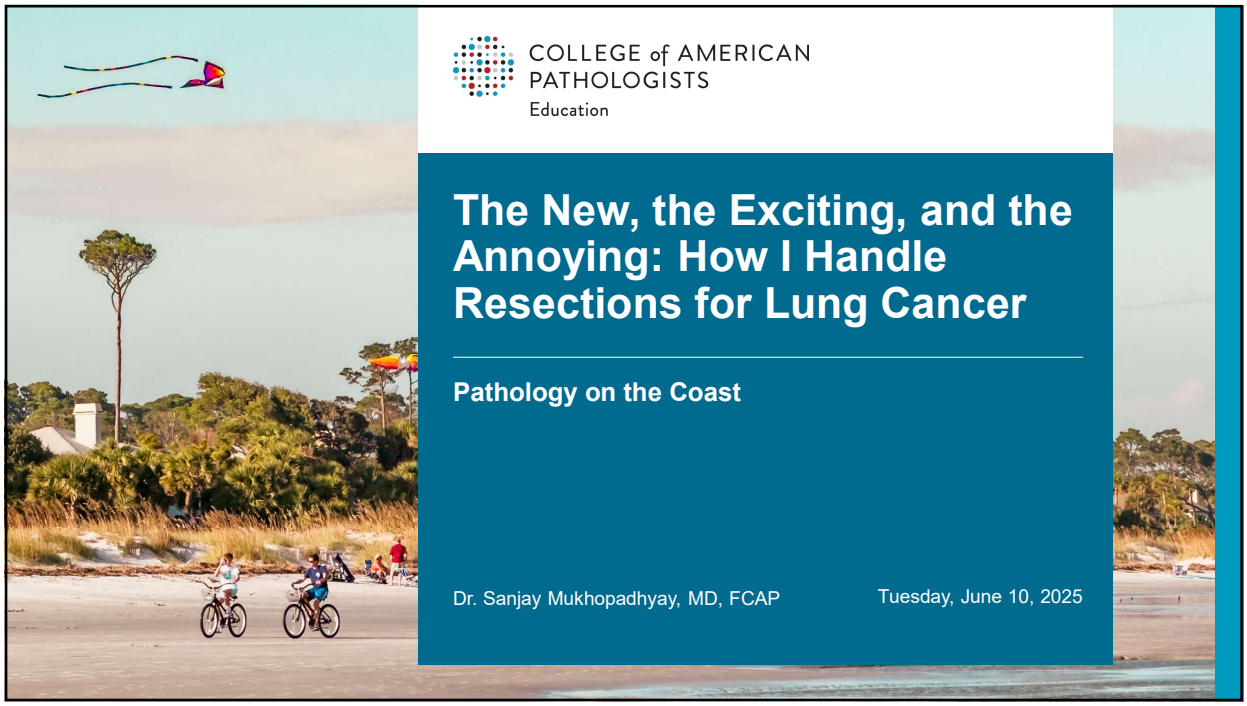

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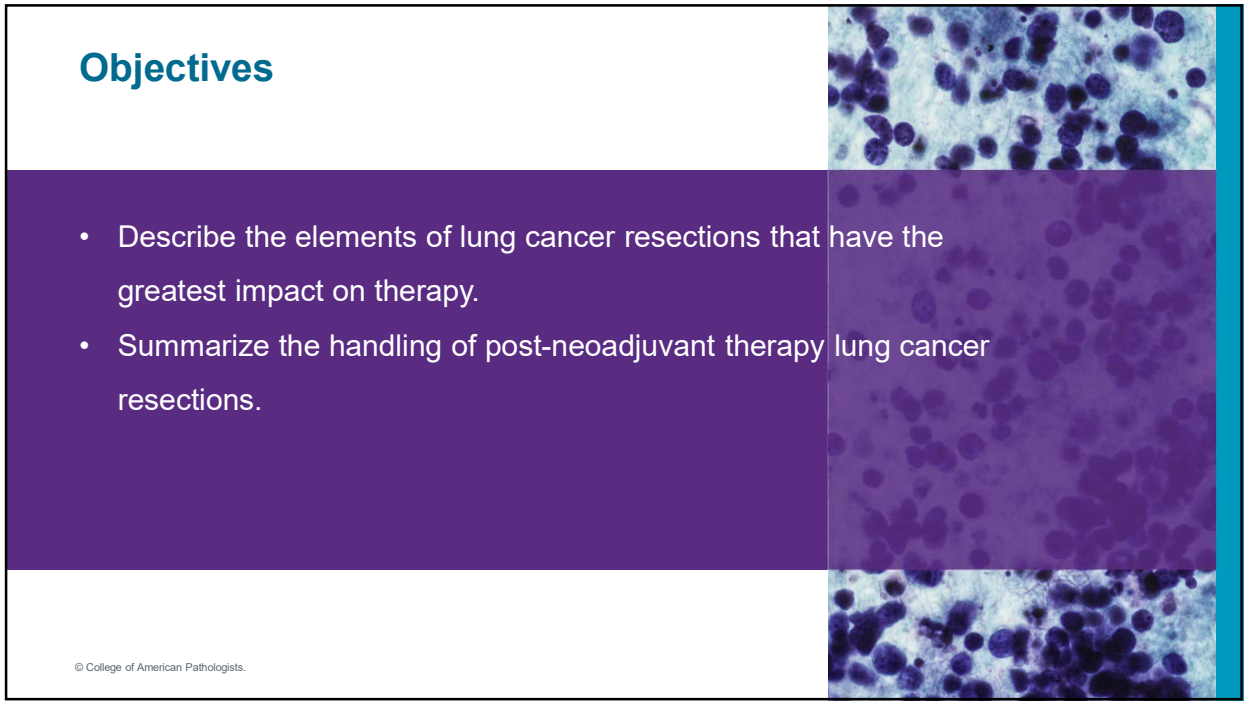


2

I am happy to answer questions about any aspect of lung cancer resection handling and reporting (no matter how routine)

But today's talk will focus on a few special areas

3

LUNG CANCER STAGING AND THERAPY

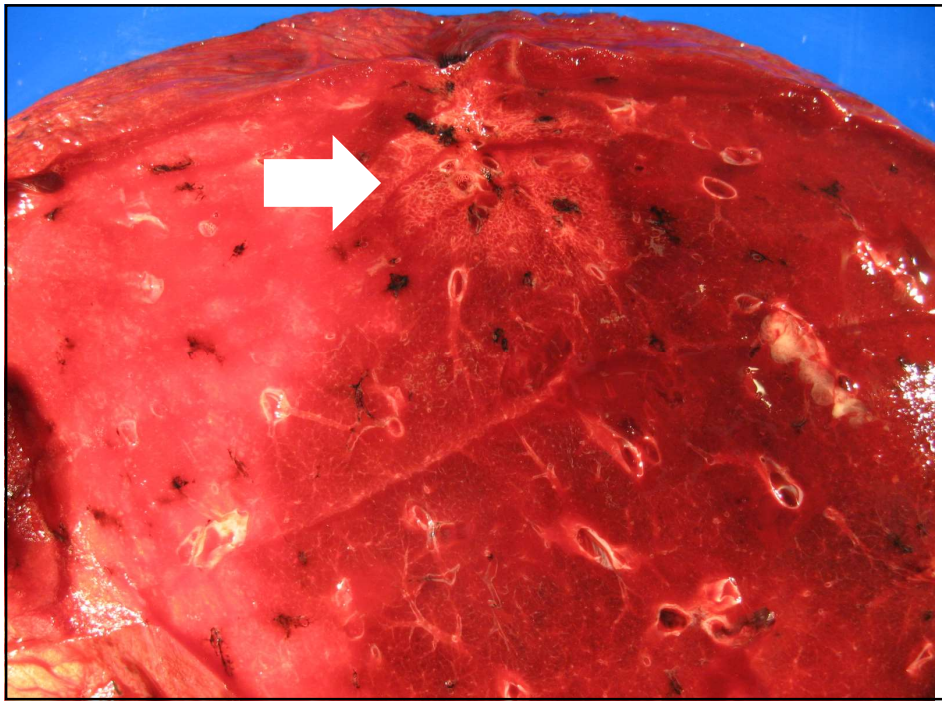
4

pT1
≤3cm
No visceral pleural invasion

Treatment
Lobectomy or wedge resection

Rami-Porta R, et al. Lung. In: AJCC Cancer Staging Manual, 8th edition

5



MINIMALLY INVASIVE ADENOCARCINOMA

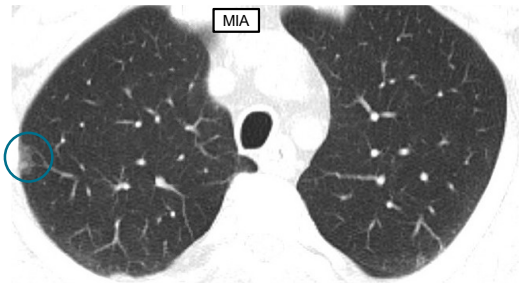
Grossly, these lesions are small, ill-defined and difficult to see

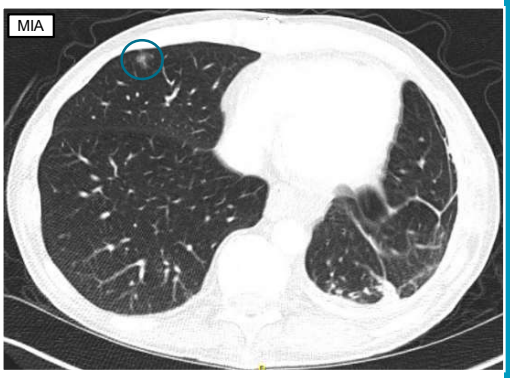
TREATMENT

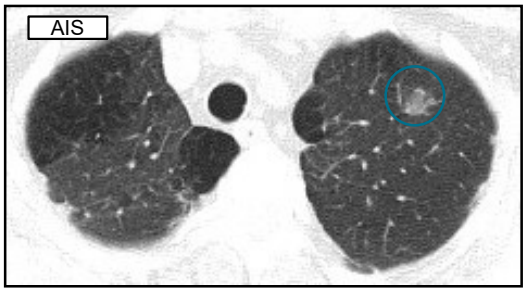
Wedge resection is enough

6

GROUND-GLASS NODULES







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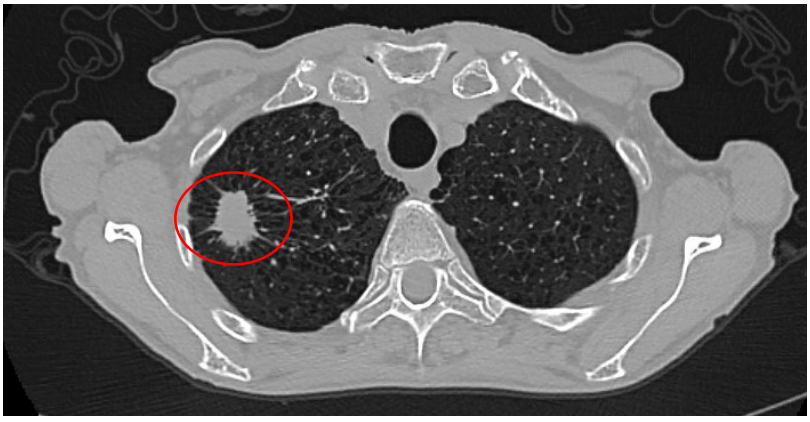
SOLID NODULE



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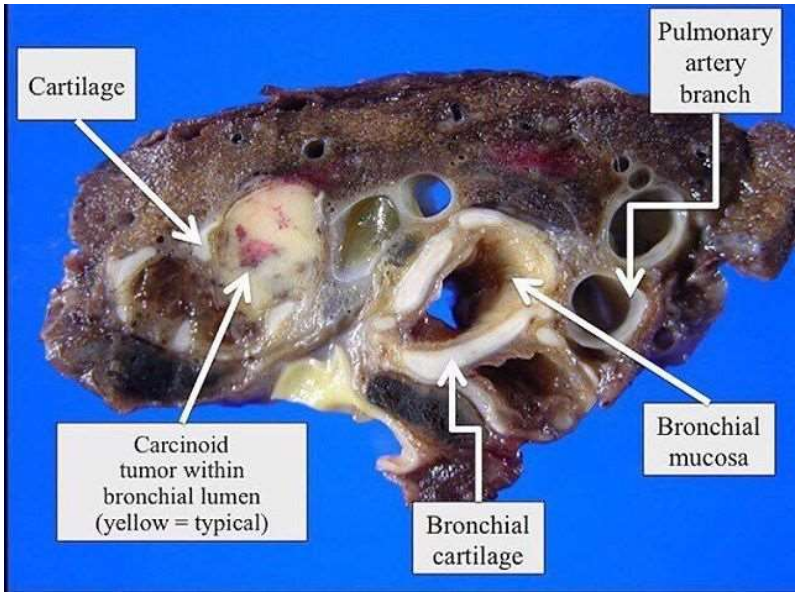
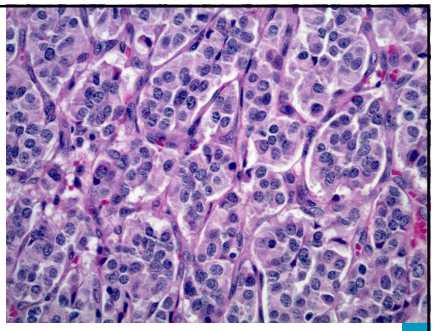
CARCINOID TUMOR





TREATMENT

Low stage: lobectomy (no further treatment needed for most cases)

9

ADENOCARCINOMA

TREATMENT

Low stage: lobectomy (no further treatment needed for most cases)

10

pT2

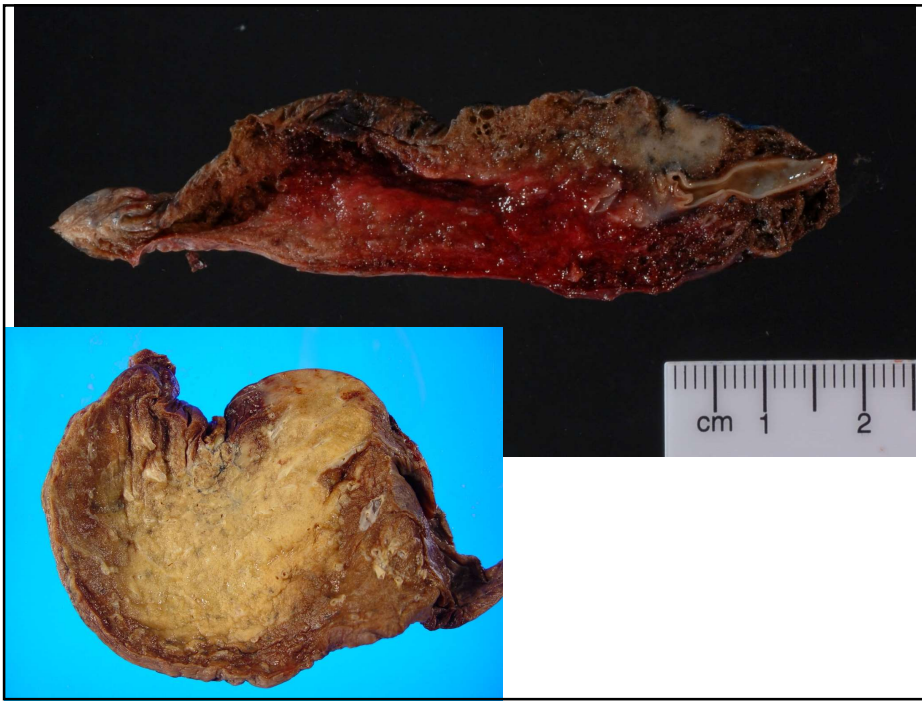
3.1 to 5 cm
OR visceral pleural invasion (pT2a)
OR involves main bronchus

Treatment

Lobectomy
Adjuvant therapy >4 cm, VPI

Rami-Porta R, et al. Lung. In: AJCC Cancer Staging Manual, 8th edition

11



ADENOCARCINOMA

TREATMENT

>4 cm tumor: lobectomy plus adjuvant therapy

12

pT3

5.1 to 7 cm
OR intrapulmonary met within same lobe
OR involves chest wall
OR involves phrenic nerve

Treatment

Lobectomy plus adjuvant therapy (traditional)

13

pT4

>7 cm
OR intrapulmonary met within different lobe on same side

Treatment

Lobectomy + adjuvant therapy (traditional)

Rami-Porta R, et al. Lung. In: AJCC Cancer Staging Manual, 8th edition

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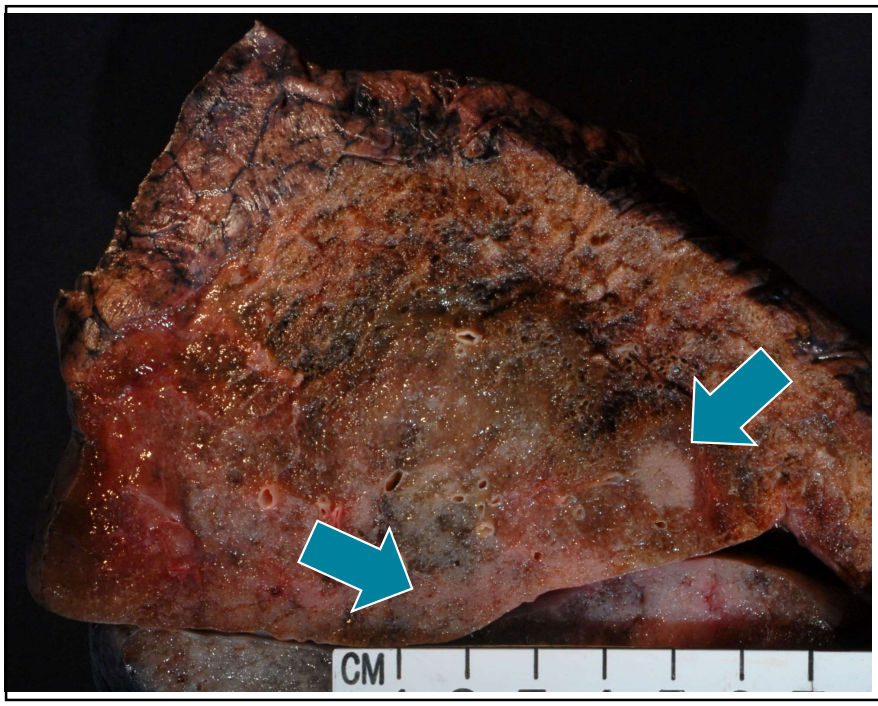


MUCINOUS ADENOCARCINOMA

TREATMENT

Intrapulmonary met: lobectomy plus adjuvant therapy

15

pN1: station 10 (or higher)
pN2: station 9 or lower (7,4,2 etc.)

The lymph nodes you dissect from the lung are N1 nodes

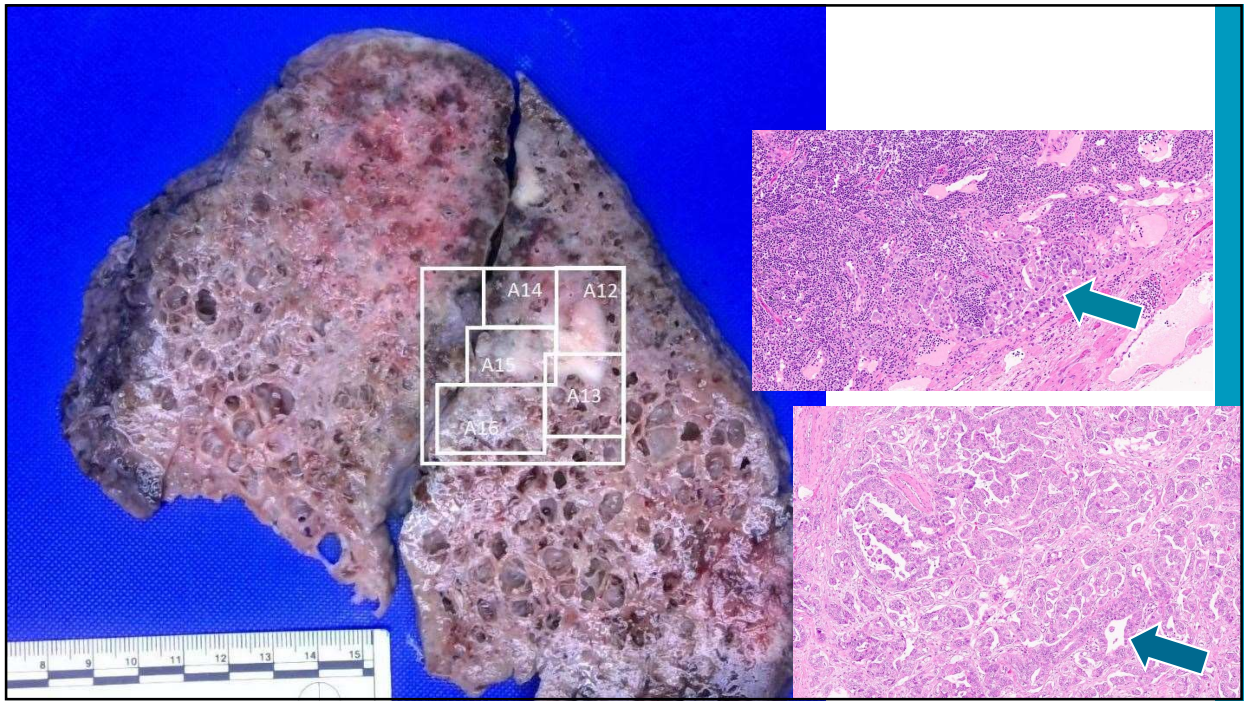
Treatment
Adjuvant therapy (traditional)

16

LYMPH NODES ARE SUPER IMPORTANT!

In lung cancer, <u>any positive lymph node (even one!)</u> you find in a lobectomy specimen buys the patient adjuvant therapy. YOU make a HUGE difference to the patient!

17



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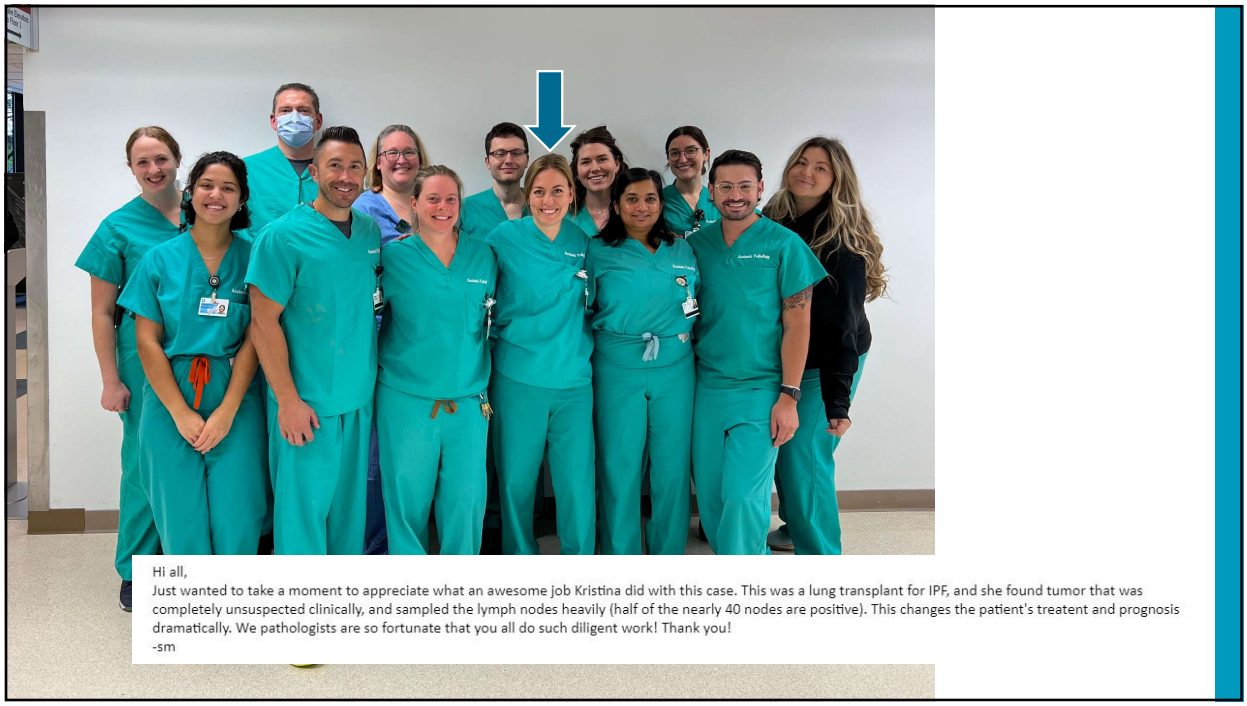


19

pM1
Distant metastases

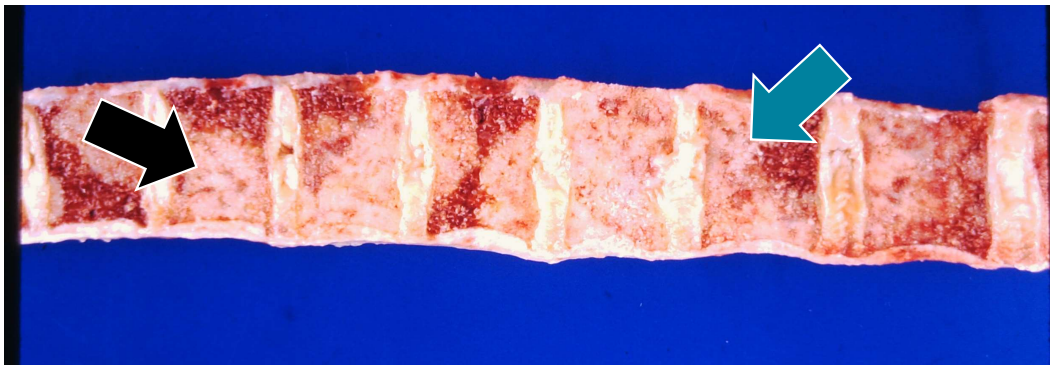
Treatment
NO RESECTION
Systemic therapy (targeted or immunotherapy or chemotherapy)

20

LUNG ADENOCARCINOMA METASTATIC TO VERTEBRA

TREATMENT

Systemic therapy



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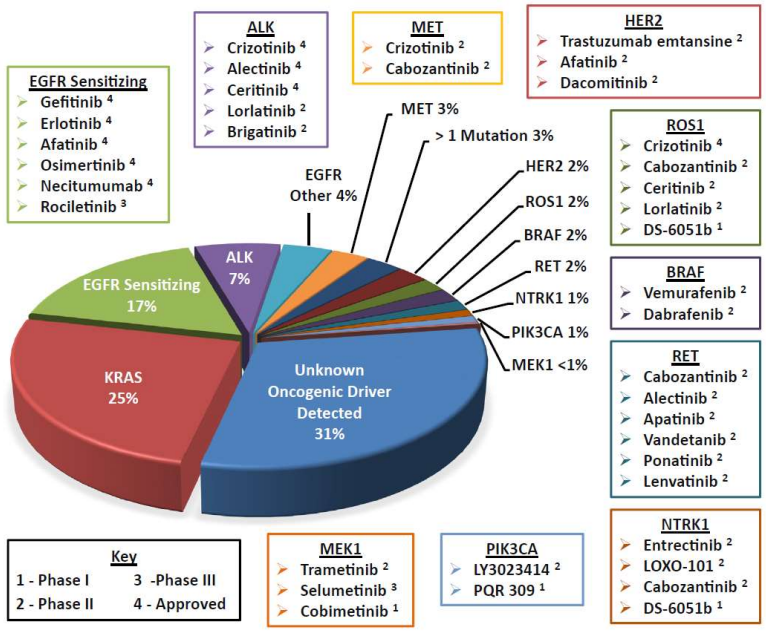
TARGETED THERAPIES FOR LUNG ADENOCARCINOMA IN LATE-STAGE or ADVANCED or METASTATIC DISEASE



Tsao AS, et al. *J Thorac Oncol* 2016;11(5):613-638

22

THE ANNOYING…

23

In 2025, how do you stage a 3.4 cm resected non-mucinous adenocarcinoma in which 50% of the tumor is invasive and 50% is lepidic?

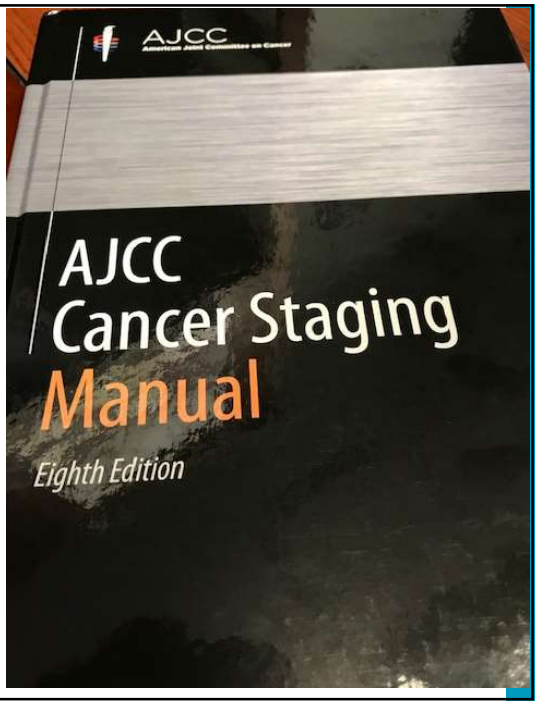
AJCC manual directs us to stage by "invasive size"

24

In non-mucinous lung adenocarcinomas with a lepidic component, AJCC 8th edition directs us to stage by "invasive size" after subtracting the lepidic component

25

"To measure tumor size in part-solid, nonmucinous adenocarcinomas, the recommendation is to follow the TNM rule to consider **only the size of the invasive component** in assigning a T category"



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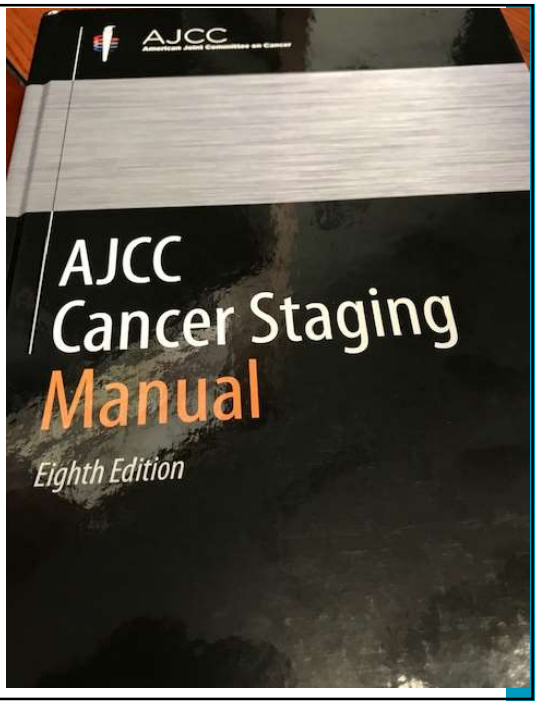
"Therefore, a lesion consisting of a 15-mm part-solid opacity with a 7-mm solid component would be classified as a cT1a lesion, because its solid component, excluding the ground-glass component, is less than 10 mm in greatest dimension"

Rami-Porta R, et al. Lung. In: AJCC Cancer Staging Manual, 8th edition



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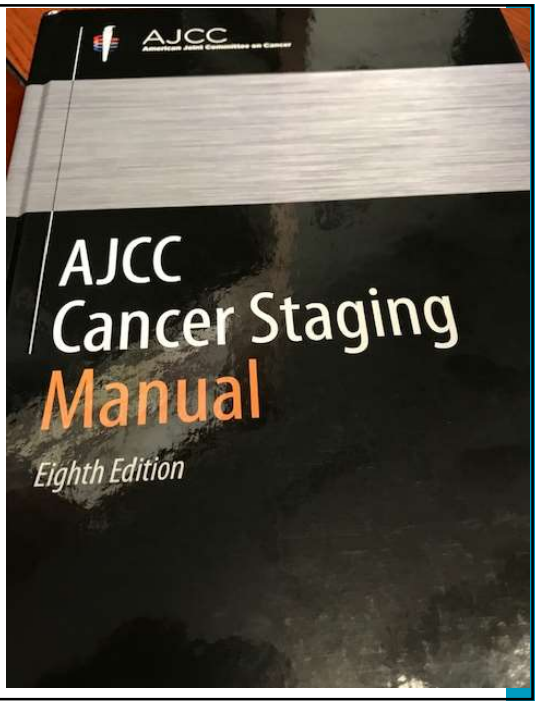
"Although this rule has been in place since 2001, **until now it has not been applied** in lung adenocarcinoma"

Rami-Porta R, et al. Lung. In: AJCC Cancer Staging Manual, 8th edition



28

THE NEW…

29

NEOADJUVANT AND ADJUVANT THERAPIES IN LUNG CANCER

30

NOW LET'S DISCUSS ADVANCES IN THE TREATMENT OF INTERMEDIATE STAGE LUNG CANCERS. THIS TYPE OF LOCALLY ADVANCED TUMOR MAY NOT HAVE BEEN RESECTABLE IN THE PAST

31

NEW NEOADJUVANT AND ADJUVANT THERAPY TRIALS HAVE IMPACTED PATHOLOGY

Neoadjuvant chemoimmunotherapy

Adjuvant EGFR-targeted therapy

Adjuvant ALK-targeted therapy

32

CHECKMATE 816: NEOADJUVANT CHEMOIMMUNOTHERAPY

Introduces:

1. Need to test for EGFR and ALK prior to initiating chemo-IO in resectable lung cancer

2. Importance of evaluation of post-chemo-IO lungs

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

BACKGROUND
Neoadjuvant or adjuvant chemotherapy confers a modest benefit over surgery alone for resectable non–small-cell lung cancer (NSCLC). In early-phase trials, nivolumab-based neoadjuvant regimens have shown promising clinical activity; however, data from phase 3 trials are needed to confirm these findings.

METHODS
In this open-label, phase 3 trial, we randomly assigned patients with stage IB to IIIA resectable NSCLC to receive nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone, followed by resection. The primary end points were event-free survival and pathological complete response (0% viable tumor in resected lung and lymph nodes), both evaluated by blinded independent review. Overall survival was a key secondary end point. Safety was assessed in all treated patients.

RESULTS
The median event-free survival was 31.6 months (95% confidence interval [CI], 30.2 to not reached) with nivolumab plus chemotherapy and 20.8 months (95% CI, 14.0 to 26.7) with chemotherapy alone (hazard ratio for disease progression, disease recurrence, or death, 0.63; 97.38% CI, 0.43 to 0.91; P=0.005). The percentage of patients with a pathological complete response was 24.0% (95% CI, 18.0 to 31.0) and 2.2% (95% CI, 0.6 to 5.6), respectively (odds ratio, 13.94; 99% CI, 3.49 to 55.75; P<0.001). Results for event-free survival and pathological complete response across most subgroups favored nivolumab plus chemotherapy over chemotherapy alone. At the first prespecified interim analysis, the hazard ratio for death was 0.57 (99.67% CI, 0.30 to 1.07) and did not meet the criterion for significance. Of the patients who underwent randomization, 83.2% of those in the nivolumab-plus-chemotherapy group and 75.4% of those in the chemotherapy-alone group underwent surgery. Grade 3 or 4 treatment-related adverse events occurred in 33.5% of the patients in the nivolumab-plus-chemotherapy group and in 36.9% of those in the chemotherapy-alone group.

CONCLUSIONS
In patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. The addition of nivolumab to neoadjuvant chemotherapy did not increase the incidence of adverse events or impede the feasibility of surgery. (Funded by Bristol Myers Squibb; CheckMate 816 ClinicalTrials.gov number, NCT02998528.)

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TRIAL OF STAGE IB to IIIA LUNG CANCER	Neoadjuvant chemotherapy alone	Chemotherapy PLUS NIVOLUMAB
Event-free survival	20.8 months	31.6 months
Pathological complete response	2.2%	24%
Grade 3 or 4 adverse events	36.9%	33.5%

34

CHECKMATE 816: BIG CHANGES!!

Patients with unresectable and/or locally advanced lung cancer can now be resected after neoadjuvant chemoimmunotherapy

Some of these cancers have complete pathologic responses

Response to therapy can be measured by pathologists (with major work by pathologists' assistants)

Patients are doing better! Some may be cured

35

LUNG CANCERS RESECTED AFTER NEOADJUVANT CHEMOIMMUNOTHERAPY NEED TO BE MAPPED; PATHOLOGISTS NEED TO PROVIDE LOTS OF INFO ON THESE CASES

COMPLETE PATHOLOGIC RESPONSE (CPR) = NO VIABLE TUMOR CELLS

MAJOR PATHOLOGIC RESPONSE (MPR) = LESS THAN OR EQUAL TO 10% VIABLE TUMOR

Diagnosis Comment [4]

Type of neoaduvant therapy: chemoimmunotherapy (checkmate 816 protocol)

Assessment of primary tumor/tumor bed (post neoadjuvant therapy):
Percentage of viable tumor: 80%
Percentage of necrosis: 10%
Percentage of stroma (inflammation/fibrosis): 10%

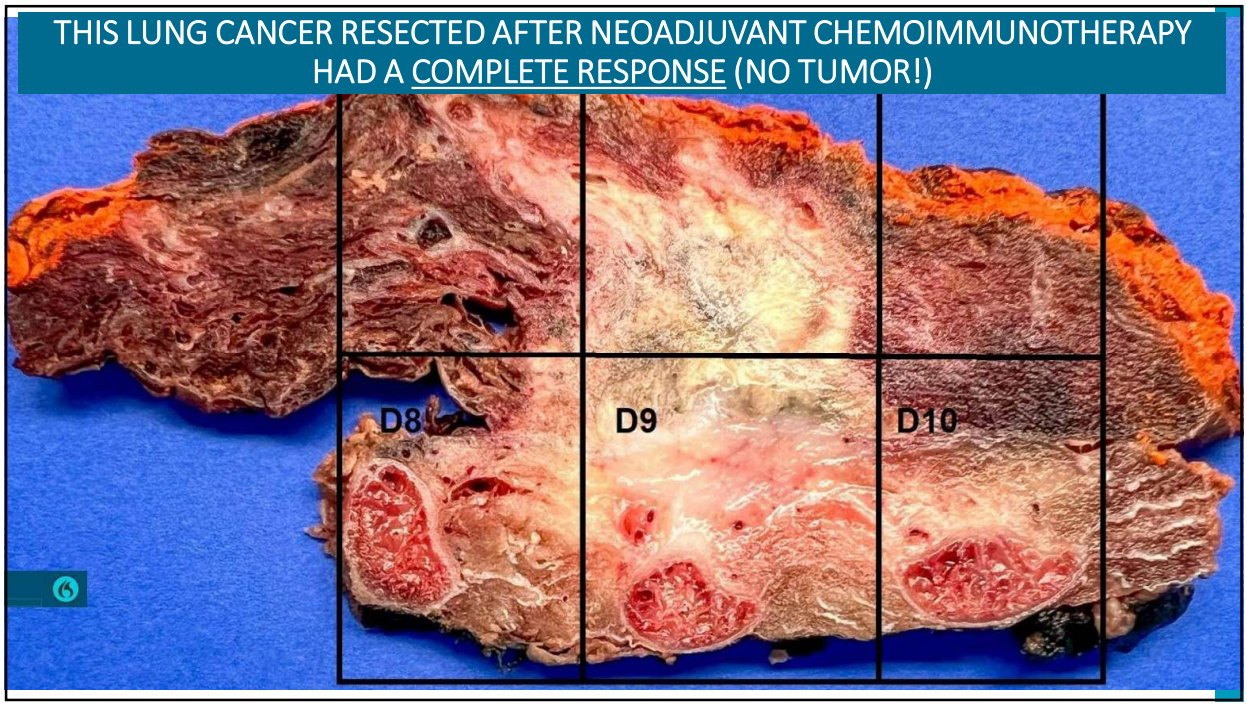
Grade of inflammation: moderate

Method:
Correlation with gross photograph: Yes
Evaluation aided by tumor mapping to match gross photograph to histologic sections: Yes
Evalution aided by correlation of pathologic findings with imaging: Yes

Overall assessment:
Complete pathologic response (CPR) present (no viable tumor cells): No
Major pathologic response (MPR) present (less than or equal to 10% viable tumor): No

Treatment effect in lymph node metastases:
Total number of lymph node stations examined: 8
Total number of lymph nodes examined: 31
Carcinoma present? No
Total number of lymph nodes with metastatic carcinoma: 0
Lymph nodes stations involved by tumor with treatment-related changes: 0
Lymph nodes stations involved by treatment-related changes without viable tumor: 1
Largest tumor focus: N/A
Extracapsular invasion: N/A

36



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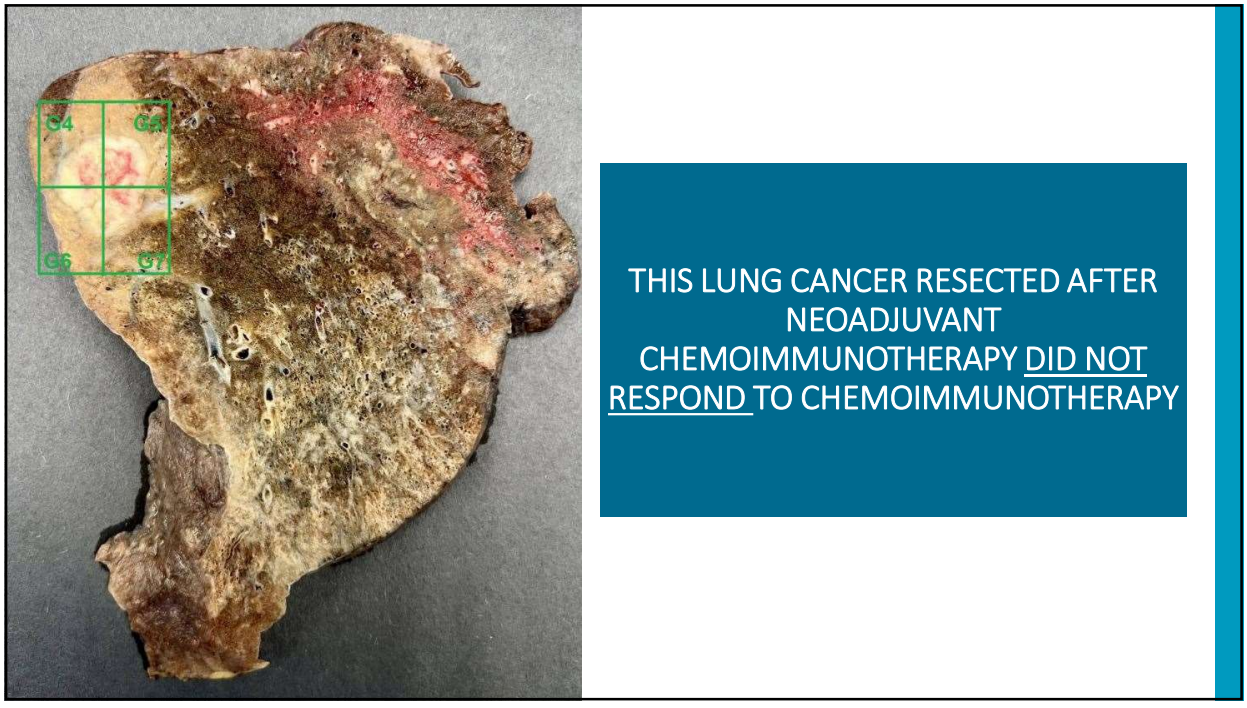

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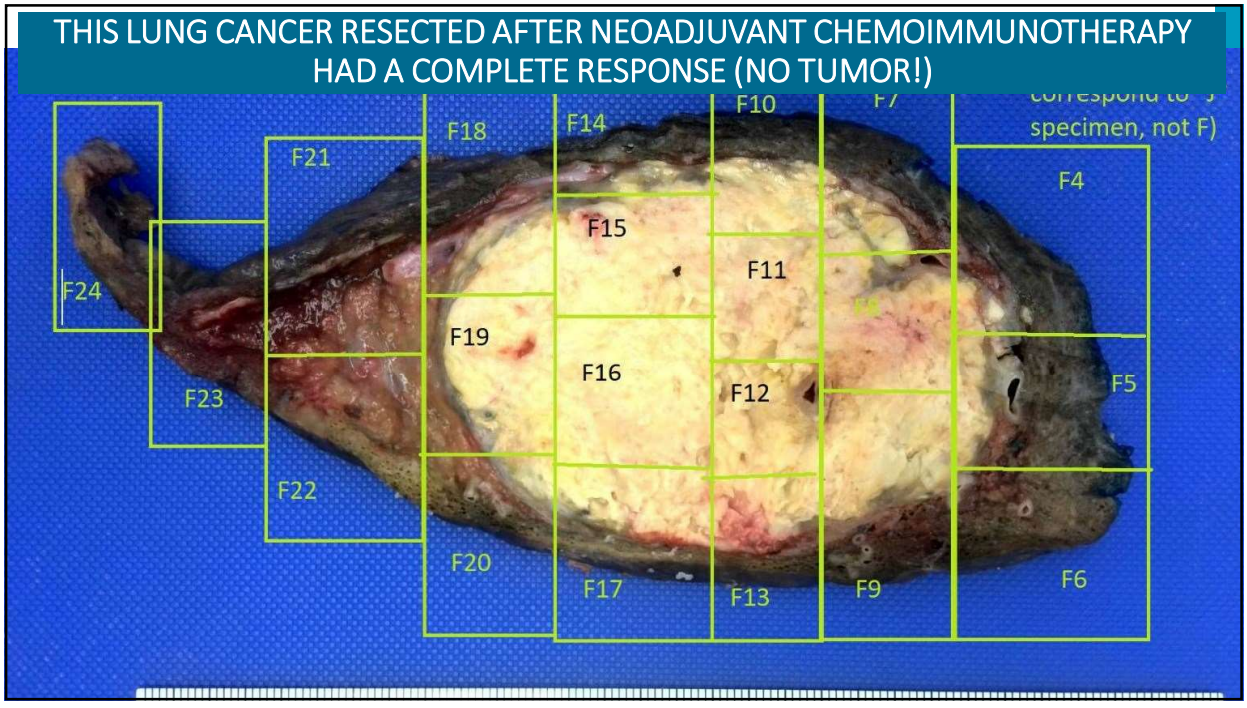

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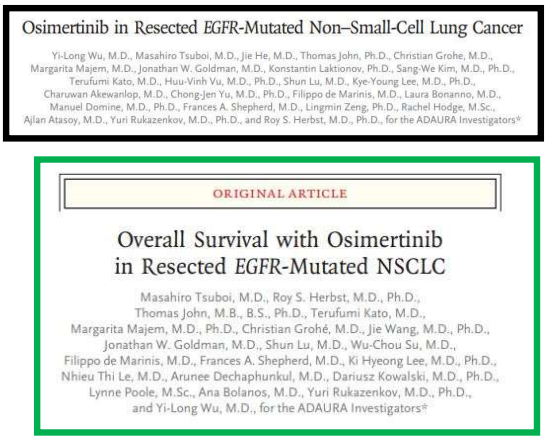
ADAURA: ADJUVANT anti-EGFR TARGETED THERAPY OSIMERTINIB

Introduces need to test for EGFR in resectable lung cancer

Wu YL, et al. *N Engl J Med* 2019;386(21):1973-1985



Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D., for the ADAURA Investigators*

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Resected *EGFR*-Mutated NSCLC

Masahiro Tsuboi, M.D., Roy S. Herbst, M.D., Ph.D., Thomas John, M.B., B.S., Ph.D., Terufumi Kato, M.D., Margarita Majem, M.D., Ph.D., Christian Grohé, M.D., Jie Wang, M.D., Ph.D., Jonathan W. Goldman, M.D., Shun Lu, M.D., Wu-Chou Su, M.D., Filippo de Marinis, M.D., Frances A. Shepherd, M.D., Ki Hyeong Lee, M.D., Ph.D., Nhieu Thi Le, M.D., Arunee Dechaphunkul, M.D., Dariusz Kowalski, M.D., Ph.D., Lynne Poole, M.Sc., Ana Bolanos, M.D., Yuri Rukazenkov, M.D., Ph.D., and Yi-Long Wu, M.D., for the ADAURA Investigators*

Tsuboi M, et al. *N Engl J Med* 2023;389(2):137-147

41

ALINA: ADJUVANT ALECTINIB

Introduces need to test for ALK in resectable lung cancer (IB-IIIA)

Wu Y-L, et al. *N Engl J Med* 2024;390(14):1265-1276

The NEW ENGLAND JOURNAL of MEDICINE

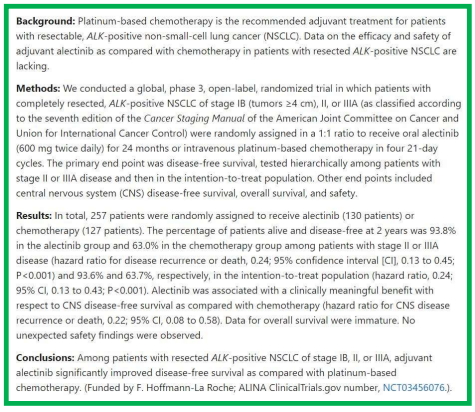
SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Alectinib in Resected *ALK*-Positive Non–Small-Cell Lung Cancer

Authors: Yi-Long Wu, M.D., Rafal Dziadziuszko, M.D., Ph.D., Jin Seok Ahn, M.D., Ph.D., Fabrice Barlesi, M.D., Ph.D., Makoto Nishio, M.D., Ph.D., Dae Ho Lee, M.D., Ph.D., Jong-Seok Lee, M.D., Ph.D., +15, for the ALINA Investigators* Author Info & Affiliations

Published April 10, 2024 | N Engl J Med 2024;390:1265-1276 | DOI: 10.1056/NEJMoa2310532 | VOL. 390 NO. 14



Background: Platinum-based chemotherapy is the recommended adjuvant treatment for patients with resectable, *ALK*-positive non-small-cell lung cancer (NSCLC). Data on the efficacy and safety of adjuvant alectinib as compared with chemotherapy in patients with resected *ALK*-positive NSCLC are lacking.

Methods: We conducted a global, phase 3, open-label, randomized trial in which patients with completely resected, *ALK*-positive NSCLC of stage IB (tumors ≥4 cm), II, or IIIA (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer and Union for International Cancer Control) were randomly assigned in a 1:1 ratio to receive oral alectinib (600 mg twice daily) for 24 months or intravenous platinum-based chemotherapy in four 21-day cycles. The primary end point was disease-free survival, tested hierarchically among patients with stage II or IIIA disease and then in the intention-to-treat population. Other end points included central nervous system (CNS) disease-free survival, overall survival, and safety.

Results: In total, 257 patients were randomly assigned to receive alectinib (130 patients) or chemotherapy (127 patients). The percentage of patients alive and disease-free at 2 years was 93.8% in the alectinib group and 63.0% in the chemotherapy group among patients with stage II or IIIA disease (hazard ratio for disease recurrence or death, 0.24; 95% confidence interval [CI], 0.13 to 0.45; P<0.001) and 93.6% and 63.7%, respectively, in the intention-to-treat population (hazard ratio, 0.24; 95% CI, 0.13 to 0.43; P<0.001). Alectinib was associated with a clinically meaningful benefit with respect to CNS disease-free survival as compared with chemotherapy (hazard ratio for CNS disease recurrence or death, 0.22; 95% CI, 0.08 to 0.58). Data for overall survival were immature. No unexpected safety findings were observed.

Conclusions: Among patients with resected *ALK*-positive NSCLC of stage IB, II, or IIIA, adjuvant alectinib significantly improved disease-free survival as compared with platinum-based chemotherapy. (Funded by F. Hoffmann-La Roche; ALINA ClinicalTrials.gov number, NCT03456076.).

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THE EXCITING…

43

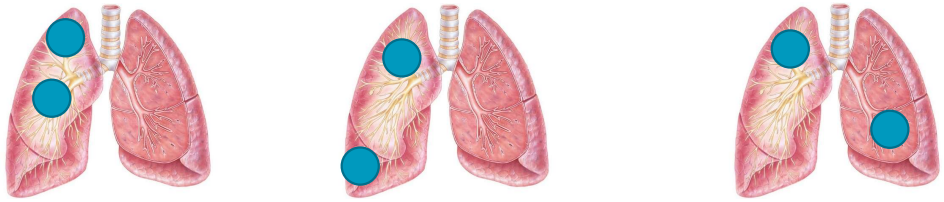
2 LUNG NODULES: WHAT'S THE BIG DEAL?

44

2 nodules of lung adenocarcinoma can

related (intrapulmonary metastasis)

unrelated (synchronous primaries)



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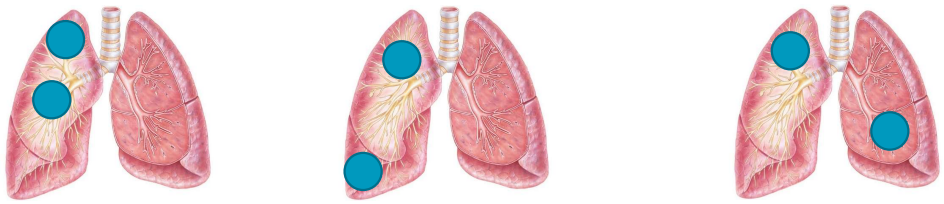
If related (intrapulmonary metastasis) they are staged as pT3, pT4 or pM1. If unrelated (synchronous primaries), each nodule is staged separately



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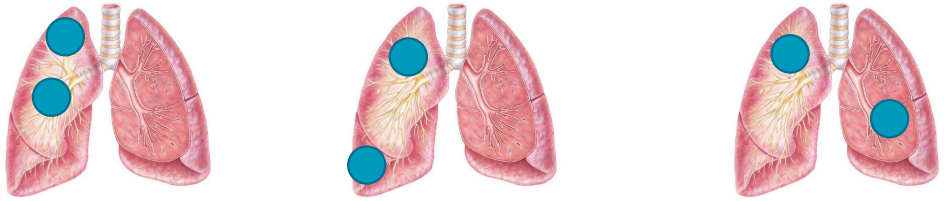
This is a BIG deal. If the tumors are deemed related (intrapulmonary metastasis) these patients are candidates for chemotherapy. If unrelated (synchronous primaries), resection may be enough



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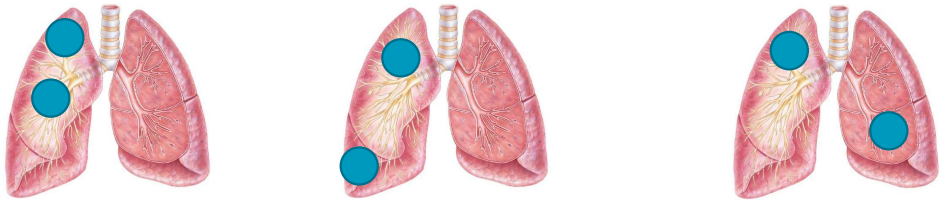
How do we know if they are related or unrelated?

For decades, we have used H&E morphology as the gold standard. If they looked similar, they were deemed related. If not, they were deemed unrelated



48

As recently as 2009, some authors argued that H&E morphology could accurately differentiate between related (intrapulmonary metastasis) and unrelated (synchronous primaries) adenocarcinomas

Girard N, et al. *Am J Surg Pathol* 2009;33:1752-64

49

Can molecular studies help?

Key concept: when lung adenocarcinomas metastasize, they retain their driver mutation

Other mutations can get added on, but the driver mutation stays the same

Yatabe Y, et al. *J Clin Oncol* 2011;29:1-6

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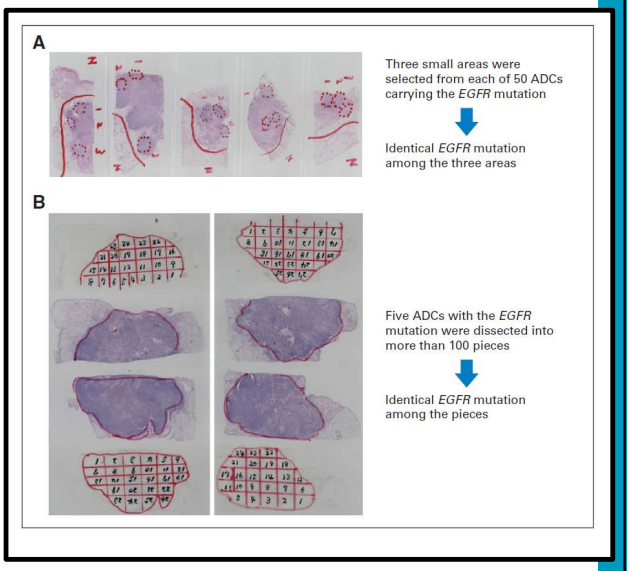
Lack of Discordant Mutation Patterns Between Primary and Metastatic Sites

Because metastasis is the spread of a clone of a primary tumor, the mutation statuses of primary tumors and metastatic lymph nodes were compared. We examined 77 such pairs with a known *EGFR* mutation in the primary tumor (Table 2), and we detected identical mutation patterns in each corresponding lymph node. Furthermore, we selected 50 patients who had lung adenocarcinomas with lymph node metastasis and in whom the *EGFR* mutation was not detected in the primary tumor despite highly suggestive clinical characteristics (including female sex, nonsmoking status, and lack of a *KRAS* mutation).[15] Despite the high likelihood of an *EGFR* mutation being present in this group of

Yatabe Y, et al. *J Clin Oncol* 2011;29:1-6



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Exercise: for the following 4 pairs of adenocarcinomas, try to guess by morphology whether they are related (intrapulmonary metastasis) or unrelated (synchronous primaries)

All pairs were in separate lobes (resected)

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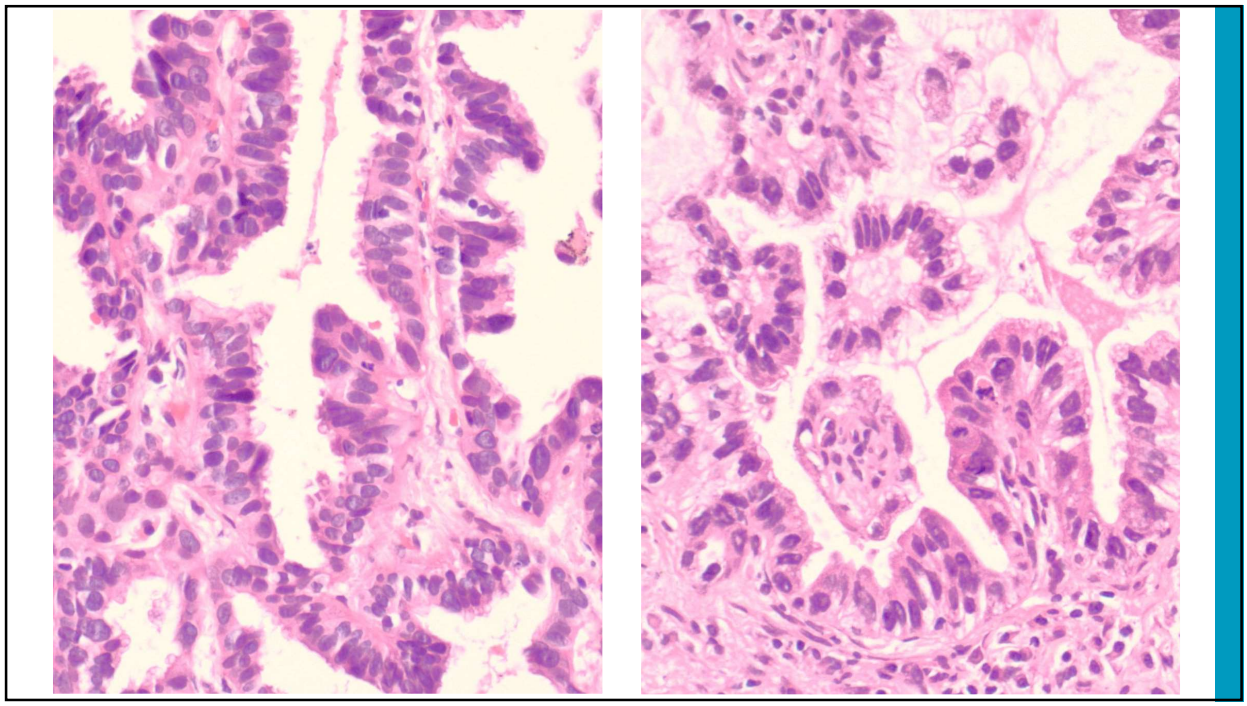

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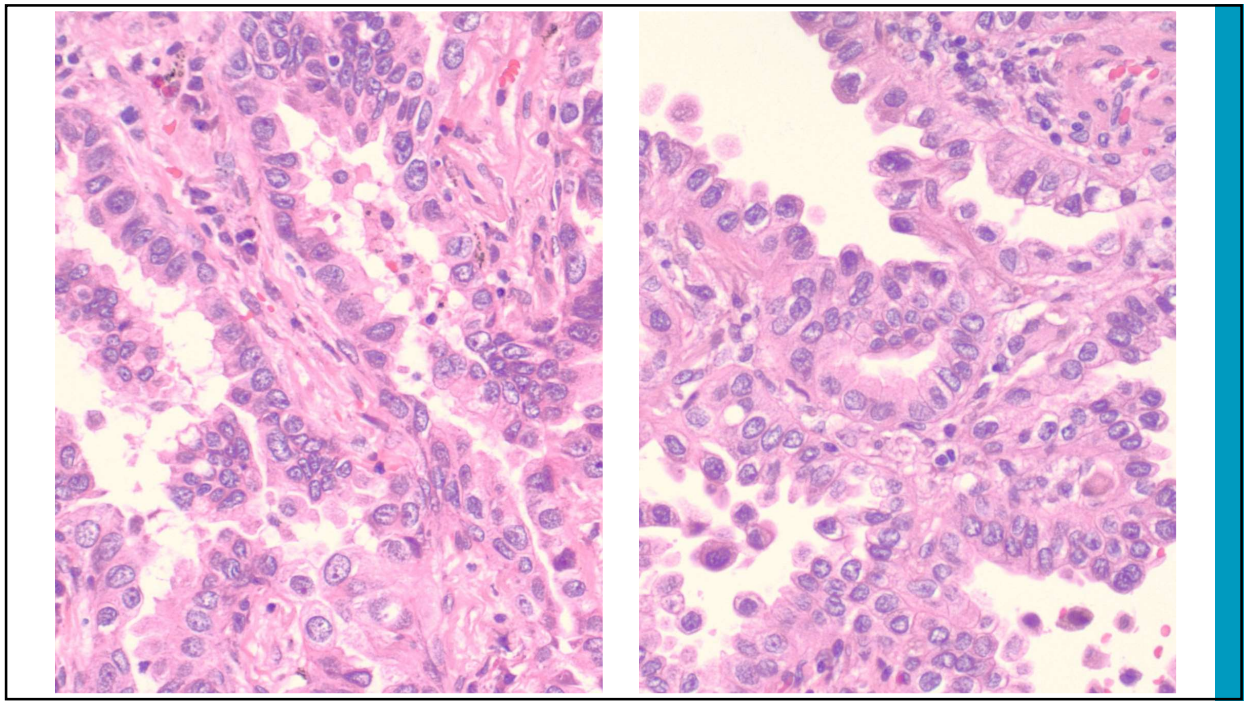

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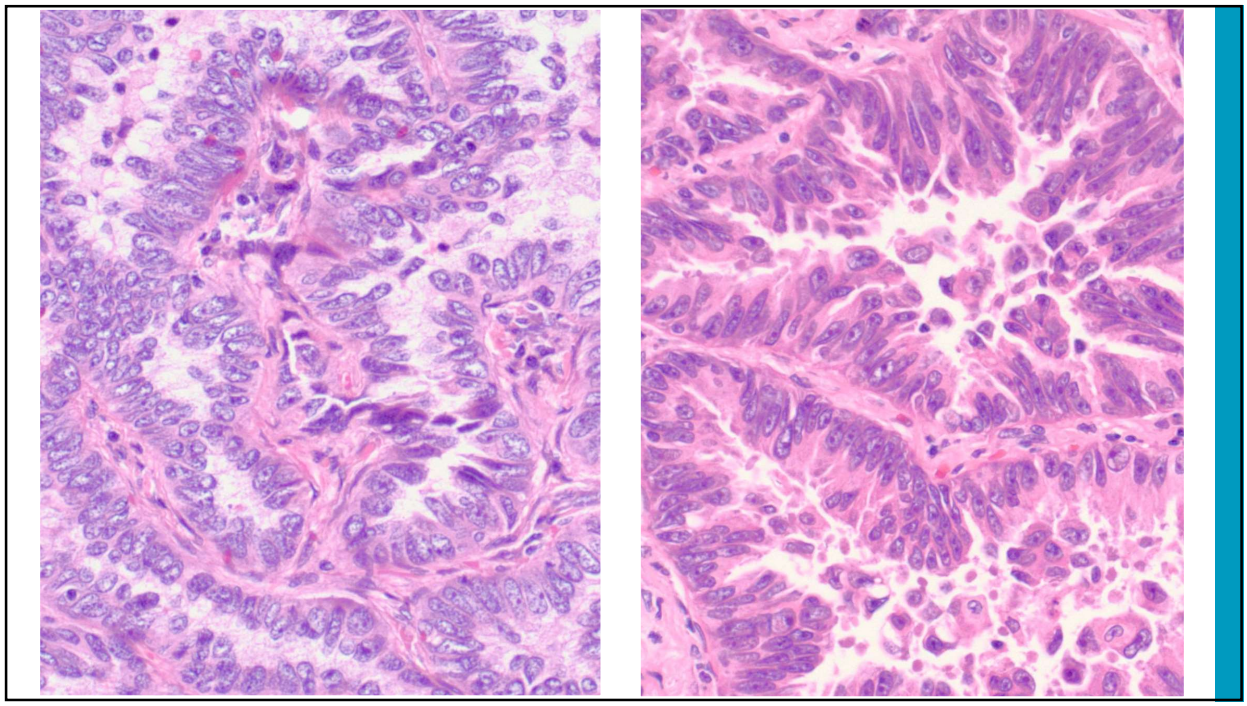

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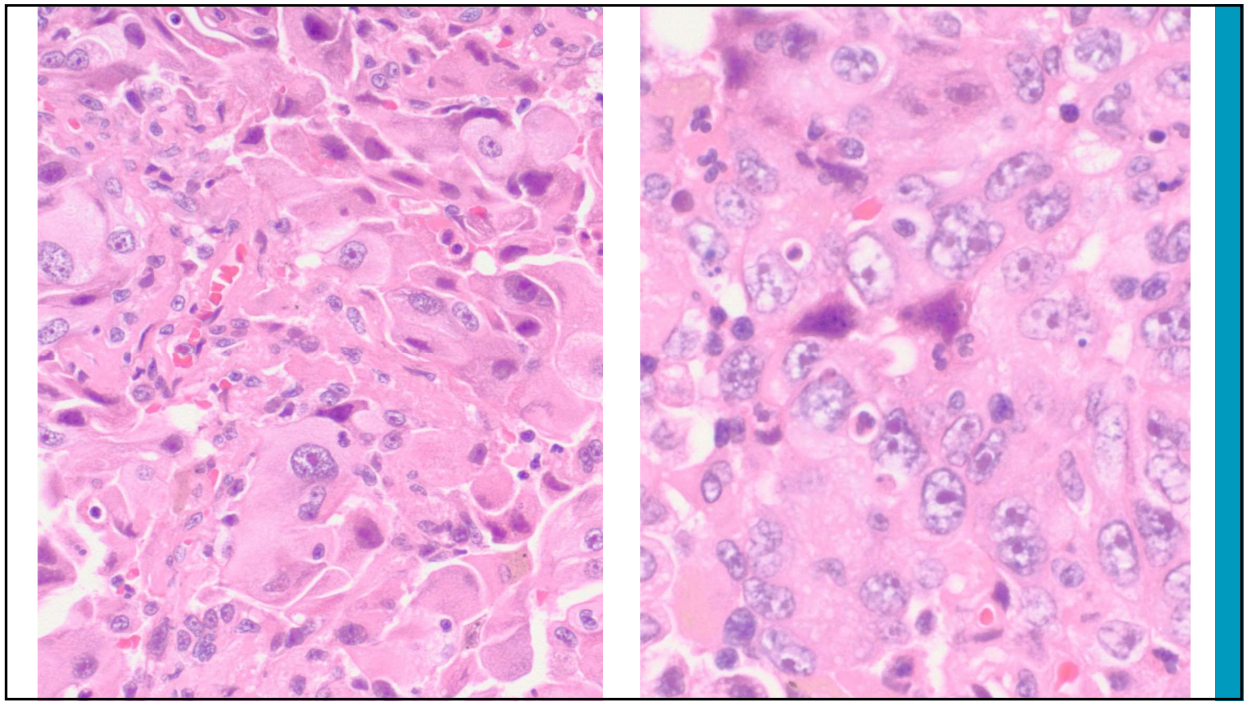

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Here are the molecular results…

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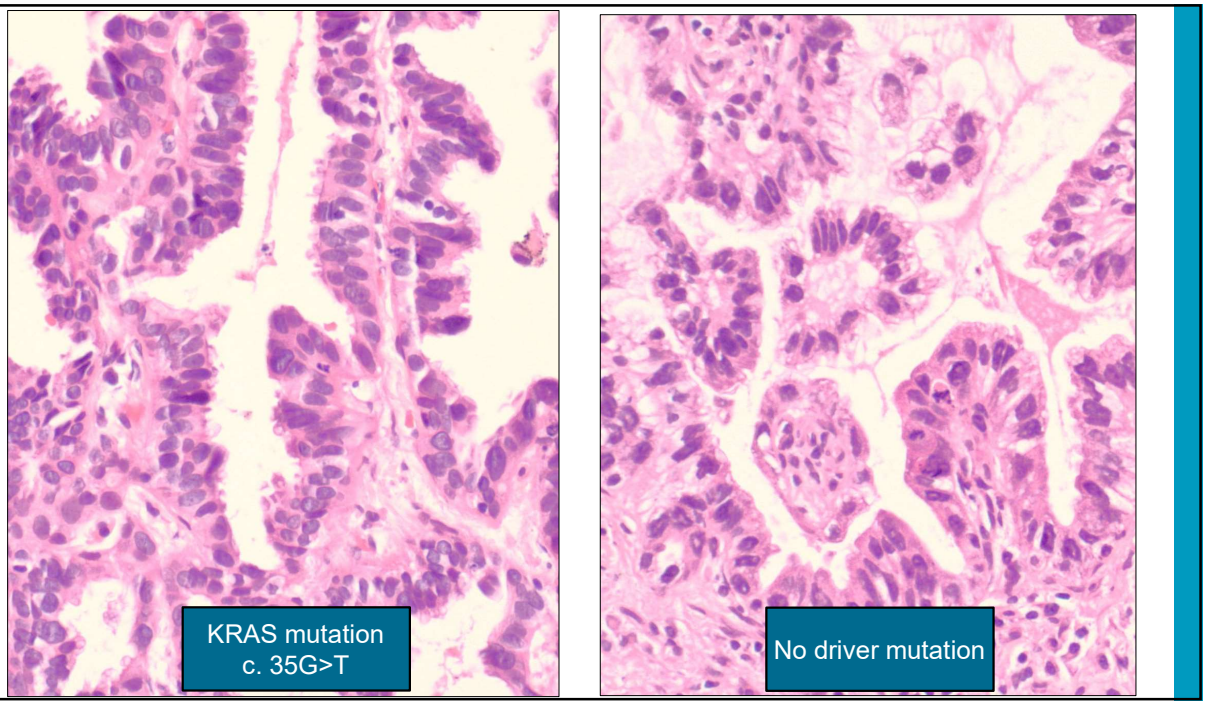

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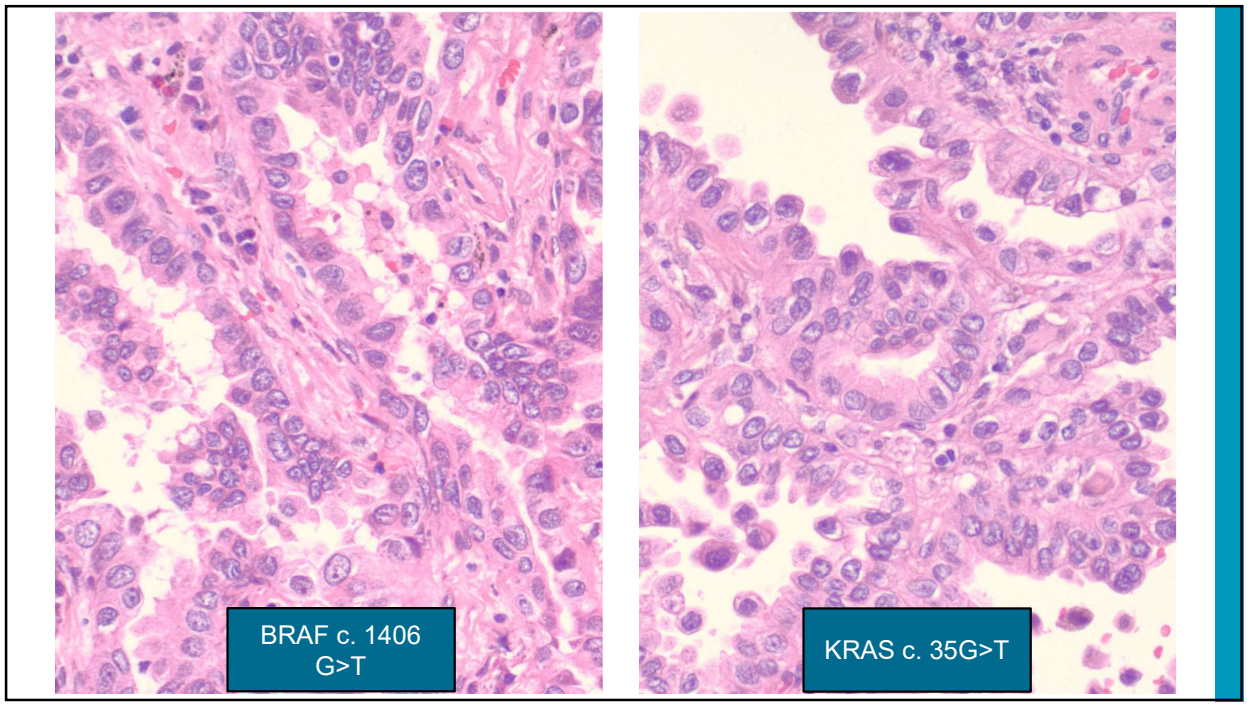

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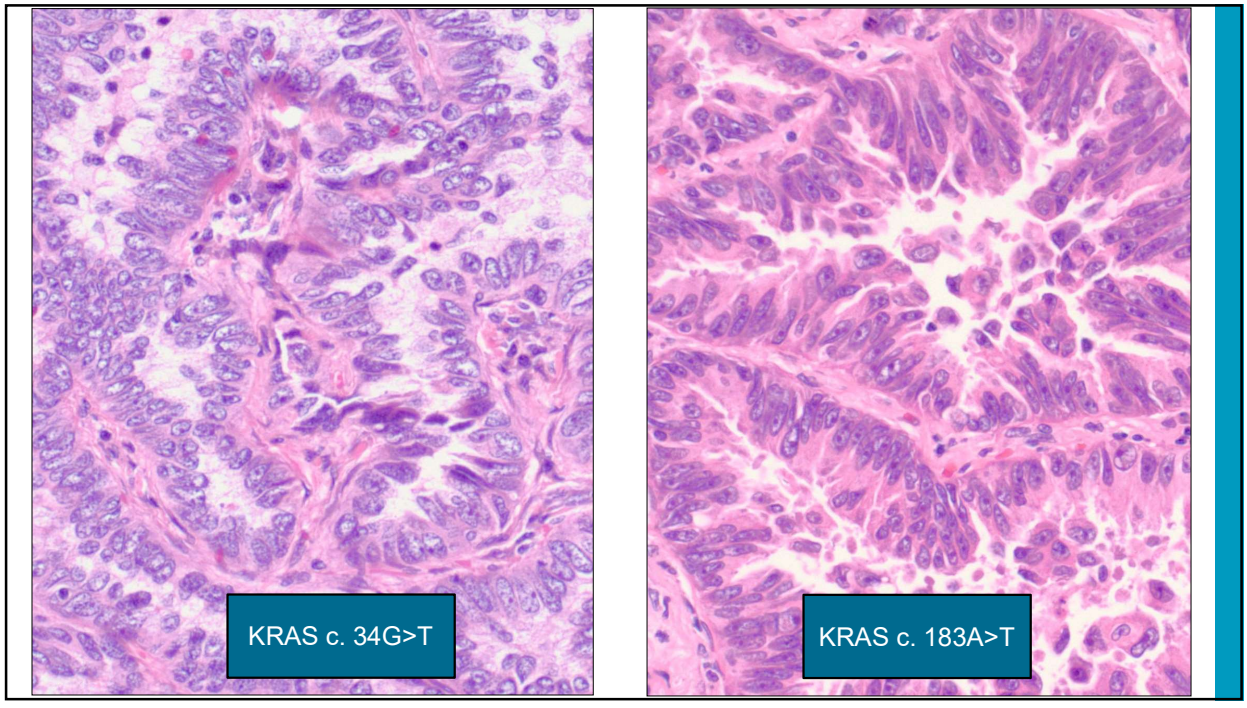

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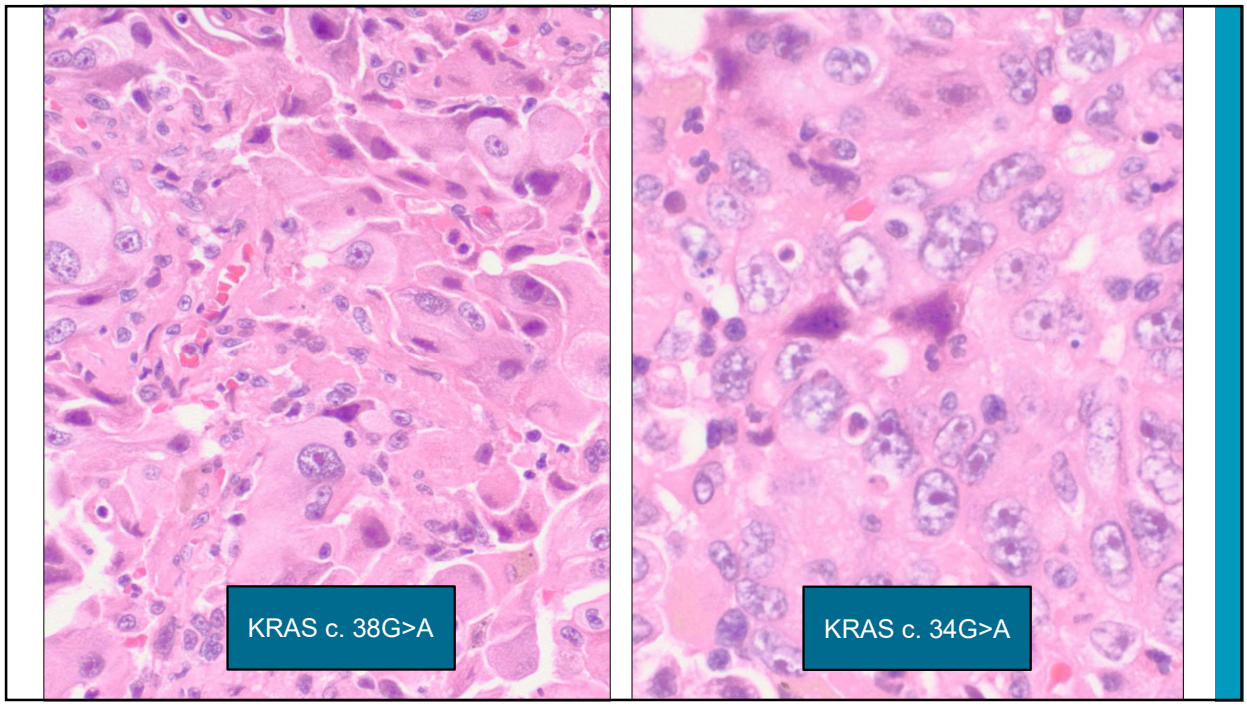

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All 4 pairs are unrelated (synchronous primaries)!!

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Does histological assessment accurately distinguish separate primary lung adenocarcinomas from intrapulmonary metastases? A study of paired resected lung nodules in 32 patients using a routine next-generation sequencing panel for driver mutations

Frido K Bruehl ,[1] Erika E Doxtader,[1] Yu-Wei Cheng,[1] Daniel H Farkas,[1] Carol Farver,[2] Sanjay Mukhopadhyay [1]

Table 3 Cases thought to be related by histology but proven to be unrelated by molecular analysis

Case	Location	Histological assessment	Driver gene variant	Tumour histology	Tumour size (mm)	Original tumour stage
1	RML	R	NVD	MP80, P10, A10, NM	30	T4N0
	RUL		*KRAS* c.35G>T	MP80, A20, MX	25	T4N0
5	RUL	R	*BRAF* c.1406G>T	P70, A30, NM	14	T4N0
	RLL		*KRAS* c.35G>T	P70, A20, MP10, NM	23	T4N0
17	LUL	R	*KRAS* c.183A>T	A60, P30, MP10, NM	20	T2aN0
	RLL		*KRAS* c.34G>T	A80, P10, MP10, NM	18	T2aN0
24	RUL	R	*KRAS* c.38G>A	S50, MP30, P20, NM	18	T1bN0
	RLL		*KRAS* c.34G>A	S50, MP30, P20, NM	17	T1bN0

A, acinar; MP, micropapillary; MX, mixed mucinous and non-mucinous; NM, non-mucinous; NVD, no variant detected; P, papillary; R, related; S, solid.

Table 2 Histological assessment of relatedness versus driver mutation status

Case	Histological assessment	Original report	Molecular analysis	Driver mutation in tumour 1	Driver mutation in tumour 2
1	R	R	UR	Negative	KRAS c.35G>T
2	R	R	I	KRAS c.34G>T	KRAS c.34G>T
3	UR	UR	UR	EGFR c.2240T>C	KRAS c.34G>T
4	UR	UR	I	KRAS c.34G>T	KRAS c.34G>T
5	R	R	UR	BRAF c.1406G>T	KRAS c.35G>T
6	UR	UR	UR	Negative	KRAS c.35G>T
7	R	R	R	MET c.3029C>T	MET c.3029C>T
8	R	R	R	EGFR c.2573T>G	EGFR c.2573T>G
9	UR	UR	UR	KRAS c.34G>T	Negative
10	UR	R	I	KRAS c.35G>T	KRAS c.35G>T
11	R	R	R	ERBB2 c.2264T>C	ERBB2 c.2264T>C
12	R	R	R	EGFR c.2240_2257del	EGFR c.2240_2257del
13	R	R	R	KRAS c.57G>T	KRAS c.57G>T
14	R	R	I	Negative (only EGFR tested)	Negative
15	R	R	I	Negative	Negative
16	R	R	R	BRAF N581S	BRAF N581S
17	R	UR	UR	KRAS c.183A>T	KRAS c.34G>T
18	UR	UR	UR	EGFR exon 19 p.Glu746_Ala750del	EGFR c.2303_2304insTGTGGCCAG
19	UR	UR	UR	KRAS c.34G>T	Negative
20	R	R	I	ERBB2 p.A775_G776insYVMA	Negative (ERBB2 not tested)
21	UR	UR	UR	KRAS c.35G>T	Negative
22	UR	UR	UR	KRAS c.183A>C	MET c.3028+2T>C
23	UR	UR	UR	KRAS c.35G>T	KRAS c.34G>T
24	R	UR	UR	KRAS c.38G>A	KRAS c.34G>A
25	UR	UR	UR	KRAS c.37G>T	KRAS c.34G>T
26	UR	UR	UR	Negative	KRAS c.34G>T
27	UR	UR	UR	KRAS c.35G>T	KRAS c.34G>T
28	UR	UR	UR	Negative	KRAS c.34G>T
29	UR	R	UR	KRAS c.34G>T	Negative
30	UR	R	UR	KRAS c.34G>T	Negative
31	UR	UR	I	Negative (only EGFR)	KRAS c.37G>T
32	R	R	I	KRAS c.34G>T	KRAS c.34G>T

I, indeterminate; R, related; UR, unrelated.

Bruehl FK, et al. *J Clin Pathol* 2022;75(6):390-396

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TAKE HOME MESSAGE:

Studies using molecular testing have shown that 2 lung nodules of adenocarcinoma cannot be assumed to be related (i.e. we can now prove that many are synchronous primaries, not pT3/T4/M1)

Chang JC, et al. *Clin Cancer Res* 2019;25(23):7113-7125

Mansuet-Lupo A, et al. *J Thorac Oncol* 2019;14(5):844-56

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Here's what you need to remember:

Neoadjuvant chemoimmunotherapy is helping lung cancer patients; these lung cancer resection specimens need to be mapped to quantitate response

Some 2-nodule lung cancer resection cases will need molecular testing (leading to downstaging and avoidance of unnecessary adjuvant Rx)

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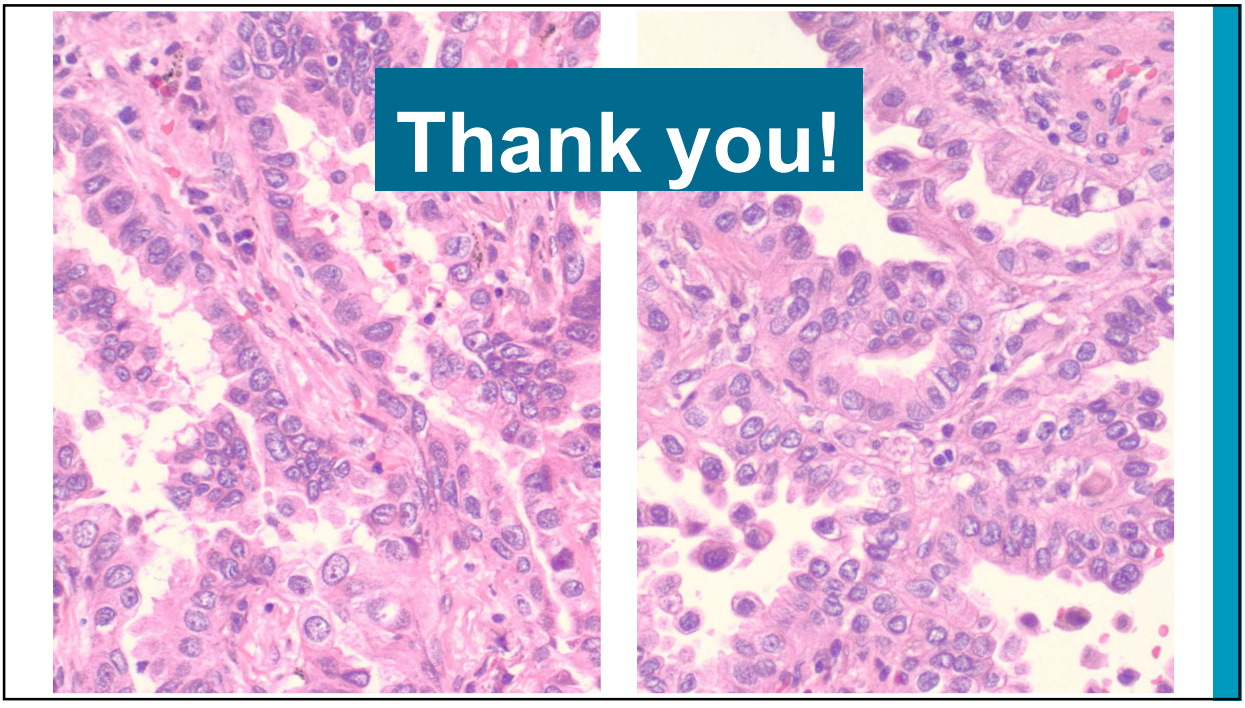

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Questions?

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