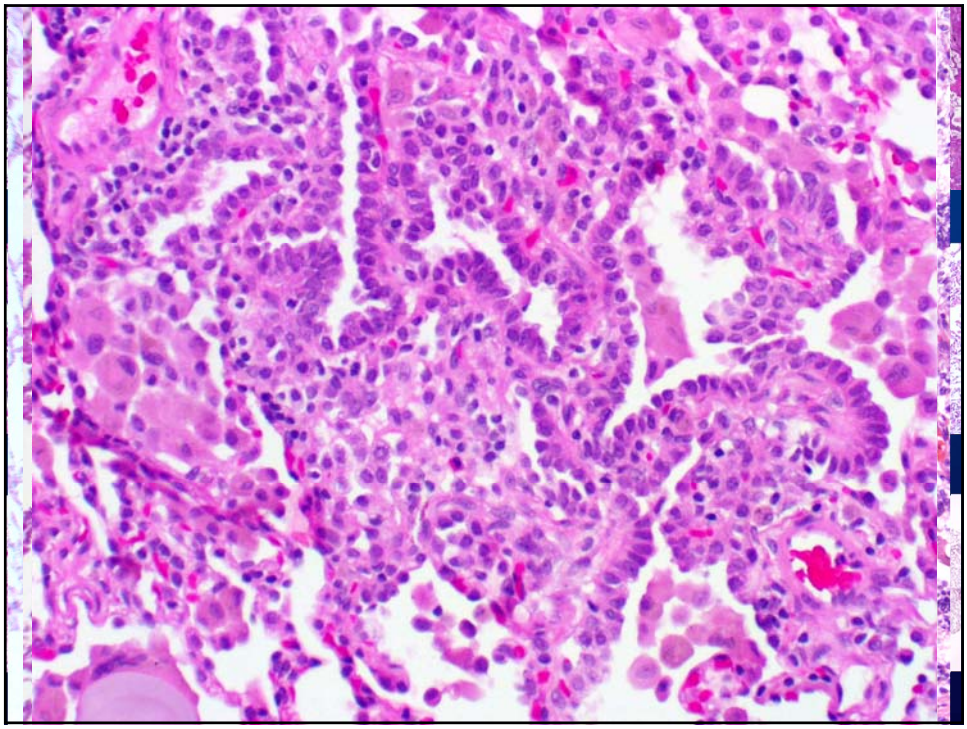


Test your skills



Helpful Tip

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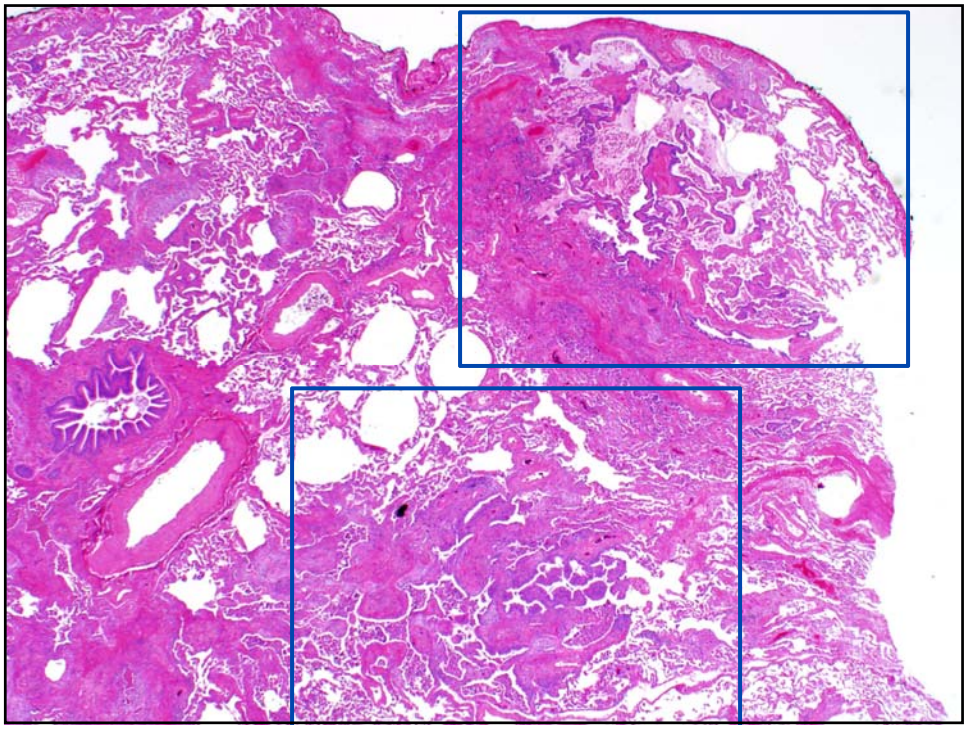
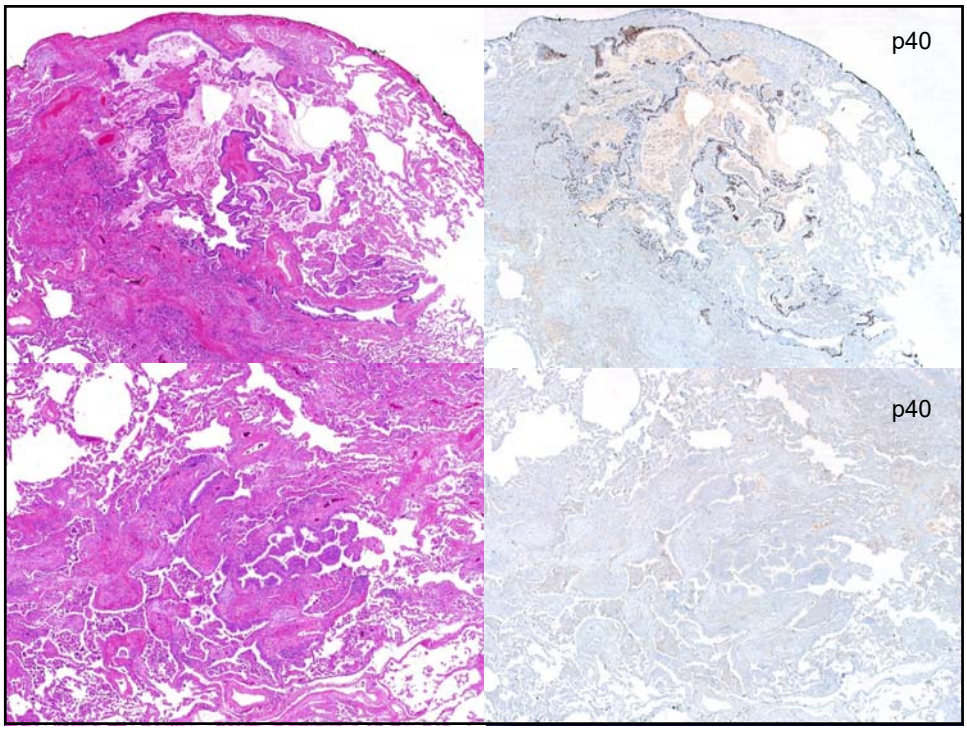
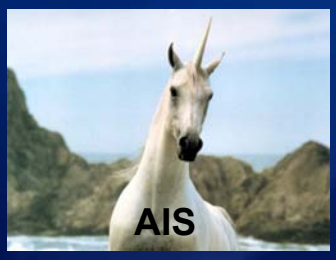



p40
p40

Final Thoughts on AIS

- Lung cancer is still a “bad” cancer in 2018, with poor survival
- **AIS is exceedingly rare** (<0.2% of Stage I tumors) -- essentially ALL resected tumors are at least focally invasive
- Have a very low threshold for diagnosing invasion; err on the side of MORE therapy, follow-up, etc.



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4 Important Thematic Questions

1. If “tissue is the issue” why is the “sample not ample”?
2. Adenocarcinoma in situ: what, when, and how?
3. Am I staging lung cancers accurately?
4. What other new entities should I know about?

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AJCC 8th Edition TNM Staging System

Based on 76,156 patient outcomes IASLC 1999-2010

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7th Edition Staging System (IASLC '07)

J Thorac Oncol. 2007 Aug ;2 (8):706-714; Histopathol 2009, 54:3

6th Ed T/M Descriptor	7th Ed T/M	N0	N1	N2	N3
T1 (≤ 3 cm)	T1a (≤ 2 cm)	IA	IIA	IIIA	IIIB
	T1b (>2 up to 3 cm)	IA	IIA	IIIA	IIIB
T2 (>3 …or larger !)	T2a or PL1, PL2	IB	IIA	IIIA	IIIB
	T2b (5 to < 7 cm)	IIA	IIB	IIIA	IIIB
	T3 (≥ 7 cm)	IIB	IIIA	IIIA	IIIB
T3 invasion	T3 or PL3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral Lung)	T4	IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

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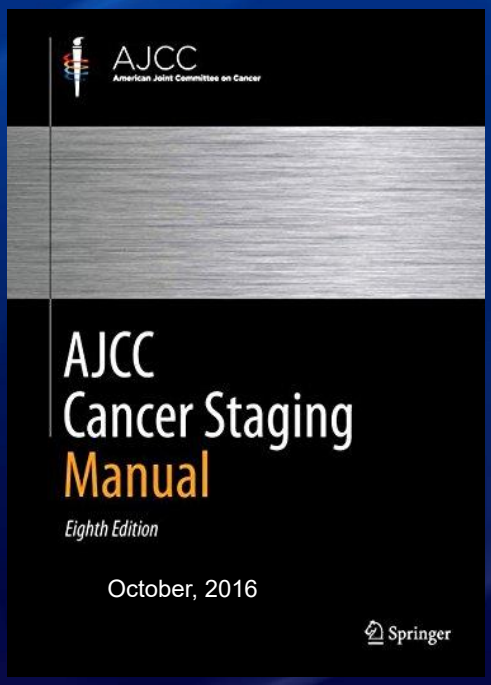

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AJCC 8th Edition Staging System

6th Ed. T/M	7th Ed. T/M	8th Ed. T/M
T1 (≤ 3 cm)	T1a (≤ 2 cm)	T1a <= 1.0 cm
	T1b (>2 up to 3 cm)	T1b > 1.0 cm up to 2 cm
T2 (>3 …or larger !)	T2a (3 to ≤ 5 cm)	T1c > 2.0 cm up to 3 cm
	T2b (5 to < 7 cm)	T2a > 3.0 cm up to 4 cm
	T3 (≥ 7 cm)	T2b > 4.0 cm up to 5 cm
T3 invasion	T3	T3 > 5.0 cm up to 7 cm
T4 (same lobe nodules)	T3	T4 > 7.0 cm
T4 (extension)	T4	
M1 (ipsilateral Lung)	T4	
T4 (pleural effusion)	M1a	Any endobronchial tumor = T2
M1 (contralateral lung)	M1a	With atelectasis or pneumonitis = T2
M1 (distant)	M1b	Invades diaphragm = T4

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AJCC 8th Edition Staging System

6th Ed. T/M	7th Ed. T/M	8th Ed. T/M
T1 (≤ 3 cm)	T1a (≤ 2 cm)	Tis Adenocarcinoma *in situ*
	T1b (>2 up to 3 cm)	T1mi Minimally Invasive Adenocarcinoma
T2 (>3 …or larger !)	T2a (3 to ≤ 5 cm)	T1a <= 1.0 cm
	T2b (5 to < 7 cm)	T1b > 1.0 cm up to 2 cm
	T3 (≥ 7 cm)	T1c > 2.0 cm up to 3 cm
T3 invasion	T3	T2a > 3.0 cm up to 4 cm
T4 (same lobe nodules)	T3	T2b > 4.0 cm up to 5 cm
T4 (extension)	T4	T3 > 5.0 cm up to 7 cm
M1 (ipsilateral Lung)	T4	T4 > 7.0 cm
T4 (pleural effusion)	M1a	Any endobronchial tumor = T2
M1 (contralateral lung)	M1a	With atelectasis or pneumonitis = T2
M1 (distant)	M1b	Invades diaphragm = T4

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Stage = Destiny!

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4 Important Thematic Questions

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New Entities To Know

- NUT carcinoma
- Primary pulmonary myxoid sarcoma

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VOLUME 22 · NUMBER 20 · OCTOBER 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Midline Carcinoma of Children and Young Adults With *NUT* Rearrangement

Christopher A. French, Jeffery L. Kutok, William C. Faquin, Jeffrey A. Toretsky, Cristina R. Antonescu, Constance A. Griffin, Vania Nose, Sara O. Vargas, Mary Moschovi, Fotini Tzortzatou-Stathopoulou, Isao Miyoshi, Antonio R. Perez-Atayde, Jon C. Aster, and Jonathan A. Fletcher

J Clin Oncol. 2004;22:4135-9.

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NUT Carcinoma

- No specific cytologic / histologic features
- Undifferentiated carcinoma, bearing translocation t(15;19) involving NUT gene
  - Small-to-medium sized malignant cells
  - Monotonous round-to-oval nuclei
  - Clear/vesicular cytoplasm
  - Prominent nucleoli
  - Might mimic small cell carcinoma
- +/- Abrupt squamous differentiation

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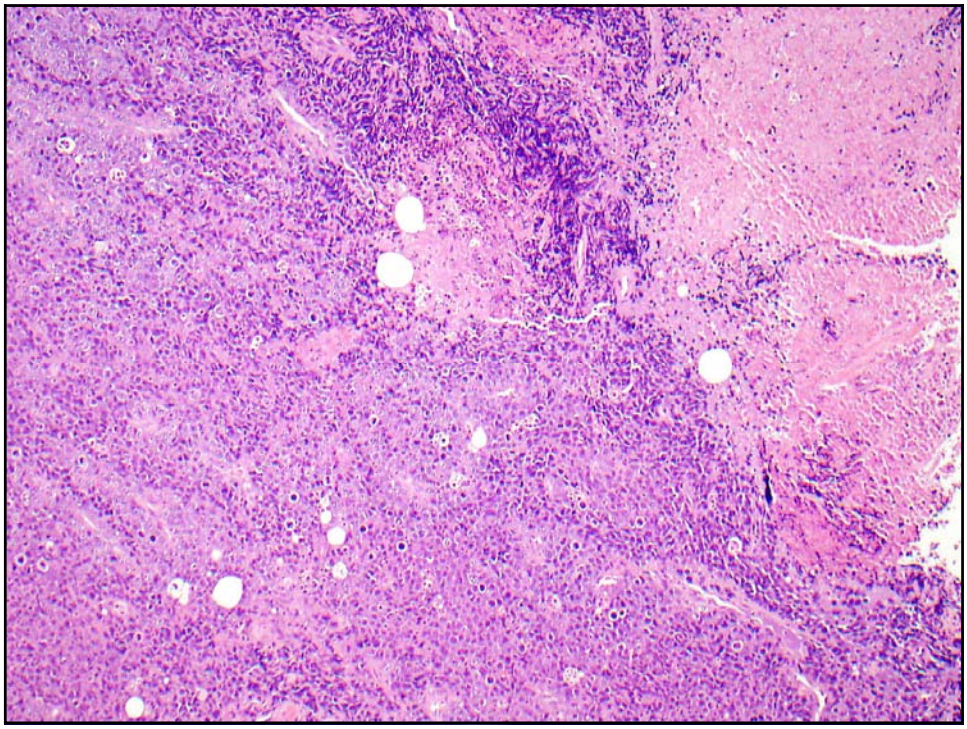
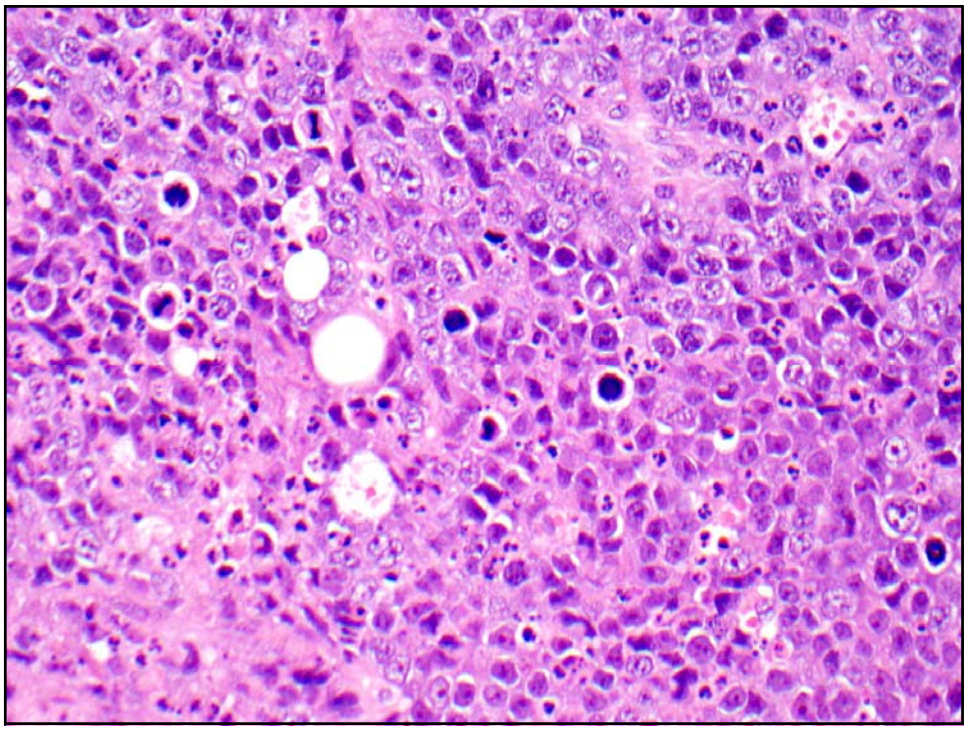
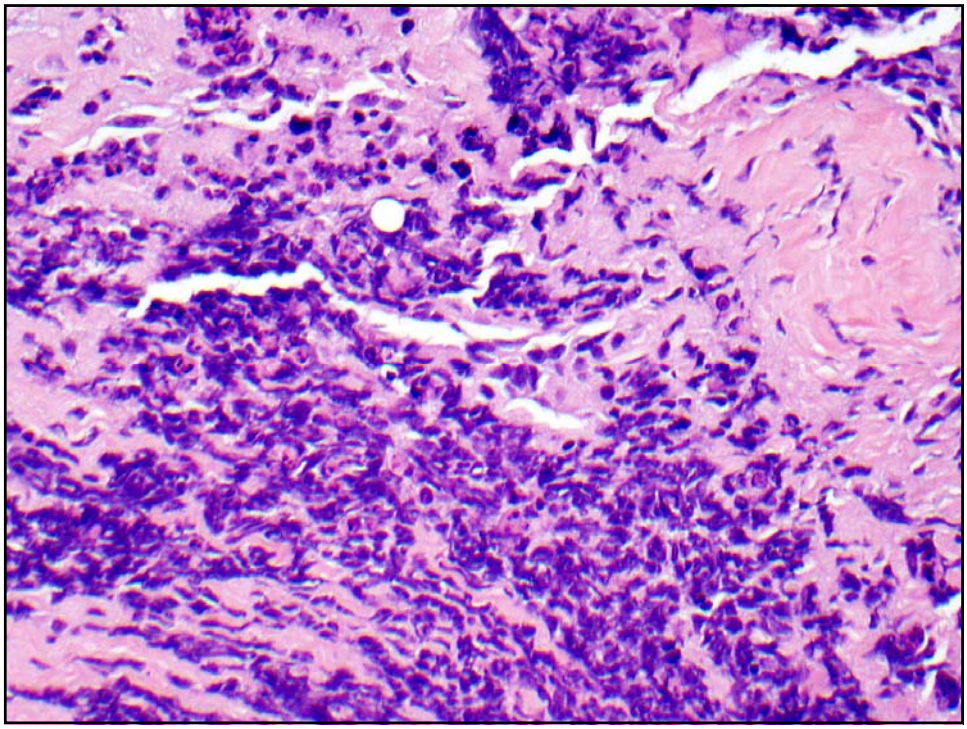
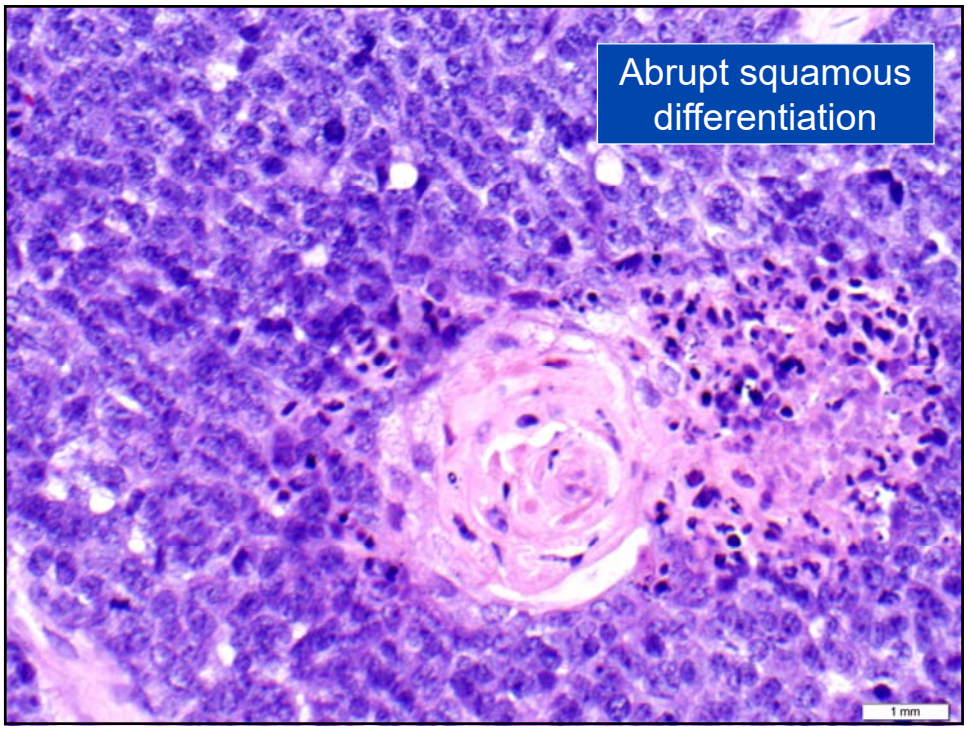
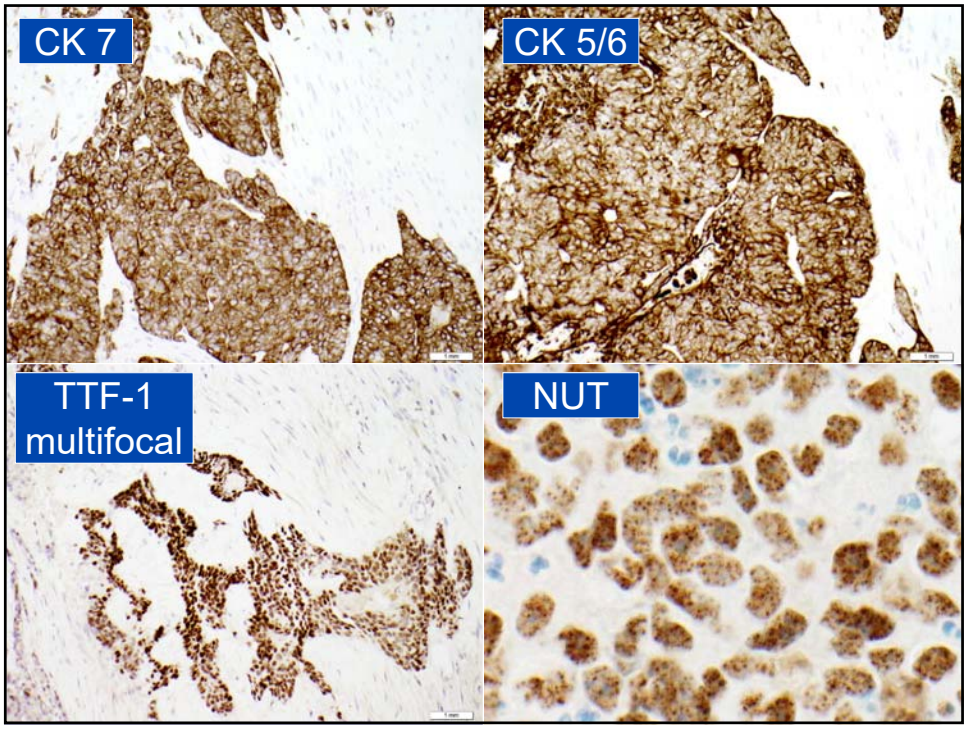
French CA . Annu Rev Pathol 2012. 7: 247-65







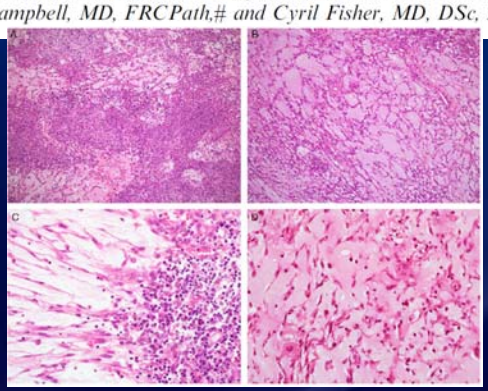

Abrupt squamous differentiation
1 mm



ORIGINAL ARTICLE

Primary Pulmonary Myxoid Sarcoma With *EWSR1-CREB1* Fusion: A New Tumor Entity

Khin Thway, FRCPath, Andrew G. Nicholson, DM, FRCPath,† Kay Lawson, MBBS,† David Gonzalez, PhD,‡ Alexandra Rice, FRCPath,† Bonnie Balzer, MD,§ John Swansbury, FRCPath,‖ Toon Min, PhD,‖ Lisa Thompson, PhD,‡ Kwame Adu-Poku, FRCPath,¶ Anne Campbell, MD, FRCPath,# and Cyril Fisher, MD, DSc, FRCPath**



Am J Surg Pathol 2011;35:1722-1732

Primary Pulmonary Myxoid Sarcoma

- Younger women (30s, 40s)
- Well-circumscribed, lobulated endobronchial mass
- Spindled, stellate, polygonal cells
- Arranged in strands and cords, myxoid stroma
- Mild to moderate atypia, low mitotic rate
- Non-specific immunophenotype
- *EWSR1-CREB1* fusion described in 79%
- Usually indolent but can metastasize and cause death

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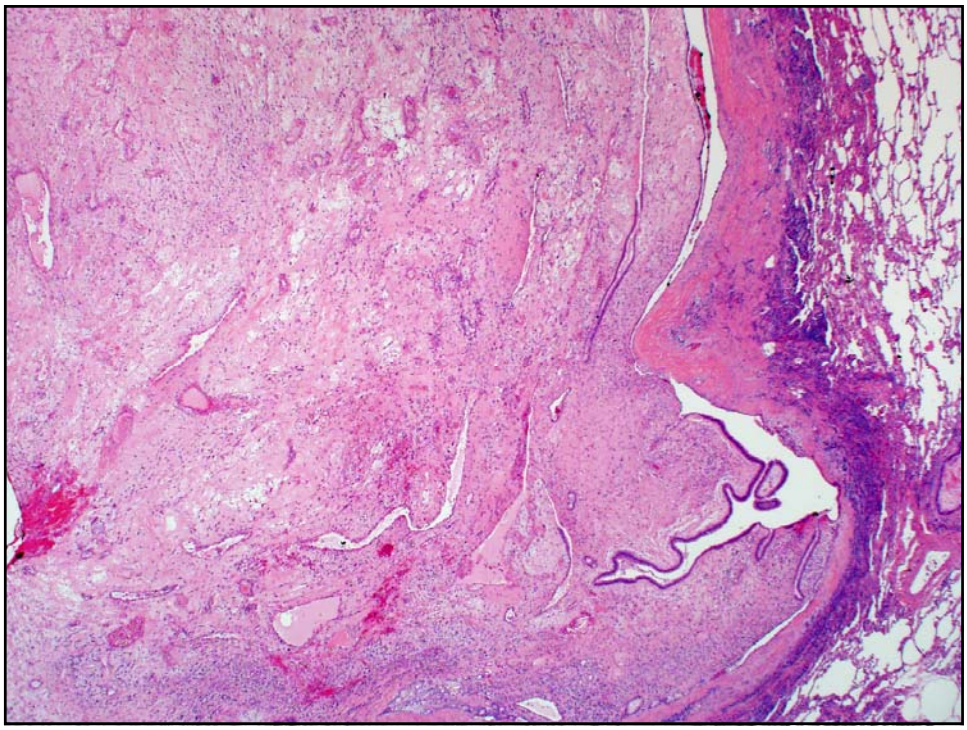

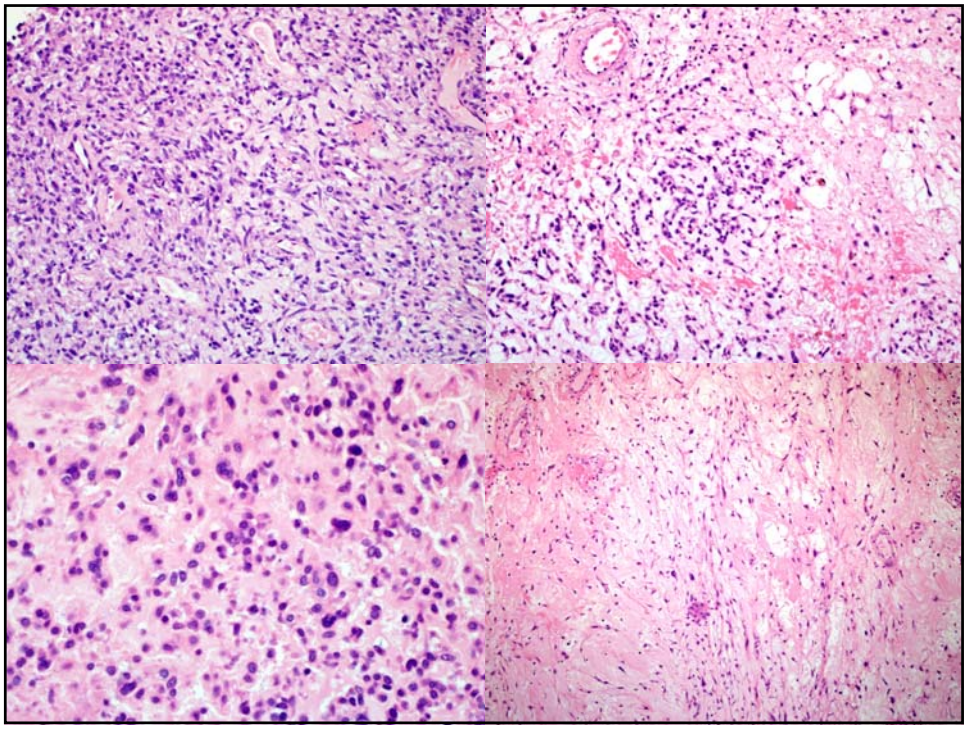

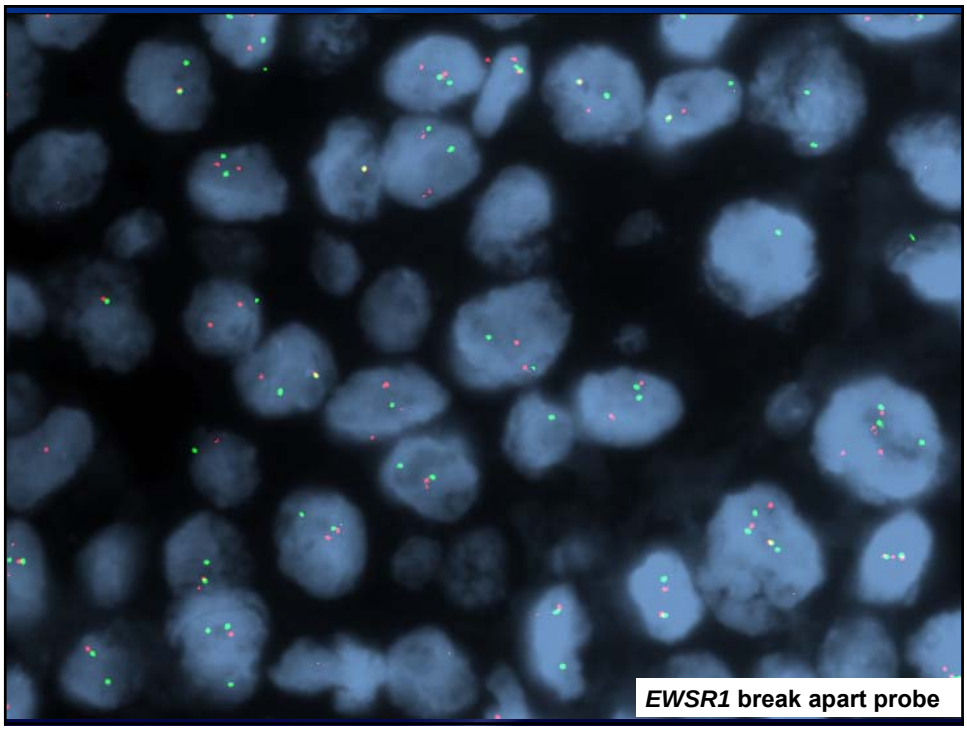
EWSR1 break apart probe

QUESTIONS?