Classification OMS 2015 des tumeurs pulmonaires : Changements de paradigme

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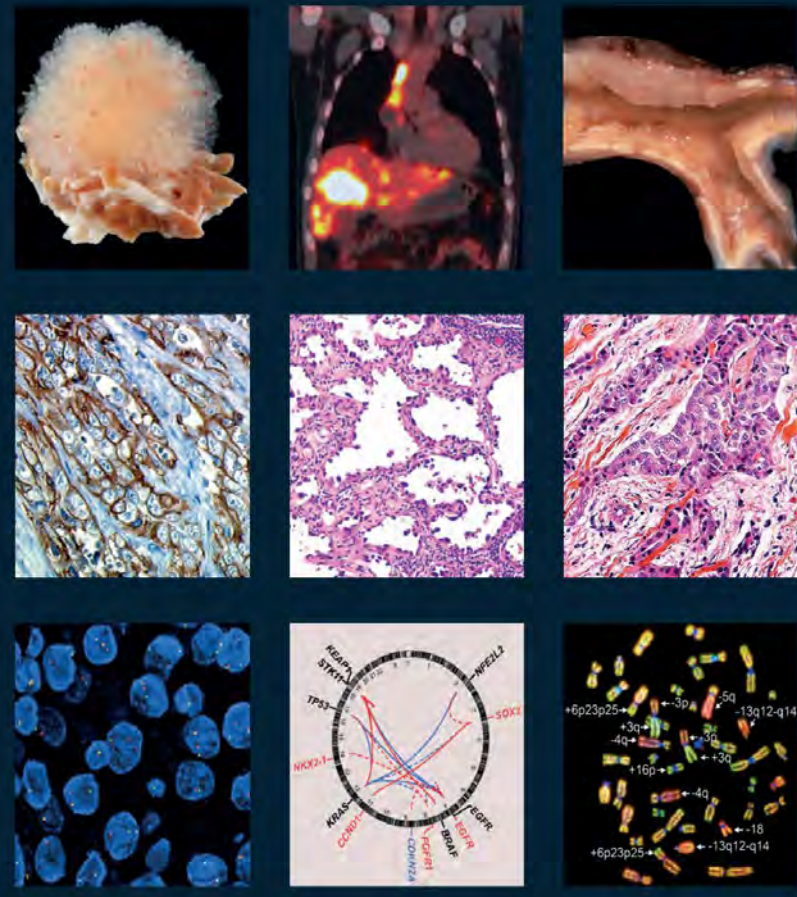
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by
William D. Travis, Elisabeth Brambilla, Allen P. Burke, Alexander Marx, Andrew G. Nicholson



WHO

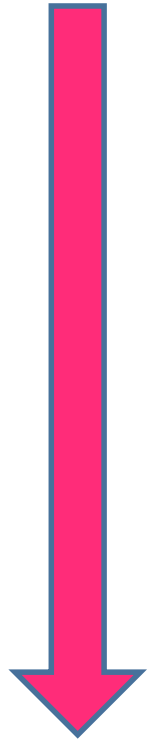
http://whobluebooks.iarc.fr/

Qu'est-ce qu'une classification OMS?

- Une classification pathologique et génétique de tumeurs humaines destinée à être acceptée et utilisée à travers le monde.
- Procure les critères standards pour
  - Le diagnostic pathologique
  - La pratique clinique
  - Les registres des cancers
  - Les études épidémiologiques
  - Les essais cliniques
  - La recherche sur le cancer

INCREASING COMPLEXITY

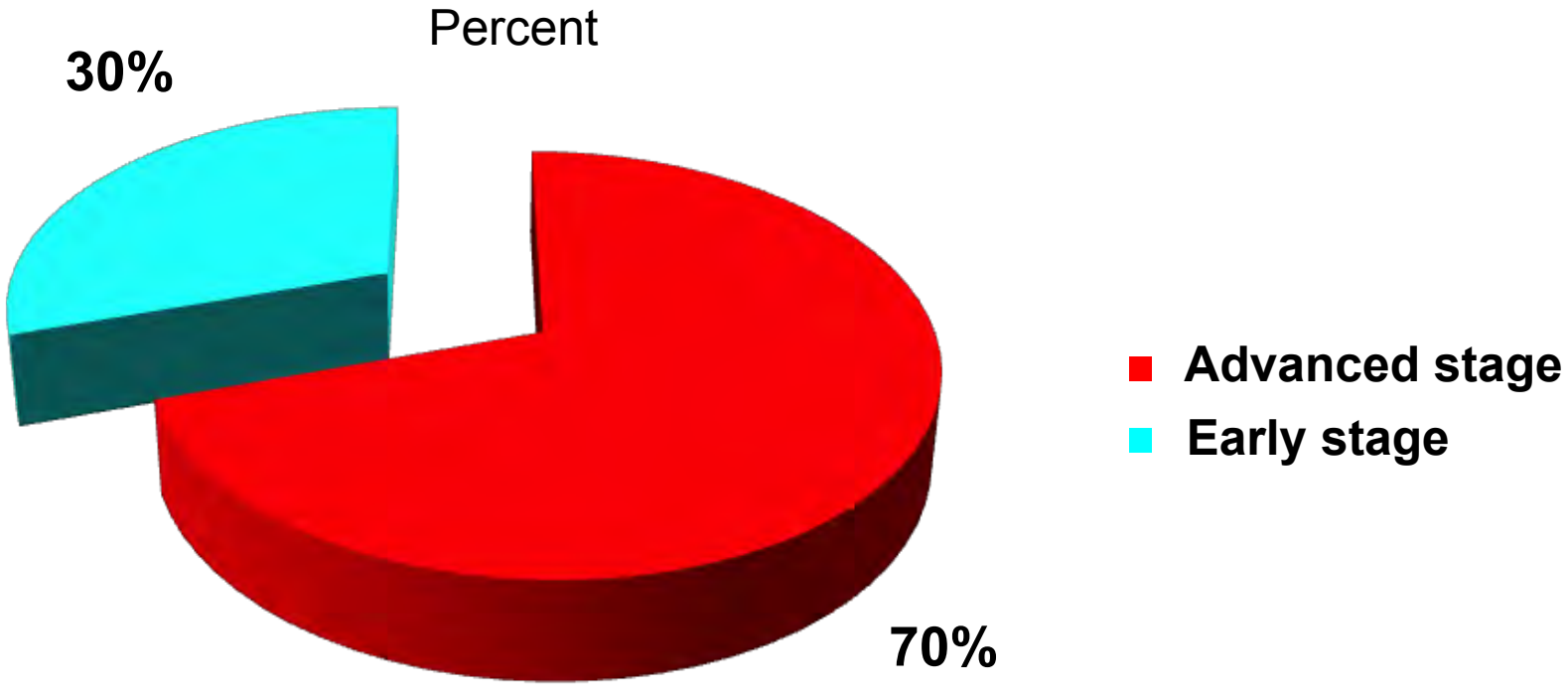
- 1967 WHO
- 1981 WHO
- 1999 WHO
- 2004 WHO
- 2015 WHO



- H&E
- H&E & Mucin
- H&E, EM & IHC
- H&E, EM, IHC & Genetics
- H&E, Cytology, IHC, Genetics, Mucin, Radiology

INCREASING RELEVANCE FOR PERSONALIZED MEDICINE

Cancer non à petites cellules : 70% diagnostiqués au stade avancé : Biopsies



Classification OMS 2015 : Impact sur la prise en charge des patients au stade avancé

- Critères / terminologie pour les petites biopsies /cytologie
- Sous typage histologique plus précis
- Stratégie de management des specimens
- Programmation rationnelle des biomarqueurs moléculaires .
- Necessité d'une équipe multidisciplinaire

Les thérapeutiques ciblées font émerger le besoin d'un diagnostic histologique précis et de tests moléculaires

- Prédiction de réponse des adénocarcinomes
  - *EGFR* mutation– TKI's
  - Adenoca or NSCC-NOS – pemetrexed
  - *ALK / Ros* fusion/ *MET* exon 14 skipping - crizotinib
- Prédiction de toxicité des ca.épidermoides
  - Bevacizumab – contrindiqué car entrainant de graves hémorragies

Changements majeurs de la classification avec un impact diagnostique chez les patients opérés

- Adénocarcinome:

  adoption de la classification IASLC/ATS/ERS
- Carcinome à grandes cellules: (large c. carcinoma) restreints aux tumeurs dépourvues de signes de différentiation claire morphologique ou immunohistochimique (phénotypique)
- Carcinomes épidermoïdes

  keratinisants, nonkeratinisants (P40 nécessaire)

  et basaloïdes
- Tumeurs NE regroupées (TC,AC,LCNEC,SCLC)

Classification OMS 2015 des adénocarcinomes adoptée à la classification multidisciplinaire IASLC/ATS/ERS

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

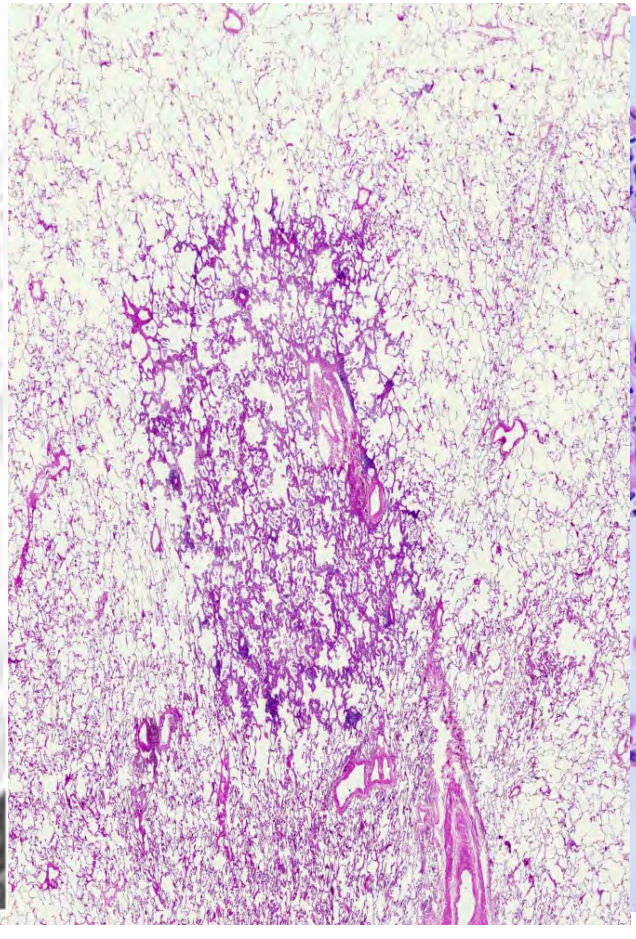
William D. Travis, MD, Elisabeth Brambilla, MD, Masayuki Noguchi, MD, Andrew G. Nicholson, MD, Kim R. Geisinger, MD, Yasushi Yatabe, MD, David G. Beer, PhD, Charles A. Powell, MD, Gregory J. Riely, MD, Paul E. Van Schil, MD, Kavita Garg, MD, John H. M. Austin, MD, Hisao Asamura, MD, Valerie W. Rusch,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

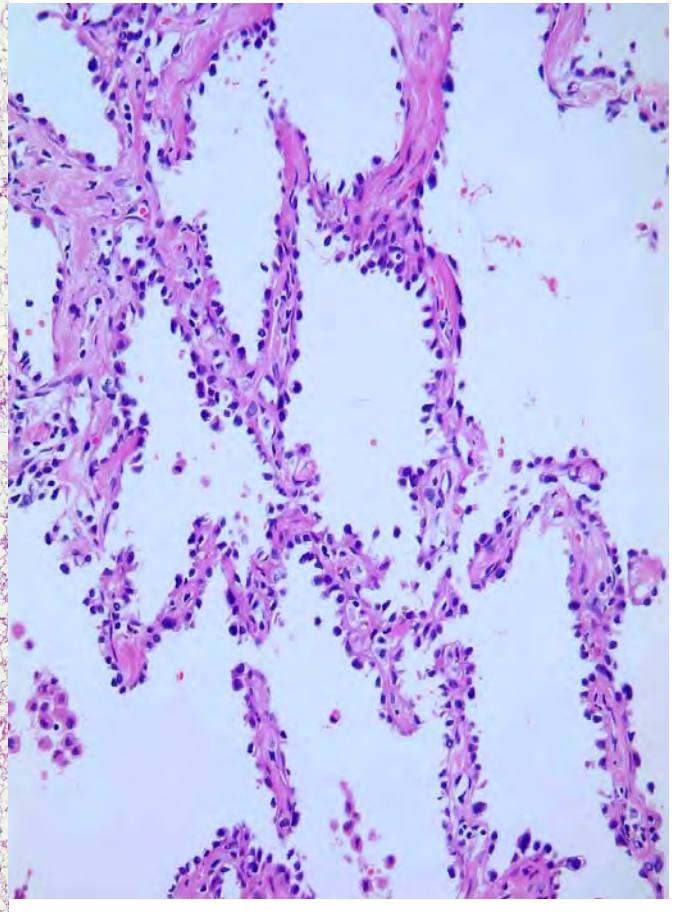
Journal of Thoracic Oncology • Volume 6, Number 2, February 2011

Classification des adénocarcinomes WHO 2015 : résections

- **Lésions préinvasives**
  - **Hyperplasie Atypique Adenomateuse**
  - **Adénocarcinome In Situ (ex BAC) : AIS**
    - **non-mucinous**
    - **mucinous**
- **Adénocarcinome à invasion minime : MIA**
- **Adénocarcinome invasif**

Adénocarcinome in situ non-mucineux





Classification des Adénocarcinomes

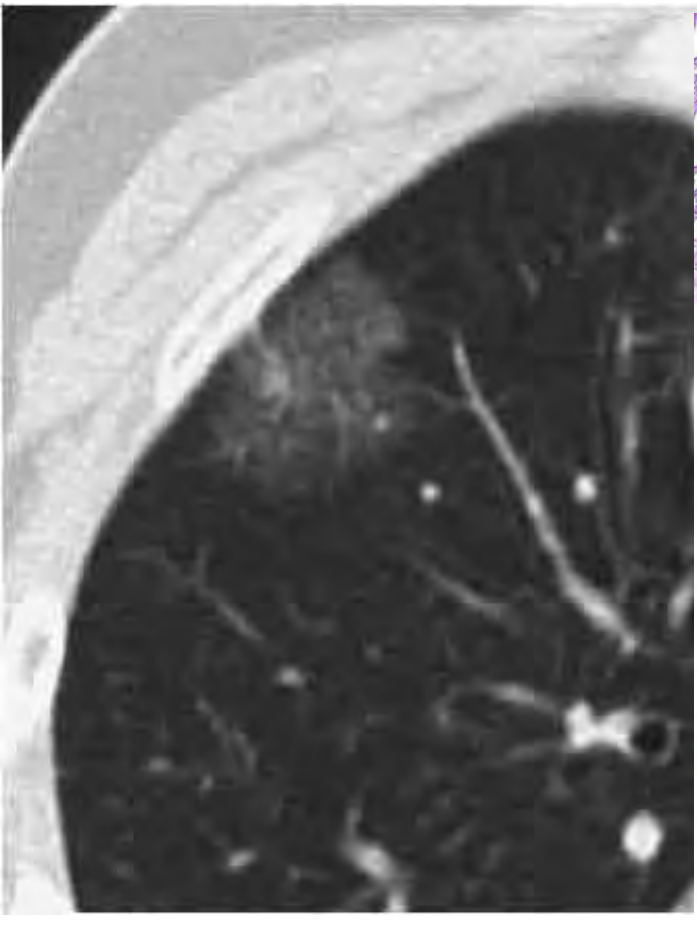
- **Lésions Preinvasives**
  Atypical Adenomatous Hyperplasia (AAH)
  Adenocarcinoma In Situ (ex BAC)
    - **non-mucineux**
    - **mucineux**
- **Adénocarcinome à invasion minime : MIA**

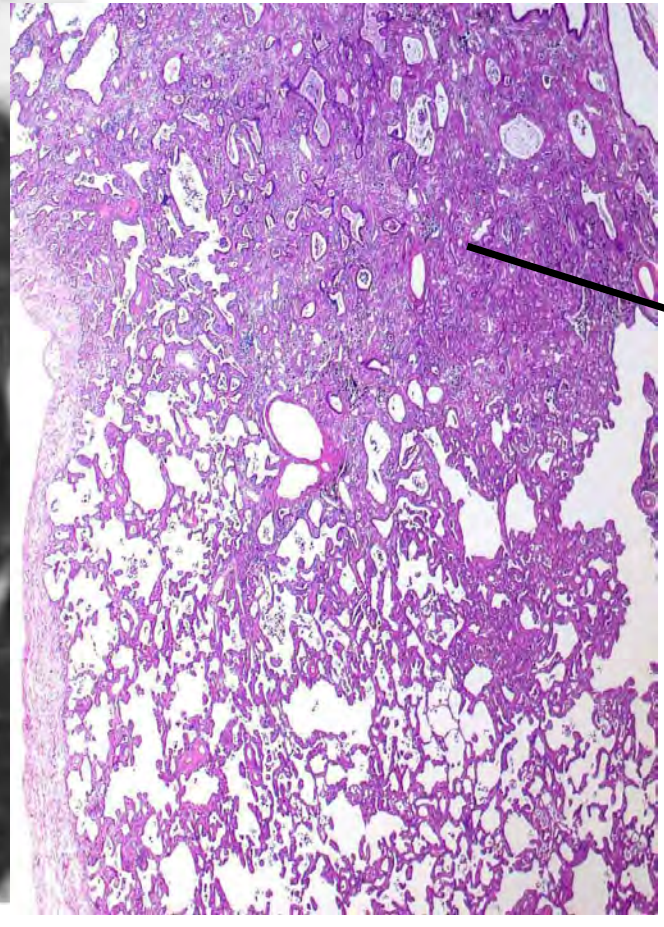
  diamètre ≤ 3cm

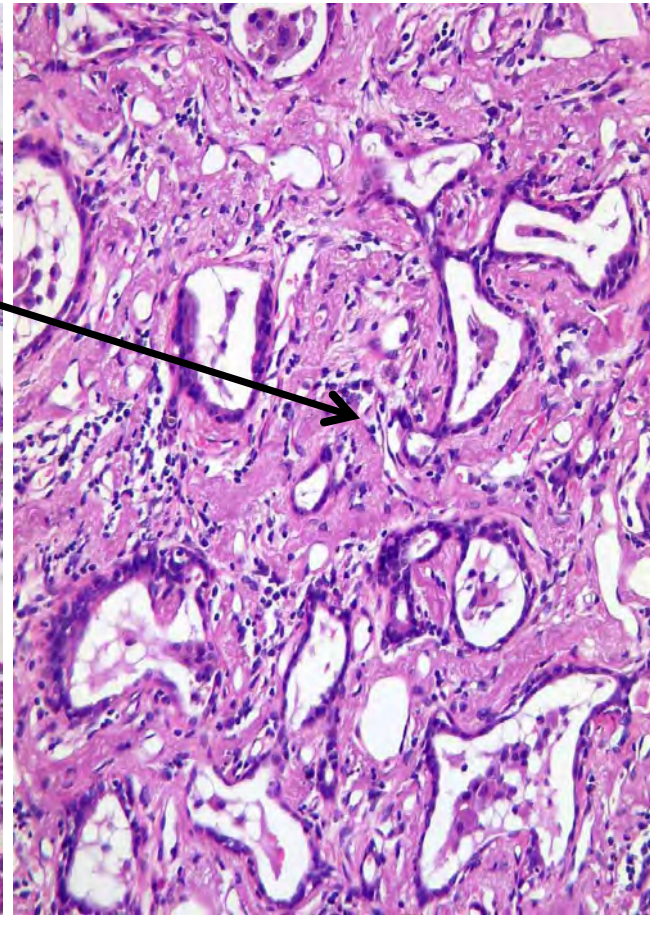
  prédominance lépidique avec ≤ 5mm invasion

  5 year survival = 100% si résection complète
- **Adénocarcinome invasif**

Adénocarcinome à invasion minime non-mucineux





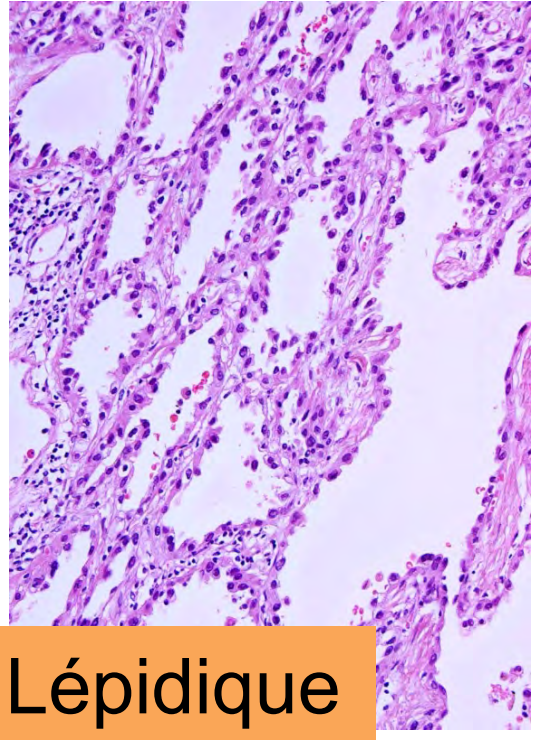


Classification OMS 2015 : Adénocarcinomes

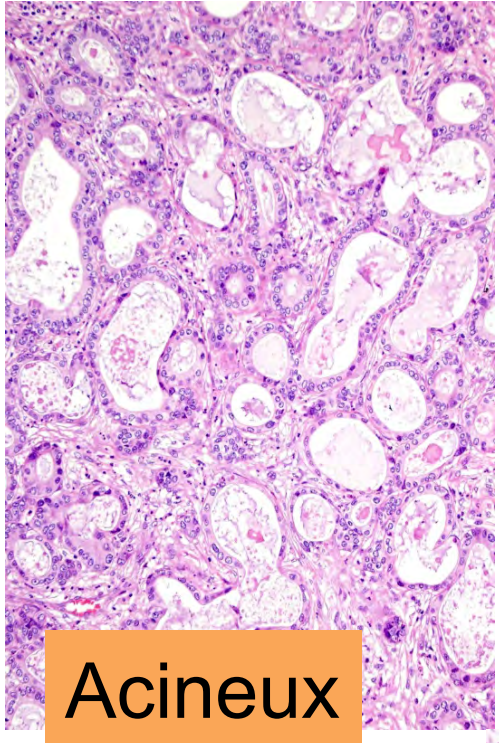
Adénocarcinomes invasifs

- **Adénocarcinome lépidique (ex BAC non-mucineux)**
- **Adénocarcinome papillaire**
- **Adénocarcinome acineux**
- **Adénocarcinome micropapillaire**
- **Adénocarcinome solide (avec mucines ou TTF1 positif)**

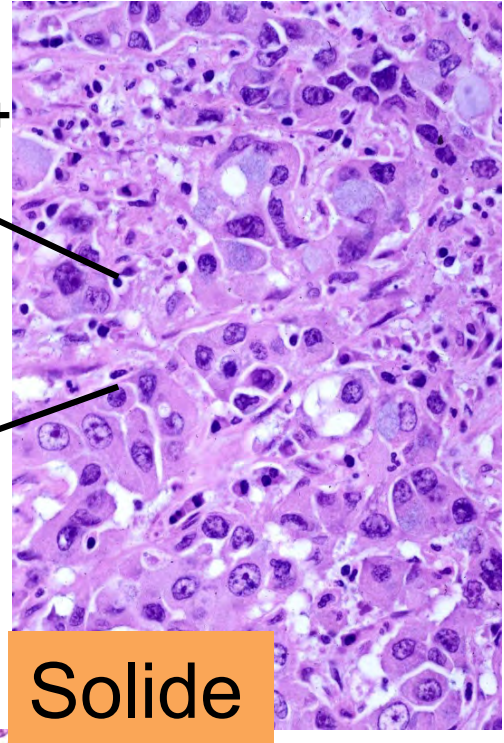
(selon l'architecture prédominante par analyse semiquantitative par intervalles de 5-10%)



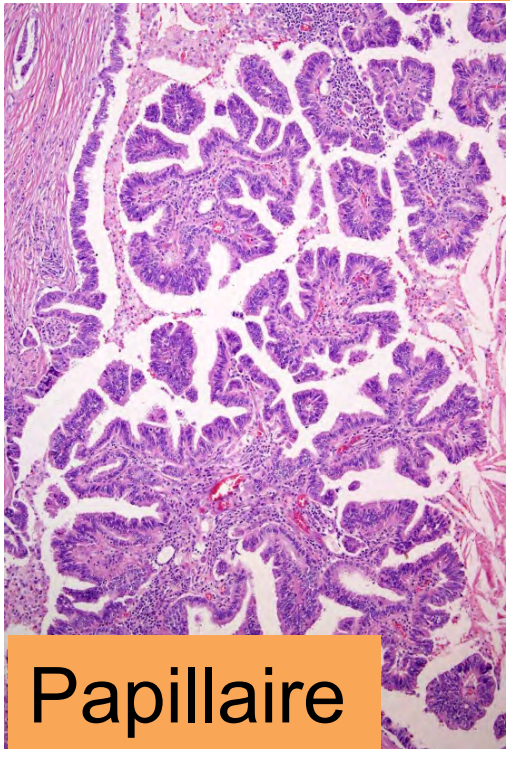
Lépidique



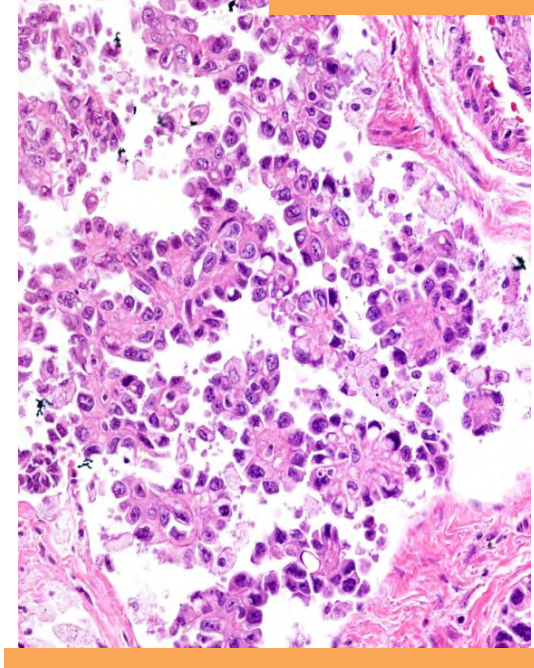
Acineux



Solide



Papillaire



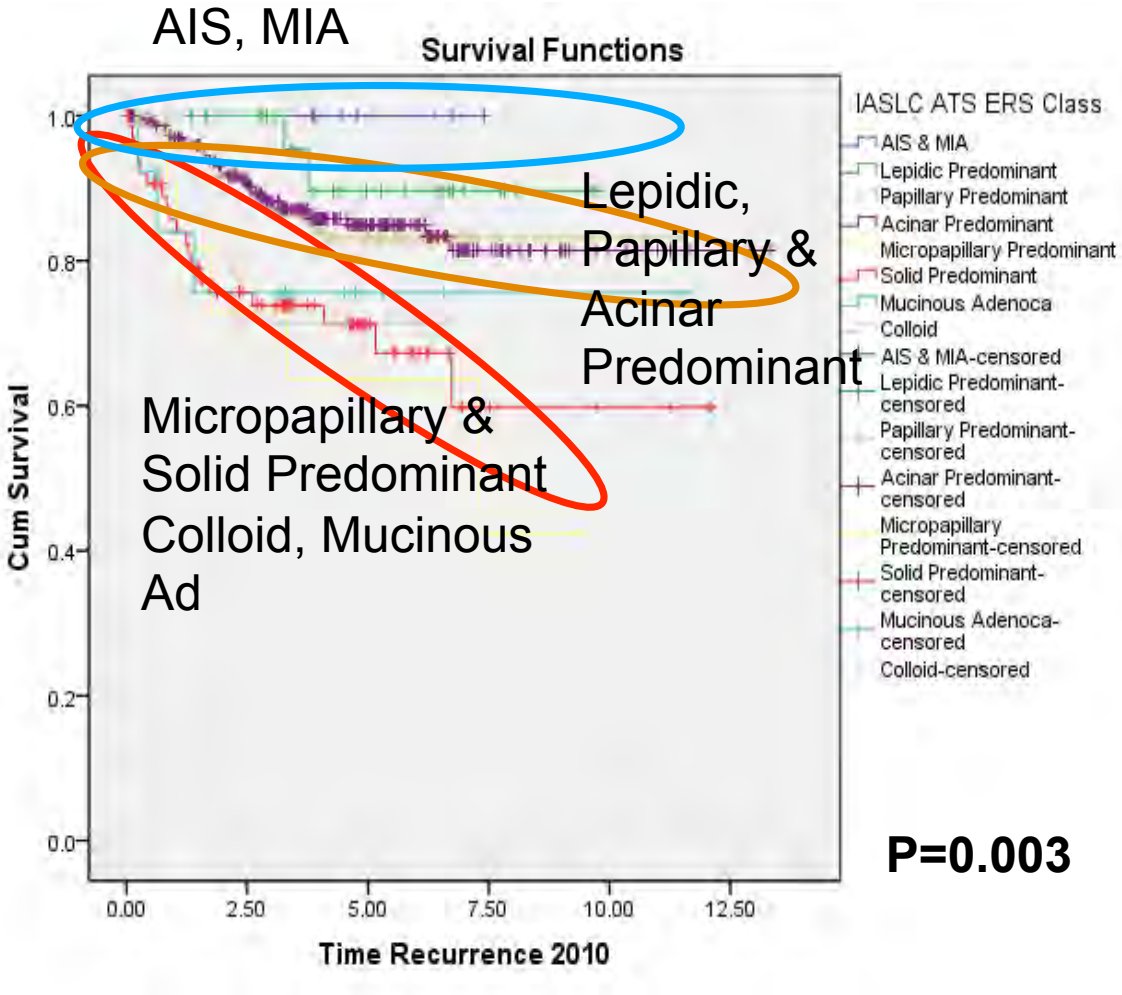
Micropapillaire

La classification participe à la gestion des patients opérés

- Prédit survie et rechute
- Définit AIS & MIA : 100% et presque 100% de survie si résection complète
- Prédit un bénéfice de survie par la chimiothérapie cisplatin-adjuvante
- Permet les correlations radio-pathologiques
- Impacte le Staging TNM
  - Taille de la zone invasive = T du TNM
  - Comparaison des tumeurs multiples = primaires ou métastases intrapulmonaires

Adénocarcinomes Stade I (N=514)

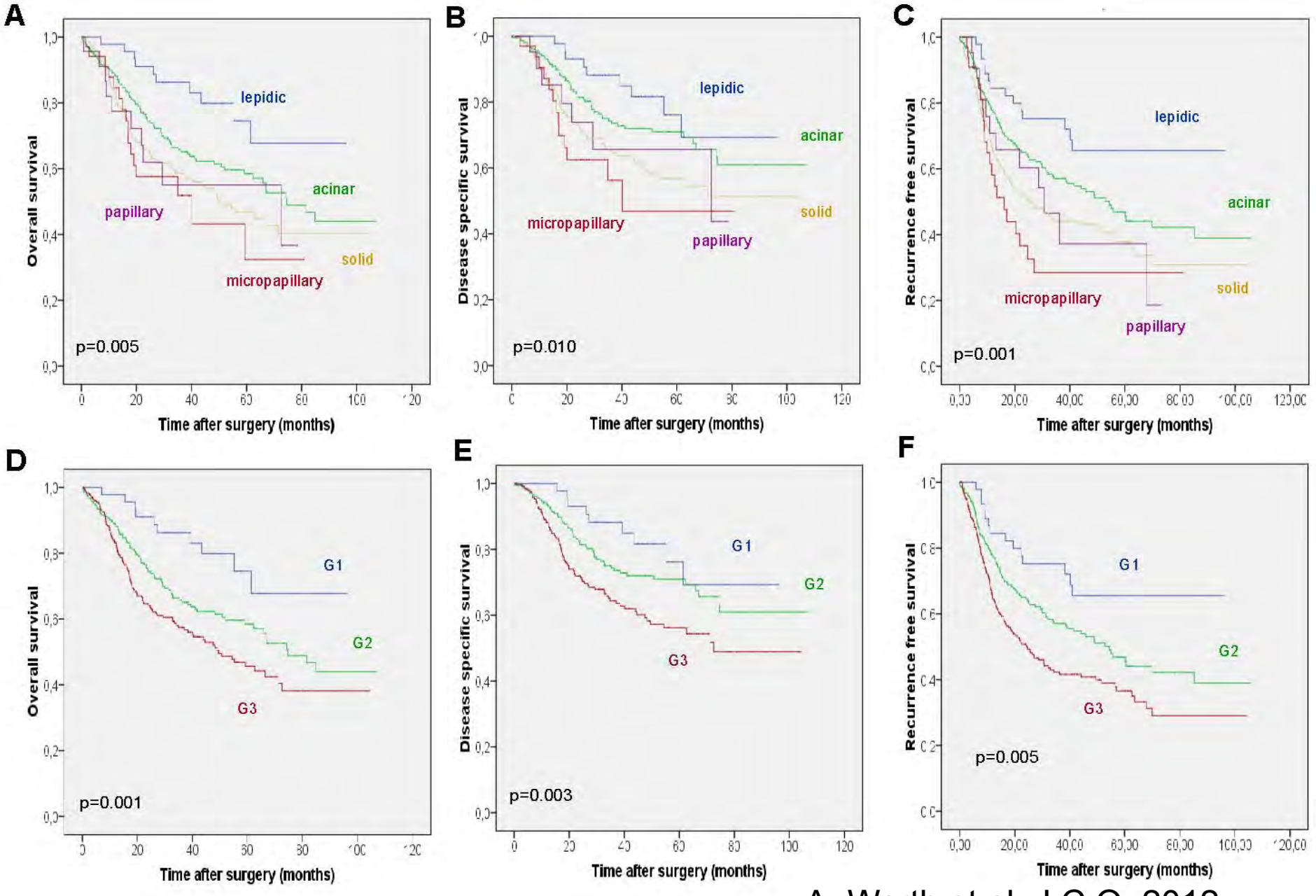
Recurrence-free survival (RFS) by histologic type



Histologic Type (N)	5 Year RFS %
AIS (1)	100
MIA (8)	100
Lepidic NM (29)	90
Papillary (143)	83
Acinar (232)	85
Inv Mucinous Ad (13)	76
Solid (67)	71
Micropapillary (12)	64
Colloid (9)	71

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011

Valeur pronostique dans 533 adénocarcinomes opérés

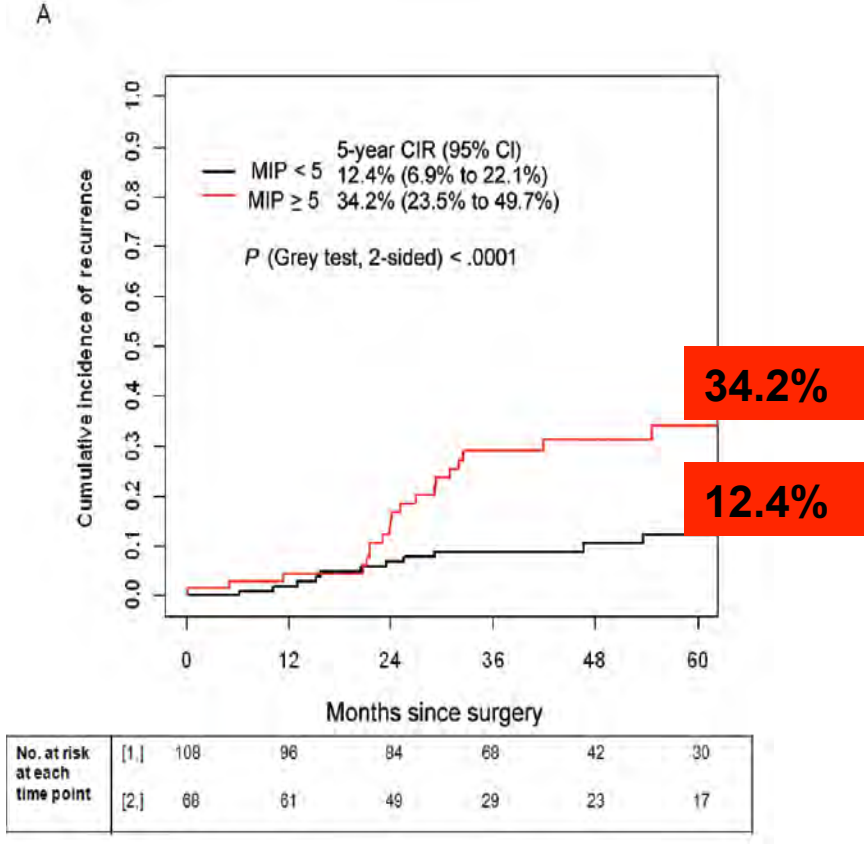


A. Warth et al. J.C.O. 2012

Impact of Micropapillary Histologic Subtype in Selecting Limited Resection vs Lobectomy for Lung Adenocarcinoma of 2 cm or Smaller

Jun-ichi Nitadori, Adam J. Bograd, Kyuichi Kadota, Camelia S. Sima, Nabil P. Rizk, Eduardo A. Morales, Valerie W. Rusch, William D. Travis, Prasad S. Adusumilli

Limited Resection : MIP ≥5%



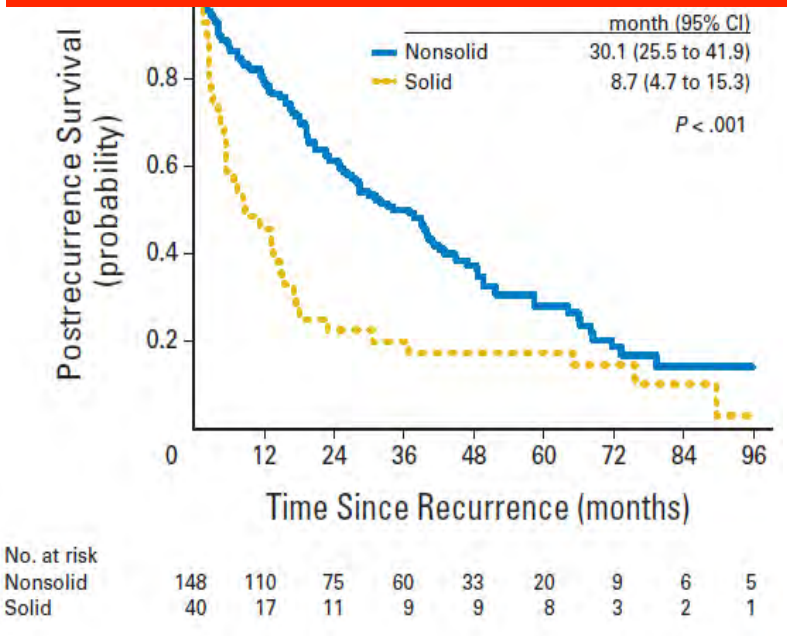
- 734 resected lung Adenoca
- MIP ≥5% associated with increased risk of recurrence in limited resection but not lobectomy patients (p<0.001)
- MV Analysis: independent predictor HR 3.11 (CI 1.48-6.54) p=.003
- In MIP ≥5% tumors local recurrence strongly associated with surgical margin <1 cm.
- Suggests LR may not be appropriate for lung ADC with any MIP

Nitadori J et al: J Nat Ca Inst 105:1212-1220, 2013

Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival

Hideki Ujiie, Kyuichi Kadota, Jamie E. Chaft, Daniel Buitrago, Camelia S. Sima, Ming-Ching Lee, James Huang, William D. Travis, Nabil P. Rizk, Charles M. Rudin, David R. Jones, and Prasad S. Adusumilli

Postrecurrence survival: solid vs nonsolid



- 1120 Stage 1 ADC; 188 recurrences
- Solid predominant subtype is correlated with earlier (p=.007) distant (extrathoracic) metastasis (p=.001) and multiple-site recurrence (p=.011) in pts with primary lung adenoca
- Risk of recurrence peaked within 12 months; most occurred within 2 yrs
- MV analysis: independent predictor of post recurrence survival:
- High-grade SOL vs low or intermediate grade HR 1.76 (CI:1.11-2.77) p=0.016
- Data provides rationale for investigating adjuvant therapy

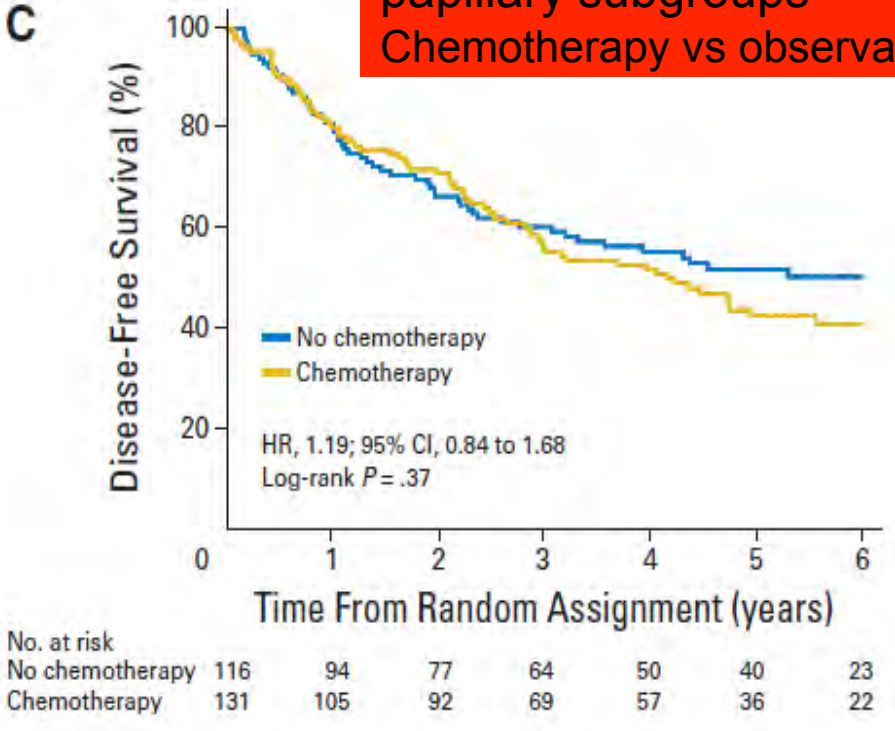
Ujiie H, et al: JCO 2015;33: epub ahead

Subtype Classification of Lung Adenocarcinoma Predicts Benefit From Adjuvant Chemotherapy in Patients Undergoing Complete Resection

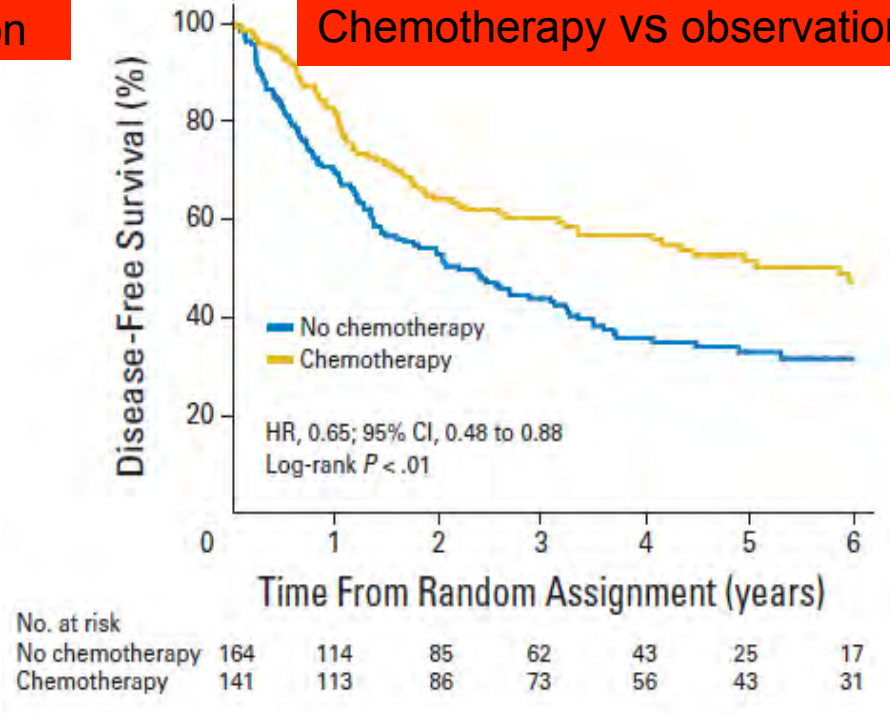
Ming-Sound Tsao, Sophie Marguet, Gwénaël Le Teuff, Sylvie Lantuejoul, Frances A. Shepherd, Lesley Seymour, Robert Kratzke, Stephen L. Graziano, Helmut H. Popper, Rafael Rosell, Jean-Yves Douillard, Thierry Le-Chevalier, Jean-Pierre Pignon, Jean-Charles Soria, and Elisabeth M. Brambilla

- 575 Resected Adenoca from LACE-Bio study

Disease free survival: Acinar/ papillary subgroups Chemotherapy vs observation



Disease free survival: Micropapillary/solid subgroups Chemotherapy vs observation



Tsao MS, et al.: J Clin Oncol 2015; epub

Subtype Classification of Lung Adenocarcinoma Predicts Benefit From Adjuvant Chemotherapy in Patients Undergoing Complete Resection

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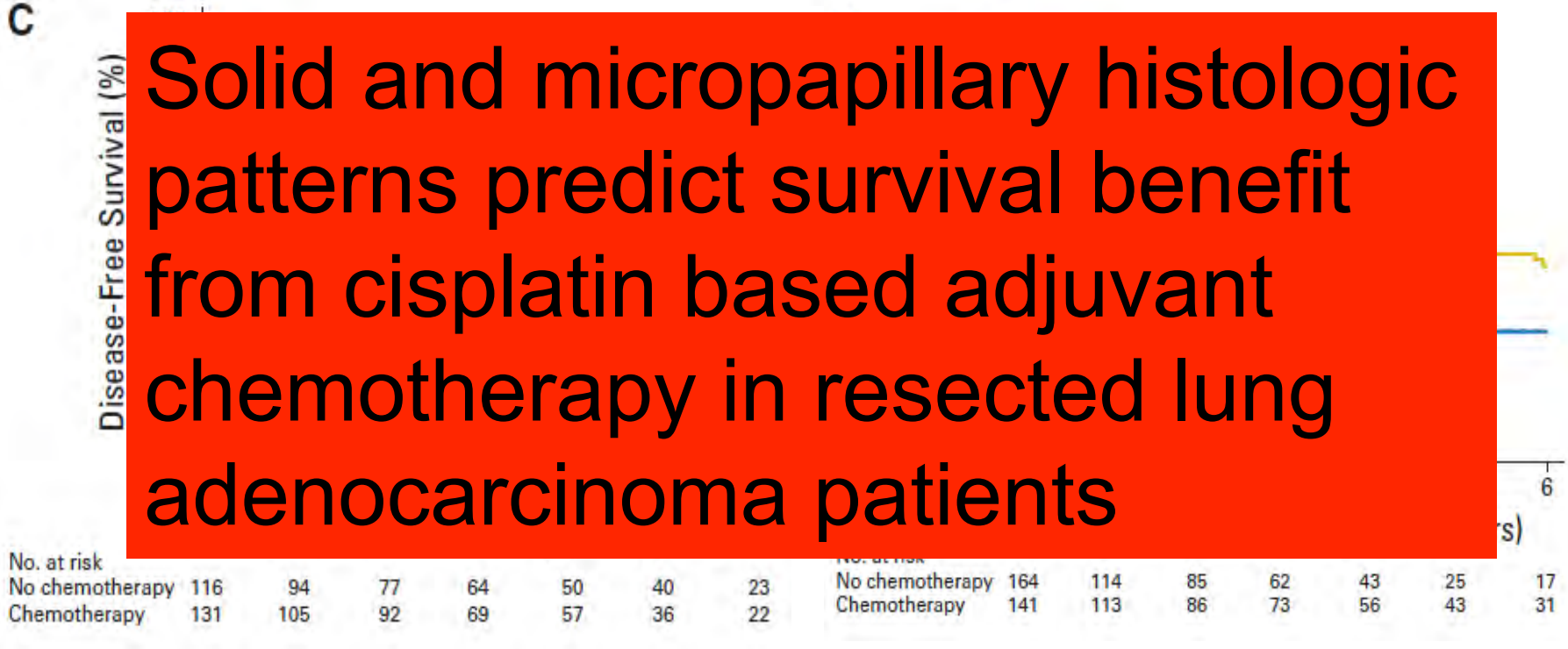


Solid and micropapillary histologic patterns predict survival benefit from cisplatin based adjuvant chemotherapy in resected lung adenocarcinoma patients

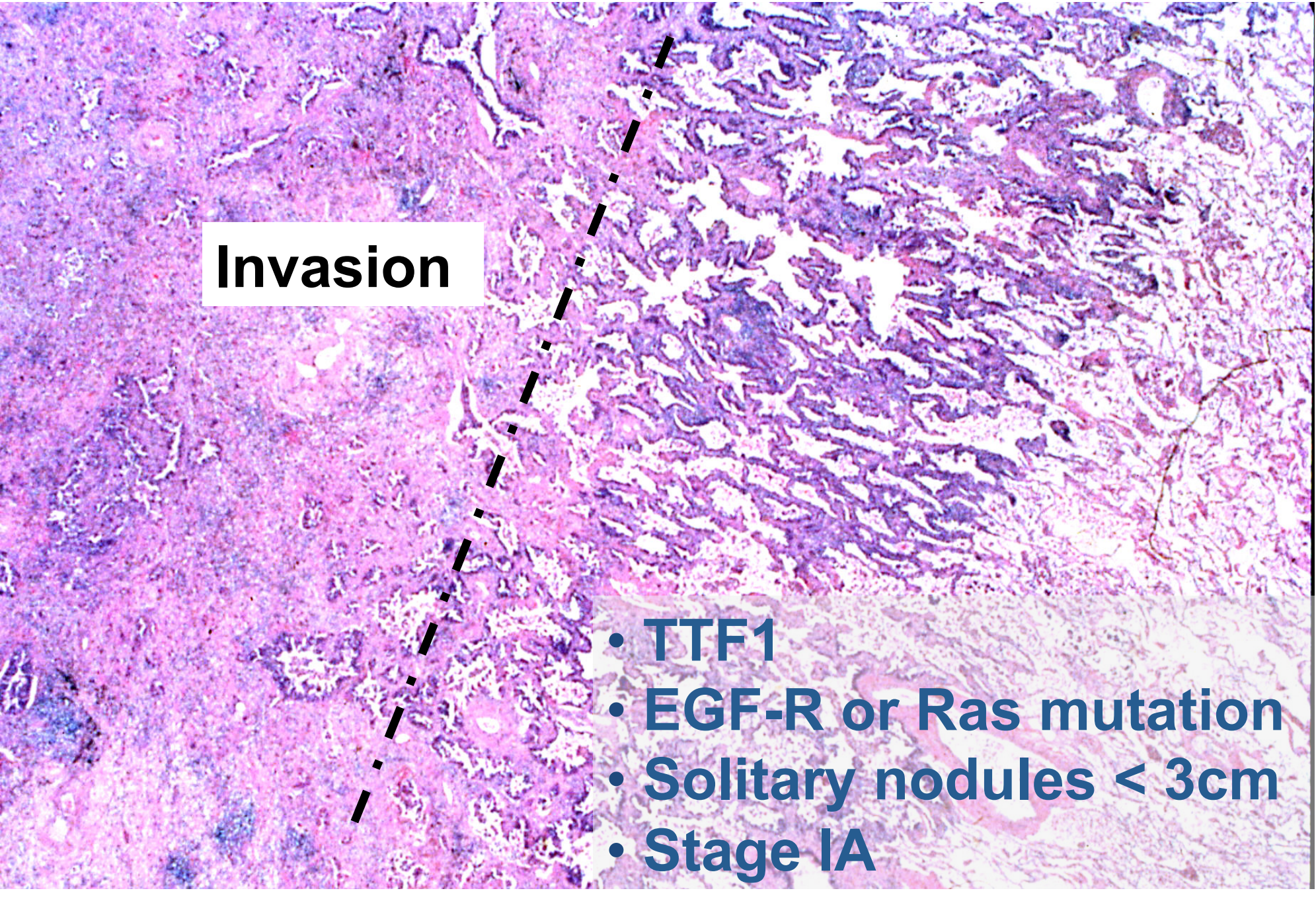
Disease free survival: Acinar/ papillary subgroups
Chemotherapy vs observation

Disease free survival: Micropapillary/solid subgroups
Chemotherapy vs observation

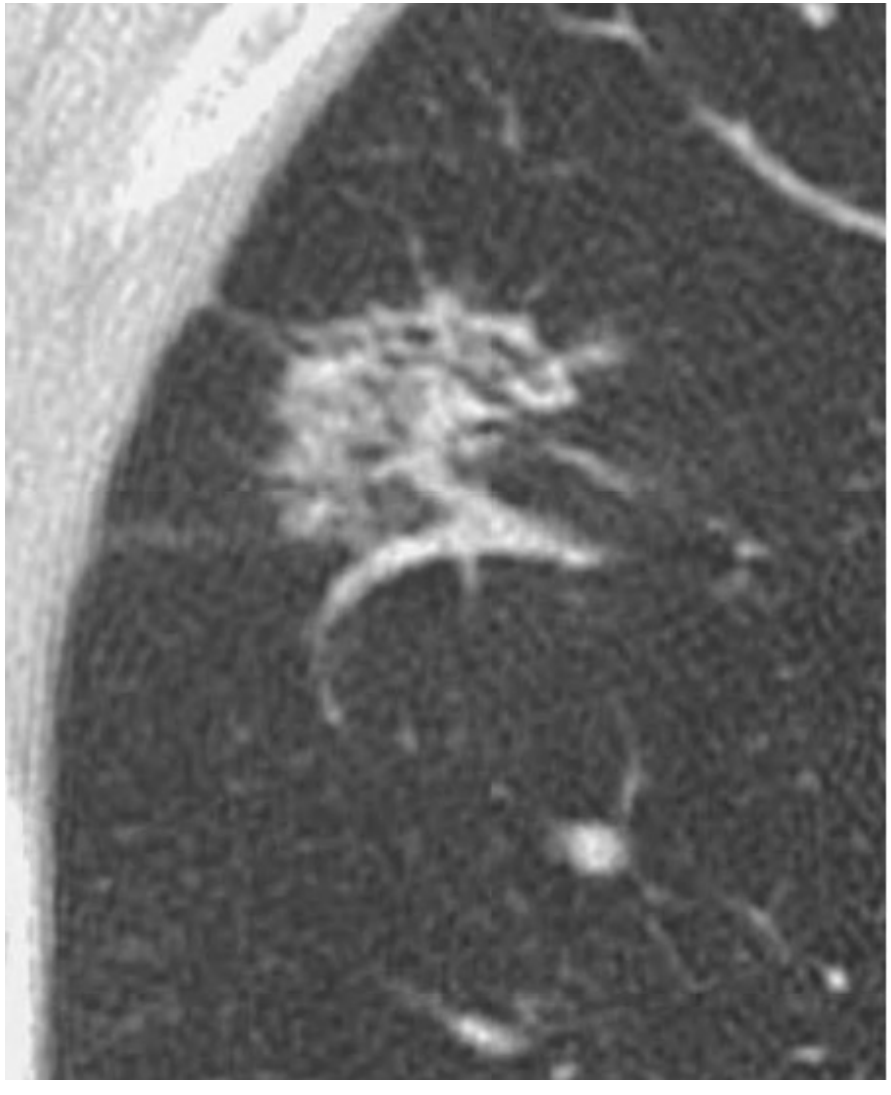
La classification participe au management des patients opérés ?

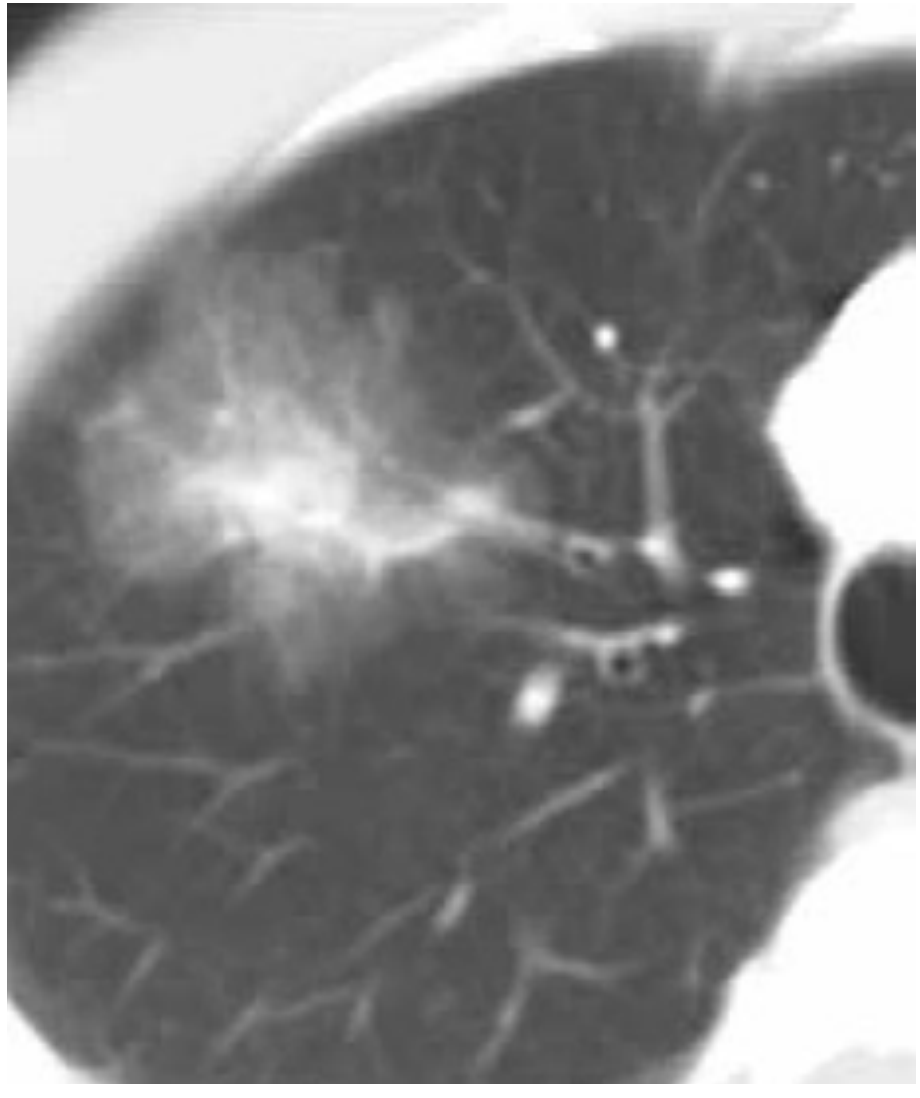
- Prédit survie et rechute
- Prédit un bénéfice de survie par la chimiothérapie cisplatin adjuvante
- Définit AIS & MIA: 100% et presque 100% de survie si resection complète
- Permet les correlations radio-pathologiques
- Impacte le Staging TNM
  - Taille de la zone invasive = T du TNM
  - Comparaison des tumeurs multiples = primaires ou métastases intrapulmonaires

Adenocarcinoma lepidic pattern predominant

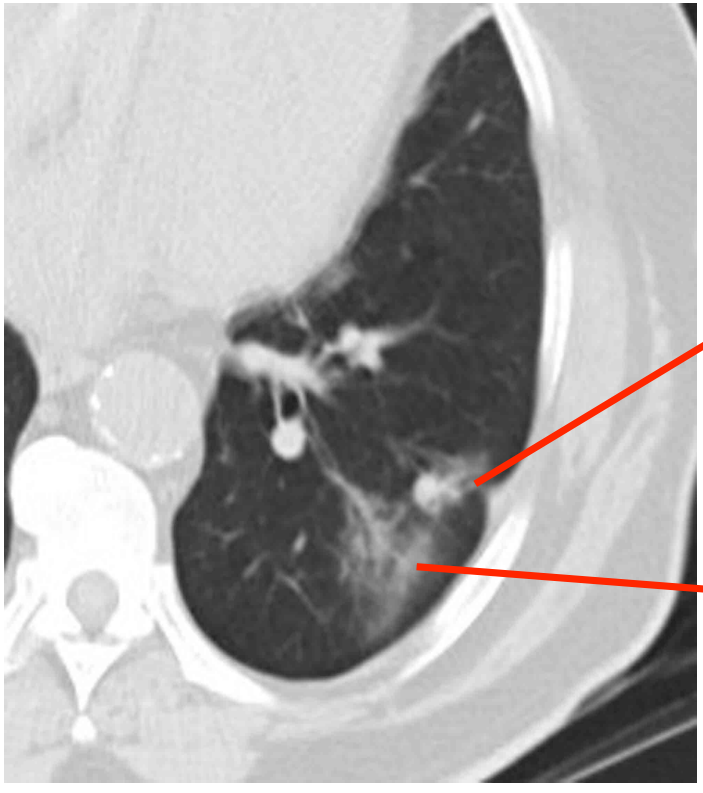


Adénocarcinome lépidique (prédominant)
CT: tumeur semi solide





Corrélations radio pathologiques



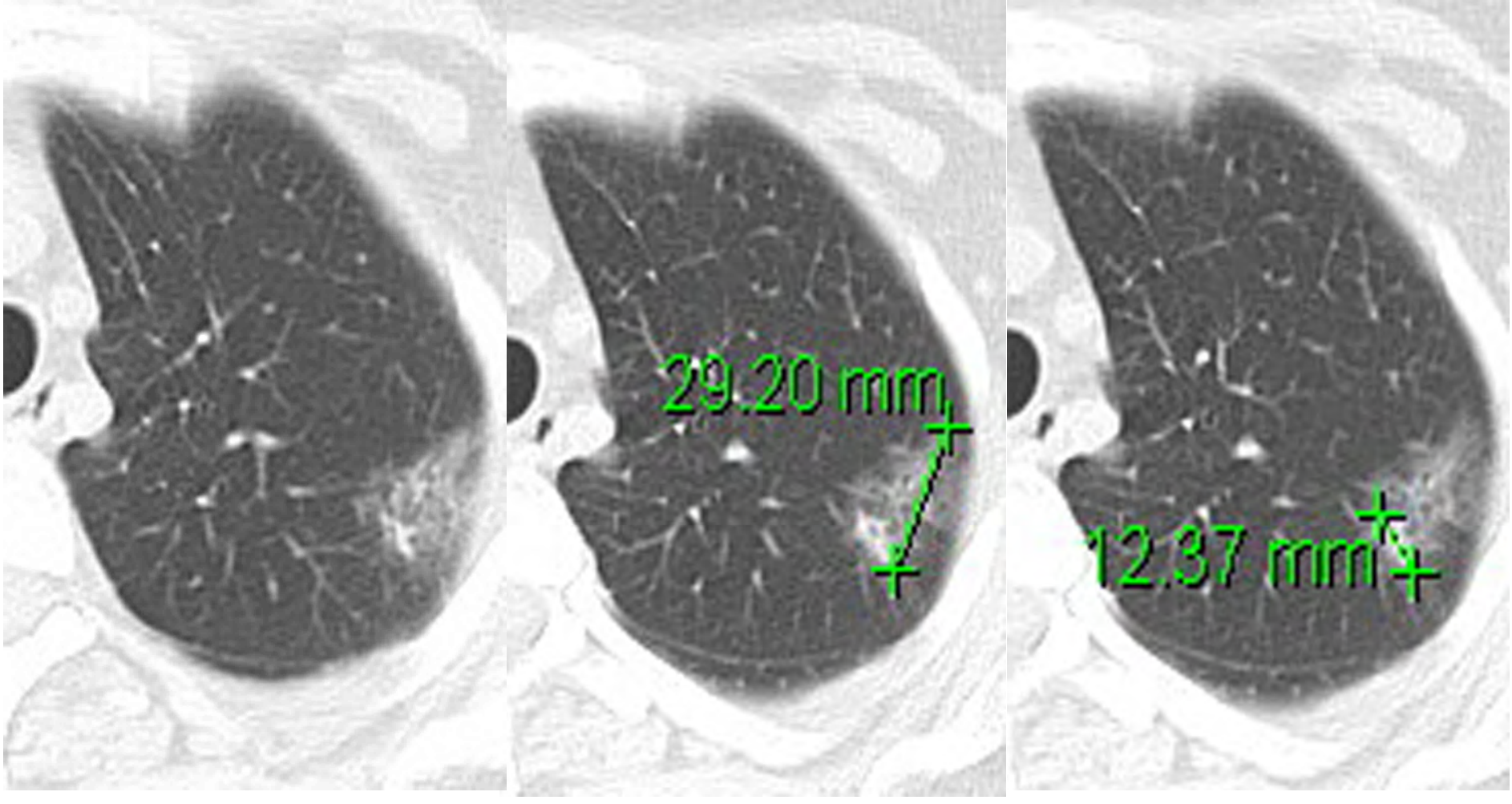
SOLIDE / CT

Histologie :
Adénocarcinome acineux, papillaire, solide, micropapillaire, mucineux invasif

VERRE DEPOLI / CT

Histologie:
le plus souvent lépidique mais peut être invasif

Case: tumor size in lepidic adca requires rad-path correlation

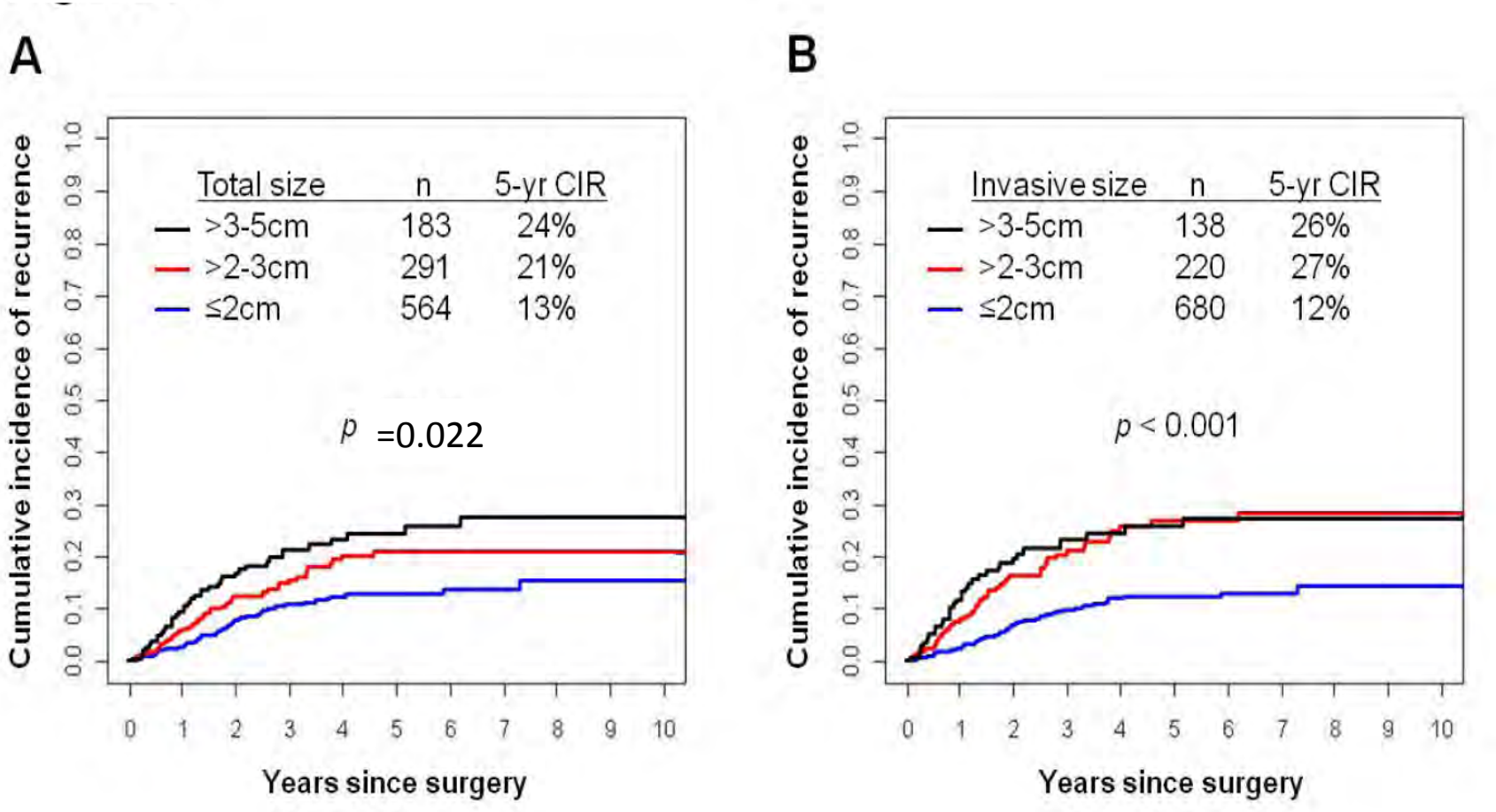


PART SOLID NODULE TOTAL SIZE SOLID COMPONENT

Reclassification du TNM par la révision du T

116 (40%) T1b (>2-3 cm) → T1a (≤2 cm)

45 (25%) T2a (>3-5 cm) → T1b (>2-3 cm)



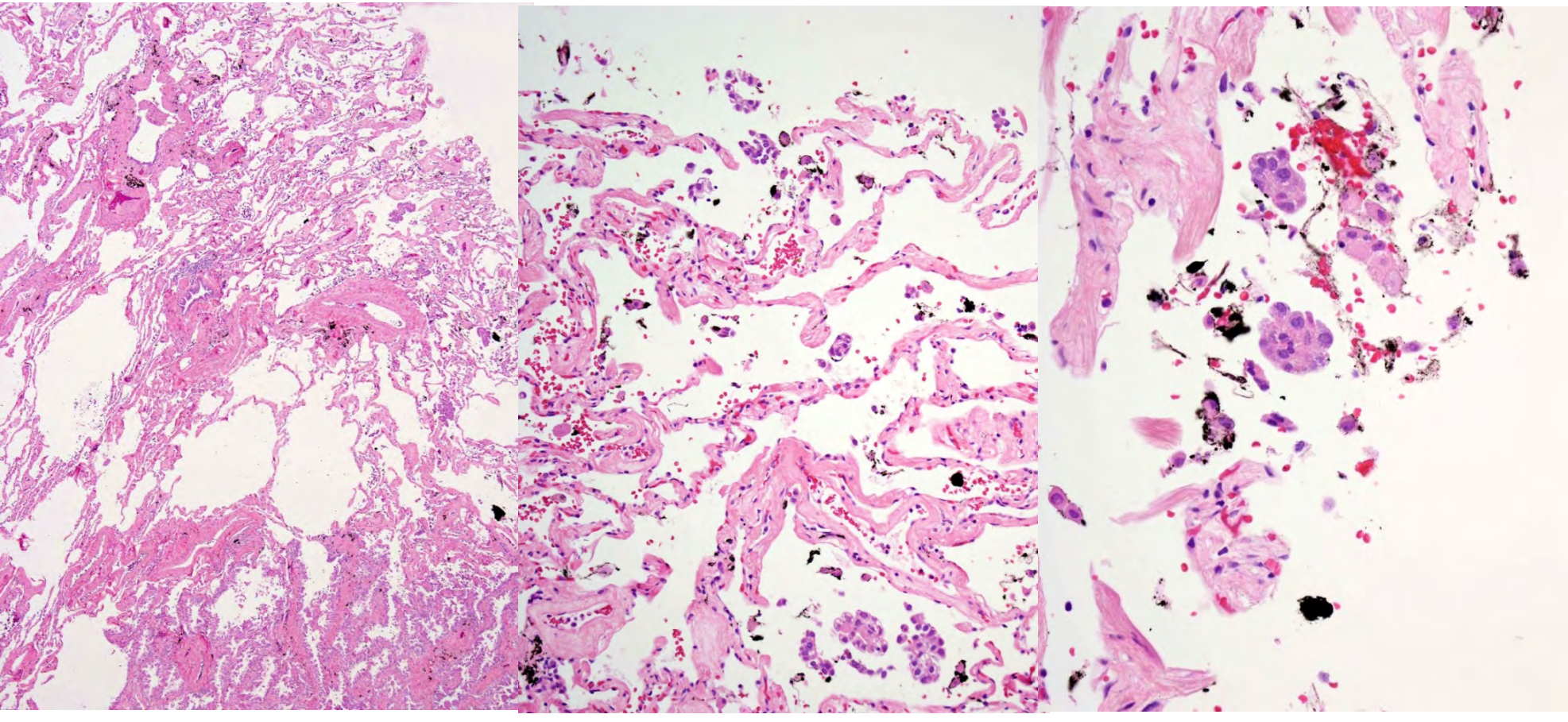
Kadota K et al, Am J Surg Path 38:448-60, 2014

Proposition pour la 8th edition TNM

- **Carcinome *In situ***
  - Tis (AIS)
  - Tis (SCIS)
- **Adénocarcinome à invasion minime**
  - T1a(mi)
  - Si multiples – T1a(mi)(m)
- **Utiliser la taille de l'invasion comme T-descriptor** dans les adénocarcinomes sub-solides CT ou les adenoca. non mucineux avec un composant lépidique en pathologie

Spread through air spaces (STAS)
in inked margin of resection

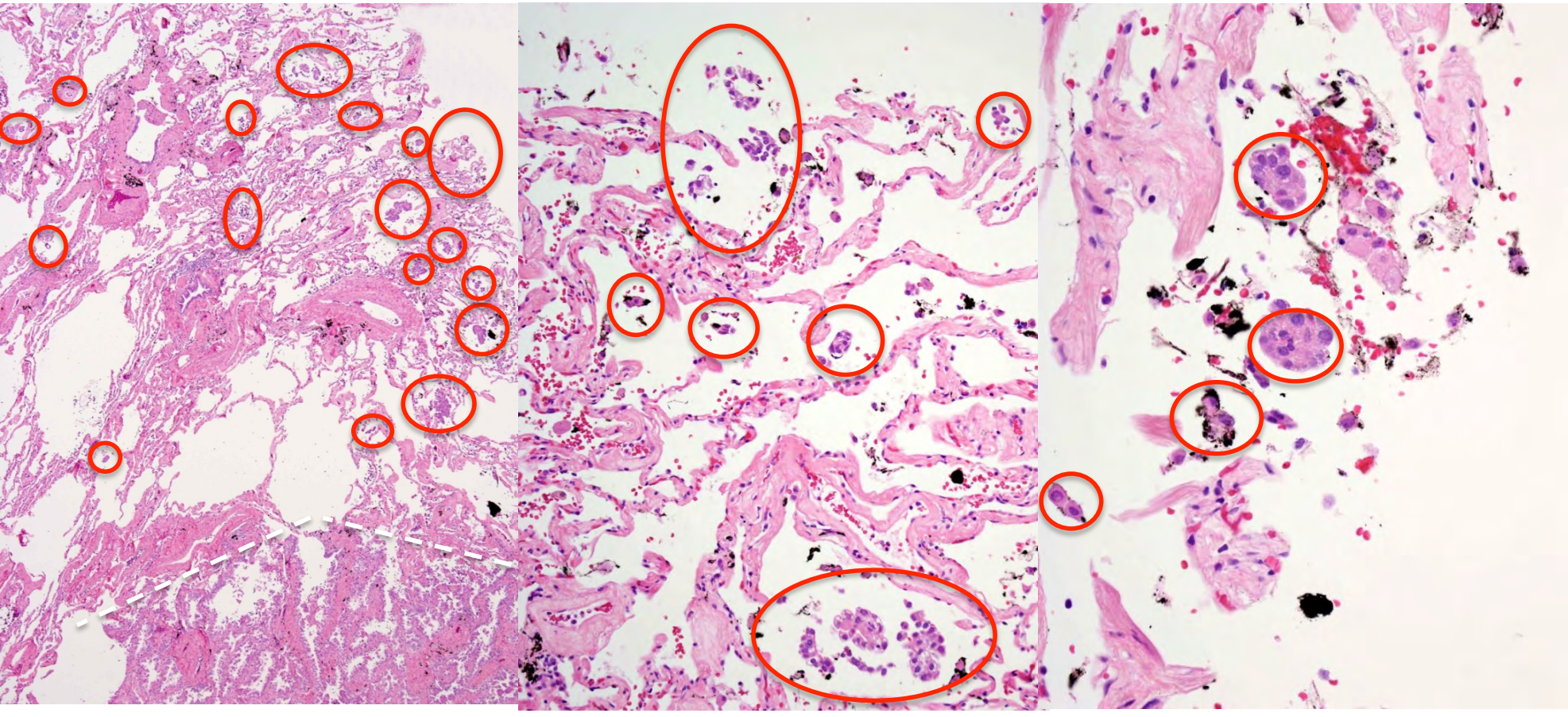
Extension à l'espace alvéolaire



Kadota K et al; JTO 2015; 10:806-14

Spread through air spaces (STAS)
in inked margin of resection

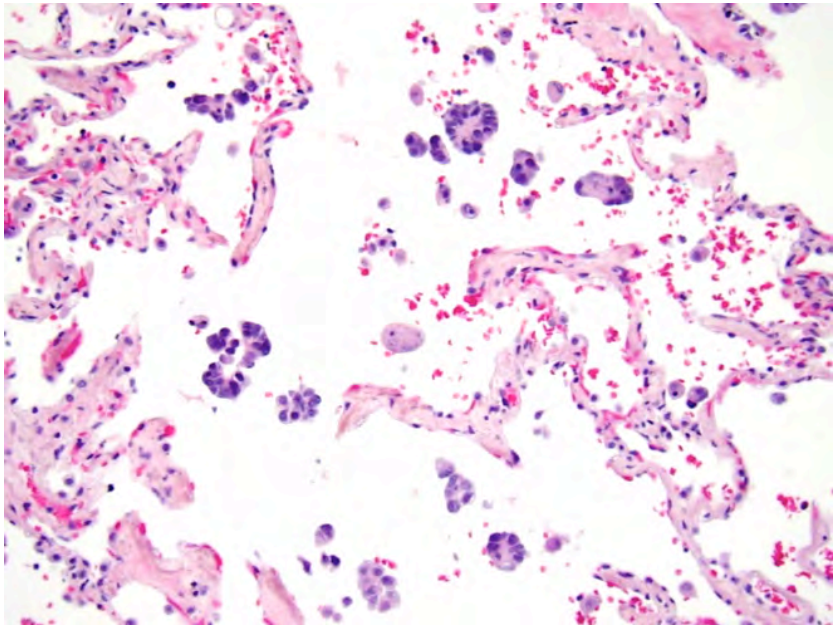
Extension à l'espace alvéolaire



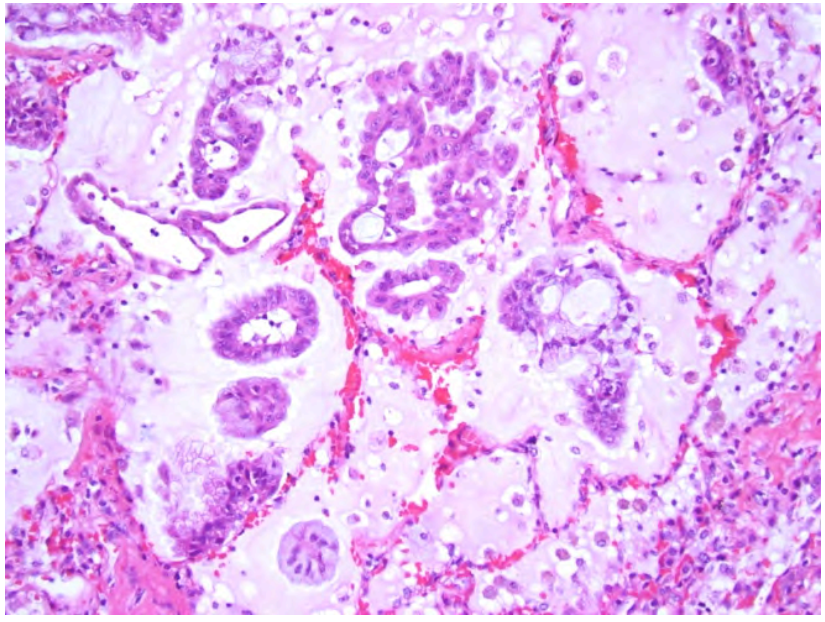
Kadota K et al; JTO 2015; 10:806-14

Histologic patterns of STAS in lung ADC

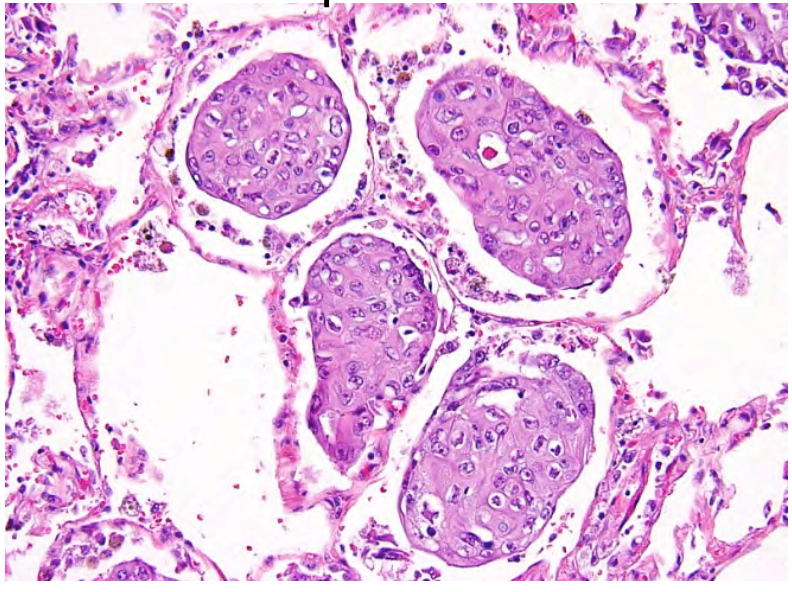
Micropapillary pattern



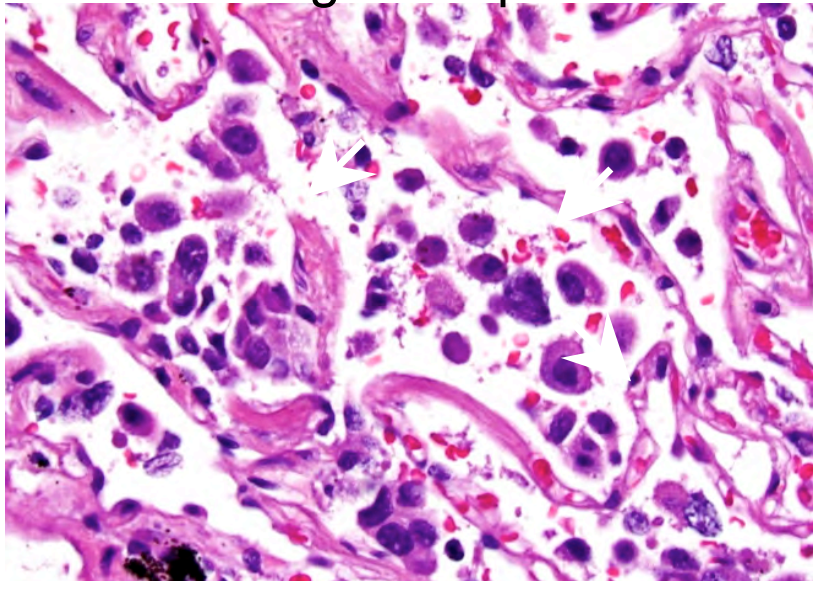
Micropapillary pattern (ring-like)



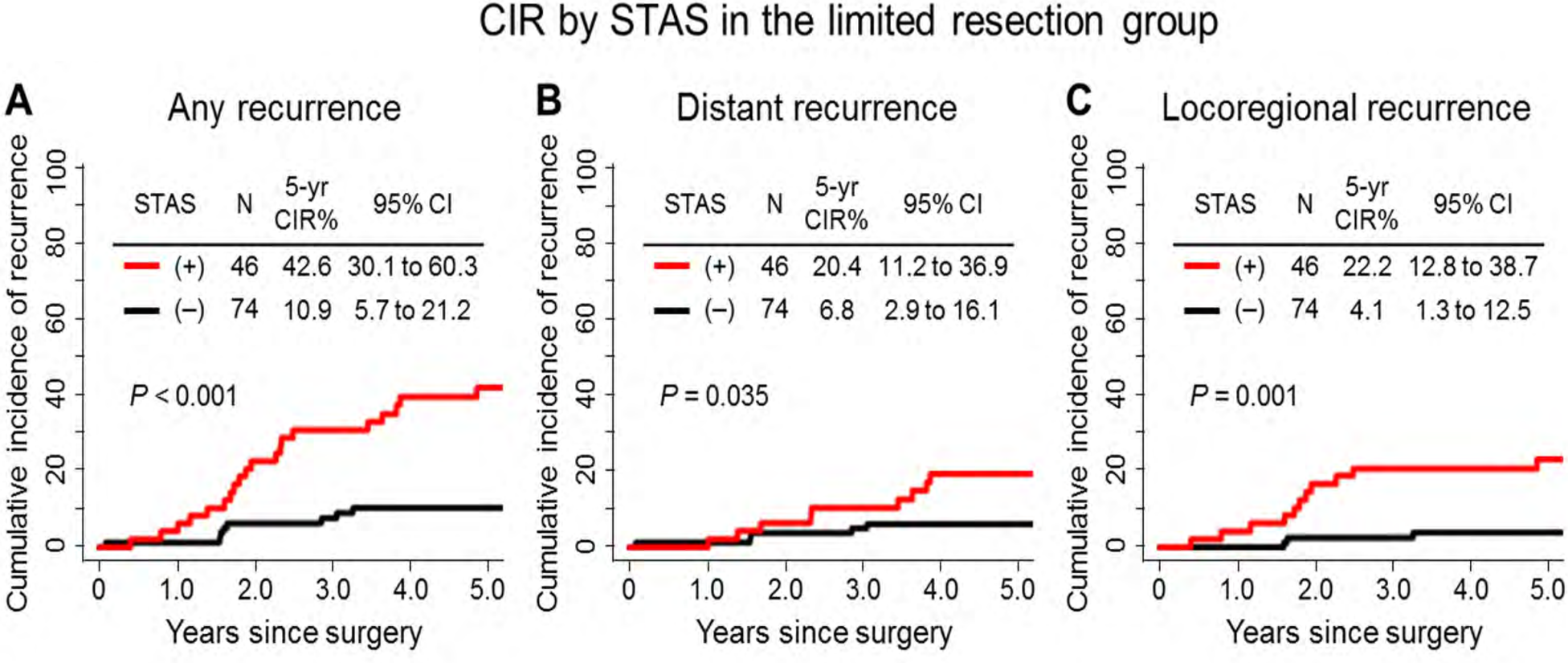
Solid pattern



Single cell pattern



STAS – incidence cumulative de rechute après resections limitées



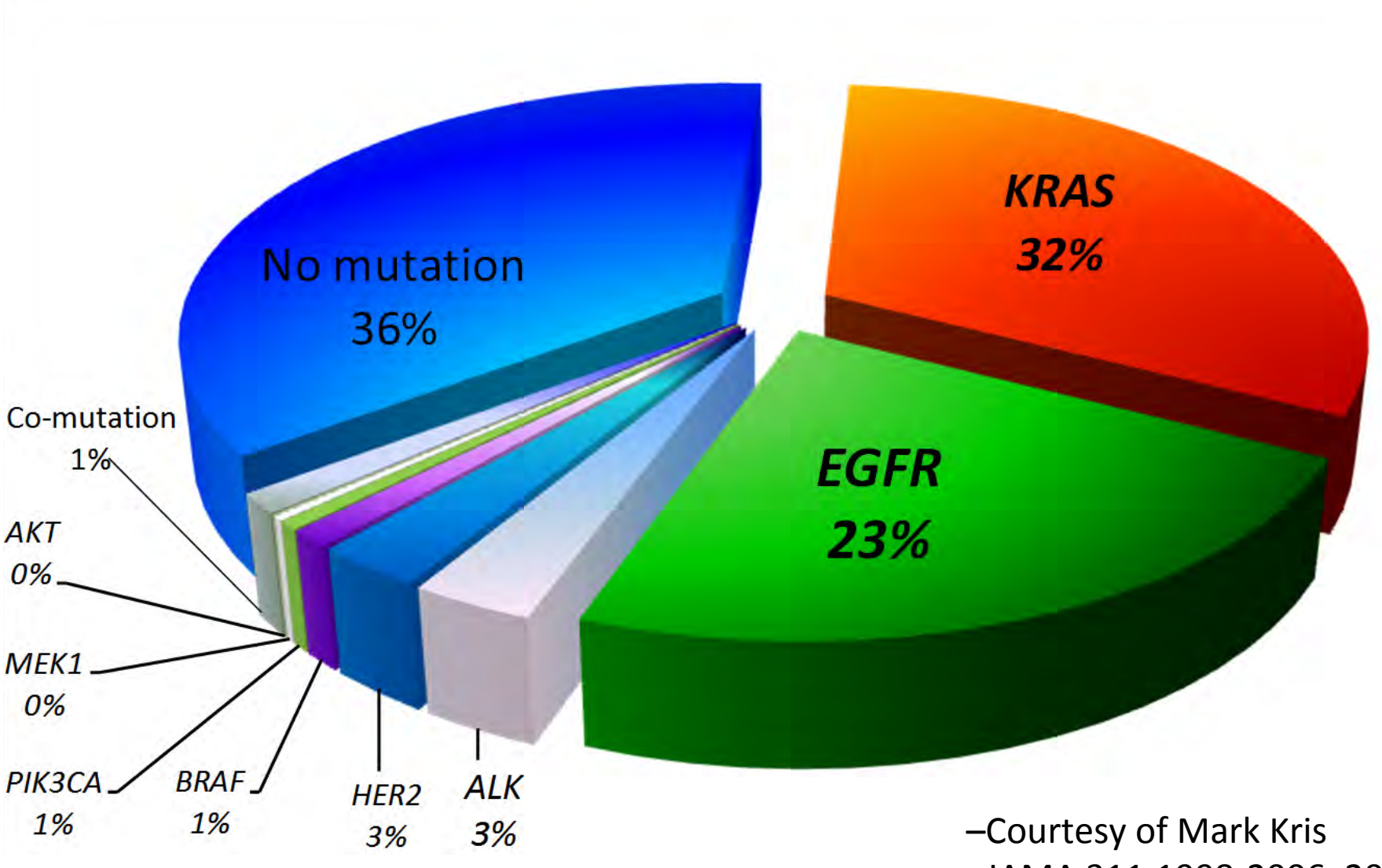
Multivariate analysis, presence of tumor STAS remained independently associated with the risk of recurrence (hazard ratio, 3.08; *P=0.014).*

Kadota K et al; JTO 2015; 10:806-14

Spread Through Air Spaces (STAS)
Extension aux espaces alvéolaires

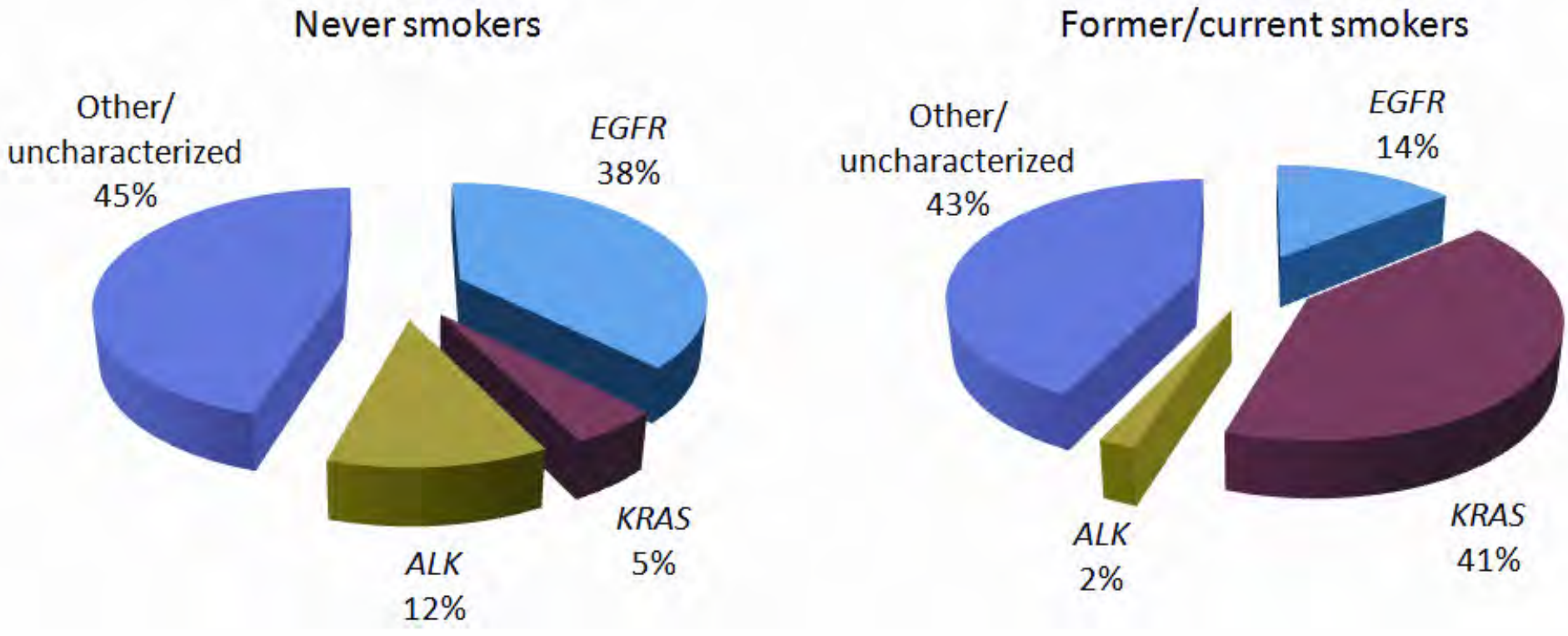
- Une invasion réelle, pas un artéfact
- Devant être incluse dans la définition de l'invasion dans les adénocarcinomes pulmonaires
- Devant être recherchée dans les specimens chirurgicaux de resection limitée (wedge) au niveau des agrafes marginales
- Nous proposons que le STAS ne soit pas inclus dans la taille tumorale ni dans l'évaluation architecturale des sous types histologiques
- Validations:
  - Warth A et al: AJSP 39:793-801, 2015
  - Onozato ML et al: AJSP 37:287-294, 2013
  - Shiono S et al: JTO 10 (Suppl):5284, 2015

Driver Mutations found in 65% of Adenocarcinoma Specimens



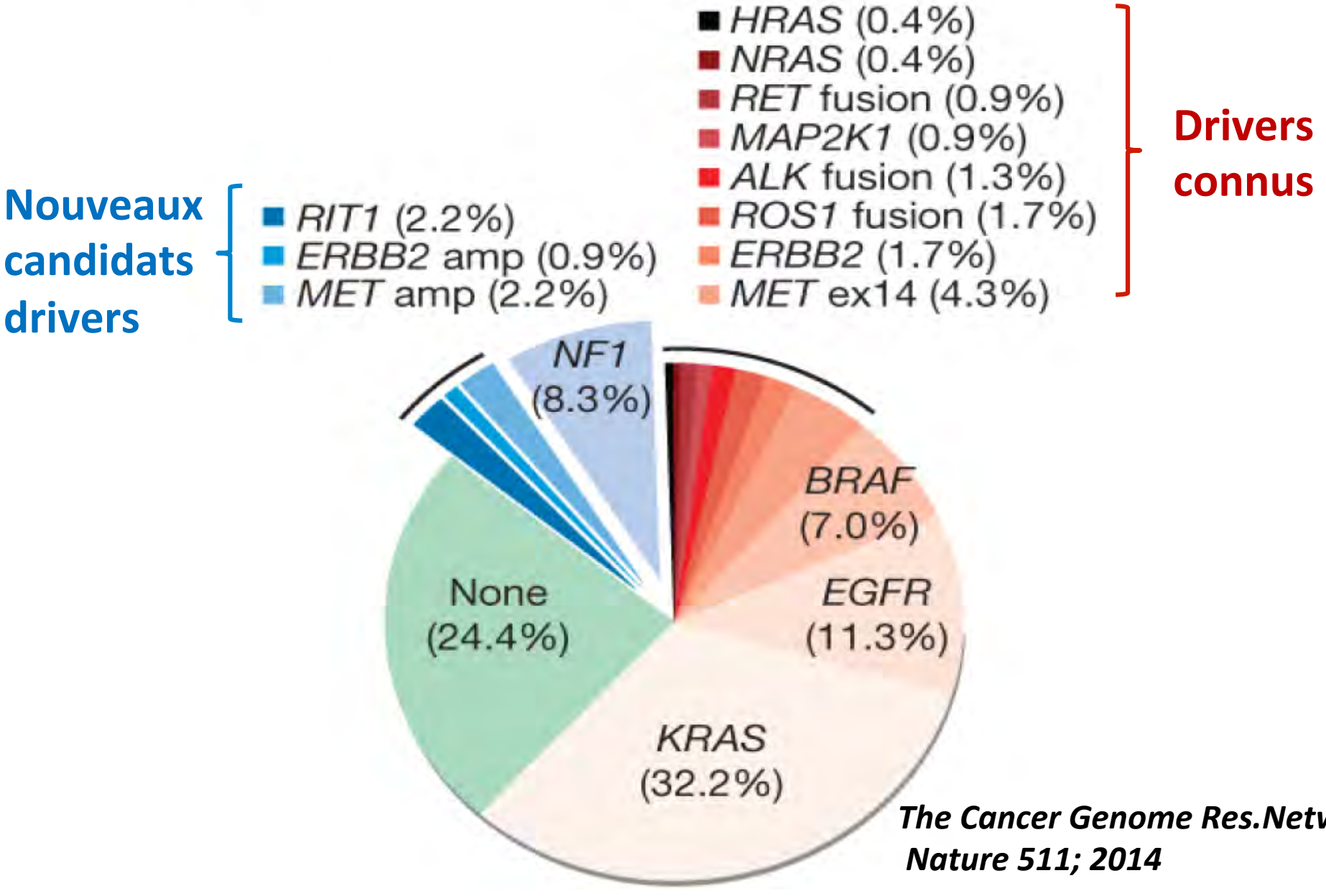
–Courtesy of Mark Kris
–JAMA 311:1998-2006, 2014

Molecular Alterations in Never Smokers *vs* Smokers



W. Pao et al. 2012 Nature Med 2012
WHO World Cancer Report : E.Brambilla,WD Travis; 2013

Adenocarcinomes : Nouveaux candidats driver oncogenes activant la voie RTK/RAS/RAF



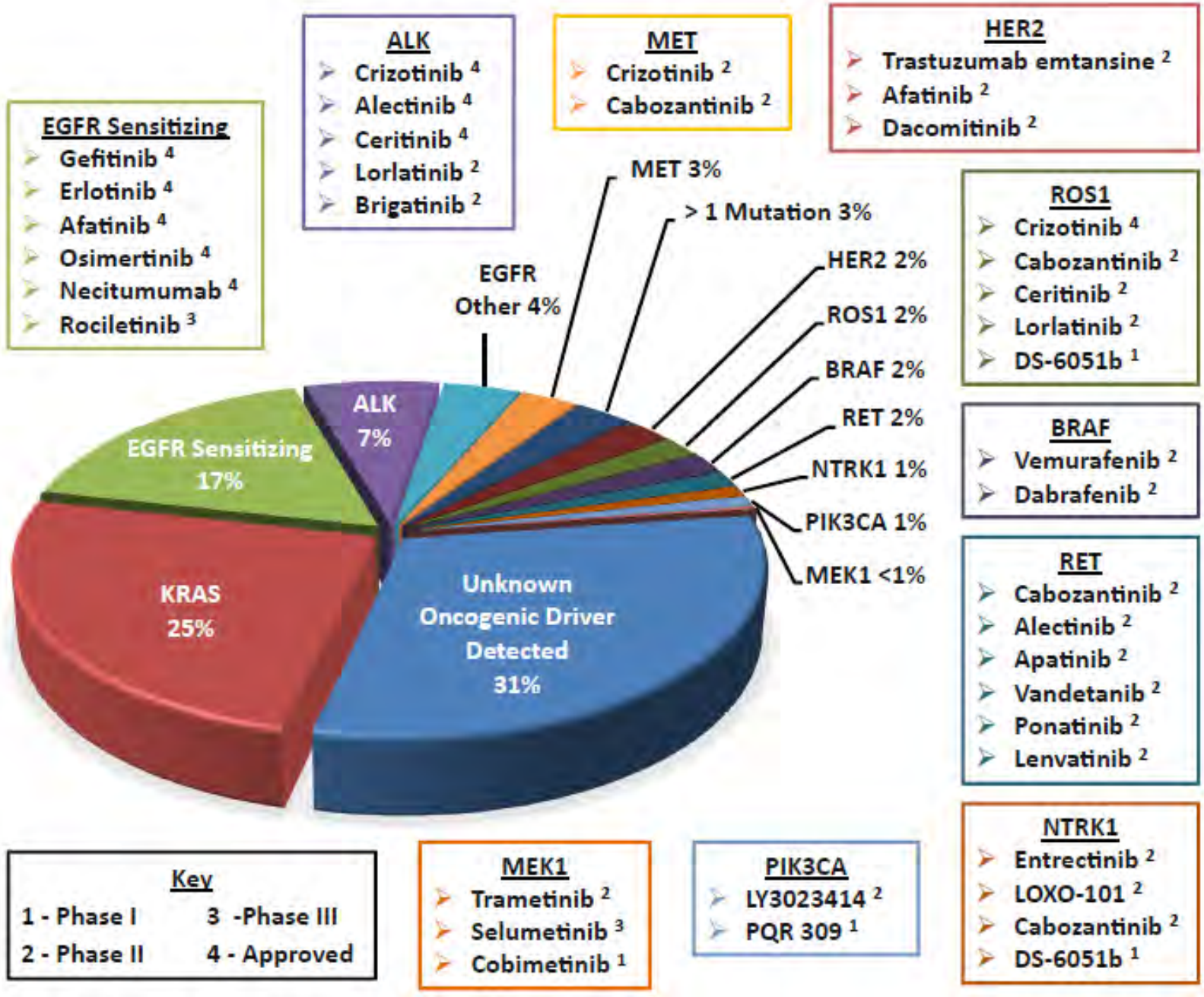
The Cancer Genome Res.Network
Nature 511; 2014

Driver mutations are targets for molecular based therapy

Target	Drug
EGFR	Erlotinib Afatinib
ALK fusions	Crizotinib Ceritinib
BRAF V600E	Dabrafenib
ROS1 fusions	Crizotinib
RET fusions	Cabozantinib
MET splice site Exon 14 mutations	Cabozantinib (and crizotinib)

Courtesy of Greg Riely

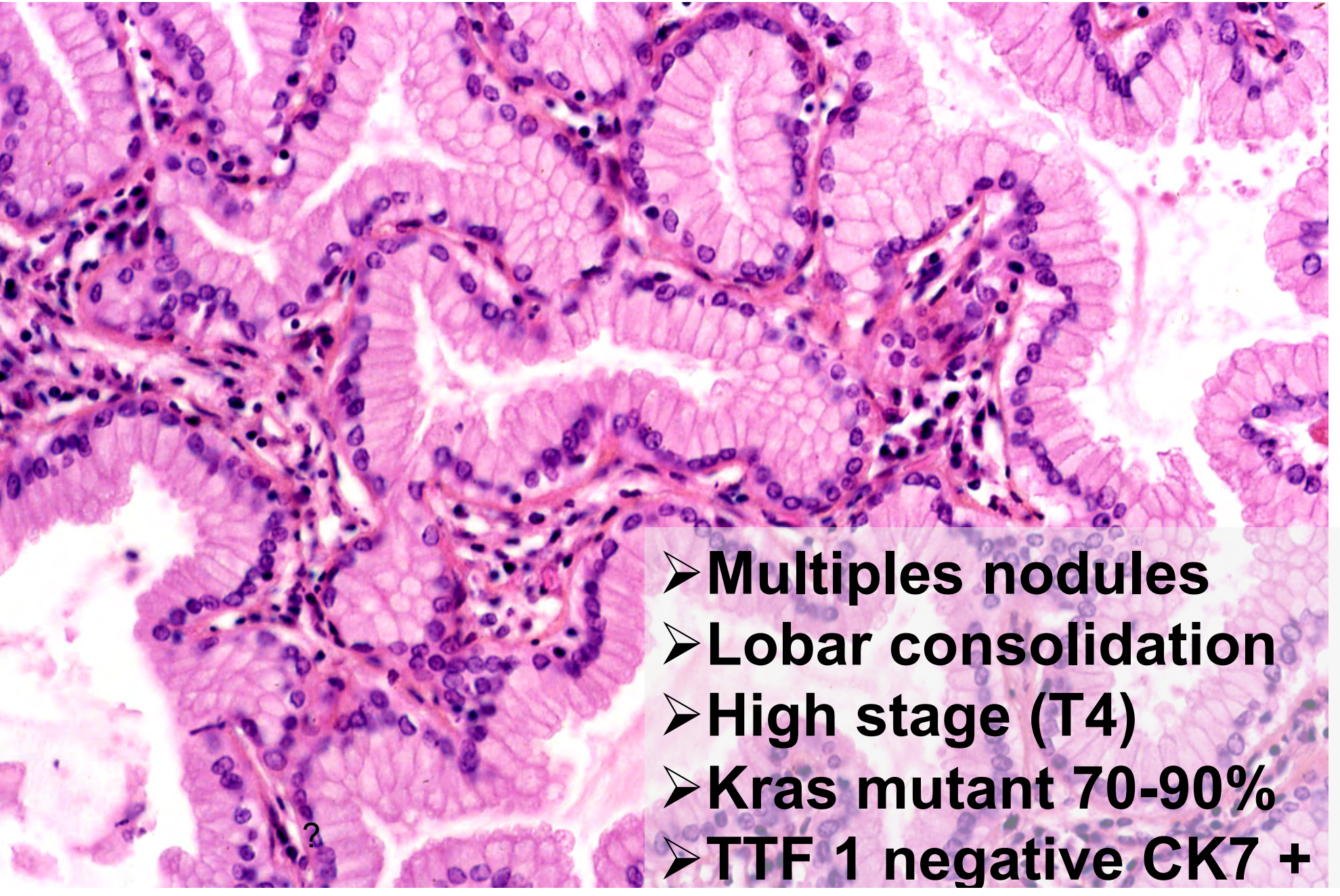
Classification of lung cancer now requires genetic testing



Specific histomolecular correlations

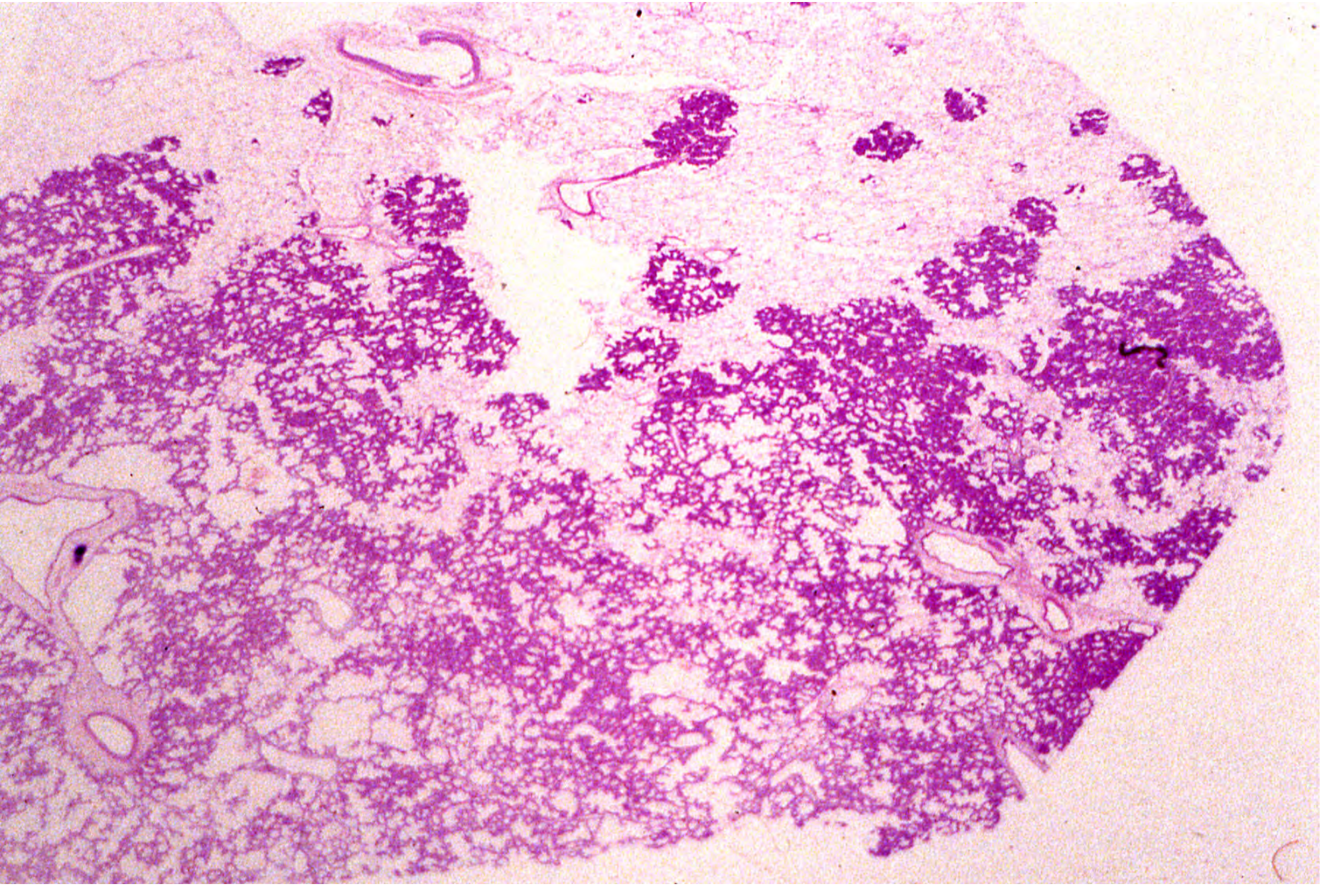
- Any strict correlation between adenocarcinoma subtype/pattern and specific genetic alteration ?
- Only one but strong correlation: invasive mucinous adenocarcinoma (IMA) never have EGFR mutation
- 75% of IMA dysplay a KRAS mutation .
- EGFR mutations , ALK and ROS1 rearrangements are restricted to TTF1 positive cases

Variant : Invasive mucinous adenocarcinoma

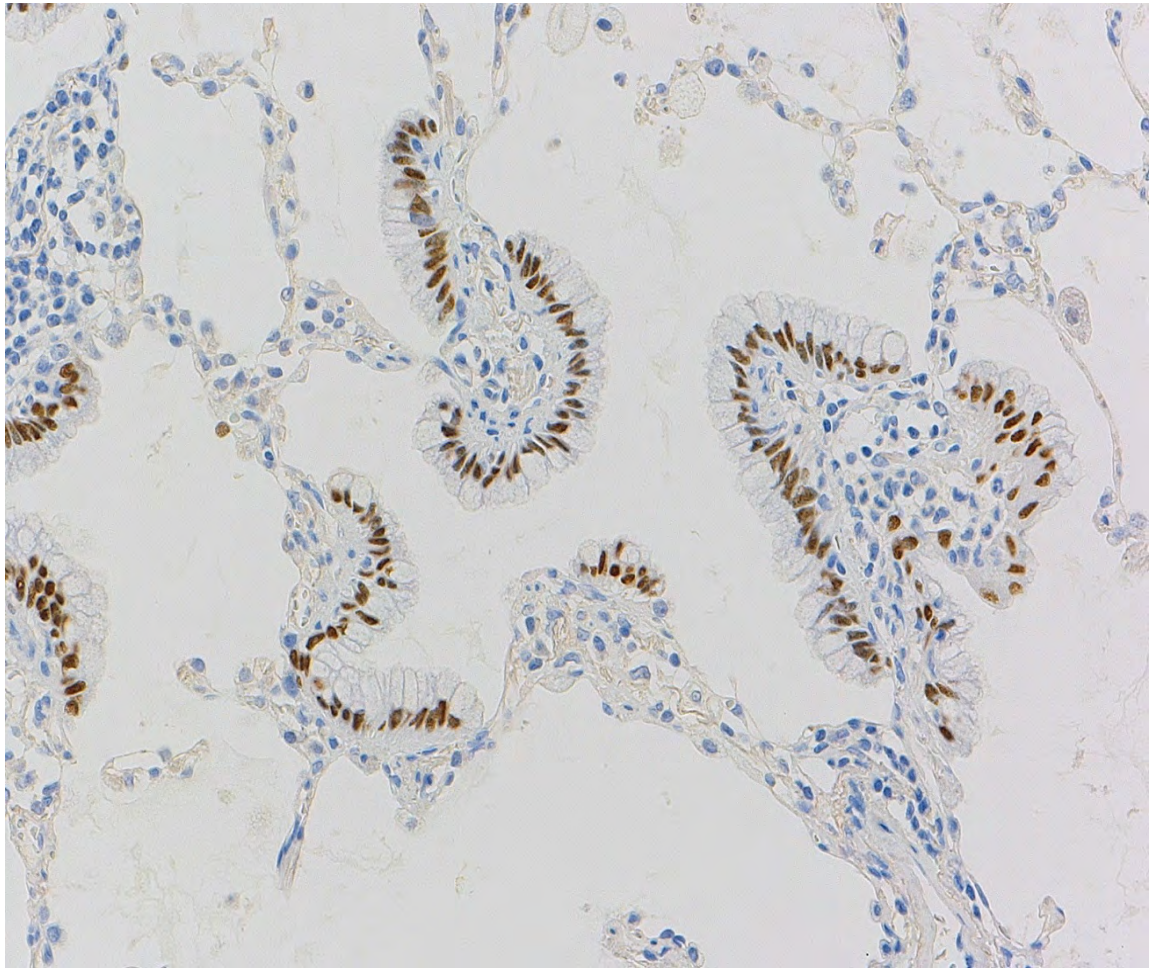


- Multiples nodules
- Lobar consolidation
- High stage (T4)
- Kras mutant 70-90%
- TTF 1 negative CK7 +

Adénocarcinomes invasifs mucineux : pseudo pneumonique

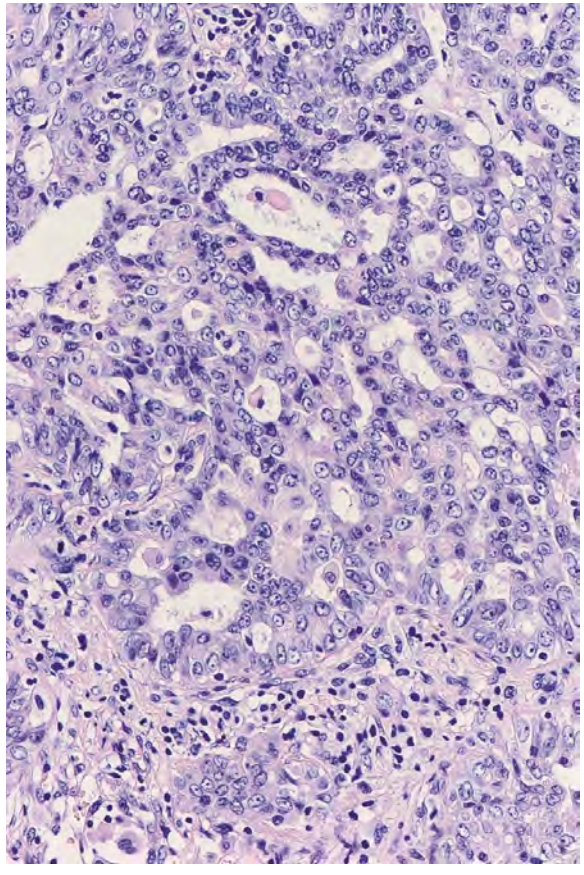


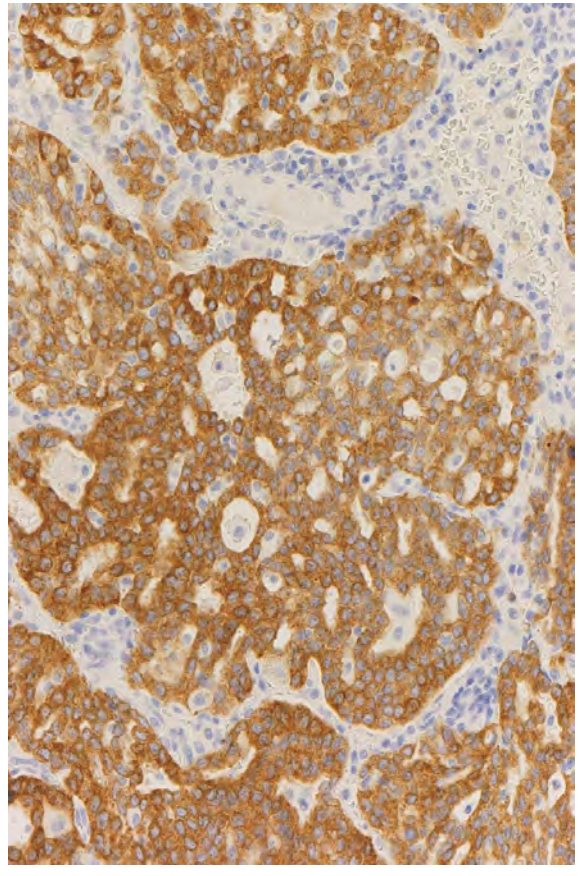
HNF4-α : Un marqueur des Adénocarcinomes invasifs mucineux



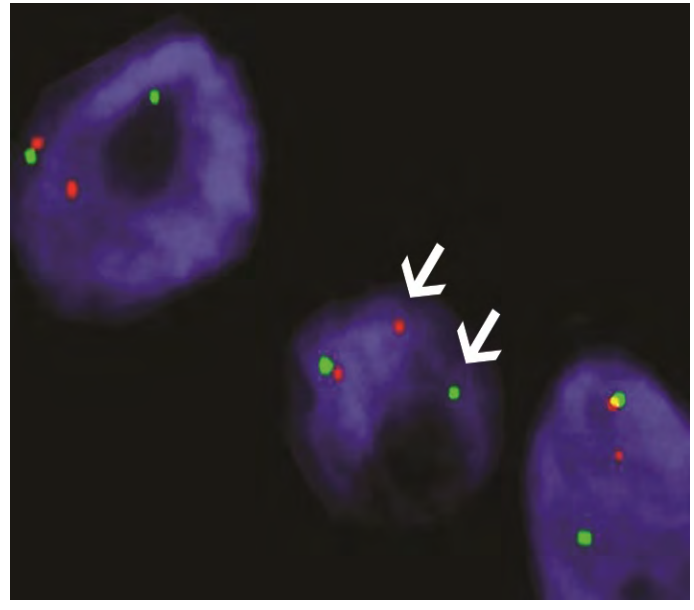
Sugano M et a: Am J Surg Pathol 37:211-8, 2013

Adenocarcinoma: *ALK* Fusion





ALK IHC (D5F3 ou 5A4)



ALK FISH

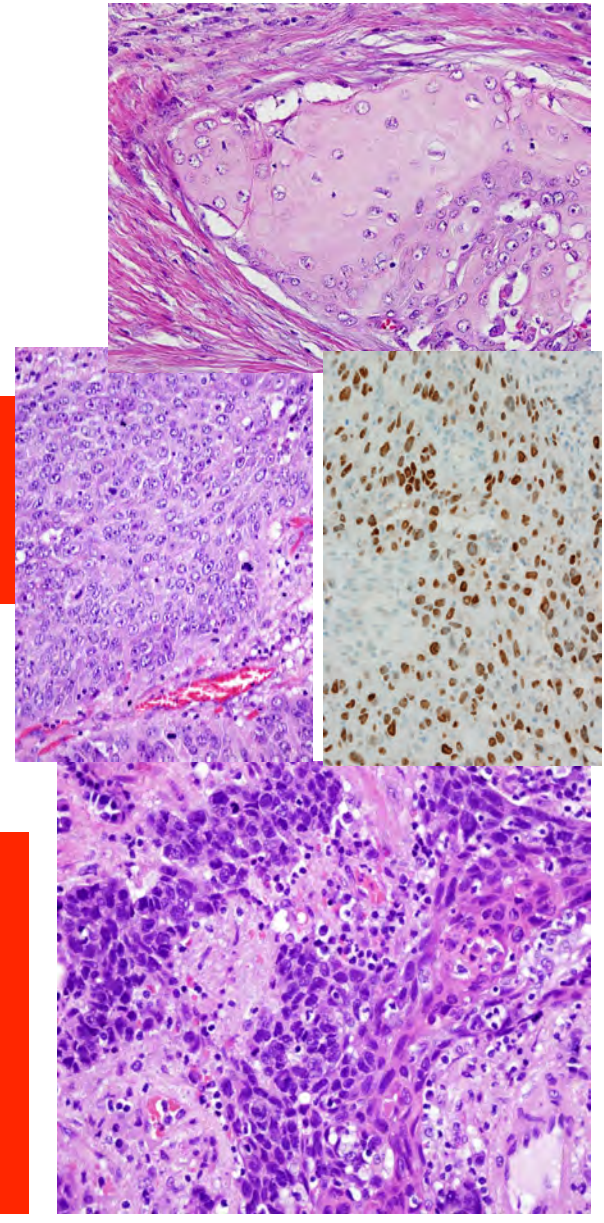
OMS 2015 :Carcinomes épidermoïdes

- Keratinisants
- Non-keratinisants

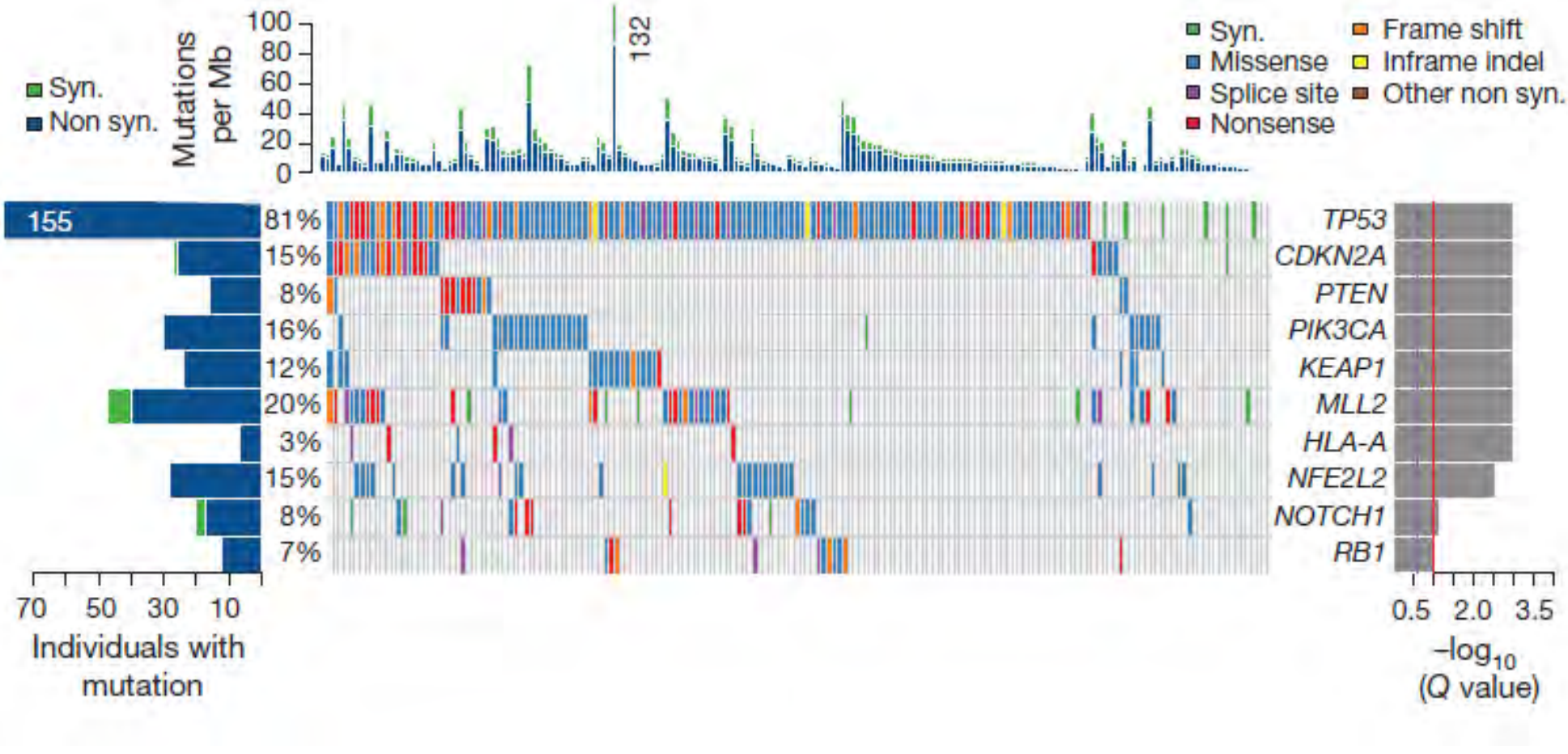
IHC P40positif,
TTF-1 negatif

- Carcinomes basaloides

IHC (+p40 , -TTF1 & NE markers)
r/o LCNEC & SCLC

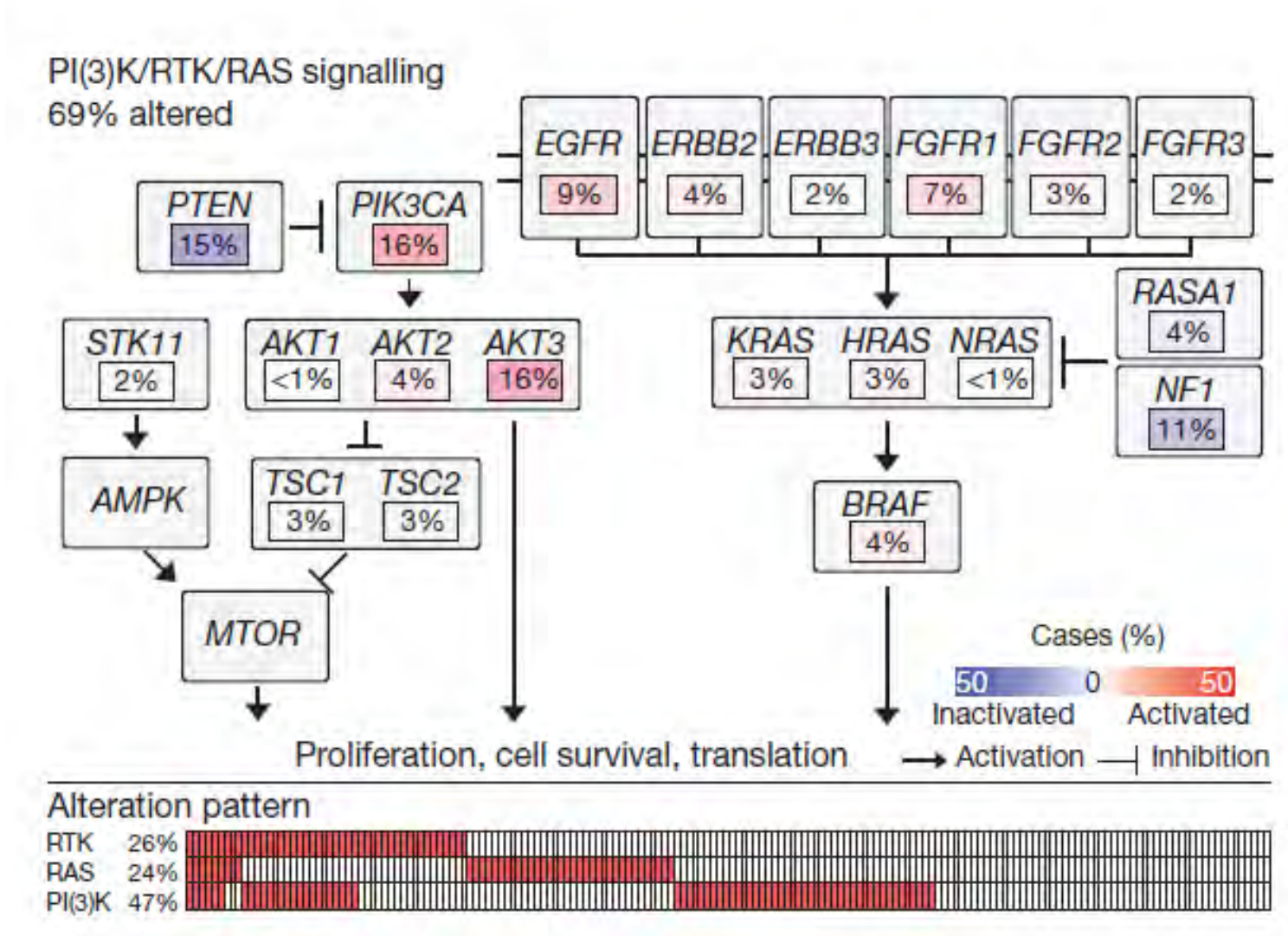


Significant mutated genes in Squamous cell carcinoma



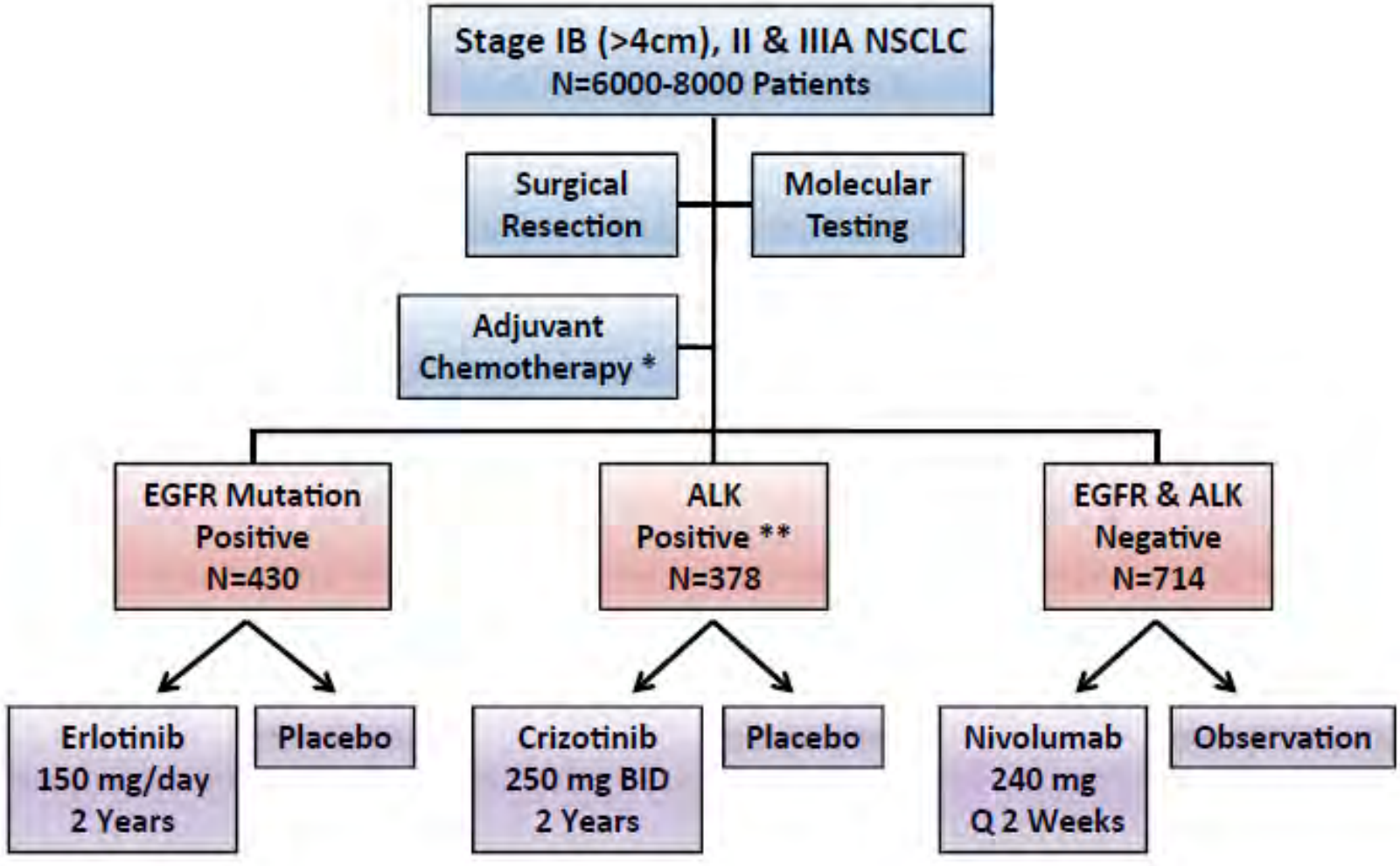
Hammerman P.S. The Cancer Genome Atlas Research Network; Nature 2012;489:519-525

Alterations in targetable oncogenic pathways in 69% of lung SQSC



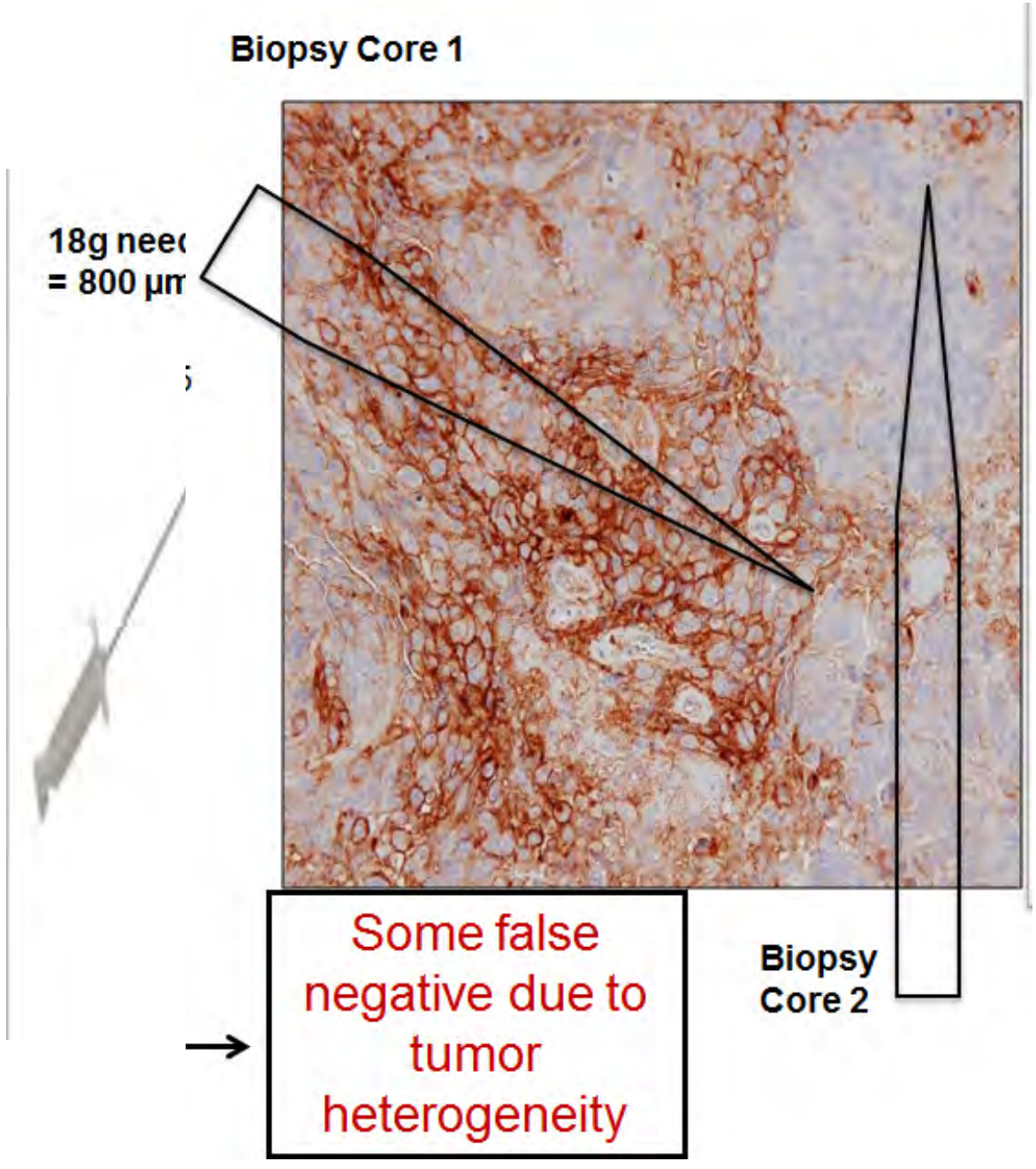
The cancer genome Atlas Research Network 2012 Nature 489; 519-25

Today therapeutic algorithm in NSCLC ALCHEMIST study (NCTN, US)



J. T. O. 2016 ; 11: 613-638

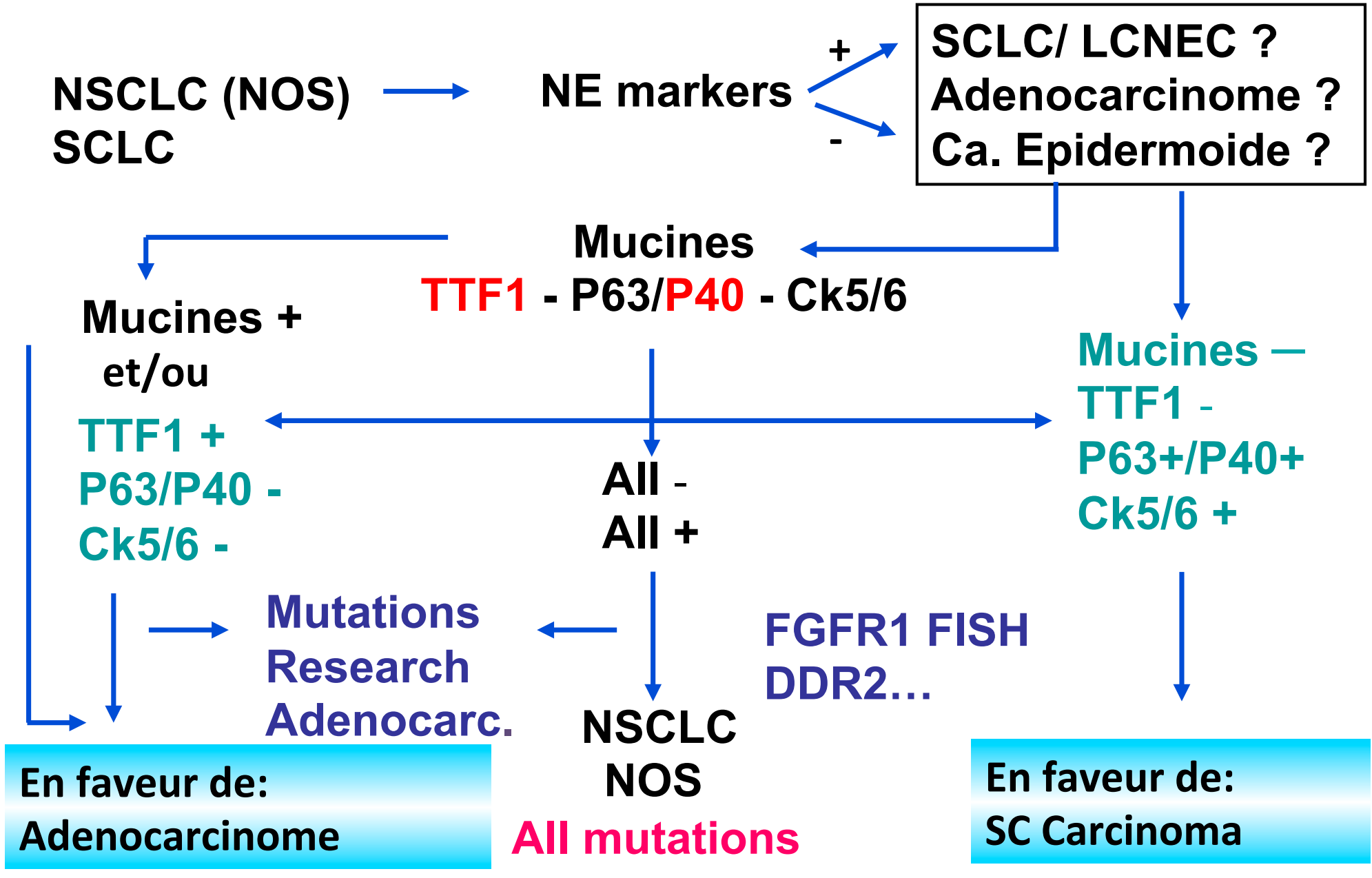
Pitfalls with heterogeneous markers :PDL1



2015 OMS : terminologie pour petites biopsies /cytologie

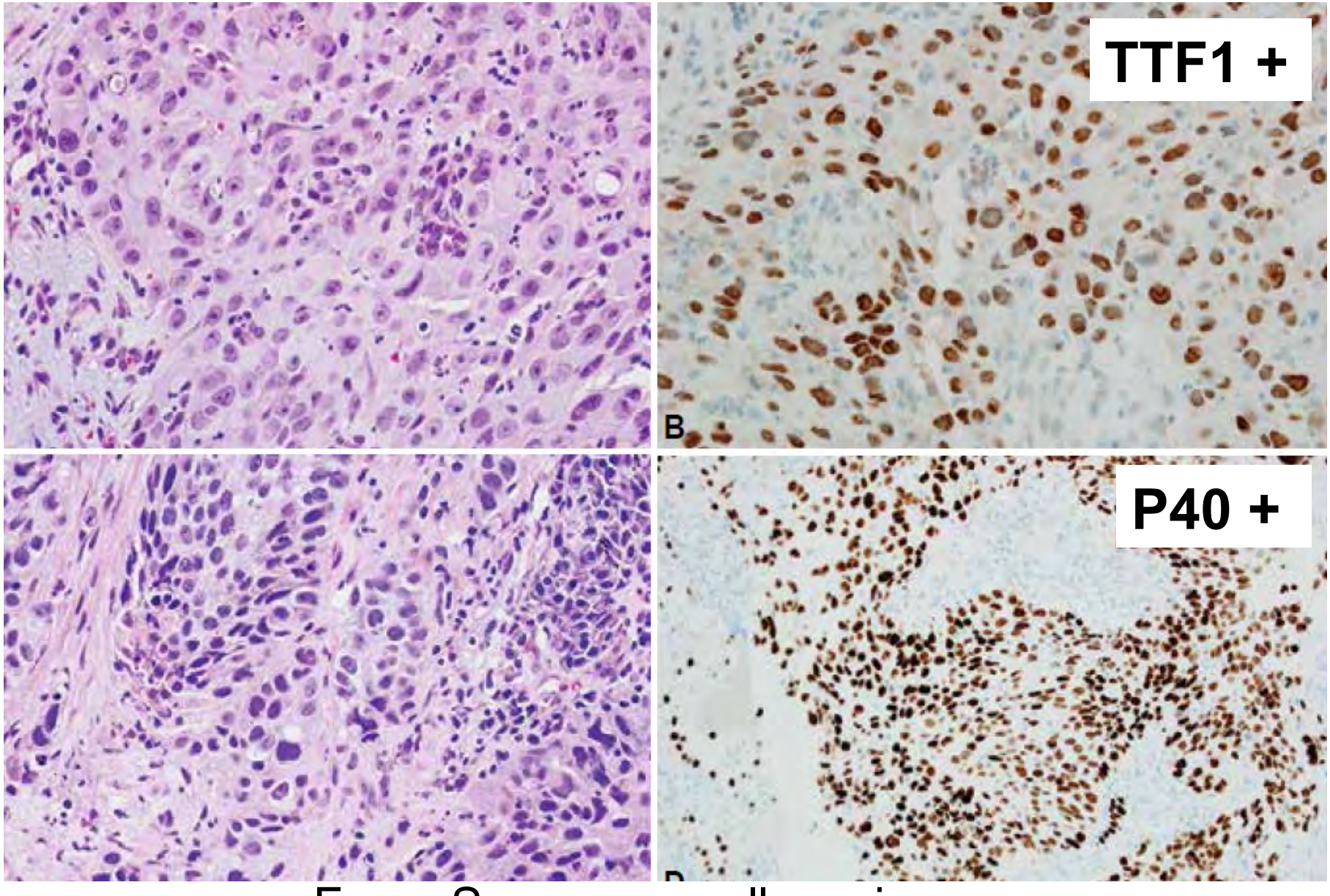
2015 WHO Resections	Small Biopsy/Cytology
ADENOCARCINOMA **Lepidic** **Acinar** **Papillary** **Micropapillary** **Solid**	***Morphologic adenocarcinoma patterns clearly present:*** **Adenocarcinoma, describe identifiable patterns present**
No 2004 WHO counterpart – most will be solid adenocarcinomas	***Morphologic adenocarcinoma patterns not present (supported by special stains; i.e TTF-1 +; p40 -):*** **Non-small cell carcinoma, favor adenocarcinoma**
SQUAMOUS CELL CARCINOMA **Keratinizing** **Nonkeratinizing** **Basaloid**	***Morphologic squamous cell patterns clearly present:*** **Squamous cell carcinoma**
No 2004 WHO counterpart	***Morphologic squamous cell patterns not present (supported by stains; i.e. p40+, TTF-1 -):*** **Non-small cell carcinoma, favor squamous cell carcinoma**
LARGE CELL CARCINOMA	**Non-small cell carcinoma, not otherwise specified (NOS)**

Diagnostic sur petites biopsies (70%)
Minimiser l'usage de NSCLC (NOS)



Carcinomes non à petites cellules: biopsies

Favor Adenocarcinoma

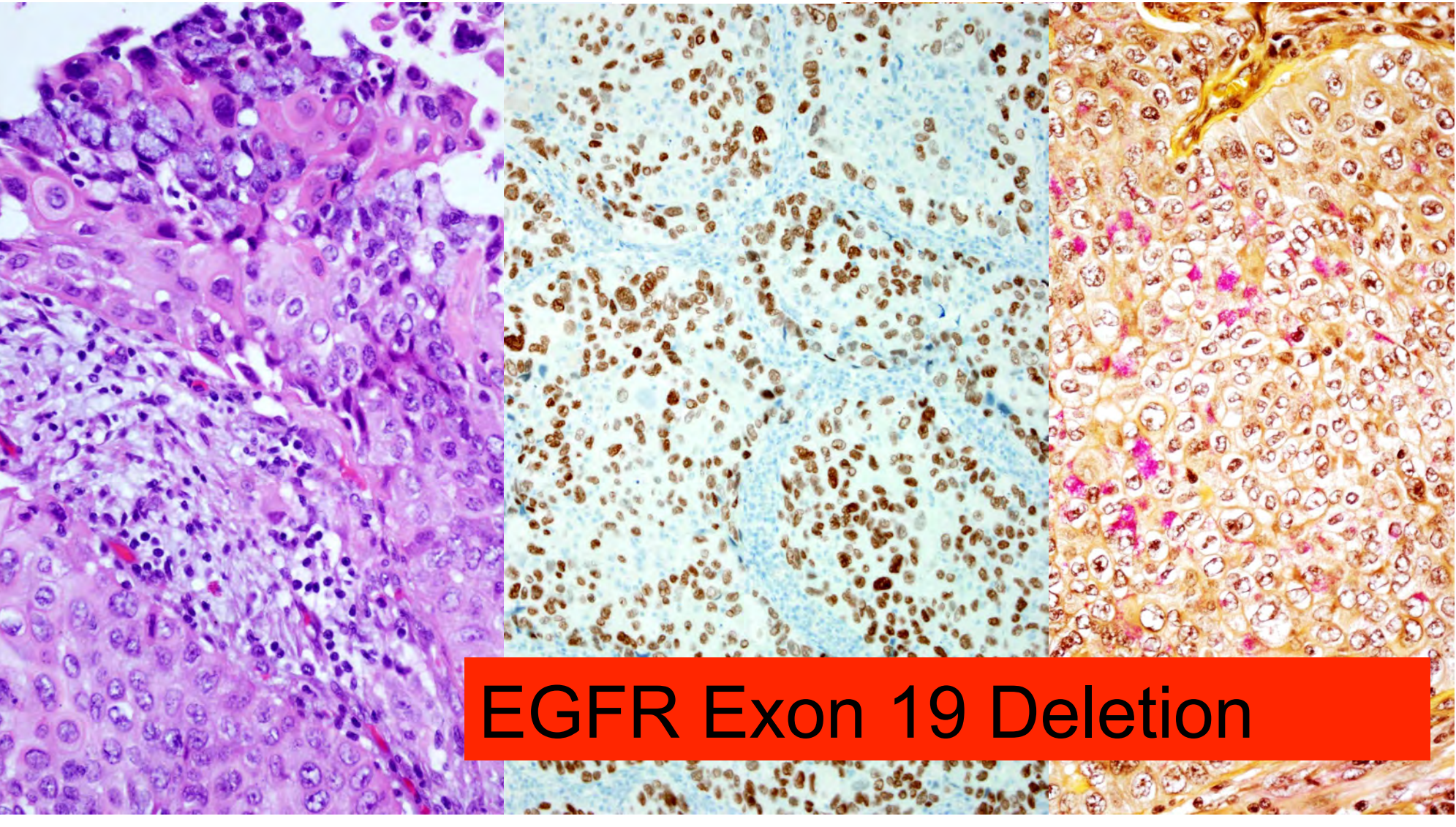


Favor Squamous cell carcinoma

Adénocarcinome solide pseudosquameux

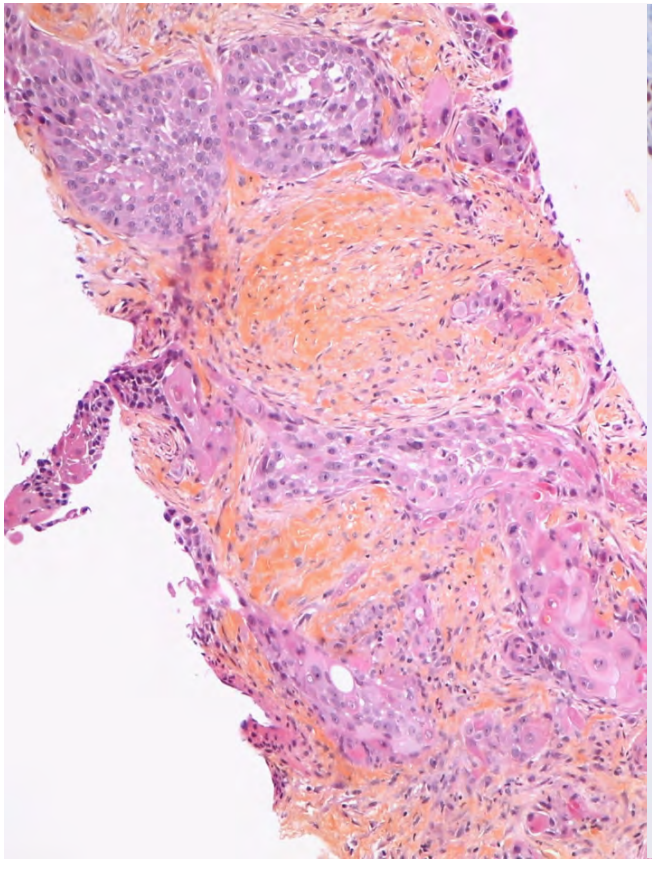
TTF-1

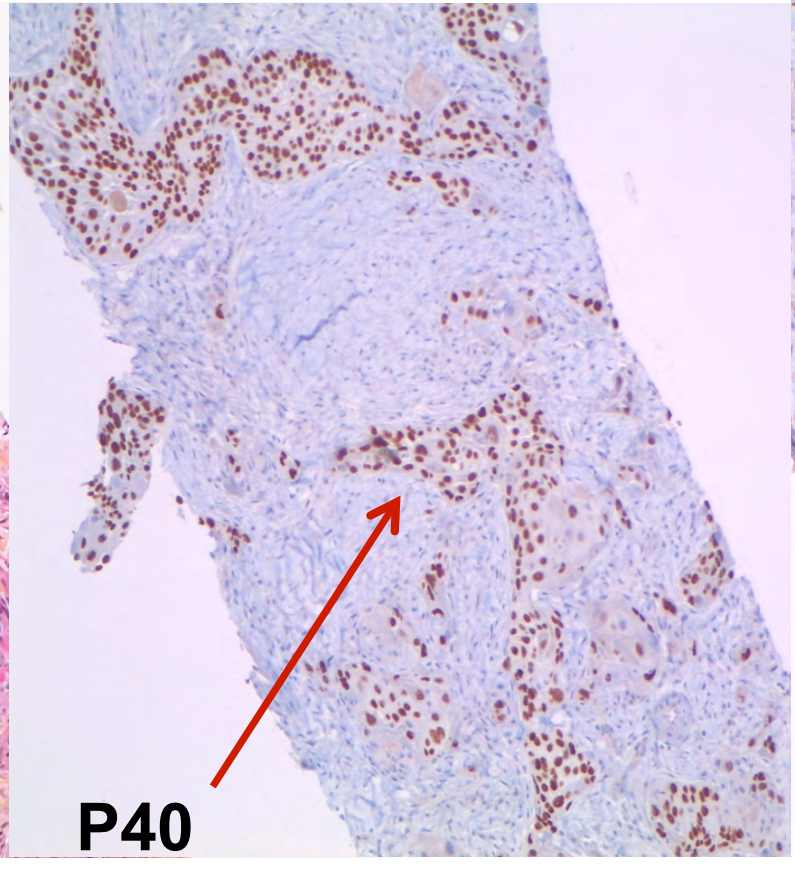
Mucicarmine

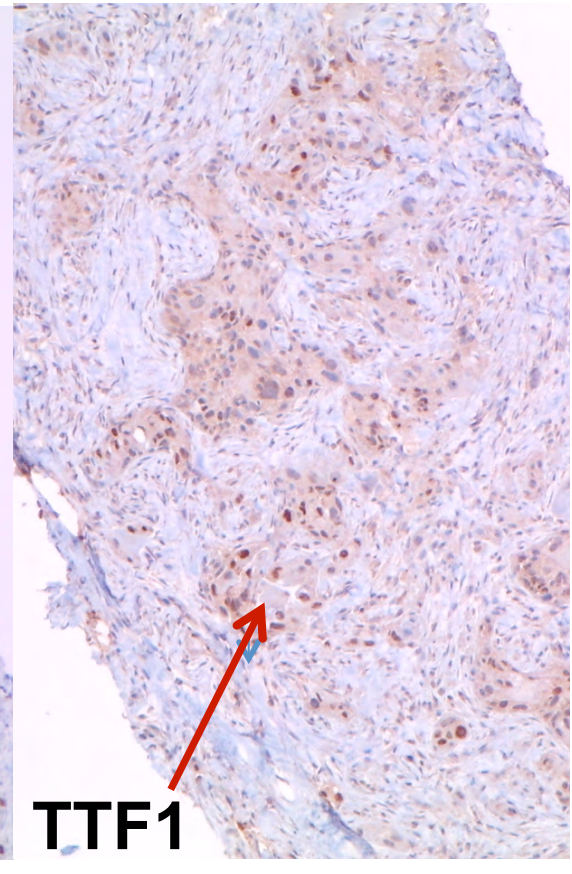


EGFR Exon 19 Deletion

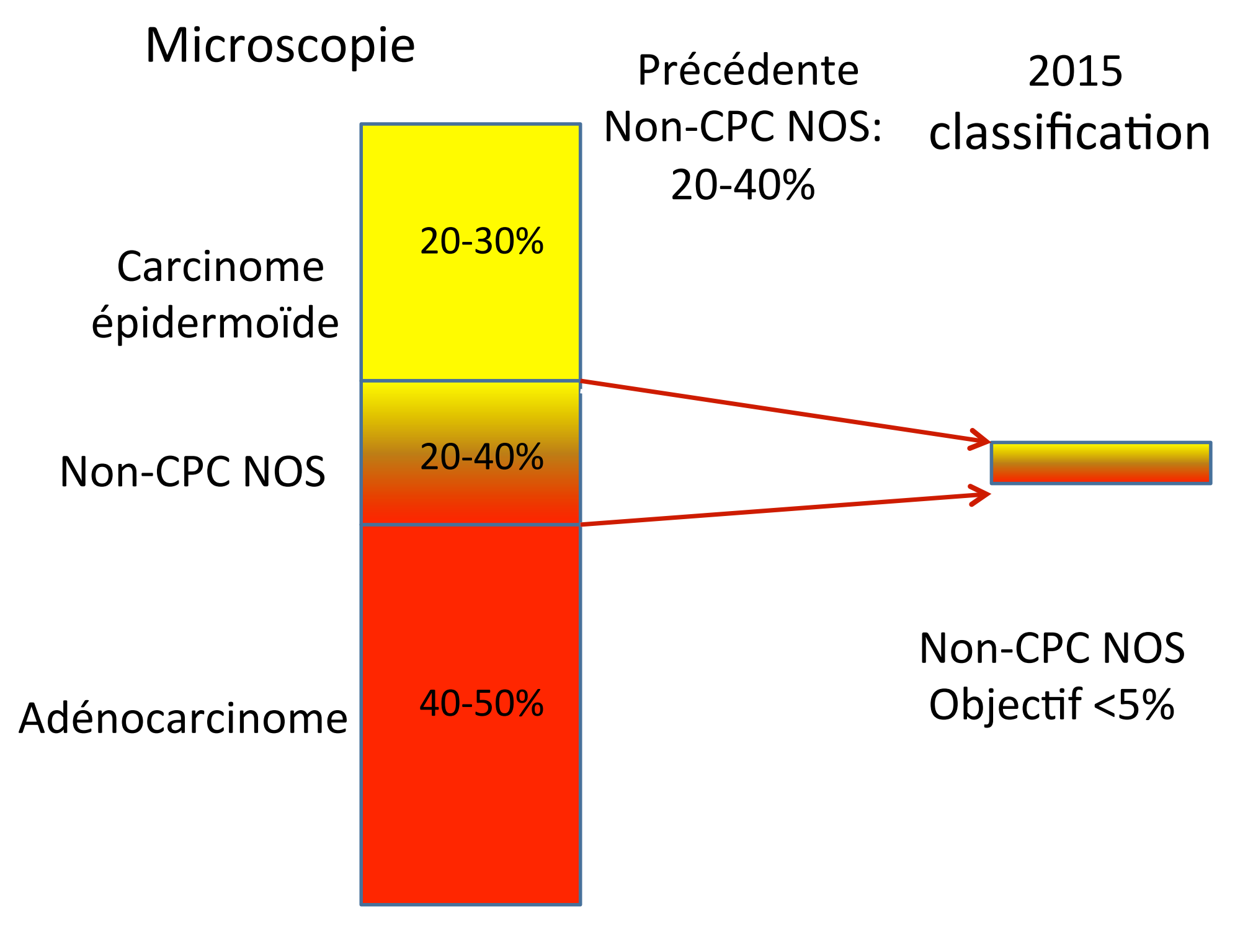
Mutant EGFR adenocarcinoma resistant to TKI



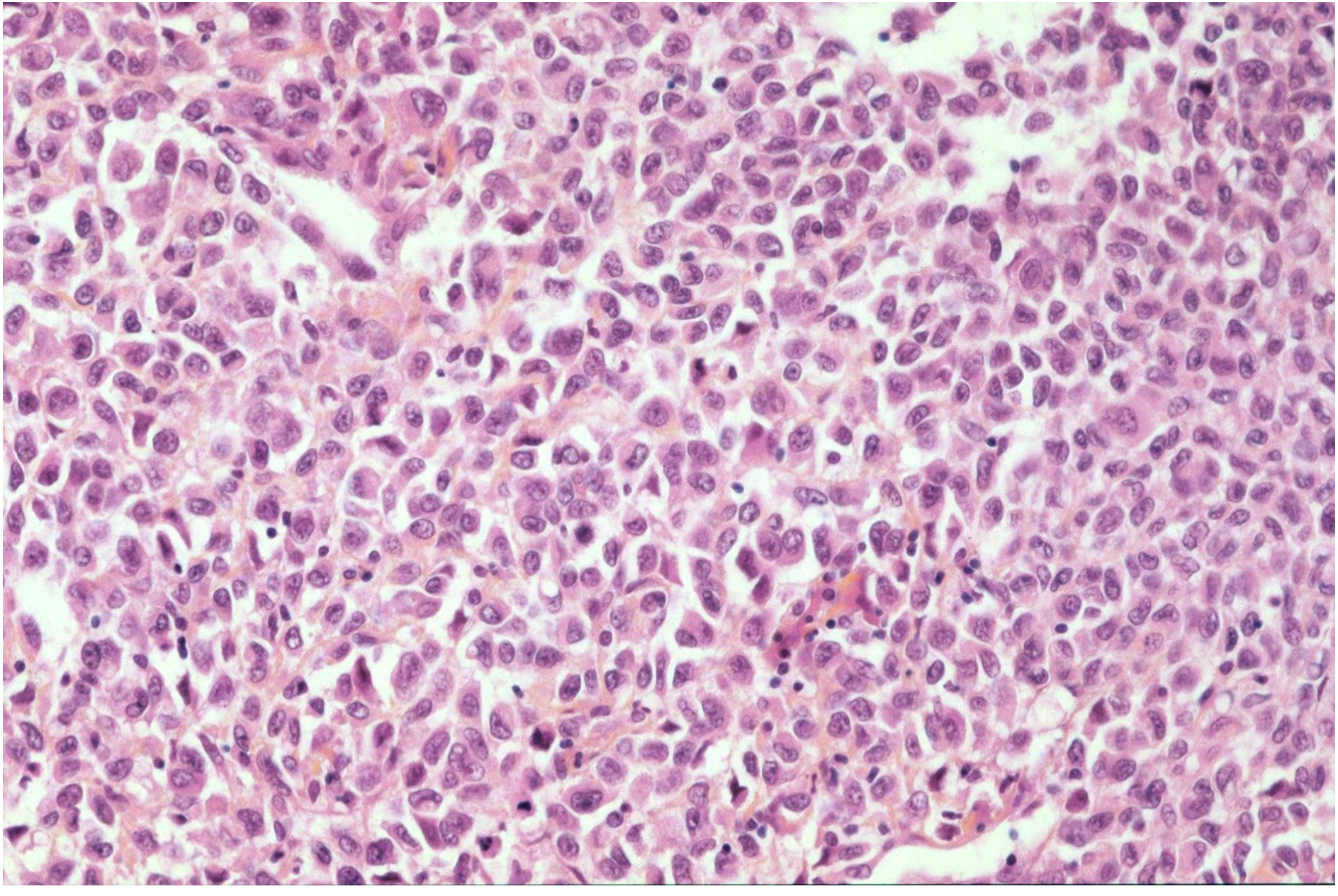




Switch (or therapeutic selection) of an adenocarcinoma phenotype ⟶ adeno-squamous carcinoma
90 % ADC / 10% SCC on original resected tumor


Microscopie
Précédente
Non-CPC NOS:
20-40%
2015
classification
Carcinome
épidermoïde
20-30%
Non-CPC NOS
20-40%
Adénocarcinome
40-50%
Non-CPC NOS
Objectif <5%

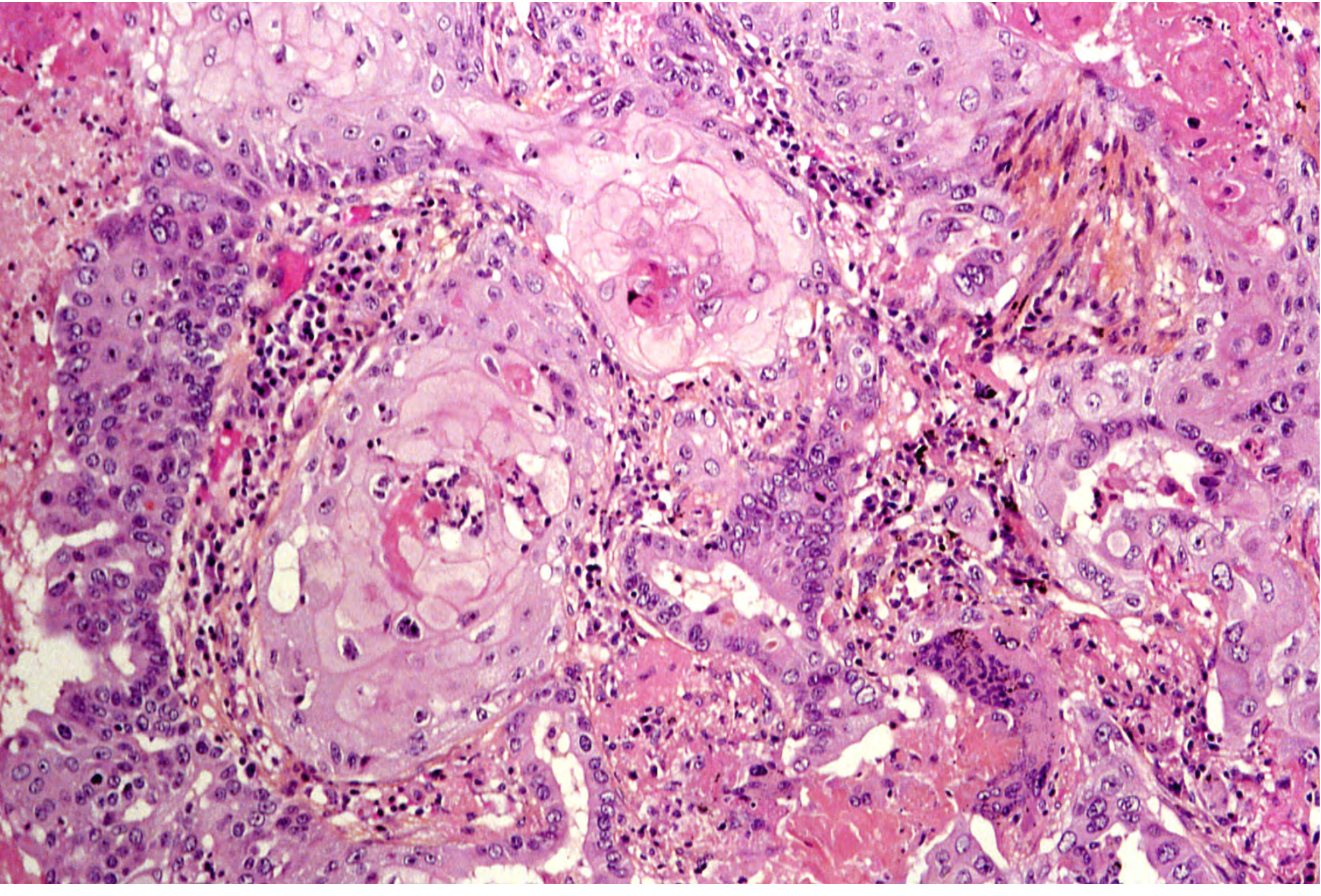
Carcinomes à grandes cellules



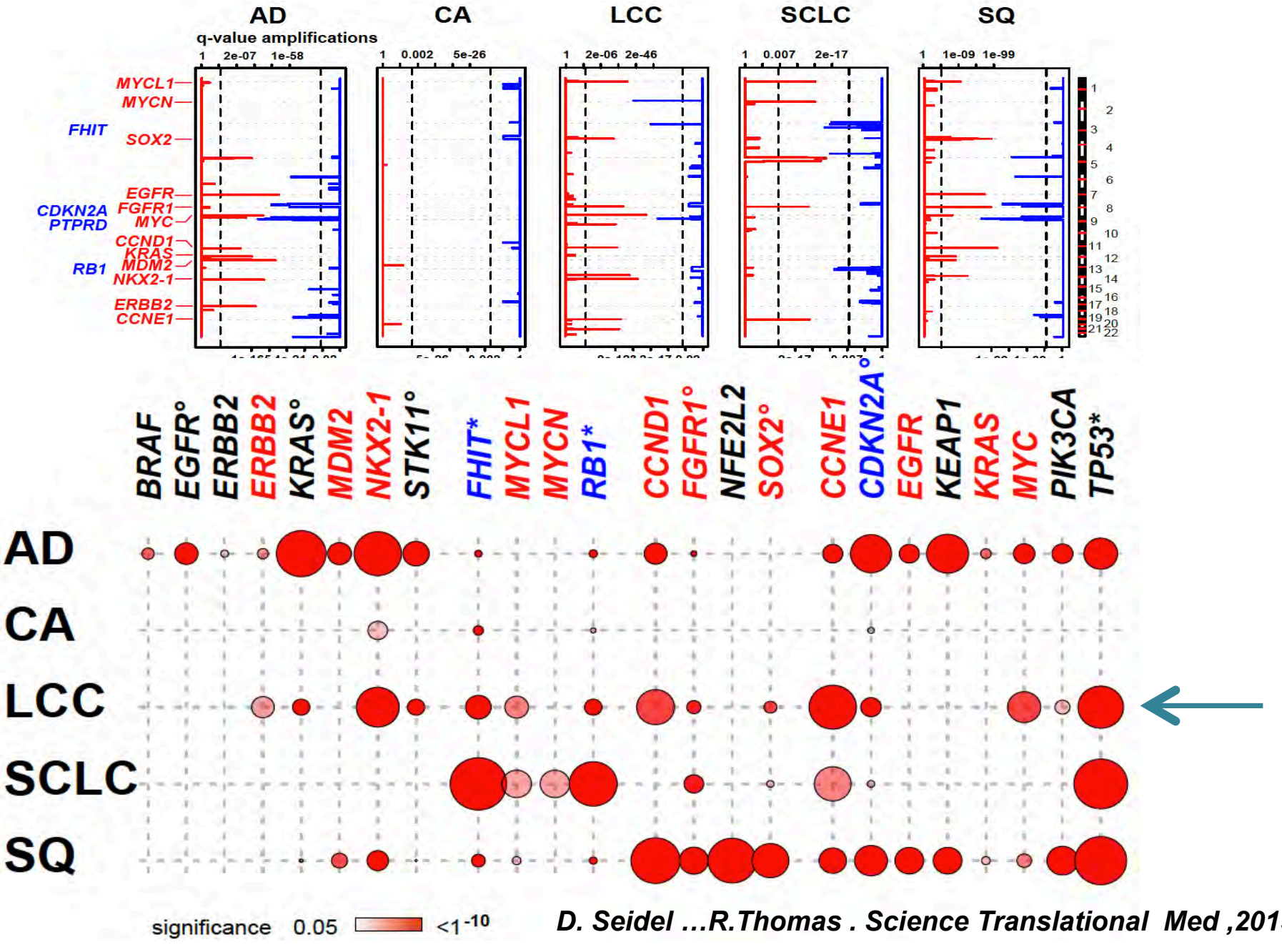
Subtyping of morphologically undifferentiated non small cell lung carcinoma (former large cell carcinoma)

Adenocarcinoma solid subtype	• Positive for TTF1 or mucin • Negative for P40/P63 ,CK5/6
Non keratinizing squamous cell C.	• Diffusely positive for P40/P63, and/or CK5/6 • Negative for TTF1 or mucin
Adenosquamous carcinoma	• Positive for both ADC and SCC in distinct populations

Adenosquamous carcinoma



Driver mutations and genomic profiles are histology- related



D. Seidel …R.Thomas . Science Translational Med ,2013

Carcinome à grandes cellules
OMS 2015 Classification

- Carcinome à grandes cellules à phénotype null et sans mucines
- Carcinome à grandes cellules avec phénotype non conclusif
- Large cell carcinoma sans phénotype recherché

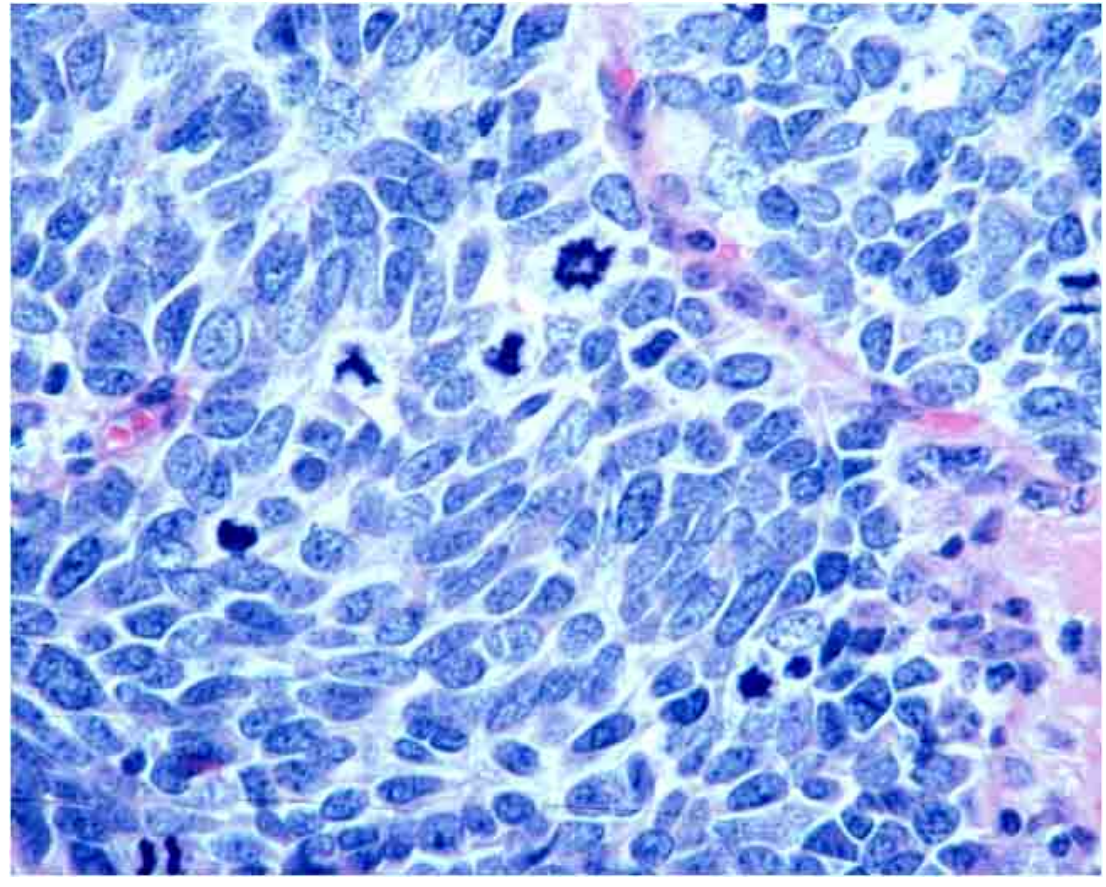
OMS 2015 : tumeurs neuroendocrines

- Carcinome à petites cellules
  - CPC composite
- Carcinome neuroendocrine à grandes cellules
  - LCNEC Composite

- Tumeur carcinoïde
  - Typical carcinoid
  - Atypical carcinoid

Pas de changements de concept ; connaissance de leur génomique confirmant que les carcinoïdes ne sont pas les étapes précoces des TNE de haut grade

SCLC: CRITERIA ARE DIFFERENT IN TEXAS



(EVERYTHING IS LARGER IN TEXAS)

Conclusions

- Appliquer la classification WHO dans les essais cliniques et les recherches oncologiques
- Essais cliniques – stratifier les adénocarcinomes par histologie (SOL/MIP) vs (LPA, AC, PAP) ou STAS
  - Résection sous-lobaire Vs lobaire
  - Chimiothérapie adjuvante
- Appliquer les nouveaux concepts au TNM (radiologique/ pathologique):
  - Mesure de la taille tumorale
  - Tumeurs multiples: multiples primaires vs métastases pulmonaires
- Nouvelles approches des petites biopsies / cytologies

The 2015 World Health Organization Classification of Lung Tumors

Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification

William D. Travis, MD, Elisabeth Brambilla, MD,† Andrew G. Nicholson, MD,‡ Yasushi Yatabe, MD,§ John H. M. Austin, MD,‖ Mary Beth Beasley, MD,¶ Lucian. R. Chirieac, MD,# Sanja Dacic, MD,** Edwina Duhig, MD,†† Douglas B. Flieder, MD,‡‡ Kim Geisinger, MD,§§ Fred R. Hirsch, MD,‖‖ Yuichi Ishikawa, MD,¶¶ Keith M. Kerr, MD,## Masayuki Noguchi, MD,*** Giuseppe Pelosi, MD,††† Charles A. Powell, MD,‡‡‡ Ming Sound Tsao, MD,§§§ and Ignacio Wistuba, MD,‖‖‖*

On Behalf of the WHO Panel

J. Thorac Oncol. 2015;10: 1243–1260)

2015 WHO editors

ELISABETH BRAMBILLA

WILLIAM TRAVIS

ANDREW NICHOLSON

ALEX MARX

THYMUS

ALLEN BURKE

HEART

Adénocarcinomes : variants WHO 2015

- Adénocarcinome invasif mucineux
- Adénocarcinome colloïde
- Adénocarcinome foetal
- Adénocarcinome enteric

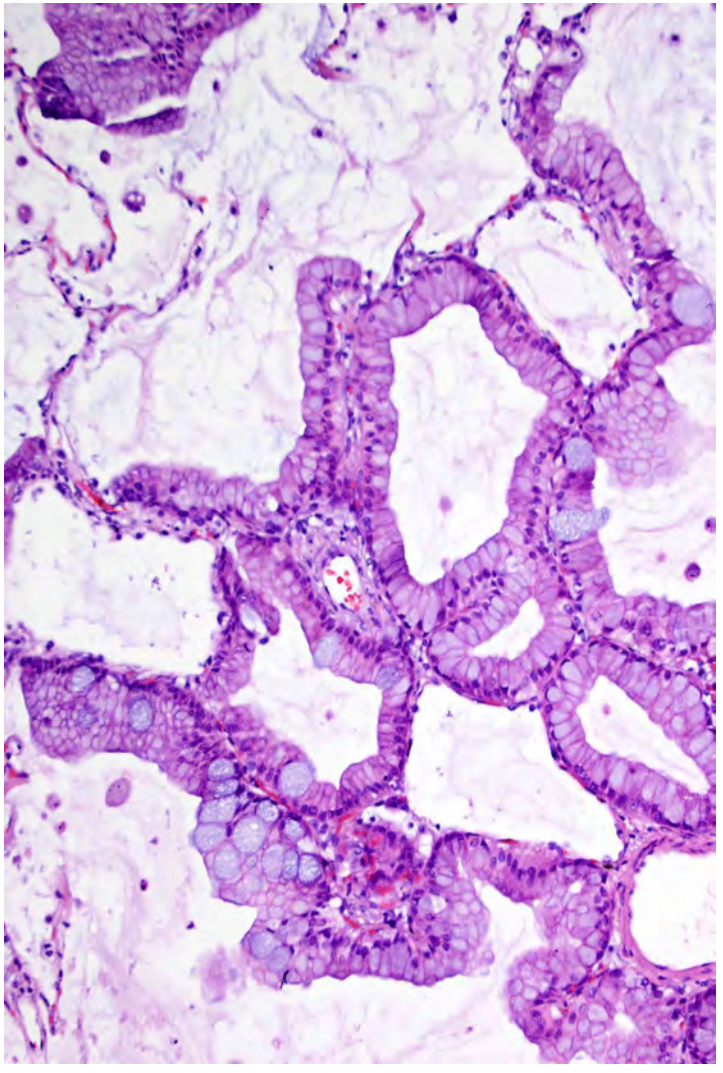
Variants 2014

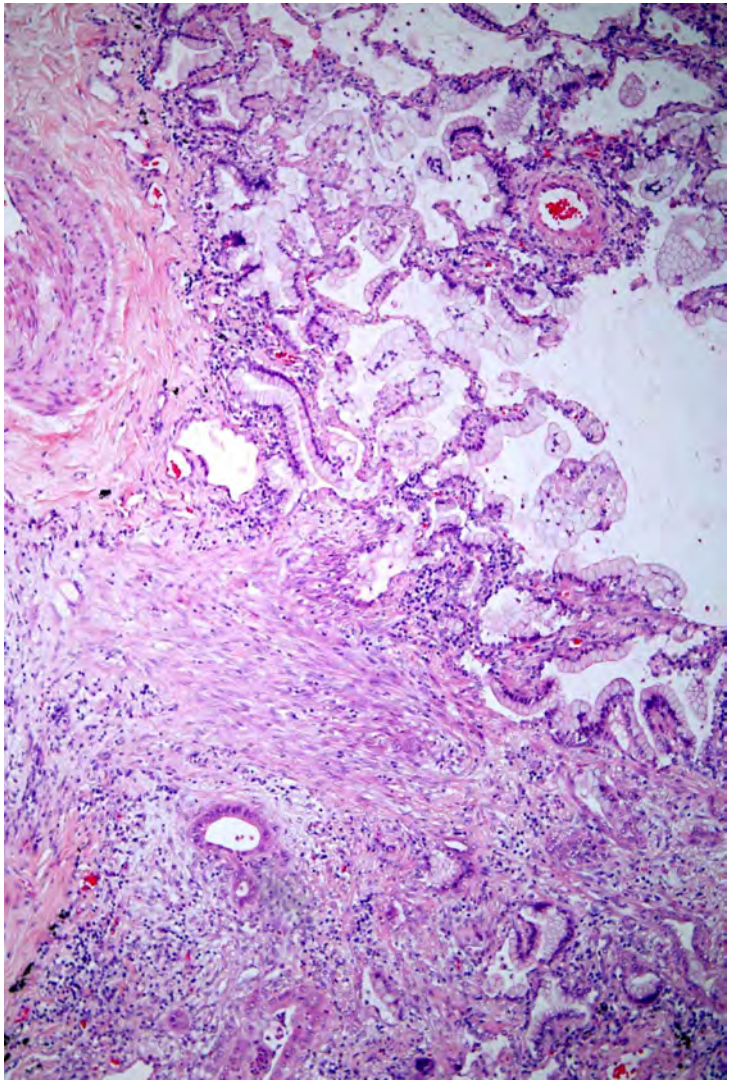
- **Adénocarcinome foetal (WDFA/99)**
- **Colloid mucineux ("colloid")**
- **Cystadenocarcinoma mucineux**
- **Signet ring**
- **Clear cell**

Adénocarcinome Invasif Mucineux

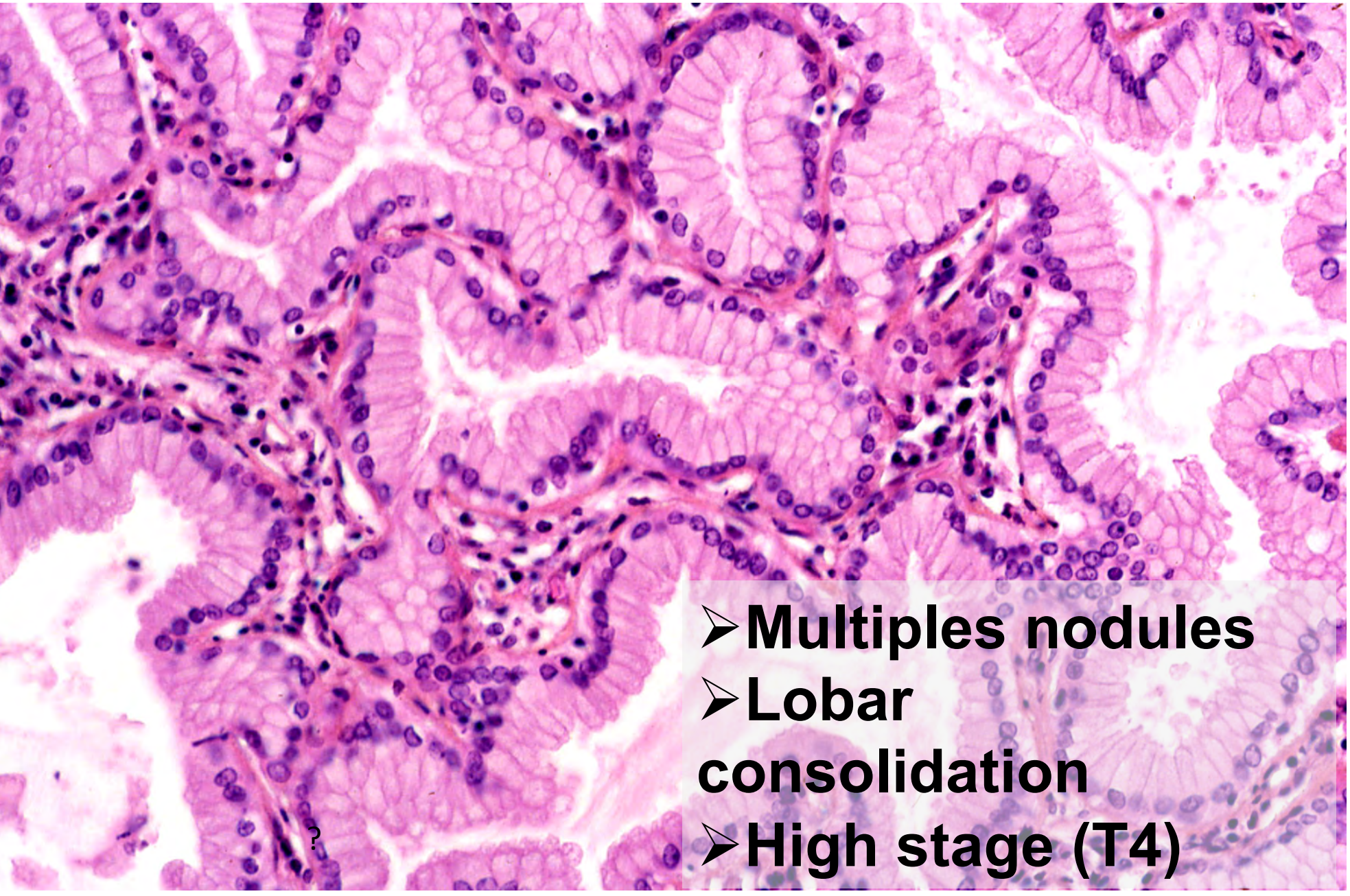
Mutations *KRAS* (75%)

Invasive Mucinous Adenocarcinoma





Variant : Invasive mucinous adenocarcinoma



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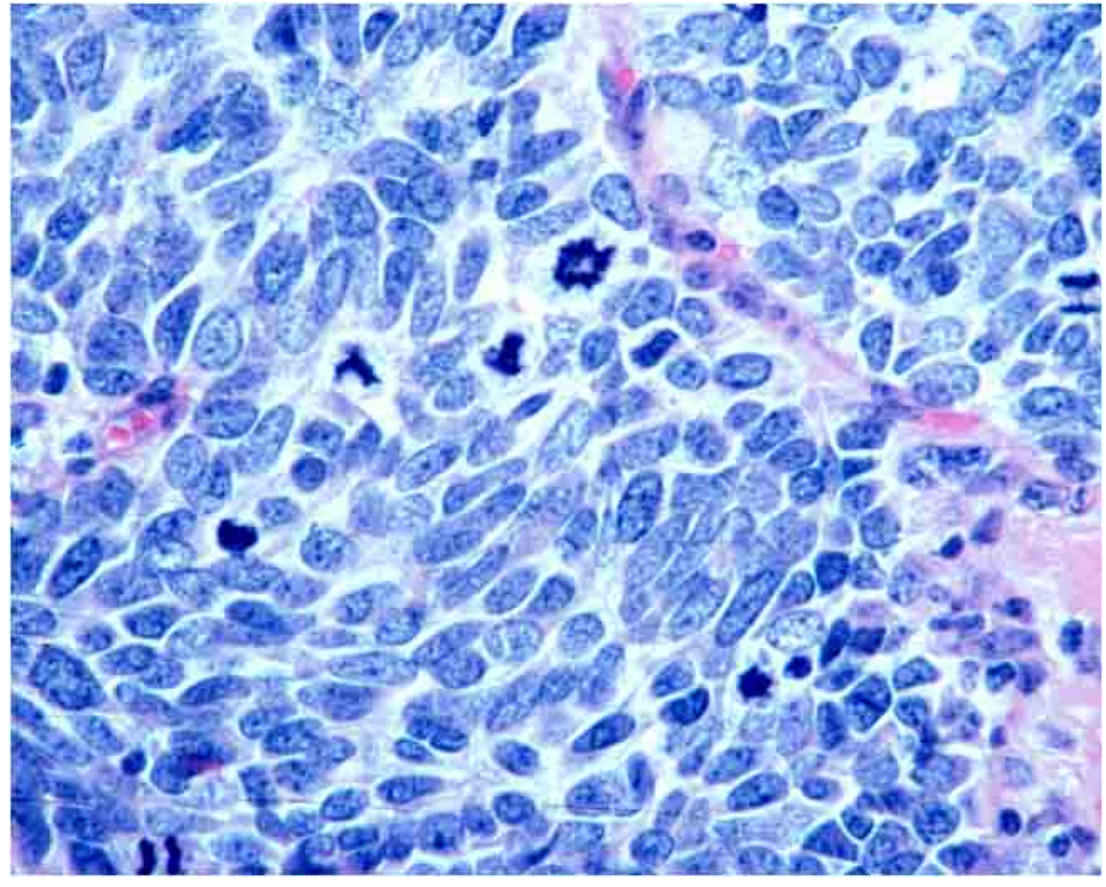

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THYMUS

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HEART

WHERE WAS WHO DEVELOPED?

157 Authors from 29 countries

2015 WHO TUMORS OF THE PLEURA: KEY AUTHORS

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VICTOR L. ROGGLI

ANDREW CHURG