Classification histomoléculaire des cancers pulmonaires 2015: Quoi de neuf en 2017 ?

Cours du GOLF Limoges 2017

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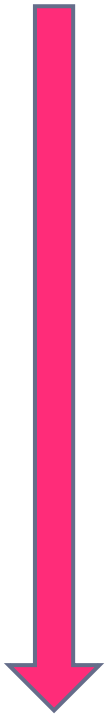
Complexité croissante des classifications

- OMS 1967
- OMS 1981
- OMS 1999
- OMS 2004

- OMS 2015



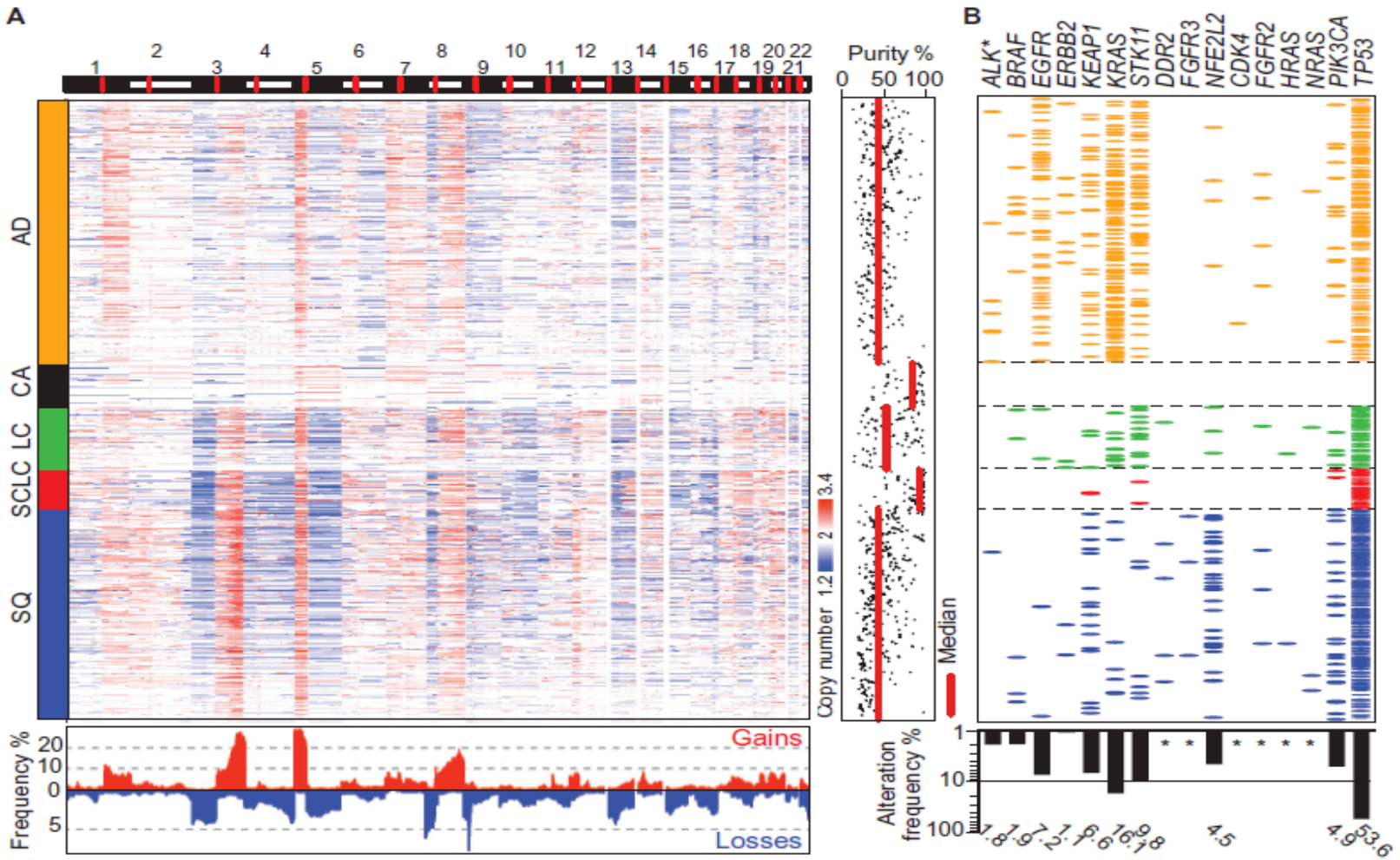
- HES
- HES & colos des mucines
- HES, ME & IHC
- HES, ME, IHC & génétique

sur pièces opératoires

- HES, cytologie et biopsies, IHC, génétique, radiologie

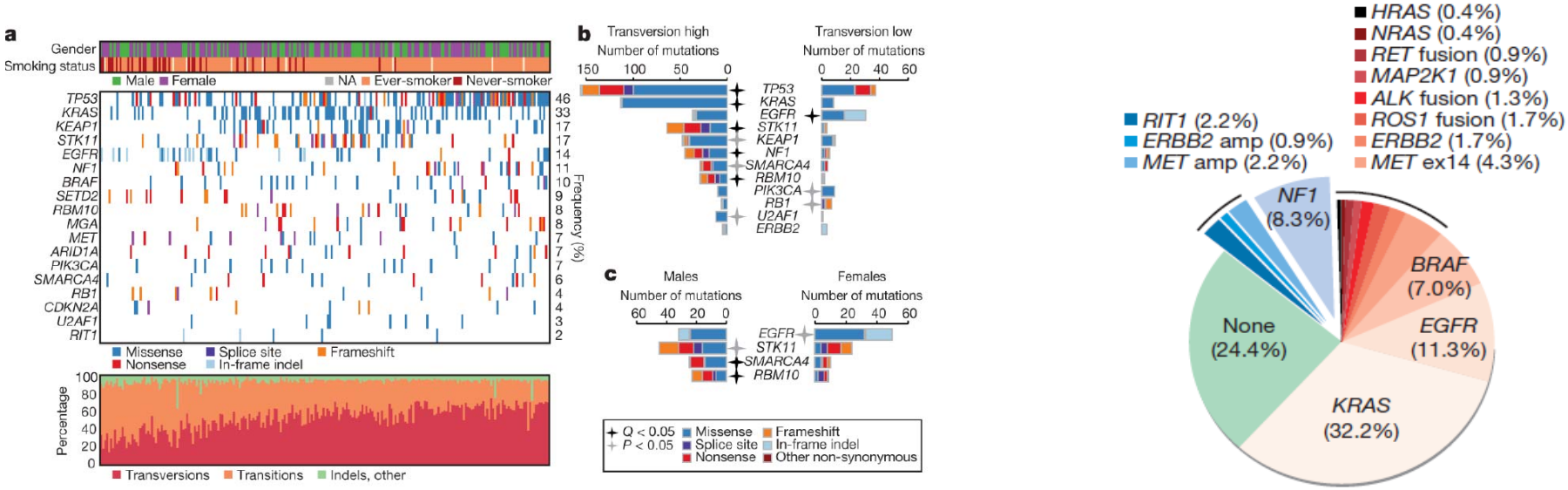
Ere de la médicine personnalisée

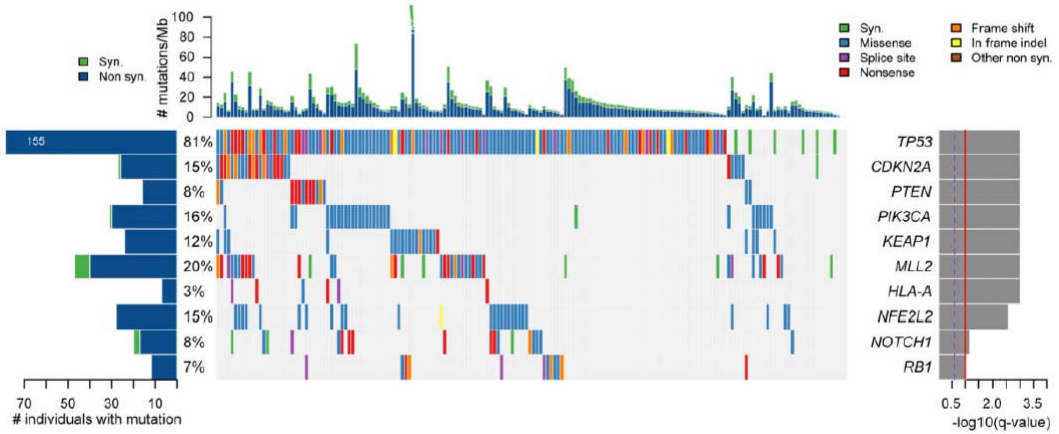
A Genomics-Based Classification of Human Lung Tumors
The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM),
Sci Transl Med **5**, 209ra153 (2013);



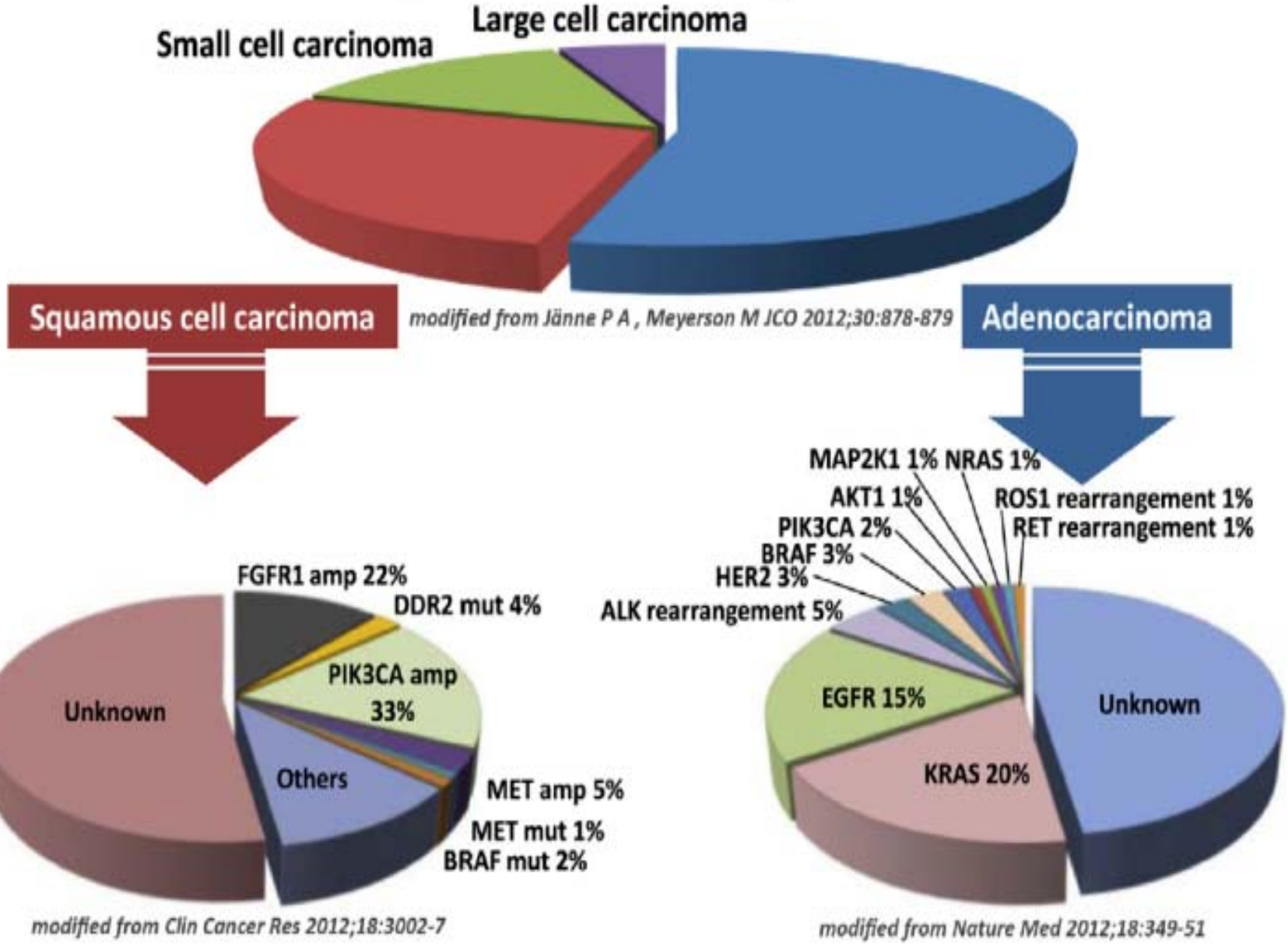
The Cancer Genome Atlas research network: comprehensive profiling of lung adenocarcinoma and squamous cell carcinoma

Nature 2014 and 2012





Histologic and molecular subtypes of NSCLC



Travis WD et al,
Journal of Thoracic Oncology
February 2011

2004 WHO Classification	SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS
ADENOCARCINOMA Mixed subtype Acinar Papillary Solid	*Morphologic adenocarcinoma patterns clearly present:* Adenocarcinoma, describe identifiable patterns present (including micropapillary pattern not included in 2004 WHO classification) Comment: If pure lepidic growth – mention an invasive component cannot be excluded in this small specimen
Bronchioloalveolar carcinoma (nonmucinous)	Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
Bronchioloalveolar carcinoma (mucinous)	Mucinous adenocarcinoma (describe patterns present)
Fetal	Adenocarcinoma with fetal pattern
Mucinous (colloid)	Adenocarcinoma with colloid pattern
Signet ring	Adenocarcinoma with (describe patterns present) and signet ring features
Clear cell	Adenocarcinoma with (describe patterns present) and clear cell features
No 2004 WHO counterpart – most will be solid adenocarcinomas	*Morphologic adenocarcinoma patterns not present (supported by special stains):* Non-small cell carcinoma, favor adenocarcinoma
SQUAMOUS CELL CARCINOMA Papillary Clear cell Small cell Basaloid	*Morphologic squamous cell patterns clearly present:* Squamous cell carcinoma
No 2004 WHO counterpart	*Morphologic squamous cell patterns not present (supported by stains):* Non-small cell carcinoma, favor squamous cell carcinoma
SMALL CELL CARCINOMA	Small cell carcinoma
LARGE CELL CARCINOMA	Non-small cell carcinoma, not otherwise specified (NOS)
Large cell neuroendocrine carcinoma (LCNEC)	Non-small cell carcinoma with neuroendocrine (NE) morphology (positive NE markers), possible LCNEC
Large cell carcinoma with NE morphology (LCNEM)	Non-small cell carcinoma with NE morphology (negative NE markers) – see comment Comment: This is a non-small cell carcinoma where LCNEC is suspected, but stains failed to demonstrate NE differentiation.
ADENOSQUAMOUS CARCINOMA	*Morphologic squamous cell and adenocarcinoma patterns present:* Non-small cell carcinoma, with squamous cell and adenocarcinoma patterns Comment: this could represent adenosquamous carcinoma.
No counterpart in 2004 WHO classification	*Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components* Non-small cell carcinoma, NOS, (specify the results of the immunohistochemical stains and the interpretation) Comment: this could represent adenosquamous carcinoma.
Sarcomatoid carcinoma	Poorly differentiated NSCLC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)

IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma

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

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (≤3 cm formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

BAC, bronchioloalveolar carcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

Travis WD et al,
Journal of Thoracic Oncology
February 2011

Adénocarcinome *In situ* à croissance lépidique Tis (ex Carcinome bronchiolo-alvéolaire)

2 à 6 % des NSCLC

OMS 2004: carcinome non invasif Tis

≤ 3 cm

respect de architecture pulmonaire

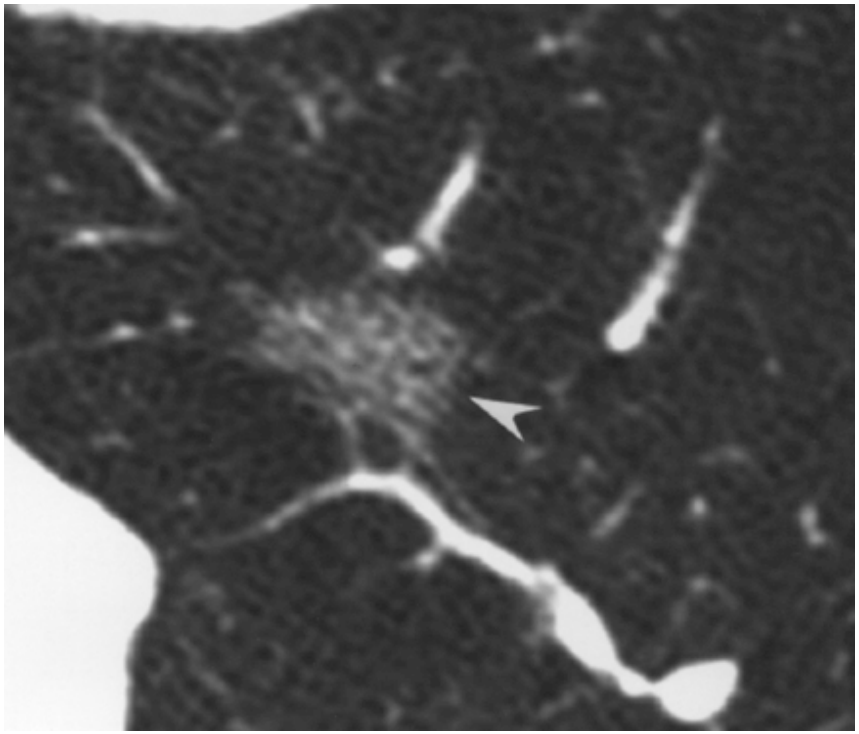
“Croissance lépidique “

stades I (p < 0,001)

absence de métastases ganglionnaires

(p < 0,001)

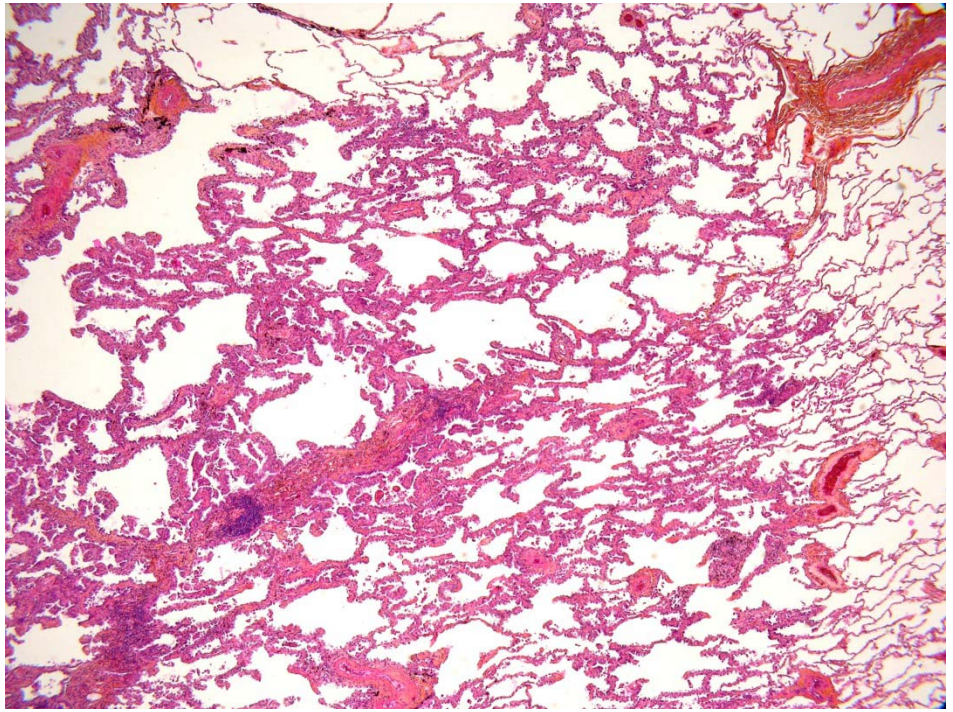
100% survie à 5 ans (p < 0,005)

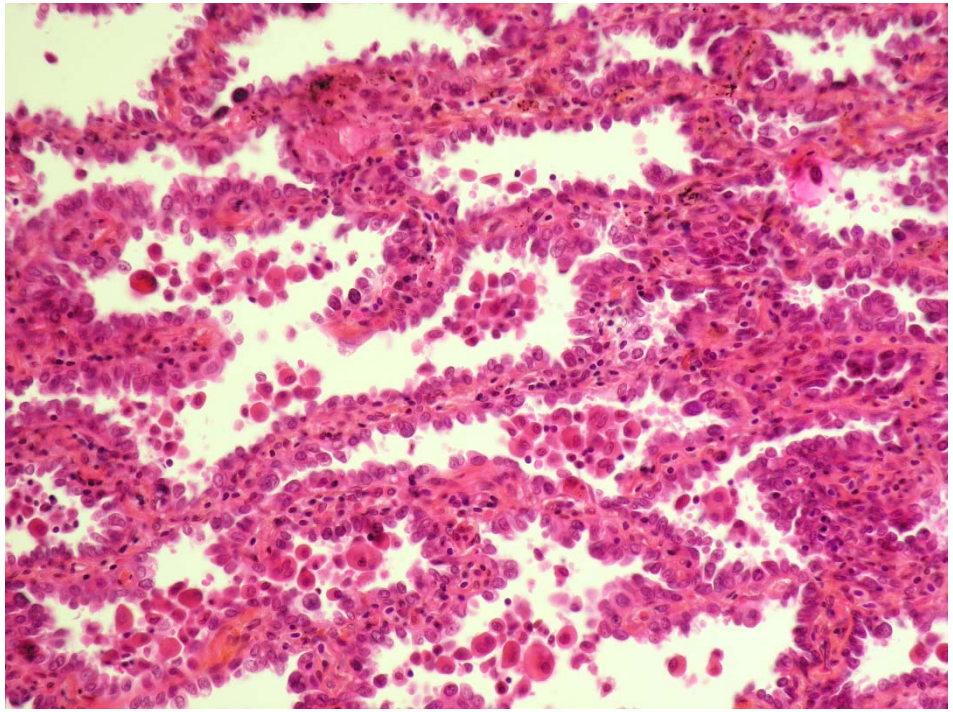


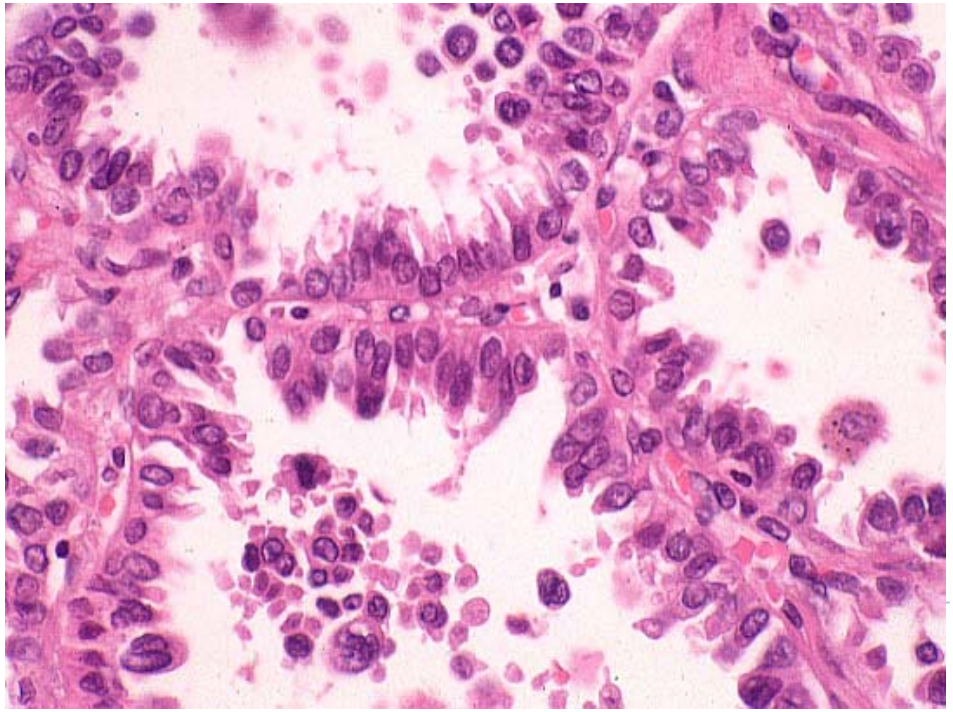
Noguchi et al Cancer 1995

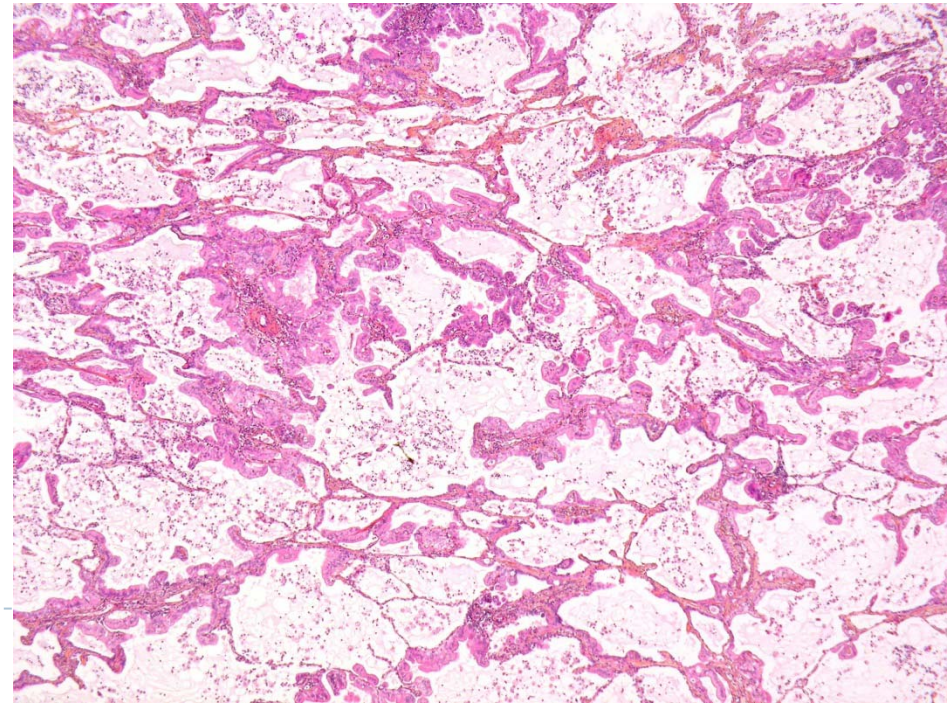
Yokose et al Lung Cancer 2000

Suzuki et al Ann Thorac Surg 2002



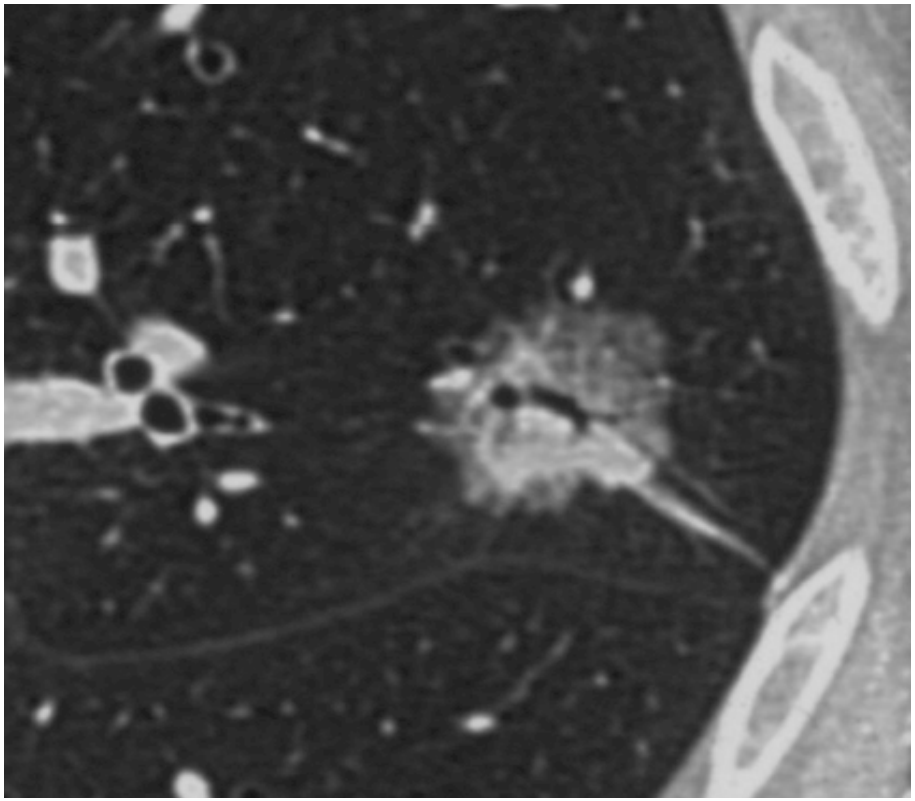


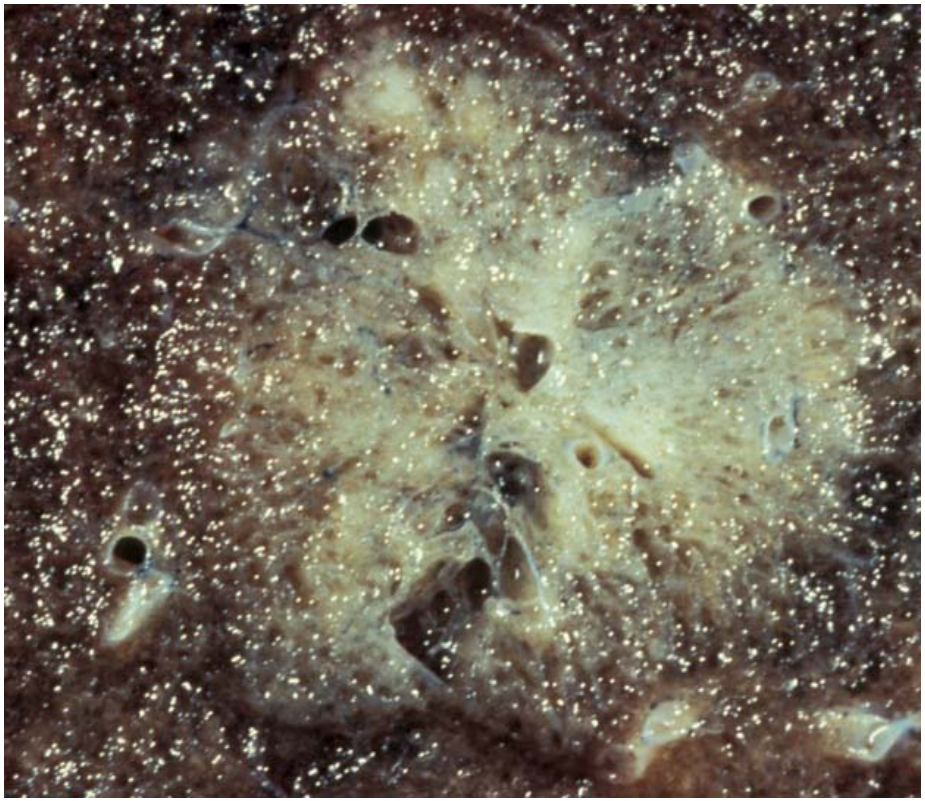




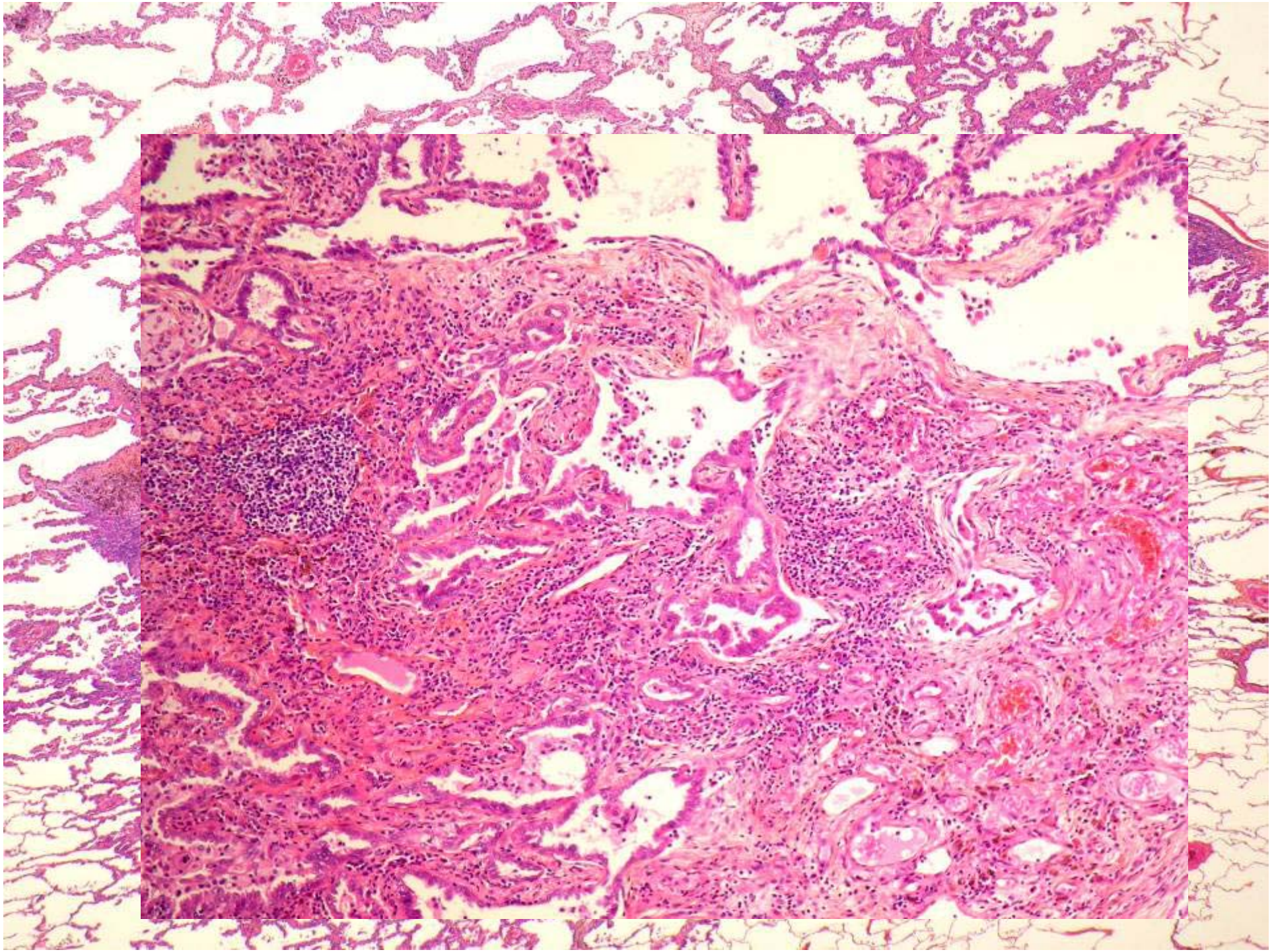
Adénocarcinome avec invasion minime (≤5mm)

T1 mi: 100% survie à 5 ans

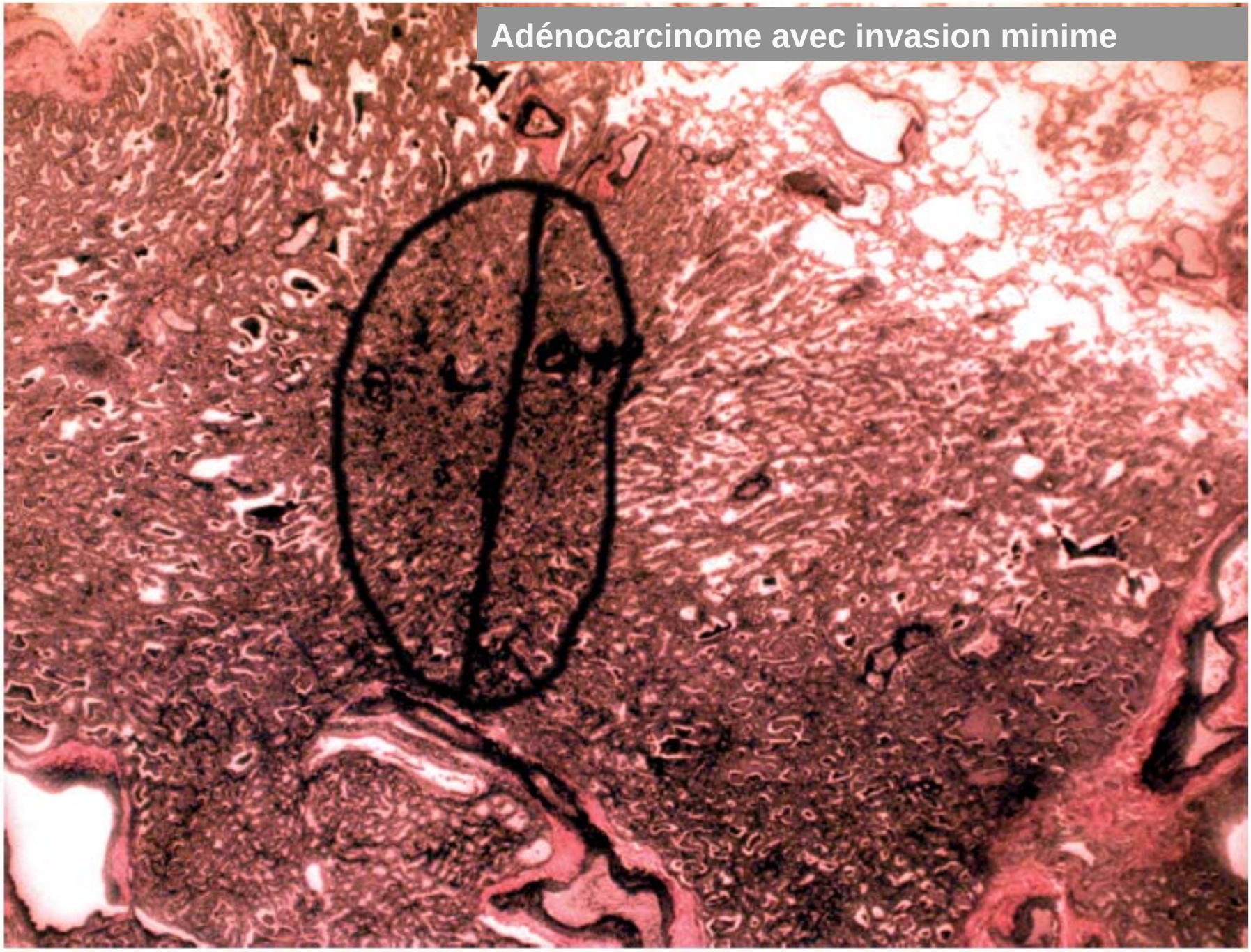




By courtesy of Prof KM Kerr

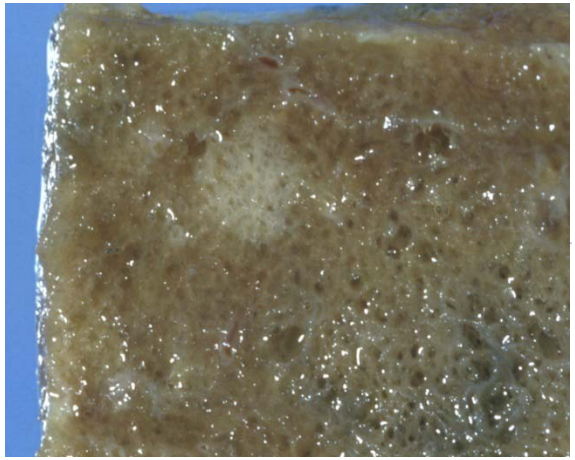


Adénocarcinome avec invasion minime

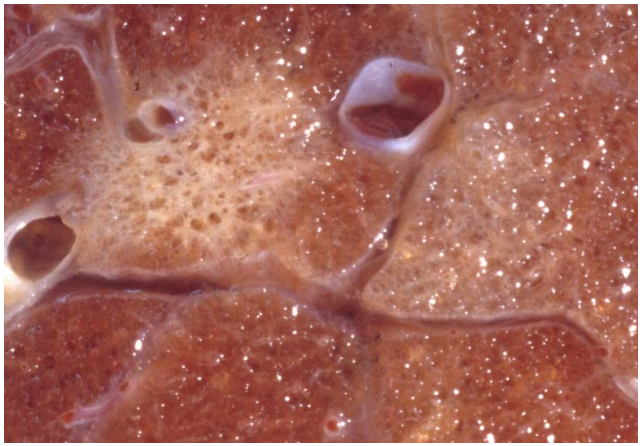


Russell et al 2011

By courtesy of Prof KM Kerr

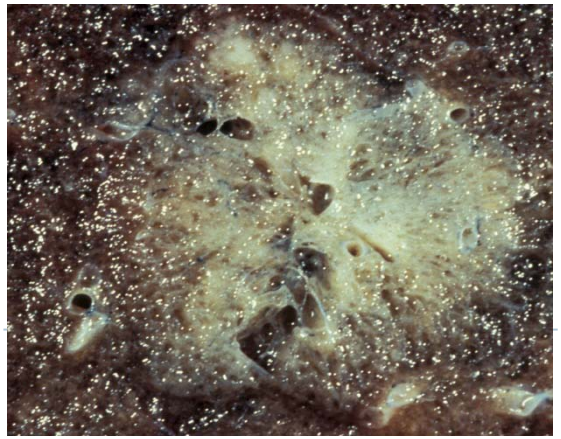


Hyperplasie Atypique Adénomateuse

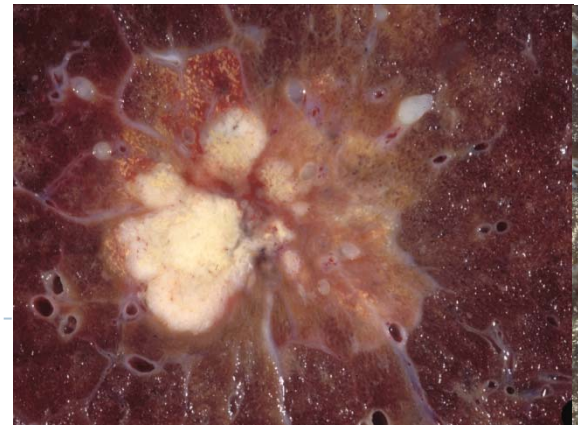


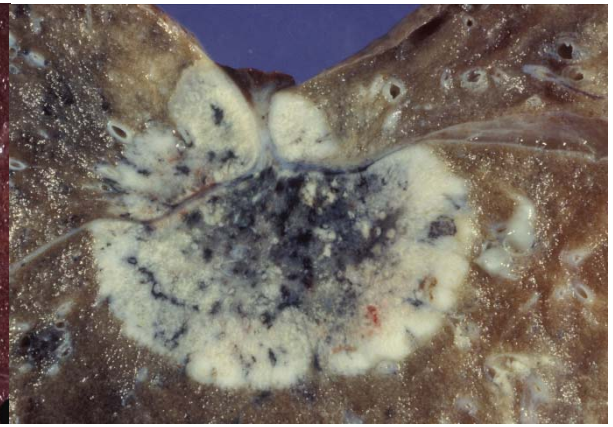
Adénocarcinome *in situ*

ADC invasion minime

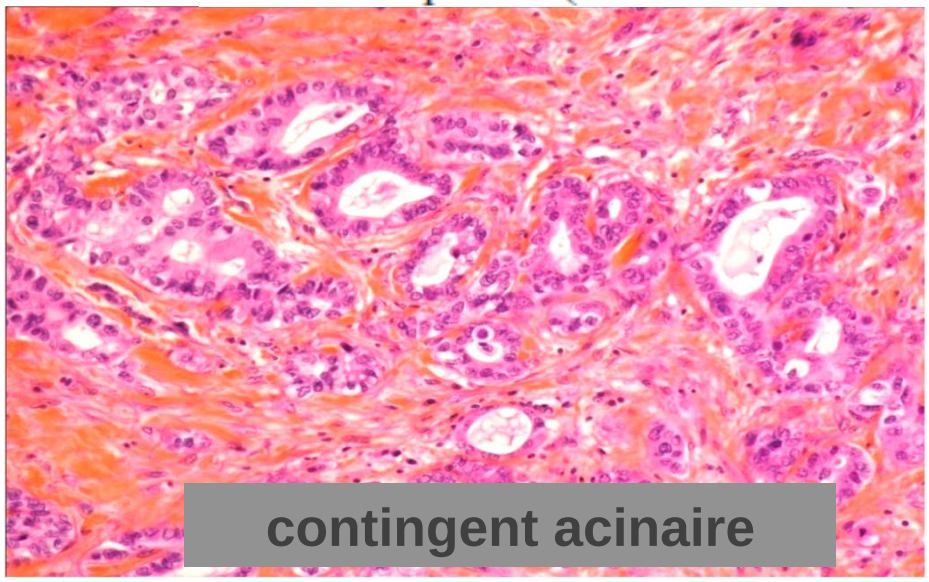


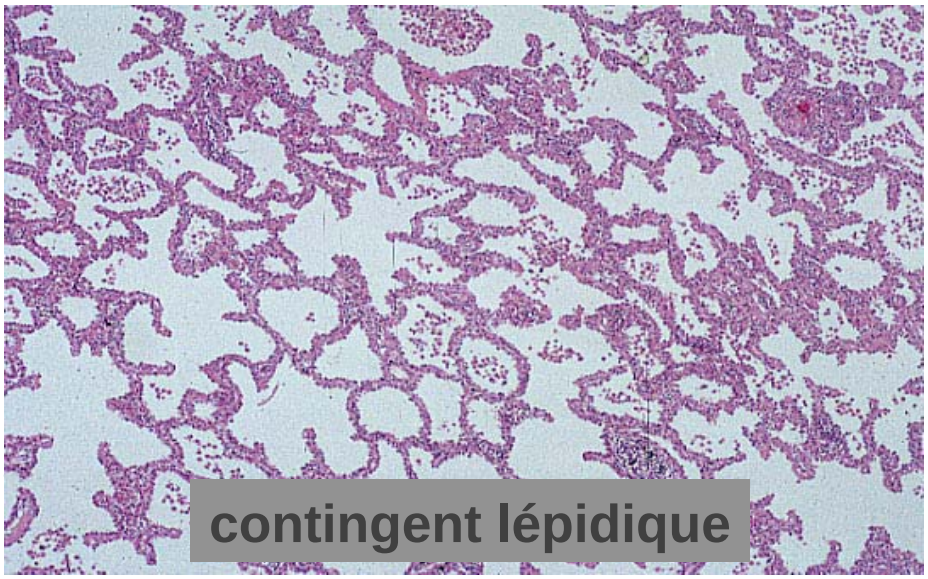
Adénocarcinome Invasif



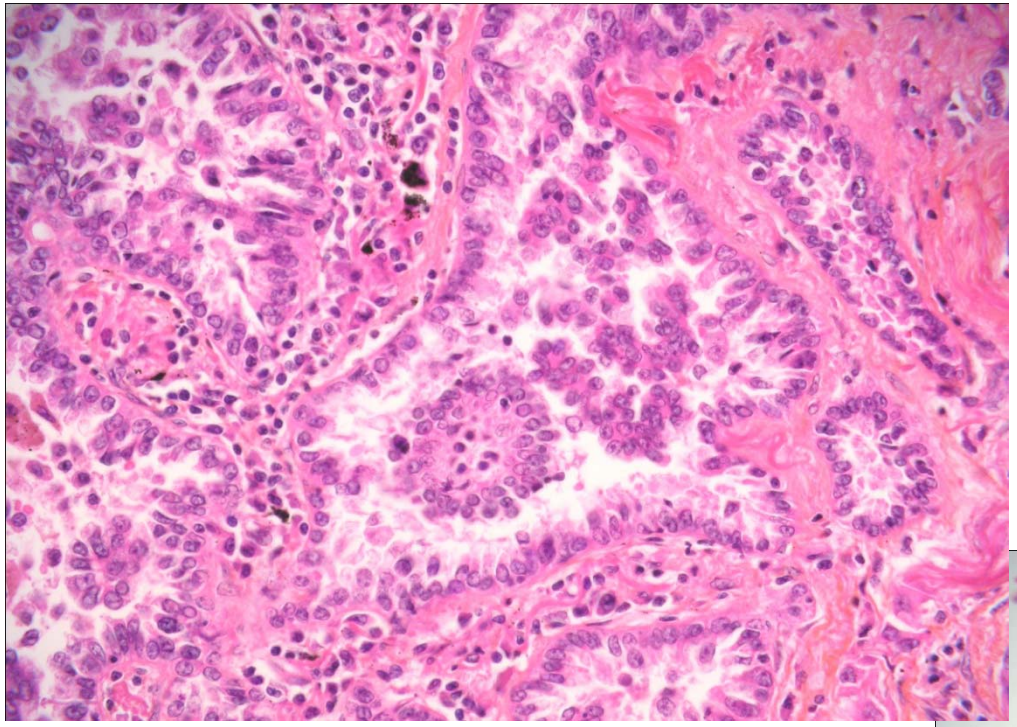


For invasive adenocarcinomas, we suggest comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments, choosing a single predominant pattern. Individual tumors are then classified according to the predominant pattern and the percentages of the subtypes are also reported (weak recommendation, low-quality evidence).

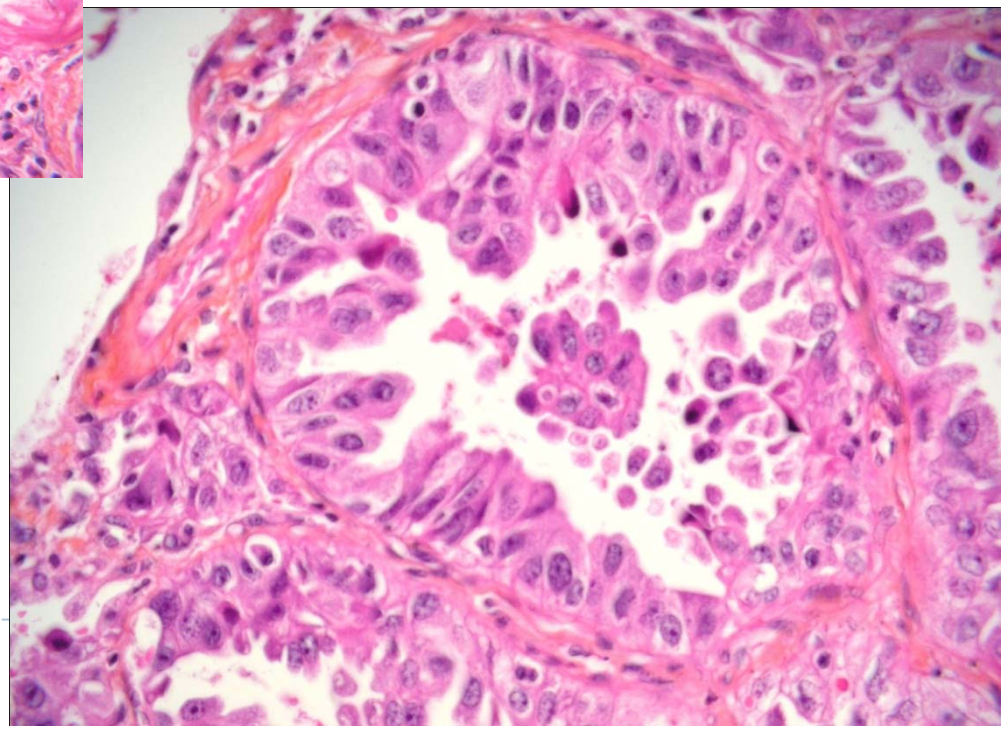


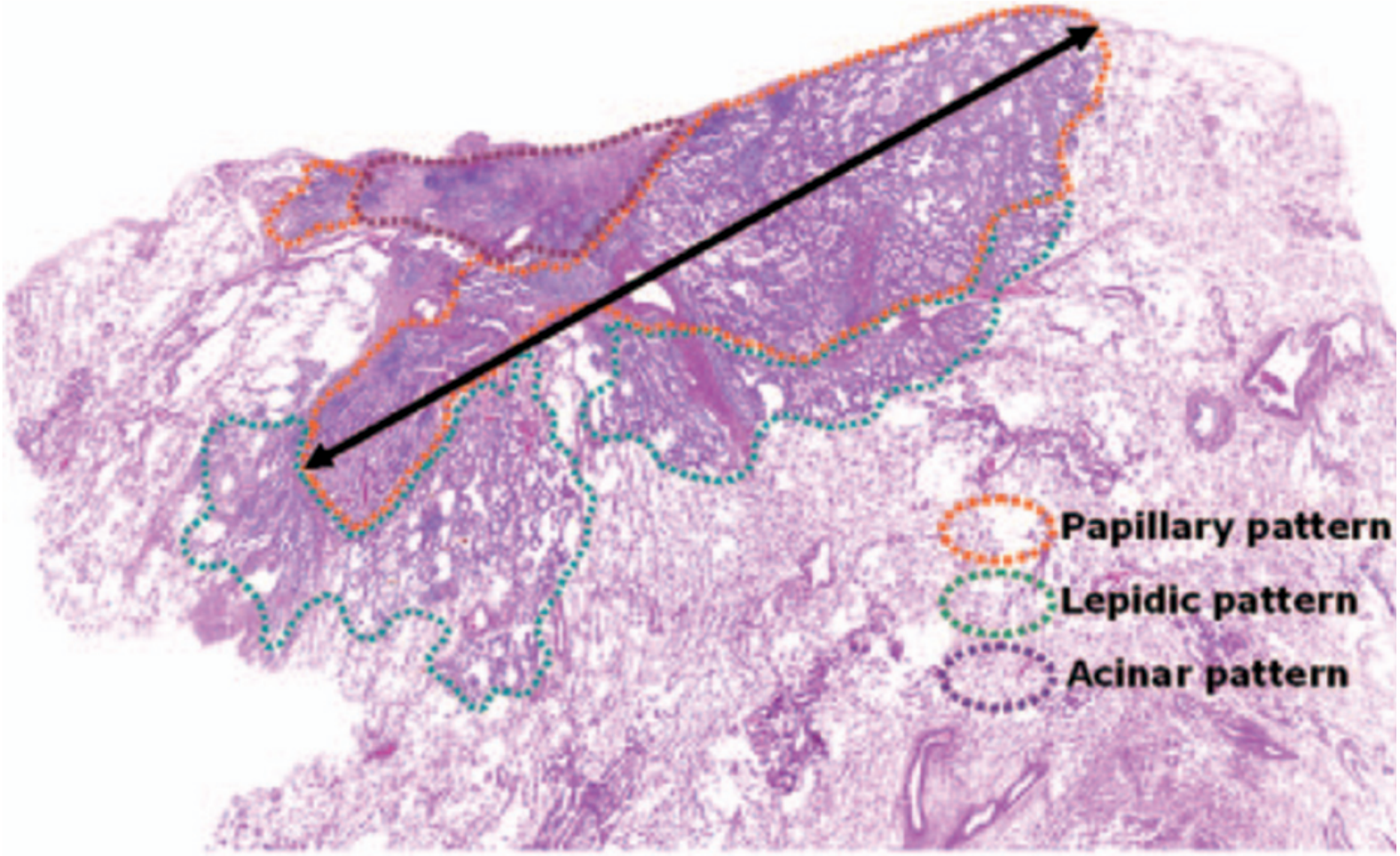


Micropapillaire



Cellules tumorales assemblées en amas ou touffes
mais sans axes fibrovasculaires
Parfois agencées en anneaux

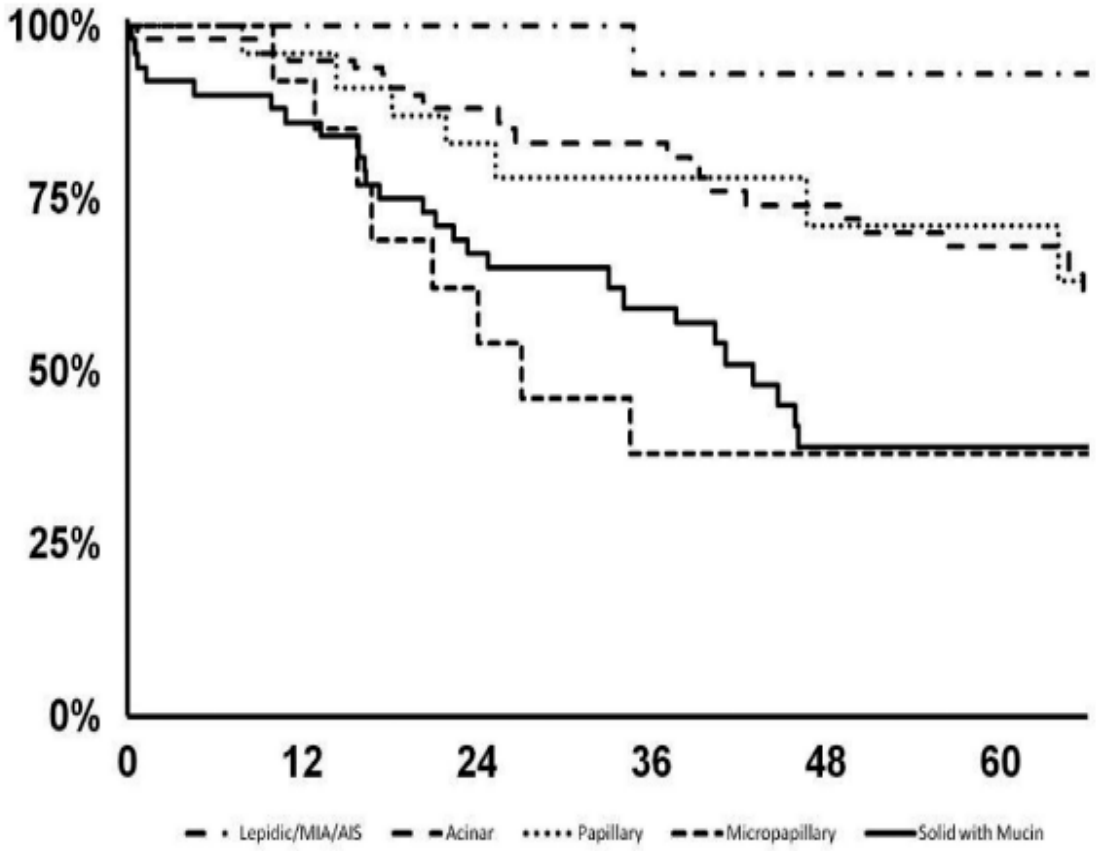




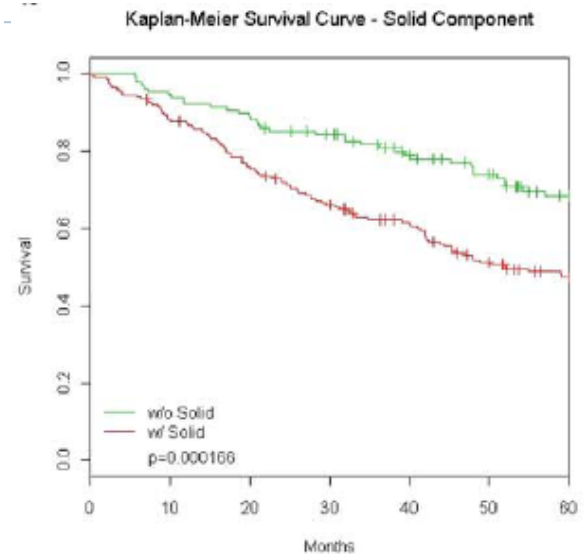
Yoshizawa et al. J Thorac Oncol 2013

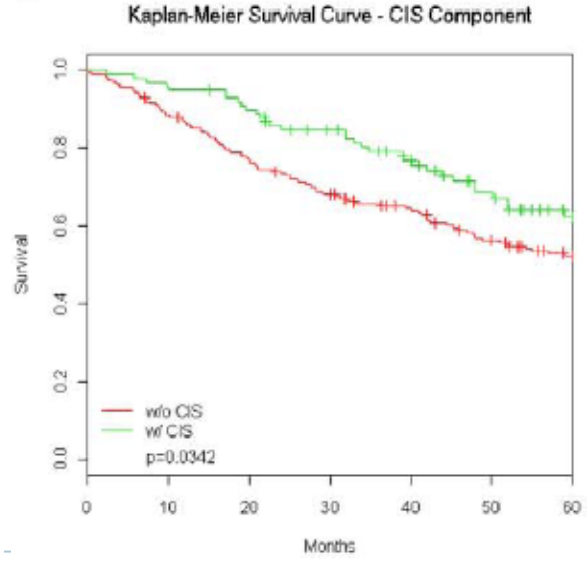
Does Lung Adenocarcinoma Subtype Predict Patient Survival?

A Clinicopathologic Study Based on the New International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society International Multidisciplinary Lung Adenocarcinoma Classification



Russell et al,
Journal of Thoracic Oncology
Sept 2011

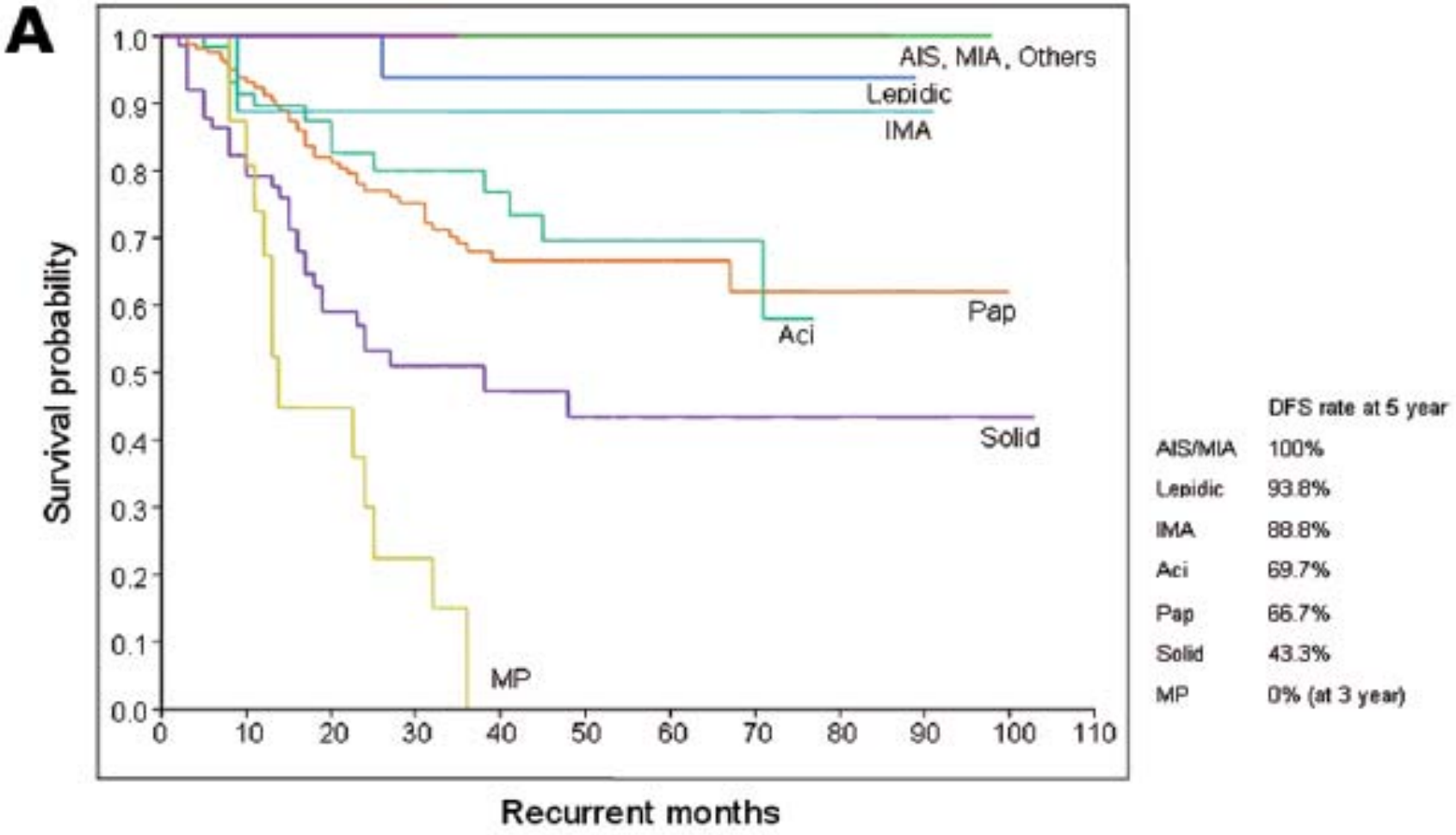




Bryant et al, PLoS One 2010

Série japonaise de 440 adénocarcinomes

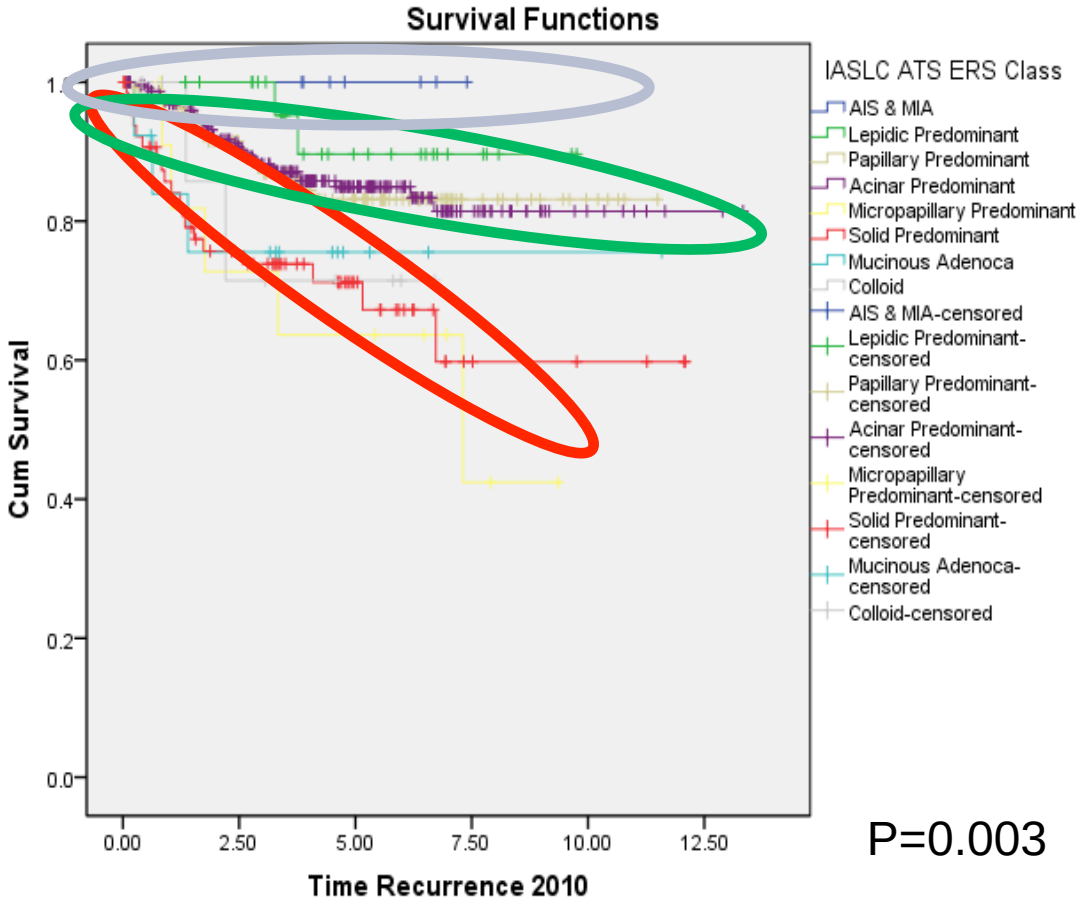
Yoshizawa JTO 2013



	DFS rate at 5 year
AIS/MIA	100%
Lepidic	93.8%
IMA	88.8%
Aci	69.7%
Pap	66.7%
Solid	43.3%
MP	0% (at 3 year)

Stage I adenocarcinoma (n=514)

Recurrence-free survival (RFS) by IASLC histologic type



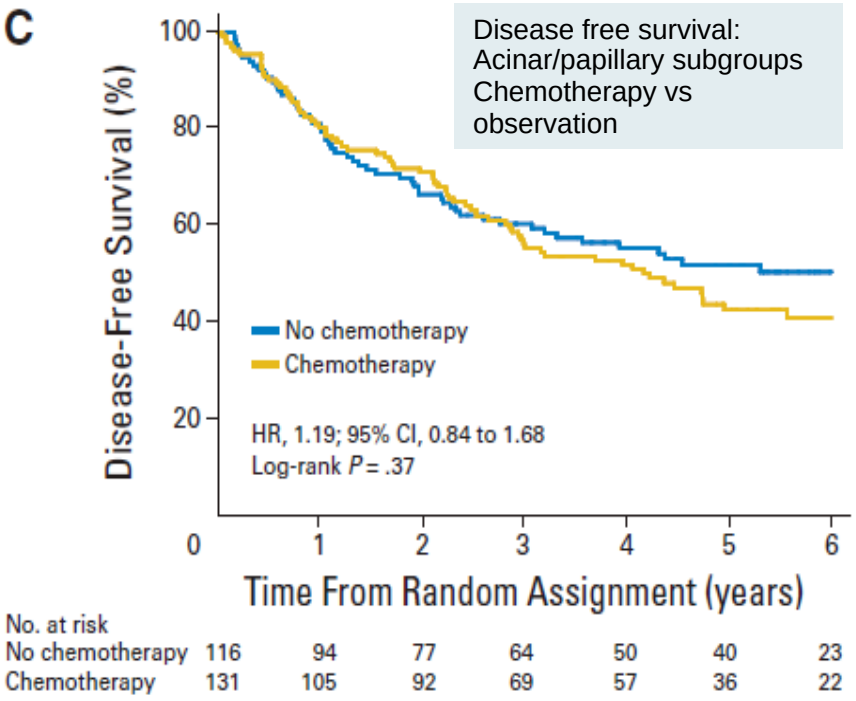
P=0.003

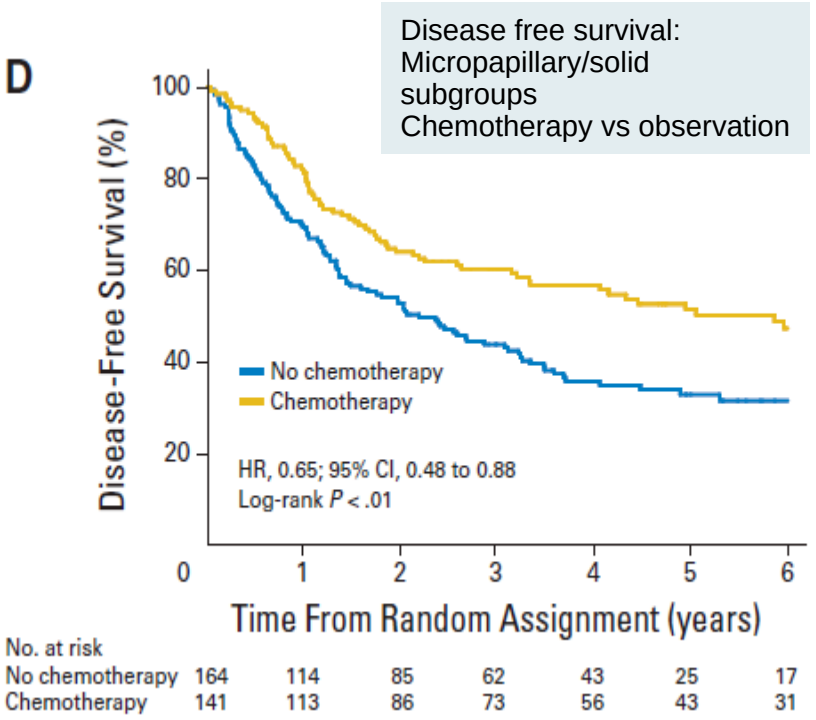
Histologic Type (N)	5 Year RFS %
AIS (1)	100
MIA (8)	100
Lepidic NM (29)	90
Papillary (143)	83
Acinar (232)	85
Inv Mucinous Ad (13)	76
Solid (67)	71
Micropapillary (12)	64
Colloid (9)	71

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 ADC from LACE-Bio study





Tsao MS, et al: J Clin Oncol 2015

Reproductibilité de la classification OMS des adénocarcinomes

Reference	ADC Subtypes	Statistics	Comments
Thunnissen E: Mod Path 25:1574, 2012	Experts Typical patterns Difficult patterns	 Kappa = 0.77 Kappa = 0.38	Selected images
Warth A: ERJ 40:1221-27, 2012	Experts Residents	Kappa (0.44-.72) Kappa (0.38-0.47)	Glass slides
Warth A:Virch Arch 461:185-93, 2012	Experts	Consensual votes: 59.6-75%	Digital Slides educational session ↓ disagreement ($p<0.001$)
Duhig E JTO 20:673, 2015	Experts & non-experts	Intraclass correlation coefficient – 88-98%	Glass slides: High degree of concordance
Nakazato Y: JTO 8:736-743	Experts	5 class – Kappa=0.46 2 class – Kappa=0.66	 LP/AC/Pap vs Sol/MP
Thunnissen E: Mod Path 25:1574, 2012	Invasive vs noninvasive Typical patterns Difficult patterns	 Kappa = 0.55 Kappa = 0.08	Selected images

Adénocarcinome mucipare invasif (MIA)

- Microinvasif ou invasif
- 58% femmes; 45% fumeurs
- Svt multifocal
- CK7, CK20 +; TTF1 neg
- 70% mutations K-ras

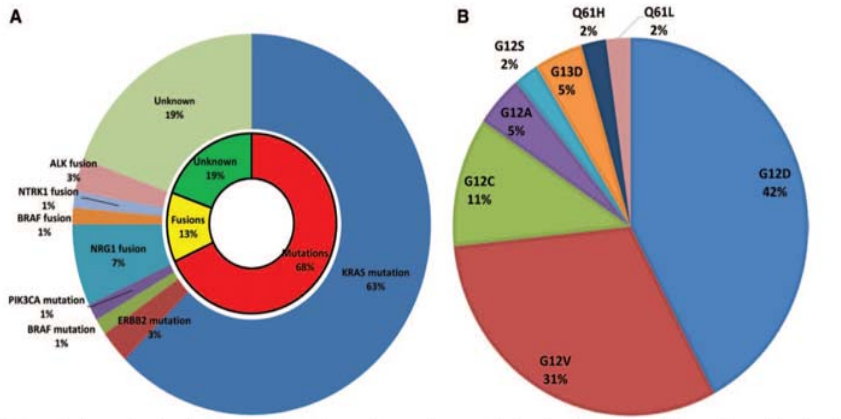
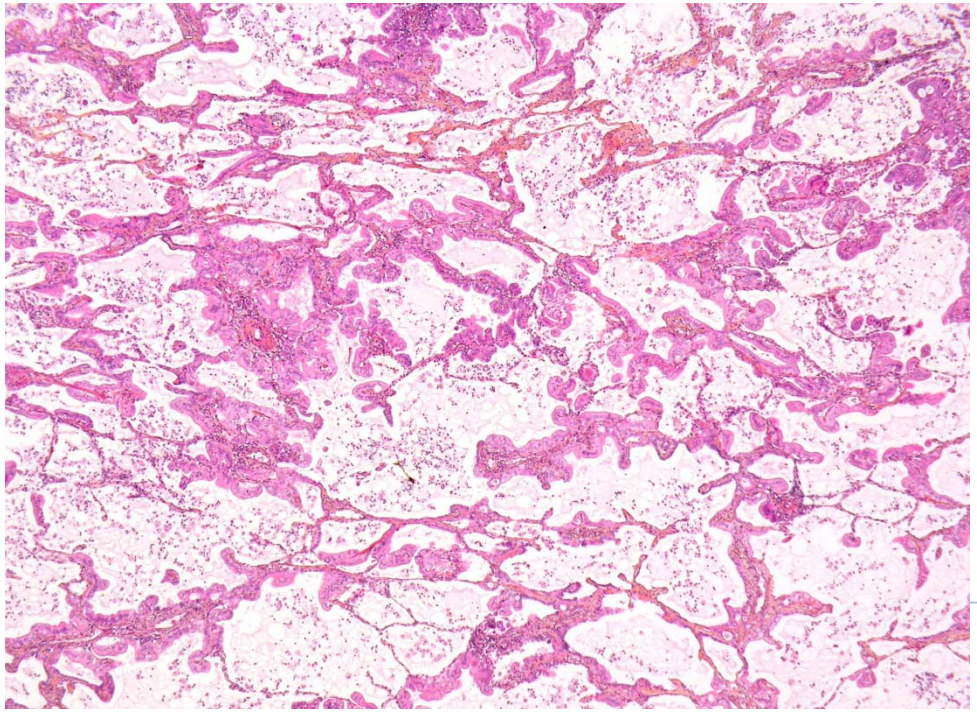
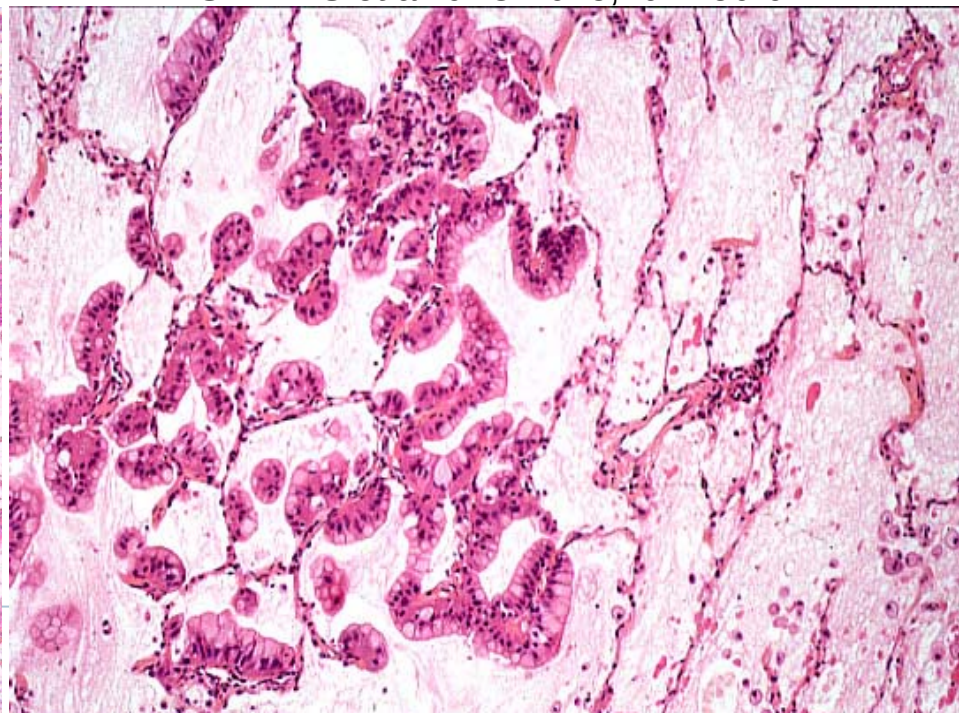


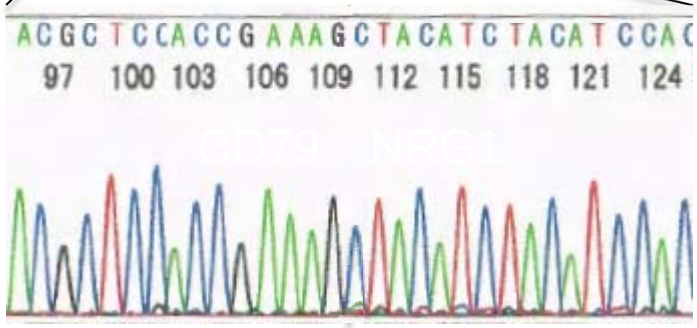
FIGURE 2. Pie charts showing the fraction of mucinous adenocarcinomas that harbor the indicated drivers (*A*) and the fraction of subtypes of *KRAS* mutations (*B*).

Shim HS et al: JTO 2015;10:1156-62





Invasive Mucinous denocarcinoma in non-smokers harbor *CD74-NRG1* fusion (ERBB2-ERBB3 pathways)

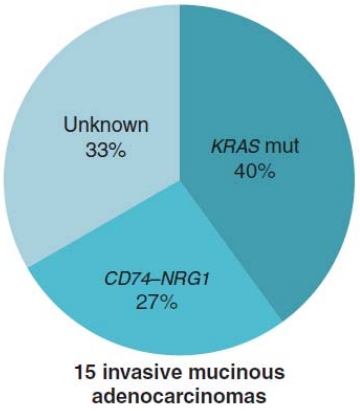


A

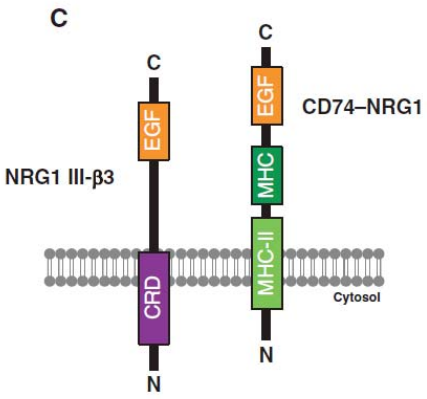
Sample	Age	Sex	Stage	Smoking status	AD subtype
Index-case	64	Female	Ib	Never	Invasive mucinous
Case-A	73	Female	Ia	Never	Invasive mucinous
Case-B	72	Female	Ia	Never	Invasive mucinous
Case-C	66	Female	Ia	Never	Invasive mucinous
Case-D	31	Female	Ia	Never	Invasive mucinous

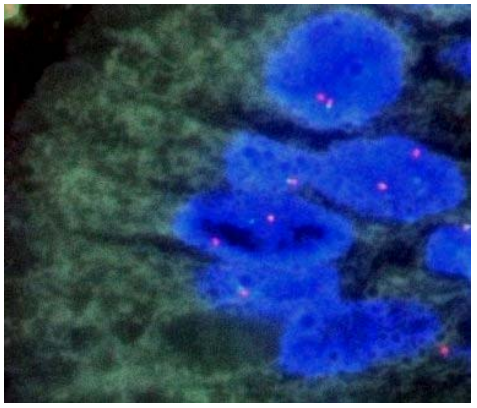
EGFR, KRAS, BRAF, HER2, ALK, ROS, RET negative

B

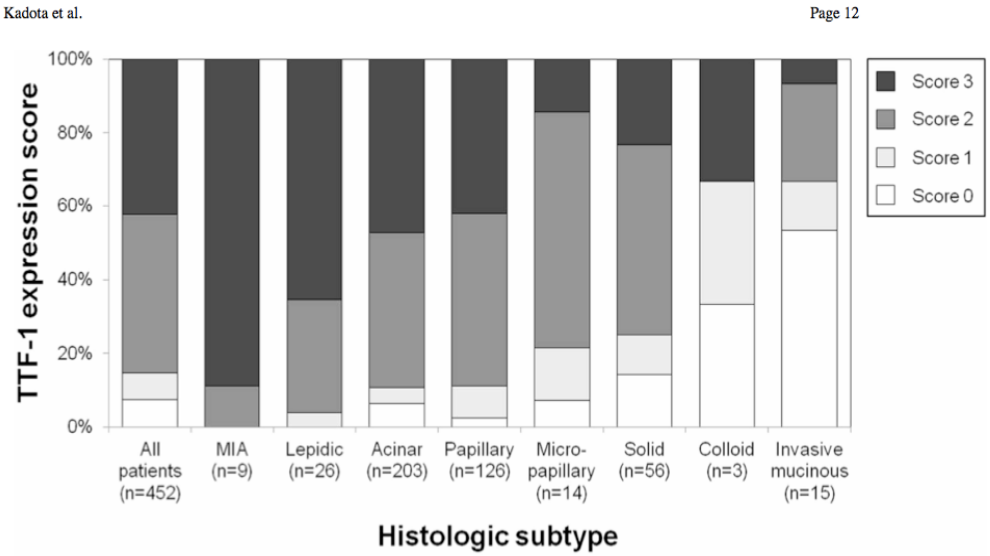


C

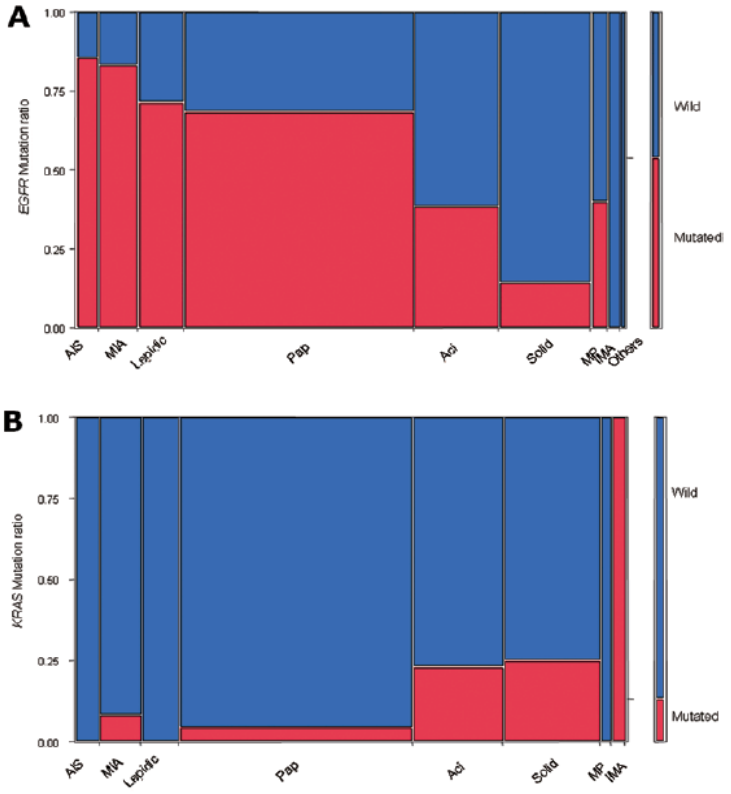




Histology is correlated with TTF1 expression and EGFR and K-RAS mutations



Kadota et al 2013

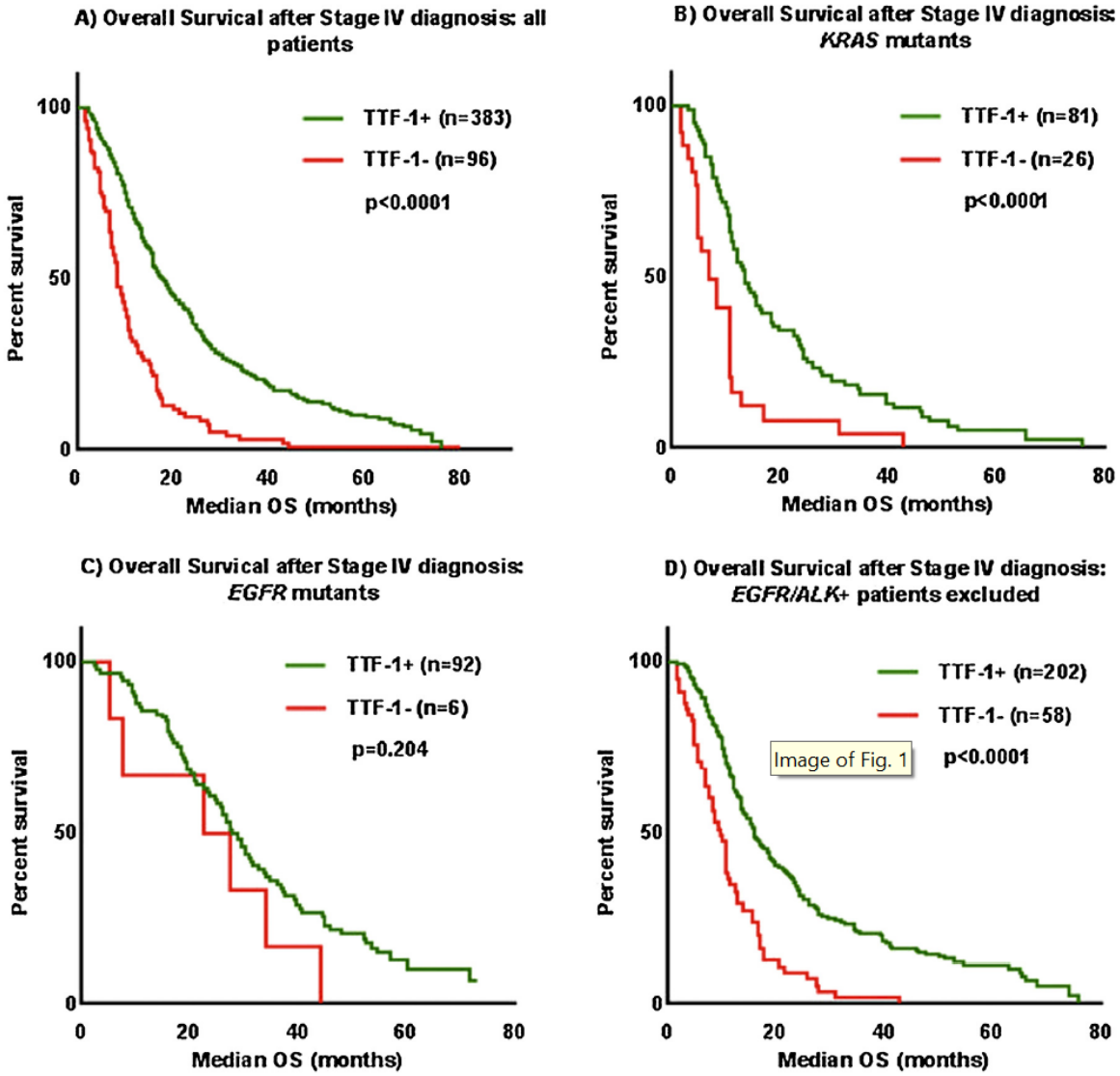


Yoshizawa JTO 2013

Prognostic impact of TTF-1 expression in patients with stage IV lung adenocarcinomas

Juliana B. Schilsky[a], Ai Ni[b], Linda Ahn[a], Sutirtha Datta[a], William D. Travis[c,d], Mark G. Kris[a,e], Jamie E. Chaft[a,e], Natasha Rekhtman[c,d,**], Matthew D. Hellmann[a,e,*]

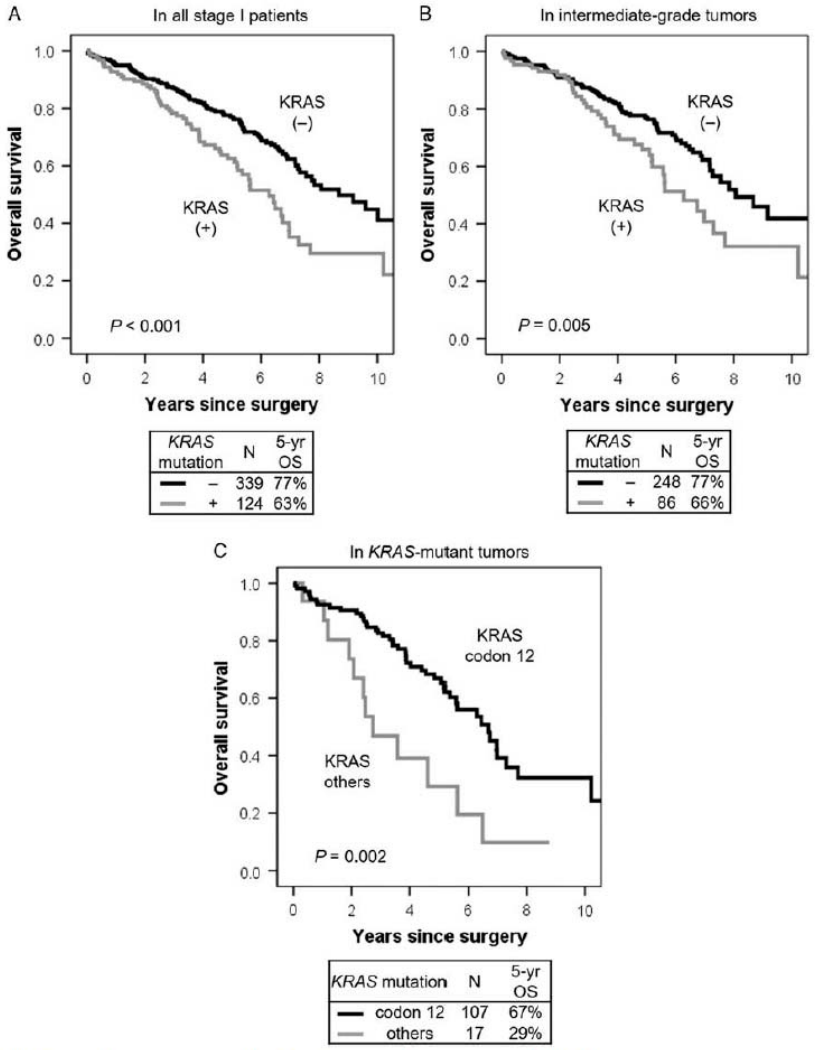
Lung Cancer 2017

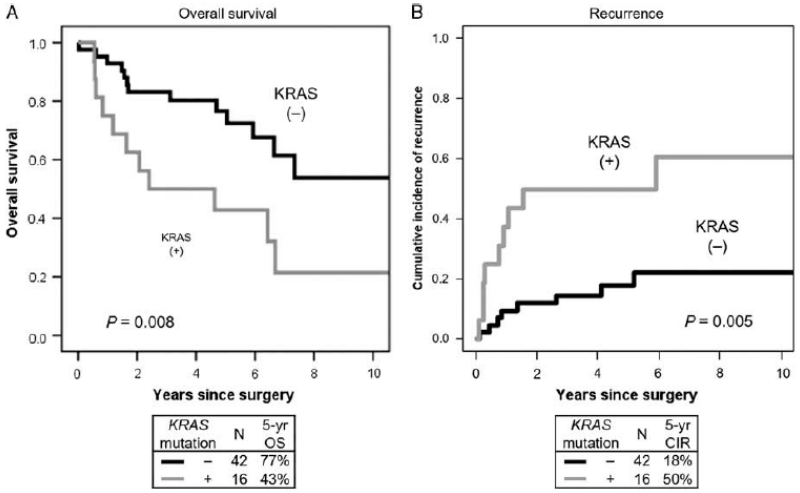


KRAS Mutation Is a Significant Prognostic Factor in Early-stage Lung Adenocarcinoma

Kyuichi Kadota, MD, PhD,†‡ Camelia S. Sima, MD, MS,§ Maria E. Arcila, MD,† Cyrus Hedvat, MD,† Mark G. Kris, MD,‖ David R. Jones, MD,* Prasad S. Adusumilli, MD, FACS, FCCP,*¶ and William D. Travis, MD†*

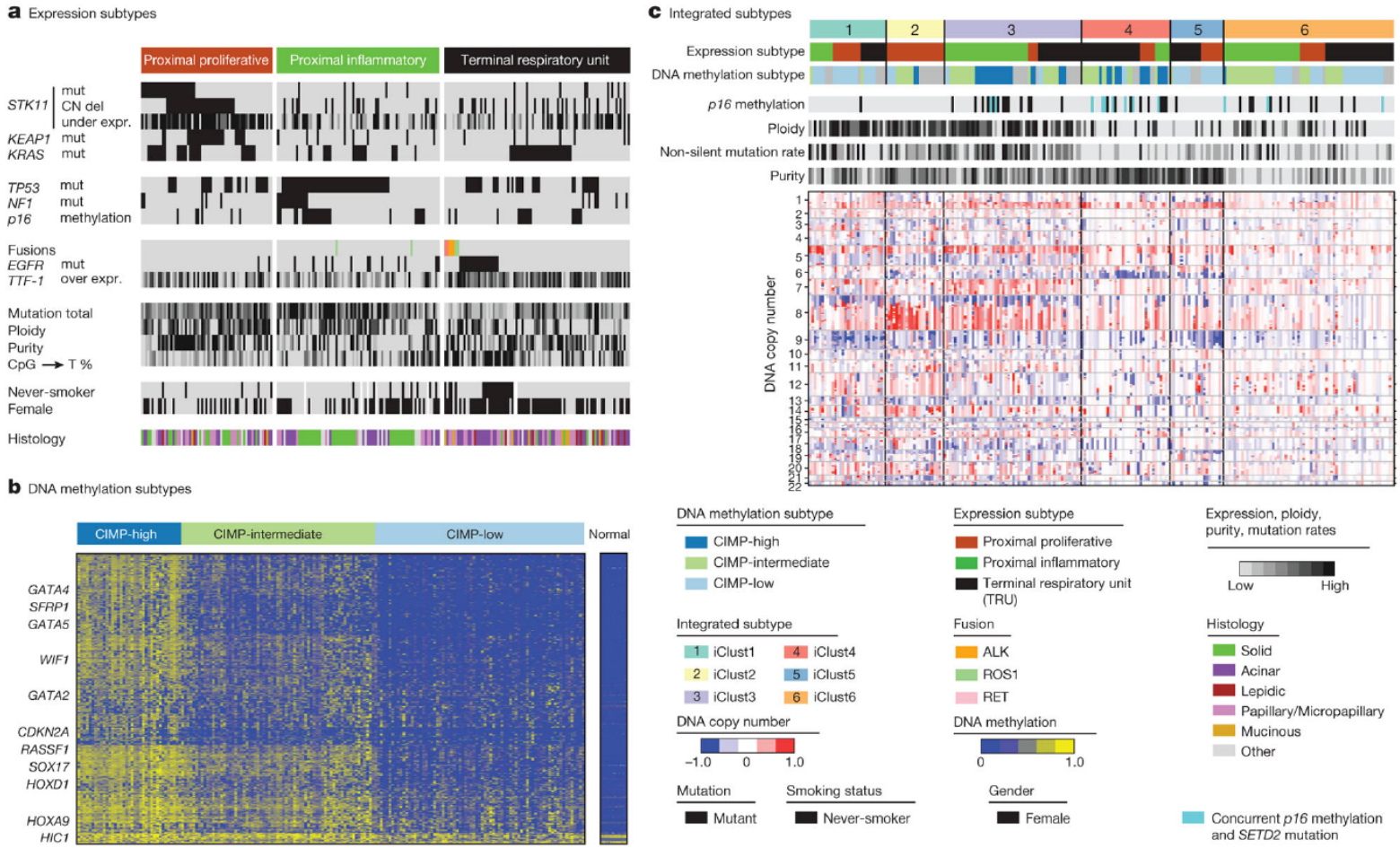
Am J Surg Pathol 2016





The Cancer Genome Atlas research network: comprehensive profiling of lung adenocarcinoma

Nature 2014

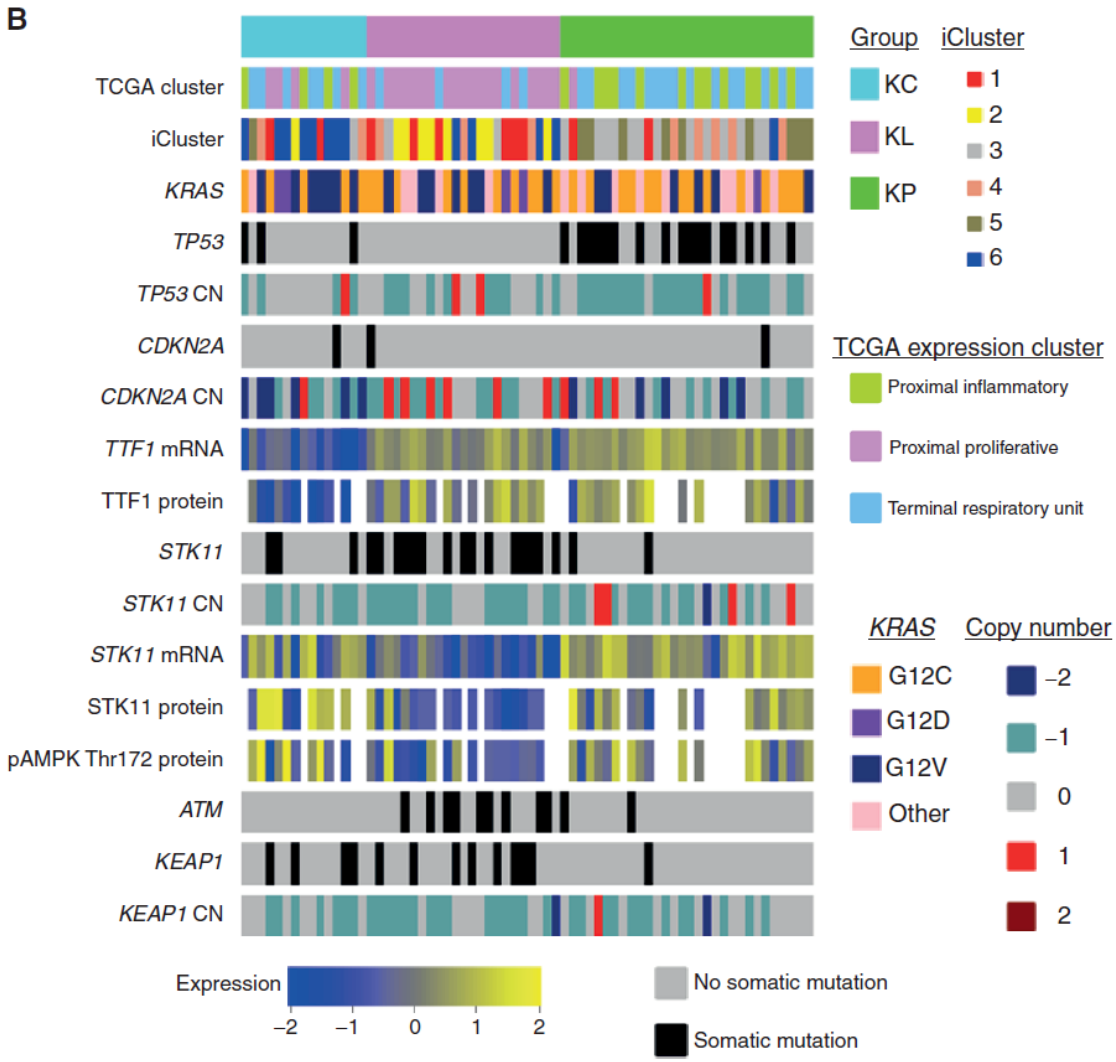


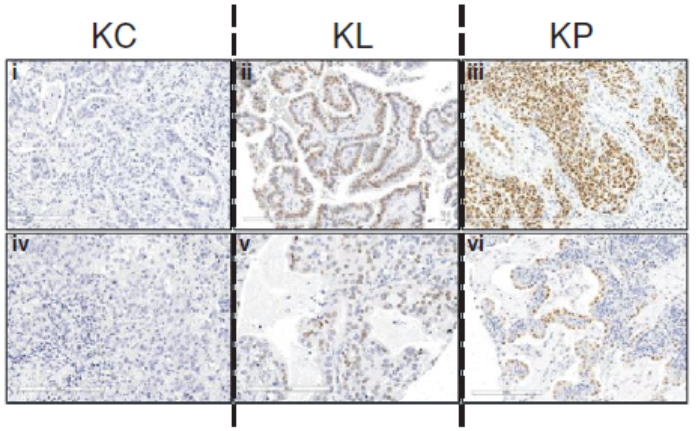
Major Subsets of *KRAS*-Mutant Lung Adenocarcinoma with Distinct Biology, Immune Profiles, and Therapeutic Vulnerabilities

Ferdinandos Skoulidis[1], Lauren A. Byers[1], Lixia Diao[2], Vassiliki A. Papadimitrakopoulou[1], Pan Tong[2], Julie Izzo[3], Carmen Behrens[1], Humam Kadara[3], Edwin R. Parra[3], Jaime Rodriguez Canales[3], Jianjun Zhang[4], Uma Giri[1], Jayanthi Gudikote[1], Maria A. Cortez[5], Chao Yang[1], Youhong Fan[1], Michael Peyton[6], Luc Girard[6], Kevin R. Coombes[7], Carlo Toniatti[8], Timothy P. Heffernan[8], Murim Choi[9], Garrett M. Frampton[10], Vincent Miller[10], John N. Weinstein[2], Roy S. Herbst[11], Kwok-Kin Wong[12], Jianhua Zhang[6], Padmanee Sharma[13], Gordon B. Mills[14], Waun K. Hong[15], John D. Minna[6], James P. Allison[16], Andrew Futreal[4], Jing Wang[2], Ignacio I. Wistuba[3], and John V. Heymach[1]

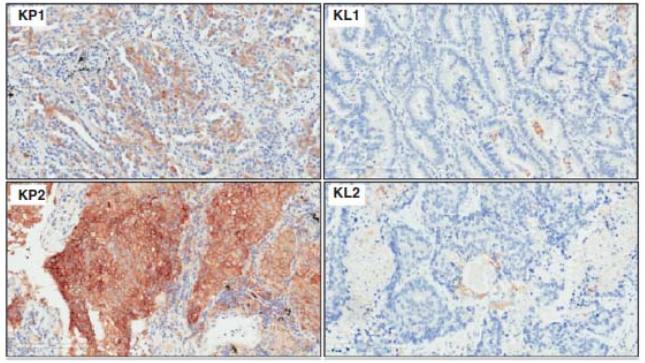
Cancer Discovery 2015

TTF1 expression





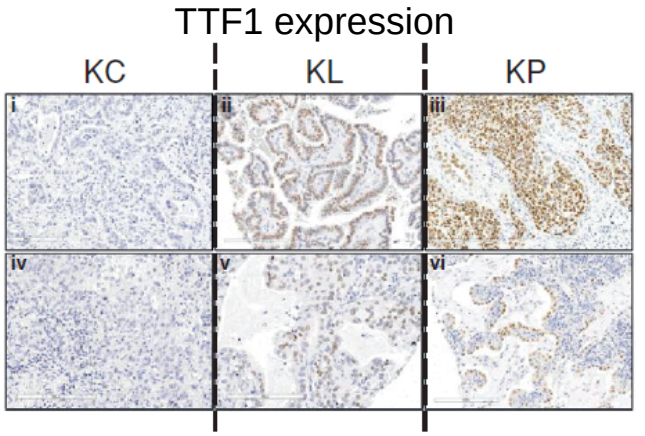
CD274 (PD-L1) IHC

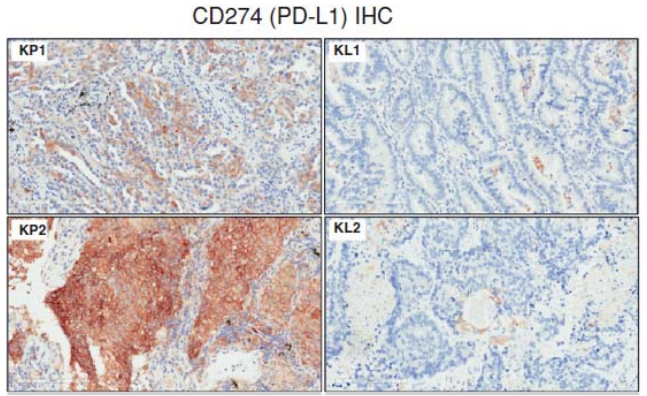


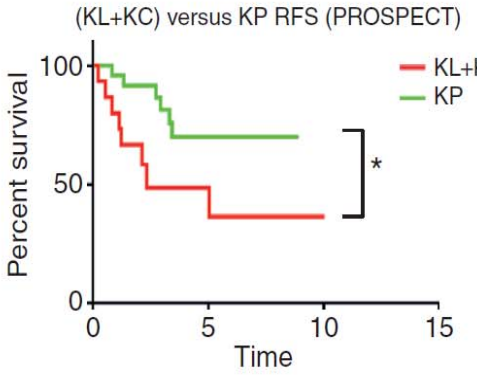
- **KP group (prox inflam): *P53* mutated, TTF1 +, expression PD-L1+ expression, *JAK-STAT* pathway and INF gamma signaling (CD3, CD8, CD45RO, PD1, CTLA4), higher mut rates**

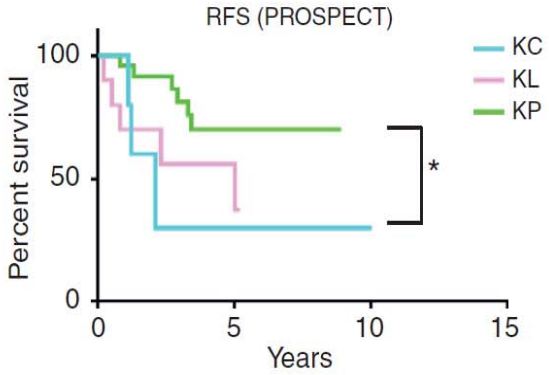
- **KL group (prox proliferative): *STK11/LKB1* mut, (co P53 co mut), *ATM* mut (ROS), *KEAP1* mut, NRF2 up regulation, *RB1* mut, TTF1 + expression, PD-L1 – expression (immune inert)**

- **KC group (TRU and invasive mucinous ADC): biallelic deletion CDKN2A and CDKN2B, NRF2 up regulation, TTF1- expression**

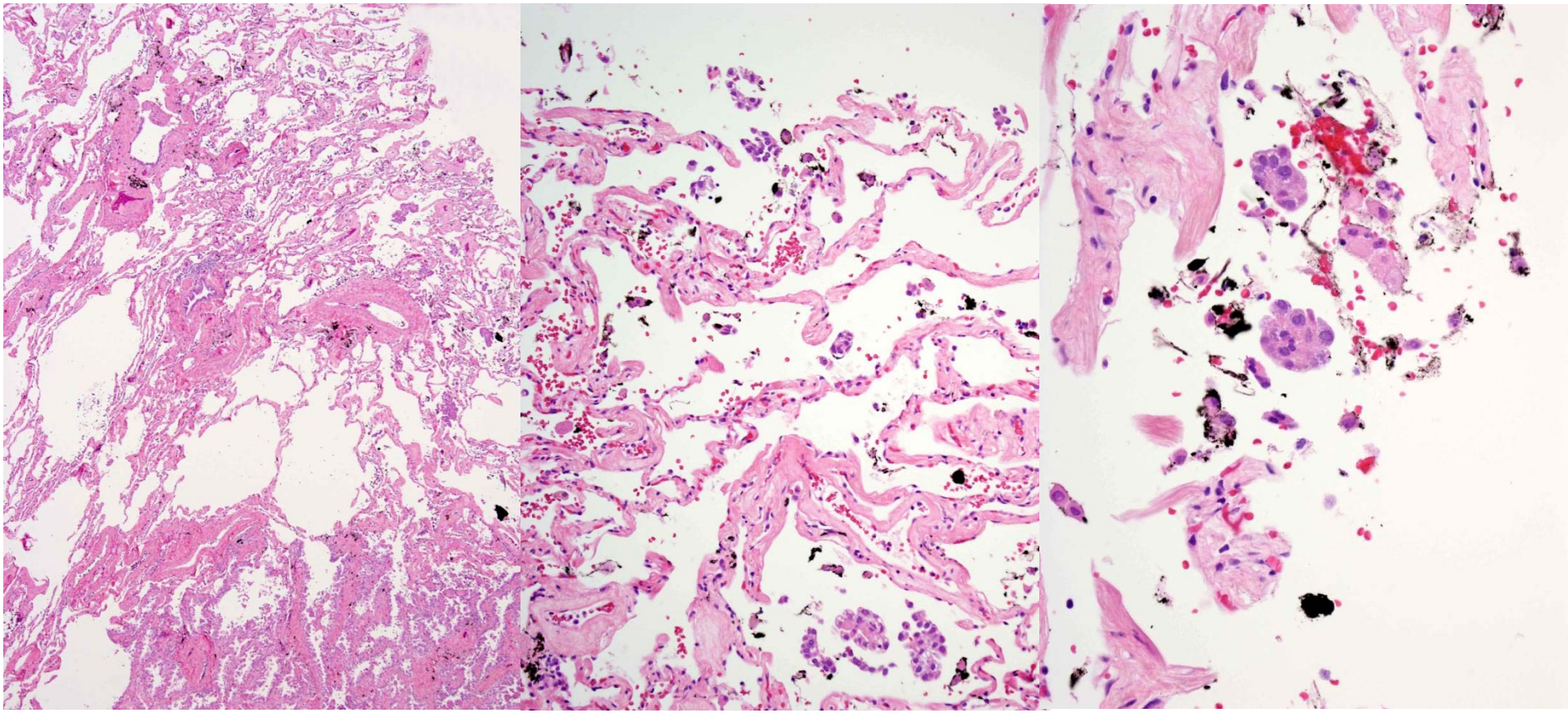




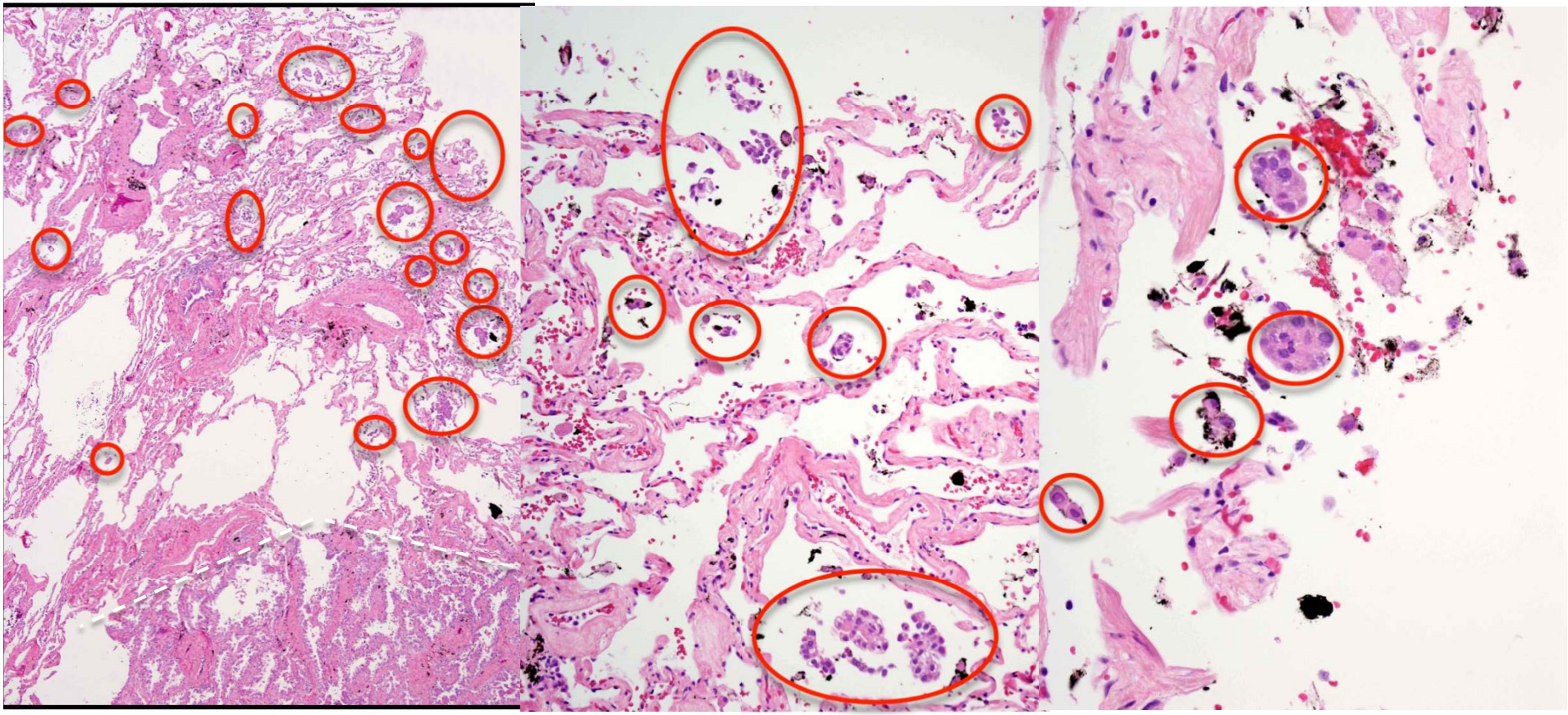




Spread Through Air Spaces (STAS) (From Travis WD)



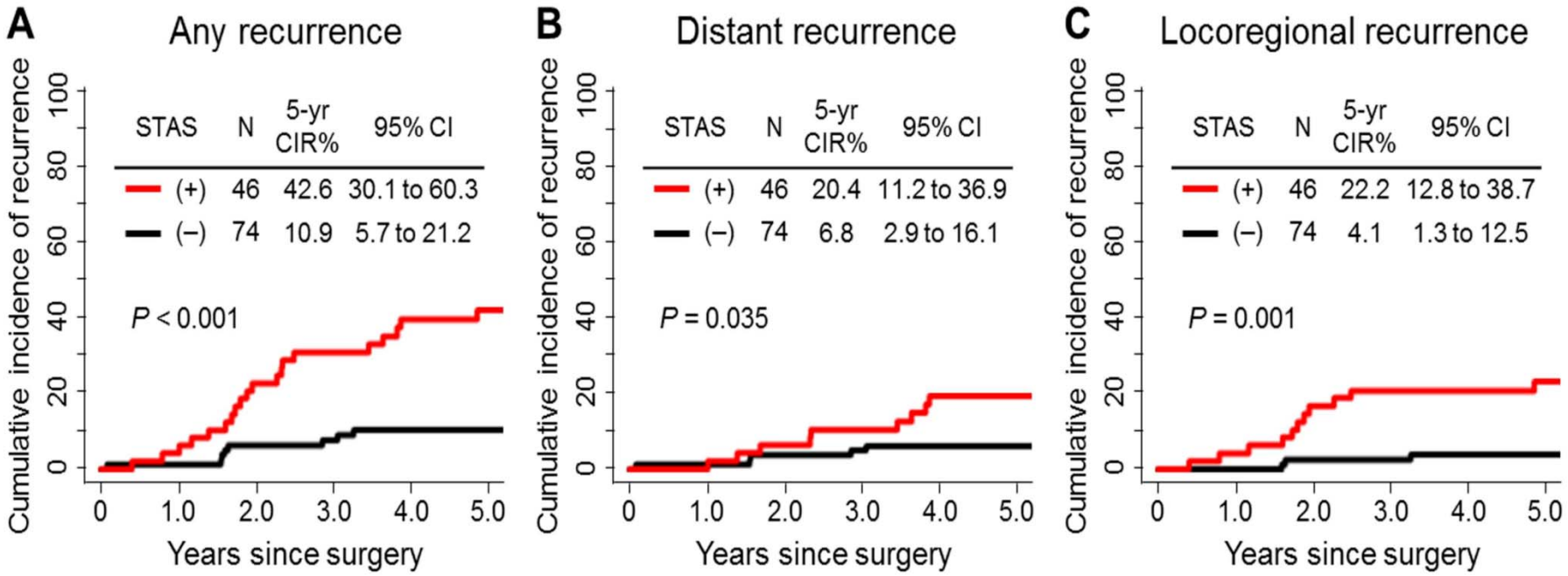
Spread Through Air Spaces (STAS)



Kadota K et al; J Thorac Oncol 2015

STAS is independently associated with risk of recurrence in limited resections

Figure 3 CIR by STAS in the limited resection group



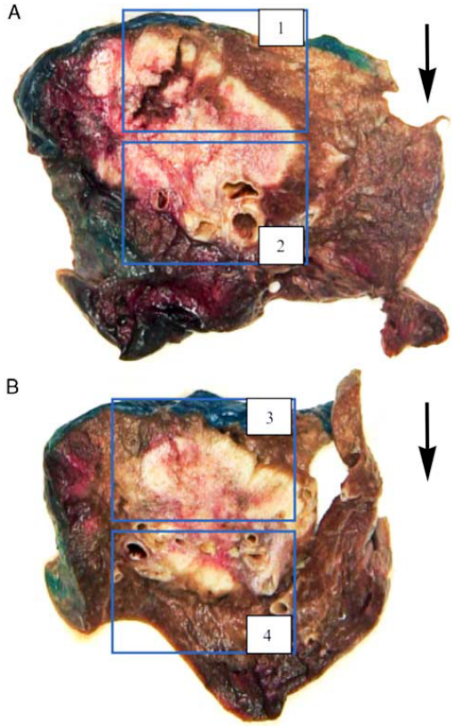
(hazard ratio, 3.08; *P=0.014).*

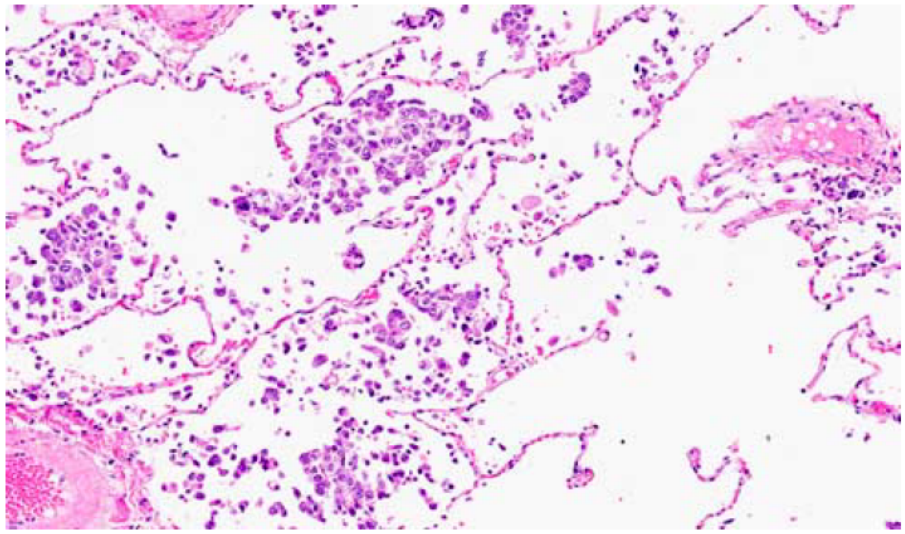
Kadota K et al; J Thorac Oncol 2015

A Prospective Study of Loose Tissue Fragments in Non–Small Cell Lung Cancer Resection Specimens

An Alternative View to "Spread Through Air Spaces"

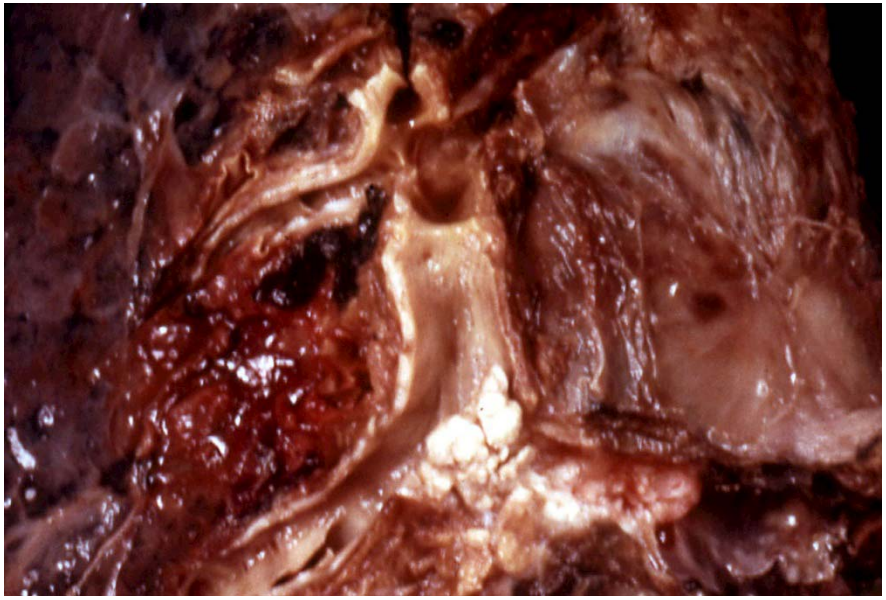
Hans Blaauwgeers, MD, Douglas Flieder, MD,† Arne Warth, MD, PhD,‡ Alexander Harms, MD,‡ Kim Monkhorst, MD, PhD,§ Birgit Witte, PhD,‖ and Erik Thunnissen, MD, PhD¶*

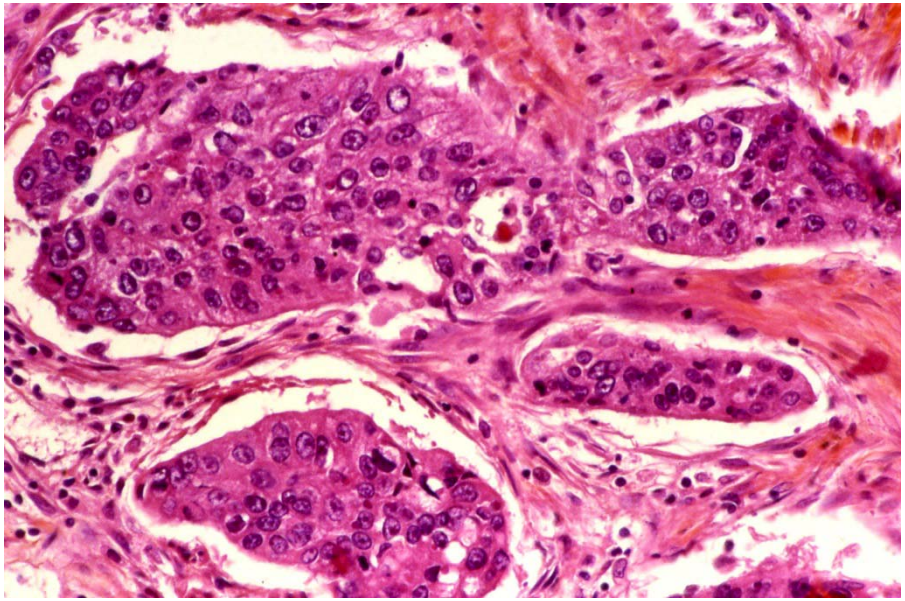


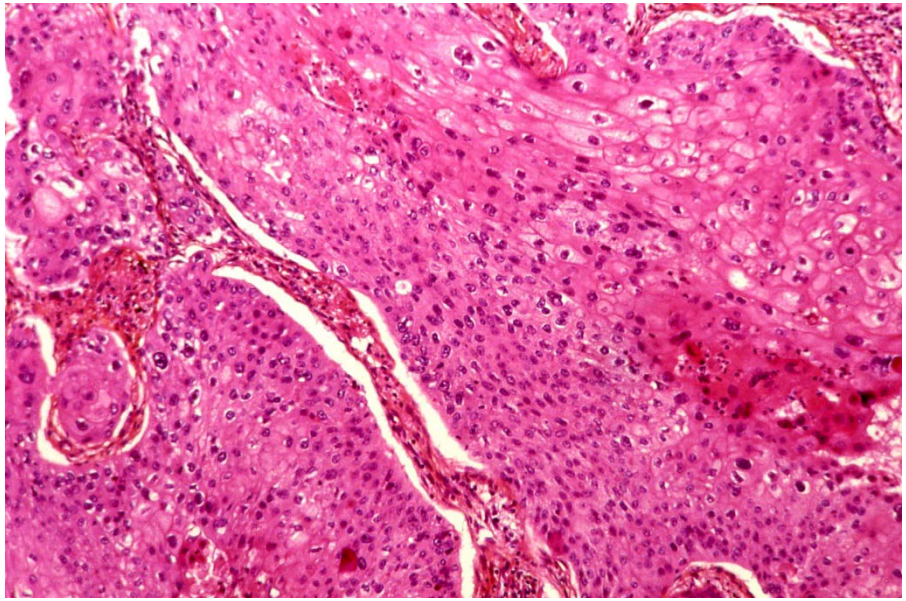


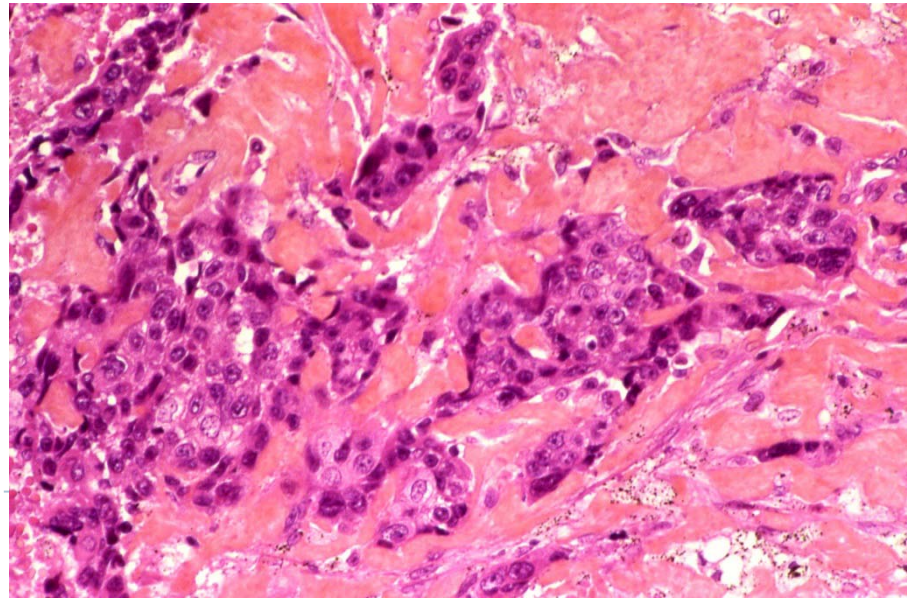
High number of tissue loose fragments (77%) particularly in sections 2,3 and 4 and when lung was freshly cut

Carcinome épidermoïde









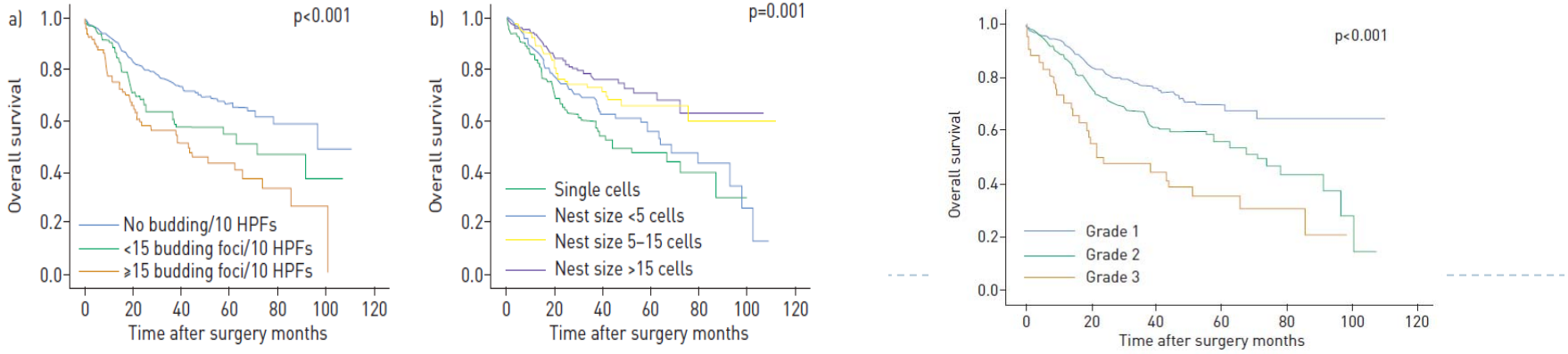
Proposal of a prognostically relevant grading scheme for pulmonary squamous cell carcinoma

Wilko Weichert[1,2,3], Claudia Kossakowski[1], Alexander Harms[1],
Peter Schirmacher[1], Thomas Muley[4,5], Hendrik Dienemann[5,6] and Arne Warth[1,5]

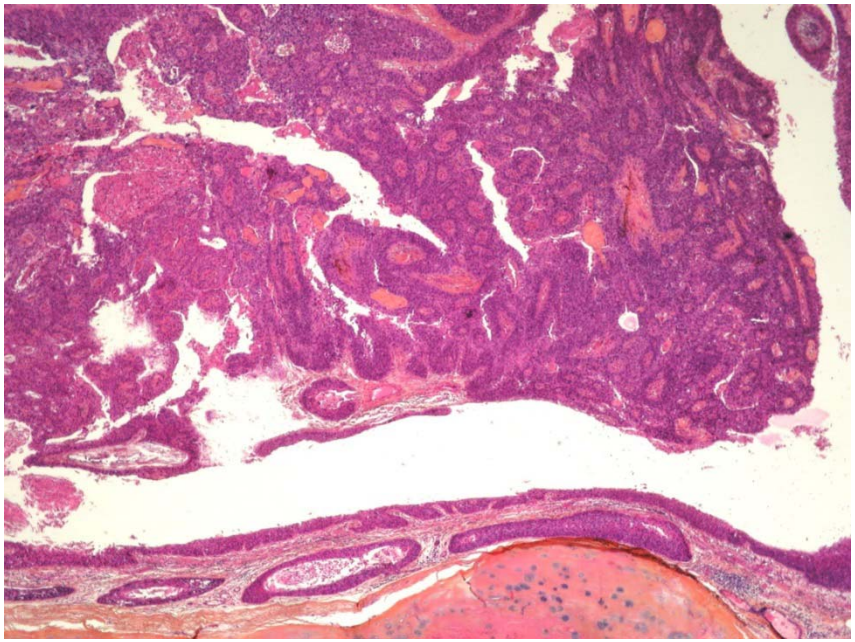
TABLE 1 Lung squamous cell carcinoma grade according to sum of scores for tumour budding and nest size

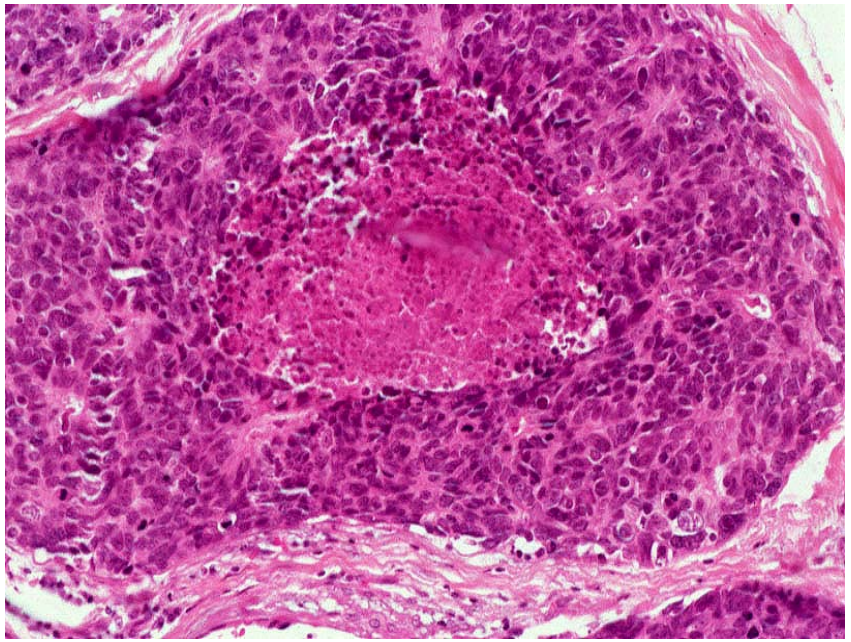
Morphologic feature	Score	Definition
Tumour budding	1	No budding in 10 HPFs
	2	<15 budding foci per 10 HPFs
	3	⩾15 budding foci per 10 HPFs
Tumour nest size	1	>15 cells (large nest size)
	2	5–15 cells (intermediate nest size)
	3	<5 (or 2–4) cells (small nest size)
	4	Single cell invasion
Combined score	2–3	Grade 1 (well differentiated)
	4–6	Grade 2 (moderately differentiated)
	7	Grade 3 (poorly differentiated)

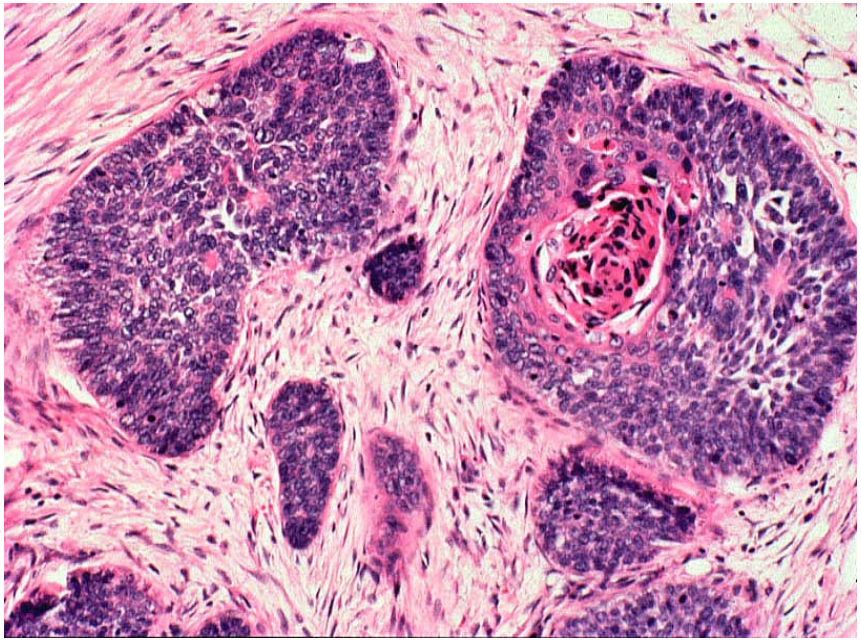
HPF: high-power field. Reproduced and modified from [33].

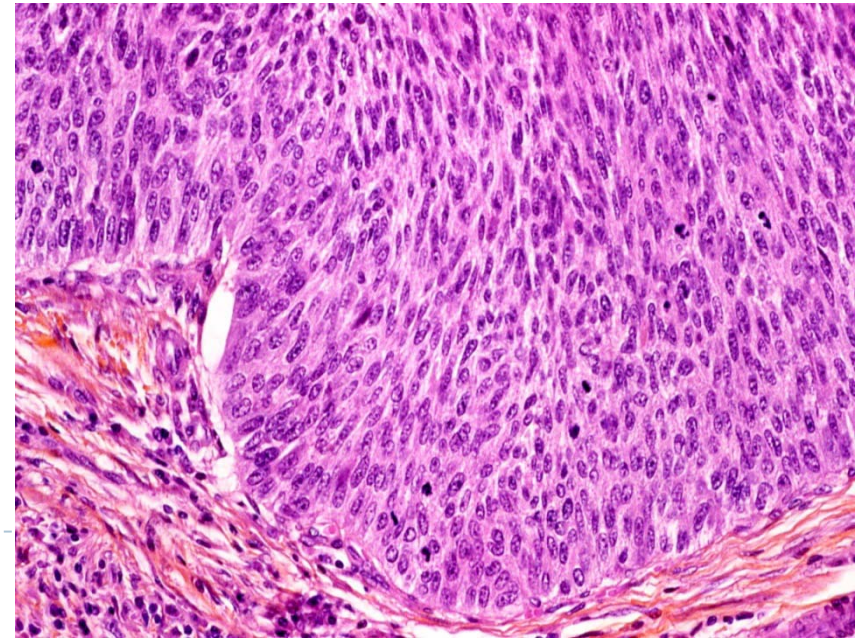


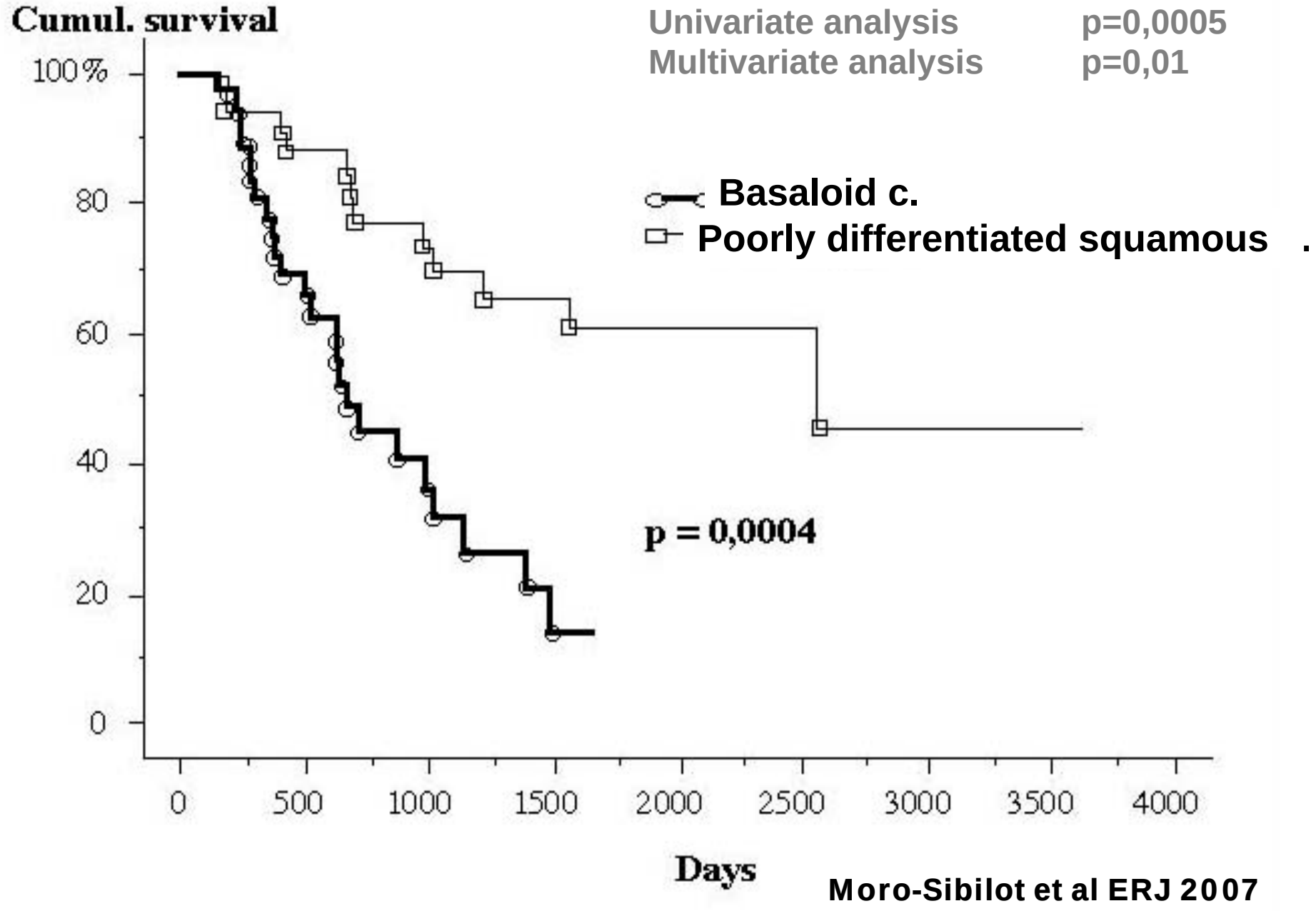
Variant basaloïde



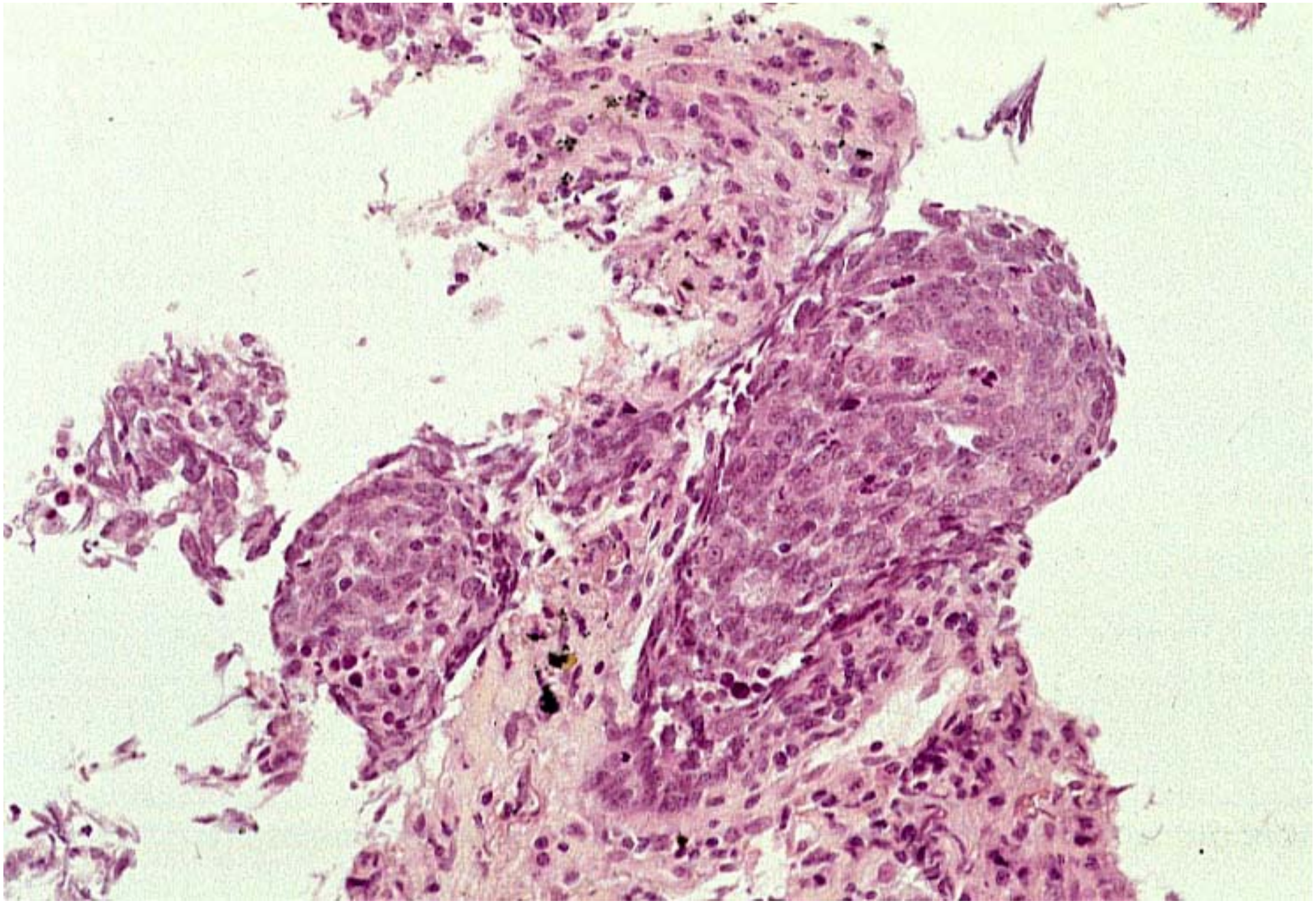


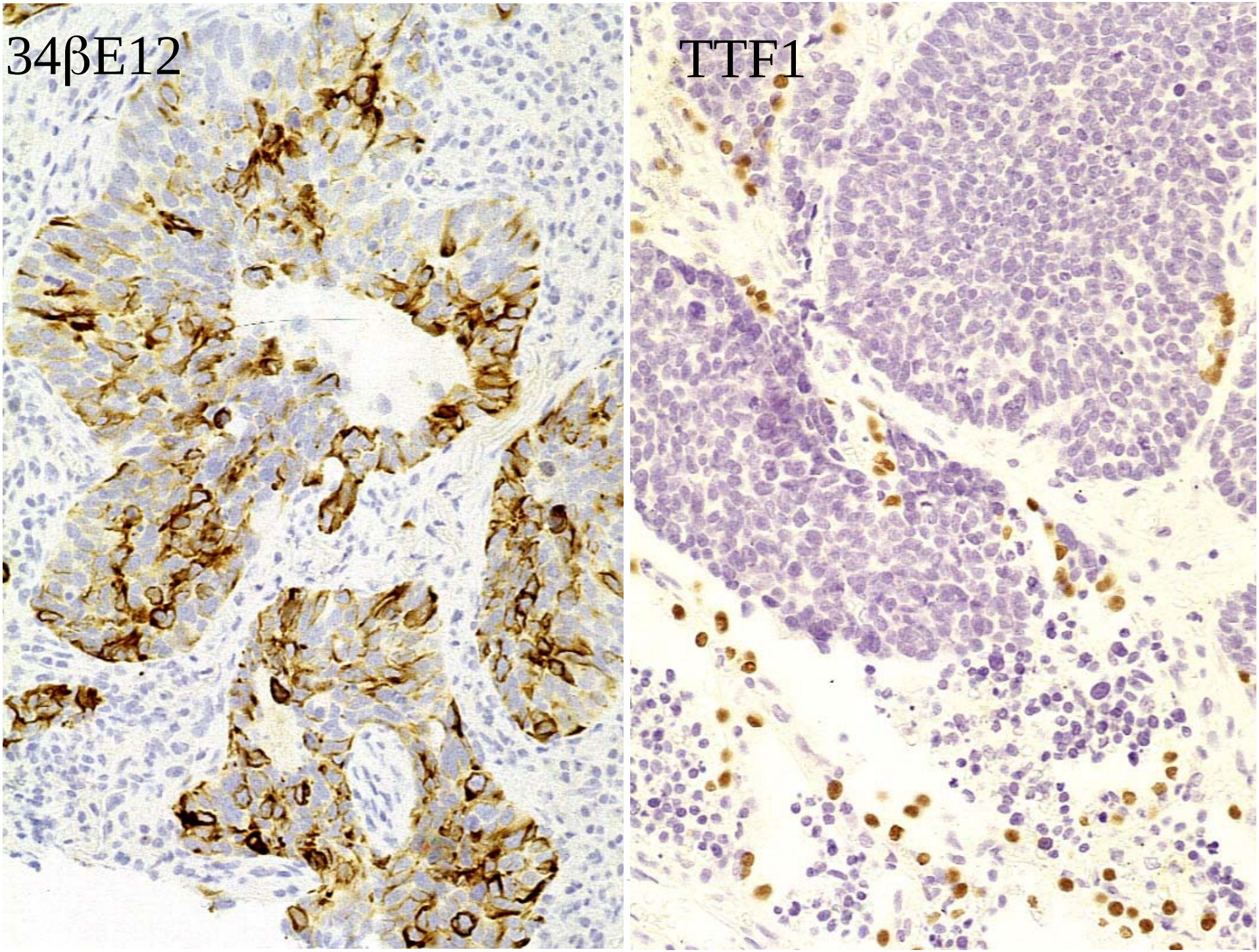






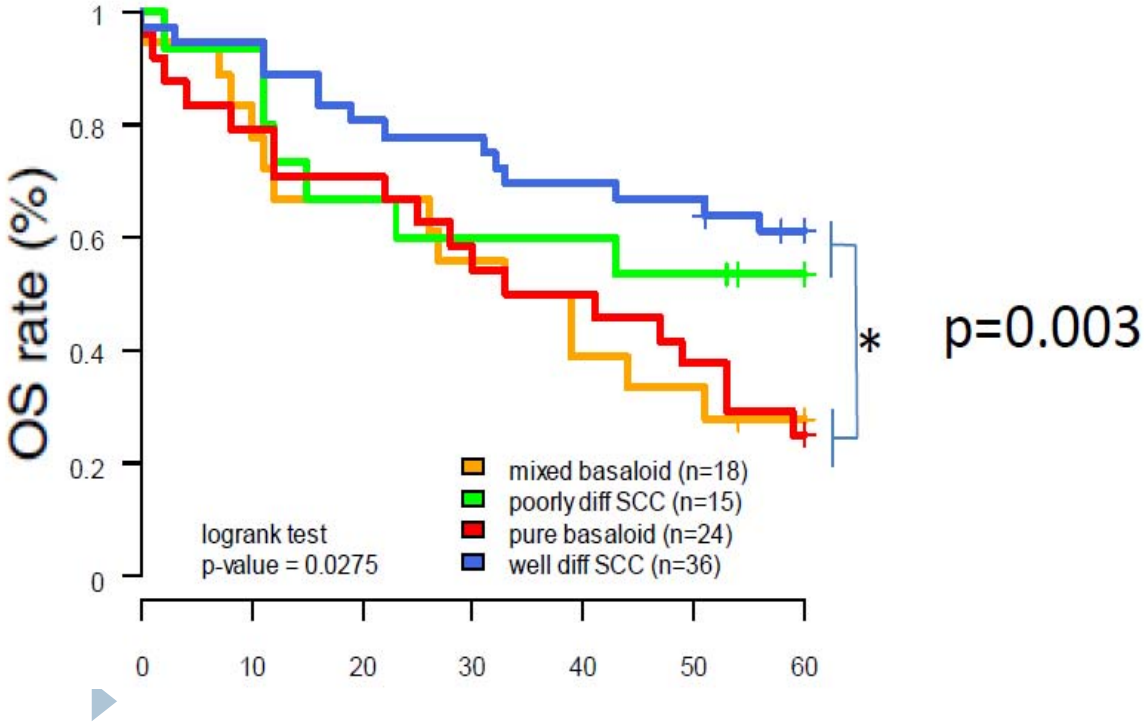
Moro-Sibilot et al ERJ 2007

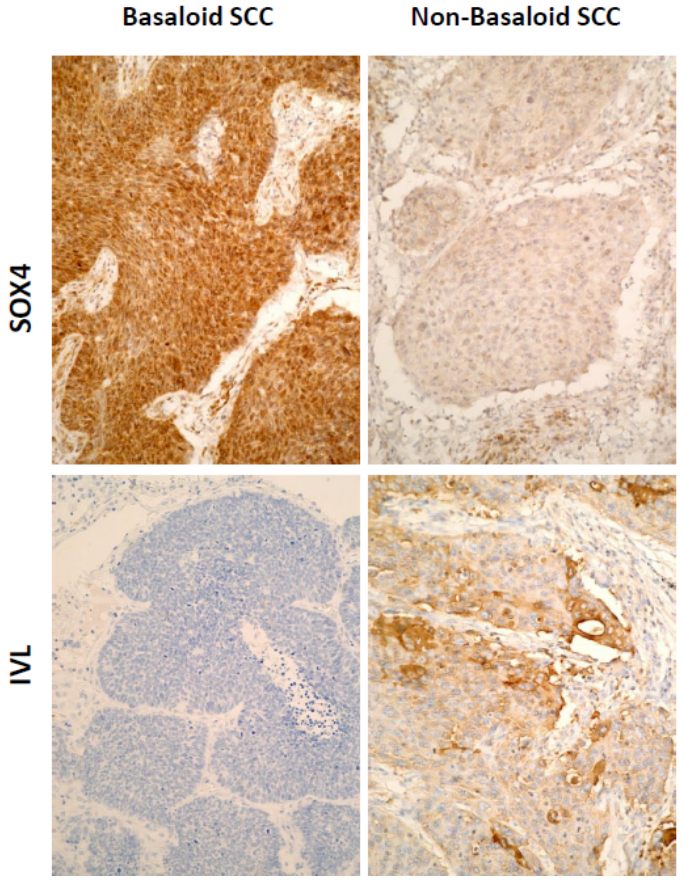



34βE12
TTF1

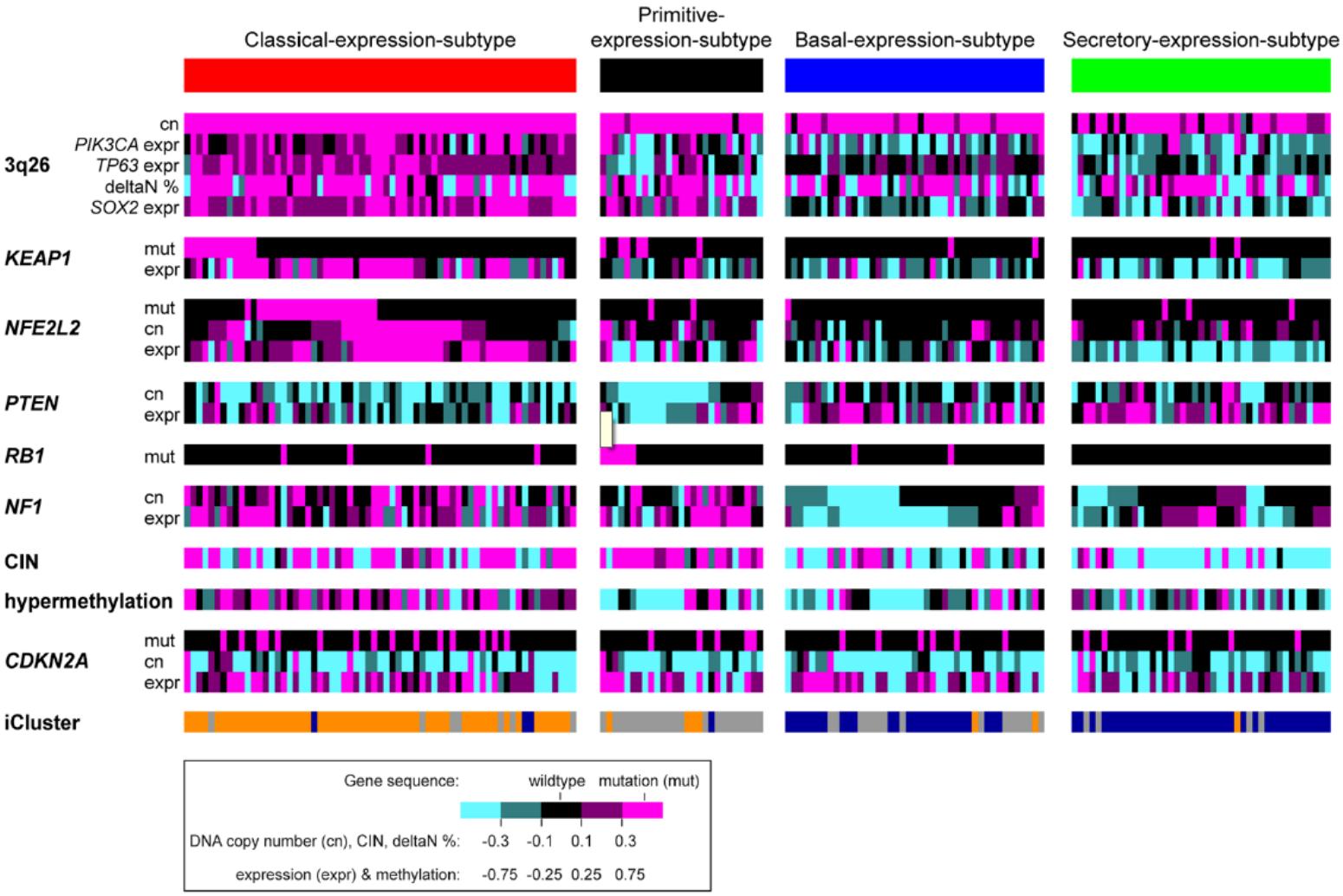
Carcinome basaloïde: entité moléculaire Analyse génomique et transcriptomique Brambilla C et al CCR 2014

- 42 BC (24 purs, 18 mixtes)
- Vs 51 SCC (36 bien différenciés, 15 peu différenciés)
- Hommes, fumeurs, âge moyen 64 ans

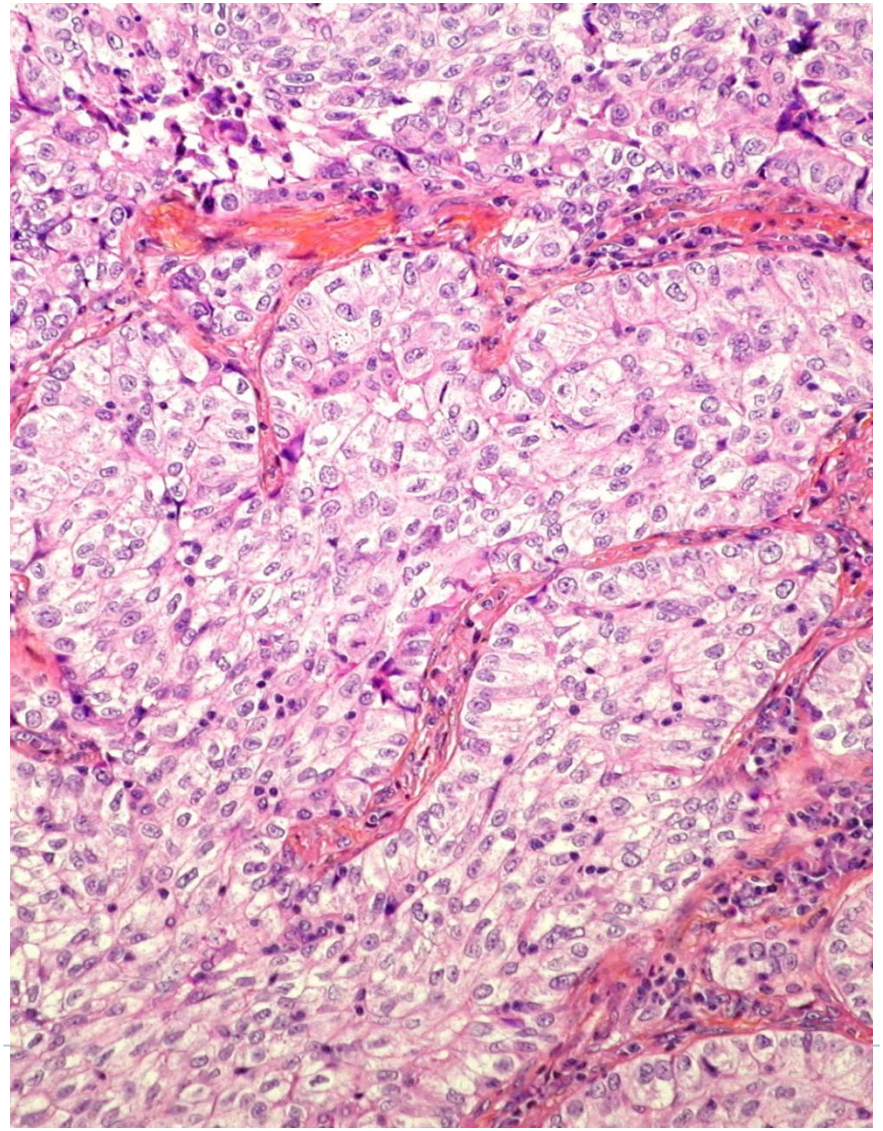




The Cancer Genome Atlas research Network: molecular profining of Squamous Cell Carcinoma of the lung
Nature 2012



Large cell carcinoma



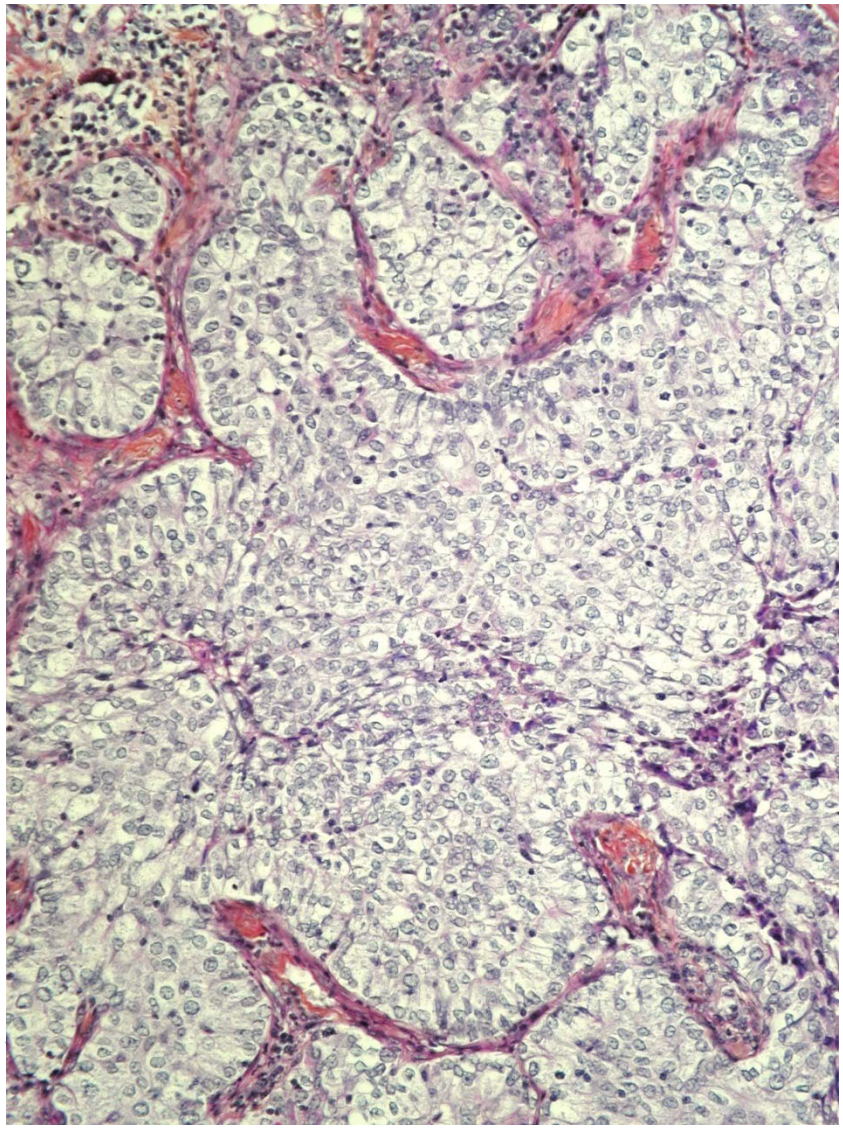


Table 1.19 Subtyping of resected, morphologically undifferentiated non-small cell carcinomas (formerly large cell carcinoma)

Adenocarcinoma, solid subtype[a]	Positive for TTF1 and/or napsin A and/or mucin Negative (or focal staining in scattered tumour cells) for p40, p63[b], and/or CK5/6
Non-keratinizing squamous cell carcinoma[a]	Negative for TTF1, napsin A, and mucin Diffusely positive for p40, p63[b], and/or CK5/6
Adenosquamous carcinoma[a]	Positive for adenocarcinoma and squamous markers in geographically distinct cell populations, each accounting for > 10% of tumour cells
Large cell carcinoma with null immunohistochemical features	Positive for cytokeratins Negative for lineage-specific markers and mucin
Large cell carcinoma with unclear immunohistochemical features (*see* Table 1.20)	Positive for cytokeratins Unclear immunoprofiles and negative for mucin
Large cell carcinoma with no stains available	No immunohistochemical or mucin staining available

[a] In cases where there is morphological evidence of either squamous cell carcinoma or adenocarcinoma, then immunohistochemistry is not required to assess undifferentiated areas.
[b] p63 (4A4) can rarely be more diffusely positive in some TTF1-positive tumours. These should be classified as adenocarcinomas.

Table 1.20 Immunohistochemical typing of cytokeratin-positive, morphologically undifferentiated non-small cell lung carcinoma (NSCLC), with mucin stains already undertaken to exclude solid pattern adenocarcinoma[a]. Focal: 0–10% of cells positive; diffuse: > 10% of cells positive.

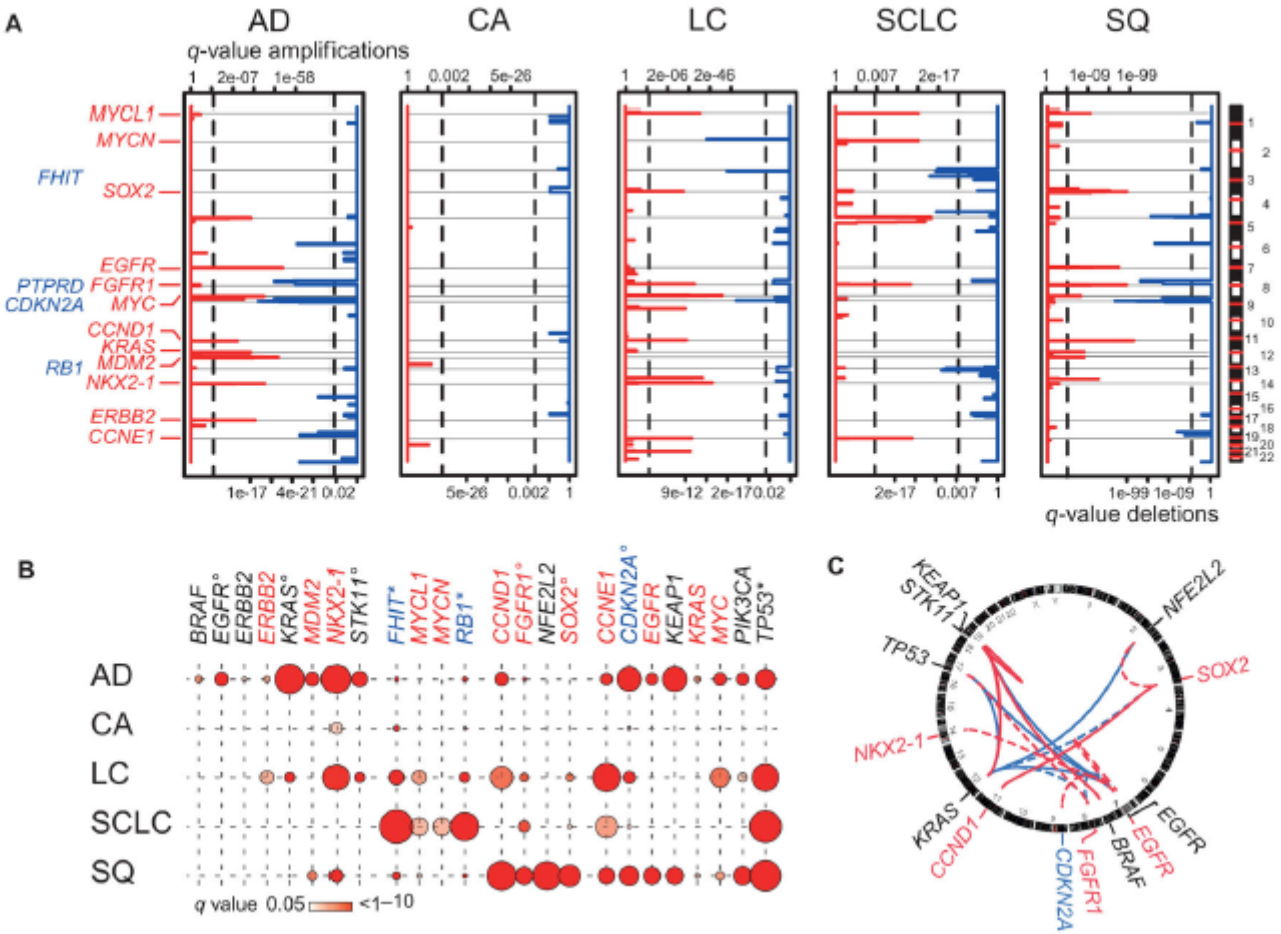
TTF1[b]	p63	p40	CK5/6	Diagnosis (resection)	Diagnosis (biopsy / cytology)
Positive (focal or diffuse)	Negative	Negative	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Negative	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Positive (focal)	Negative	Adenocarcinoma	NSCLC, favour adenocarcinoma
Positive (focal or diffuse)	Negative	Negative	Positive (focal)	Adenocarcinoma	NSCLC, favour adenocarcinoma
Negative	Any one of the above diffusely positive			Squamous cell carcinoma	NSCLC, favour squamous cell carcinoma
Negative	Any one of the above focally positive			Large cell carcinoma, unclear[c]	NSCLC, not otherwise specified
Negative	Negative	Negative	Negative	Large cell carcinoma-null[d]	NSCLC, not otherwise specified
No stains available	No stains available	No stains available	No stains available	Large cell carcinoma with no additional stains	NSCLC, not otherwise specified (no stains available)

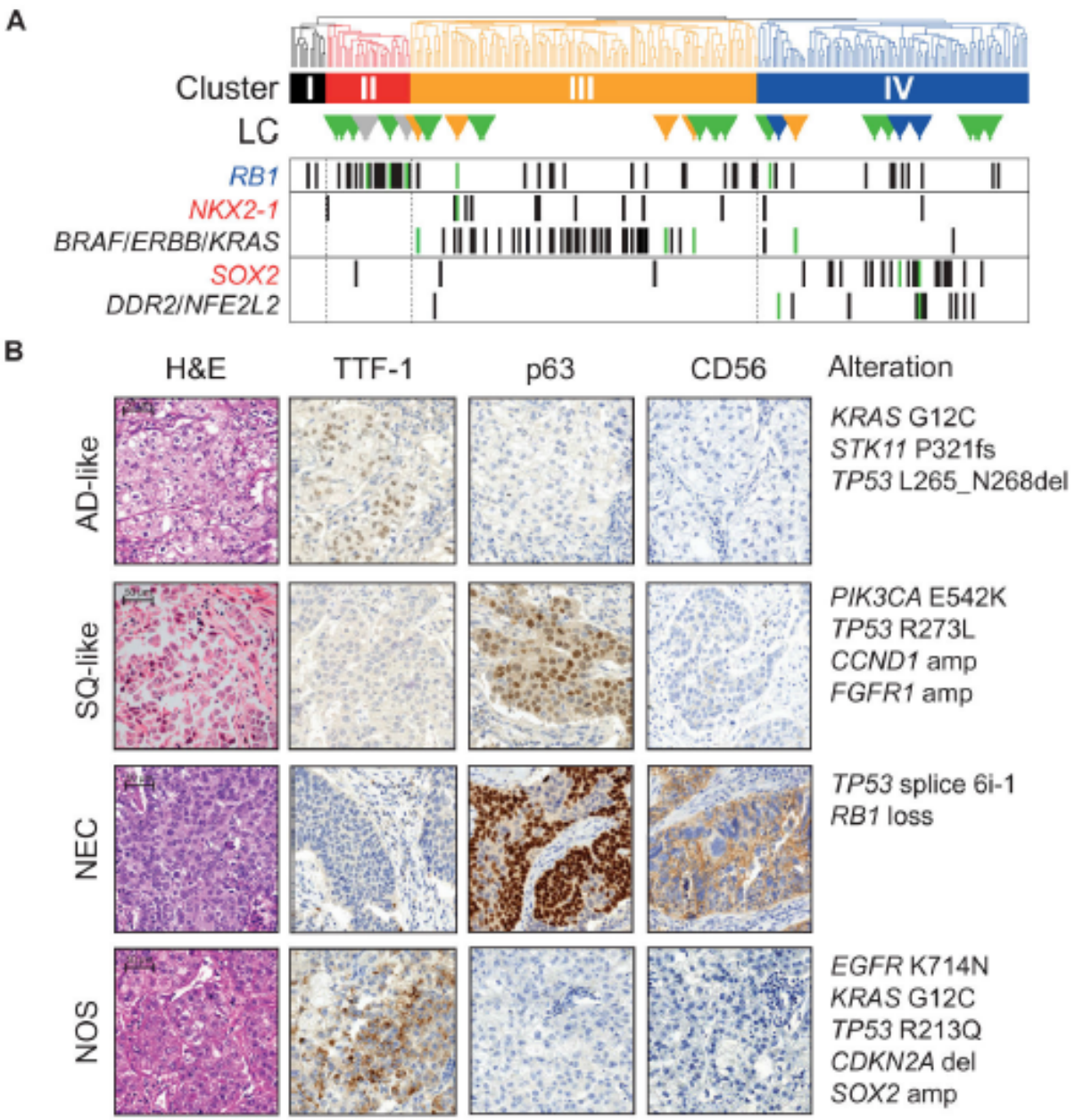
[a] Positive for mucin is defined as (≥ 5 intracytoplasmic droplets in two high-power fields in resections {2672} and mucin droplets in two or more cells within a biopsy); fewer positive cells are regarded as negative.
[b] Napsin may be used as an alternative to TTF1, although a sensitive marker (CK7) is not recommended as a marker of adenocarcinomatous differentiation due to a lack of specificity.
[c] Negativity for TTF1 and focal positivity for p63/p40/CK5/6 point to adenocarcinoma cell lineage once neuroendocrine

A Genomics-Based Classification of Human Lung Tumors

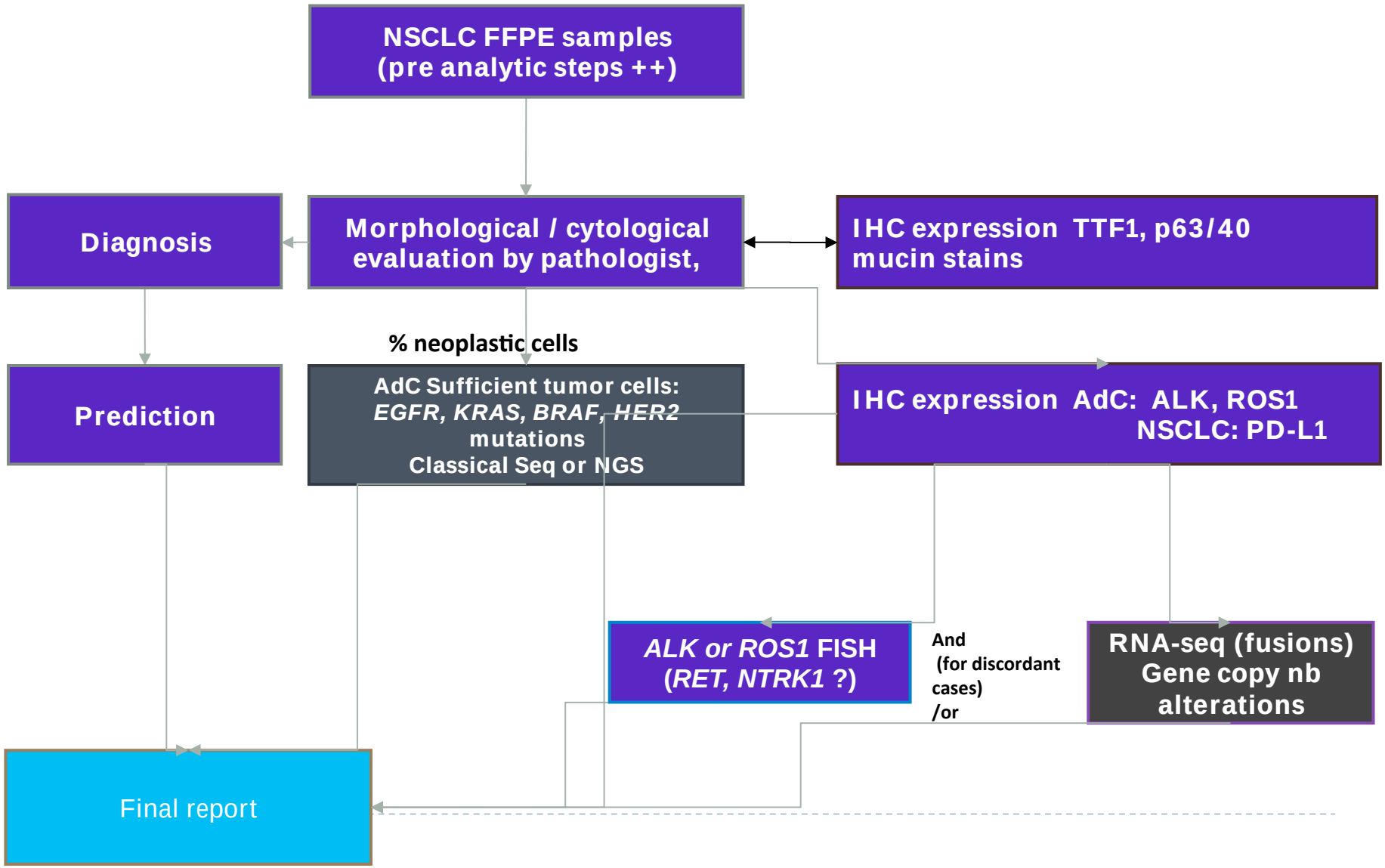
The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM) †

Sci Transl Med. 2013




A
Cluster
I
II
III
IV
LC
RB1
NKX2-1
BRAF/ERBB/KRAS
SOX2
DDR2/NFE2L2
B
H&E
TTF-1
p63
CD56
Alteration
AD-like
KRAS G12C
STK11 P321fs
TP53 L265_N268del
SQ-like
PIK3CA E542K
TP53 R273L
CCND1 amp
FGFR1 amp
NEC
TP53 splice 6i-1
RB1 loss
NOS
EGFR K714N
KRAS G12C
TP53 R213Q
CDKN2A del
SOX2 amp

Testing algorithm on diagnostic and predictive testing in NSCLC: the role of pathologist



Spectre des tumeurs NE pulmonaires

	Mitoses	Nécrose	Survie 5 ans	Survie 10 ans
Carcinoïde typique	<2	0	87%	87%
Carcinoïde atypique	2 - 10	+/-	56%	35%
CNEGC	>11	++	27%	9%
CPC	>11	+++	9%	5%

W. D. Travis et al Am. J. Surg. Pathol. 22: 934-944, 1998

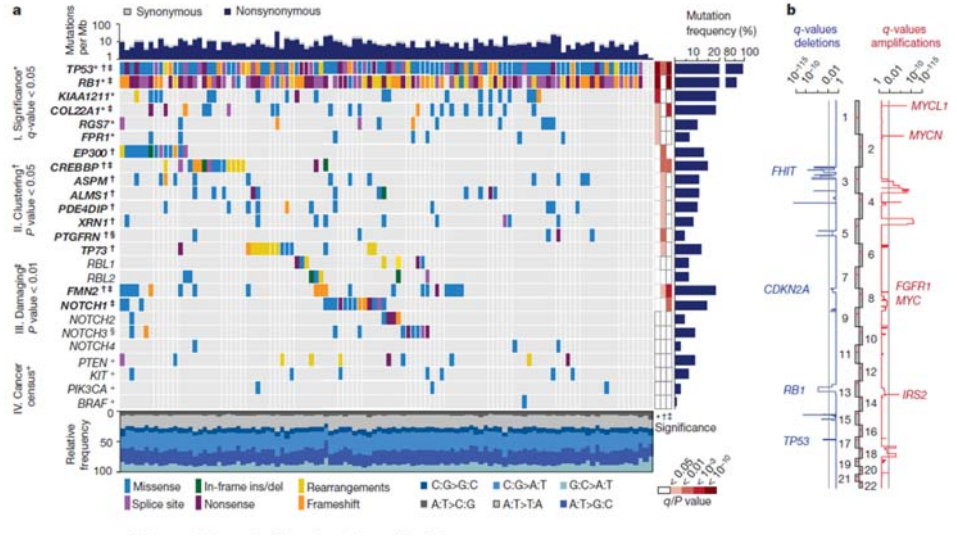
The Use of Immunohistochemistry Improves the Diagnosis of Small Cell Lung Cancer and Its Differential Diagnosis. An International Reproducibility Study in a Demanding Set of Cases

E Thunnissen et al J Thorac Oncol 2017

- 19 pathologists reviewed 79 cases (digital slides)
- Morphologic features (level 1), morphologic features along with requested IHC staining results (level 2), and all available IHC staining results (level 3).
- Rate of agreement for level 1 was 64.7%, and it increased to 73.2% and 77.5% in levels 2 and 3, respectively.
- With IHC, kappa scores for SCLC, LCNEC, carcinoid tumors increased in resection samples from 0.43 to 0.60 and in biopsy specimens from 0.43 to 0.64

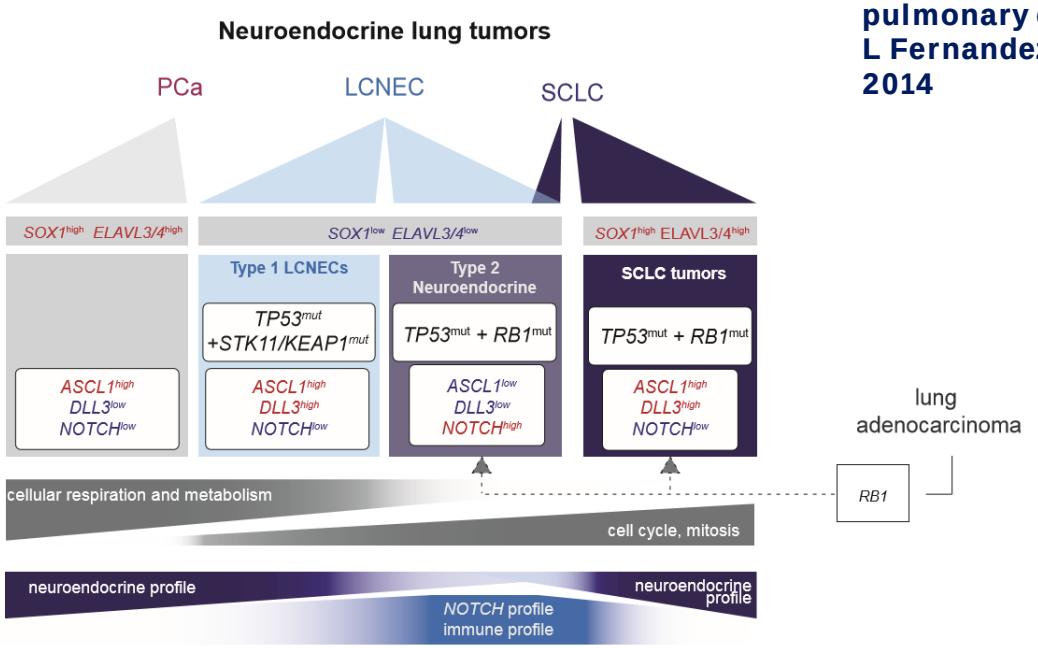
Table 2. κ Scores Calculated for All Diagnoses

κ Analysis	Level 1 κ Score	Level 2 κ Score	Level 3 κ Score	No. Cases		
				Level 1	Level 2	Level 3
Diagnoses per diagnostic category (vs. remaining diagnosis)						
(Combined) SCLC[a]	0.55	0.58	0.60	28	34	33
LCNEC	0.34	0.45	0.49	14	10	11
Atypical carcinoids	0.18	0.27	0.30	7	7	6
Typical carcinoids	0.53	0.67	0.74	22	22	22
Carcinoids (typical and atypical)	0.60	0.71	0.75	29	29	28
Poorly differentiated NSCLC	0.14	0.39	0.53	4	2	2
Small round cell sarcoma	0.09	0.03	0.81	0	0	1
Non-Hodgkin's lymphoma	0.42	0.55	0.96	3	3	3
Other	0.10	0.09	0.05	1	1	0
For all diagnoses						
All 8 categories[a] separately	0.41	0.50	0.58			
4 categories (combined): SCLC, LCNEC, (a)typical carcinoid, others	0.48	0.58	0.64			



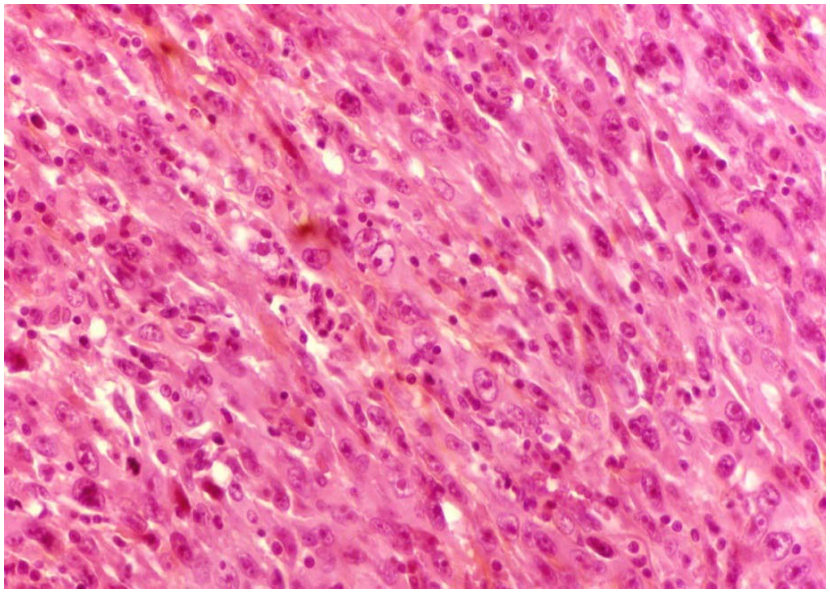
Comprehensive genomic profiles of small cell lung cancer
J George Nature 2015

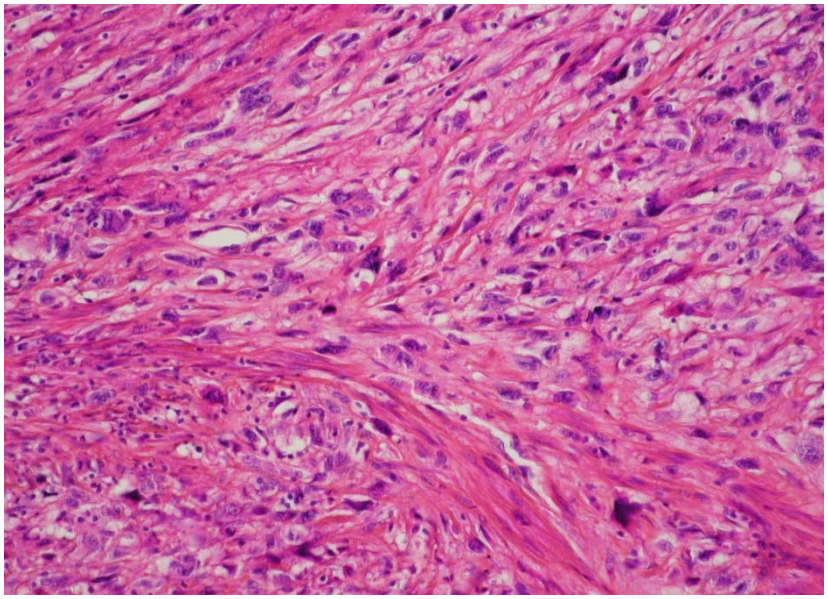
Frequent mutations in chromatin-remodeling genes in pulmonary carcinoids
L Fernandez-Cuesta Nat Comm 2014

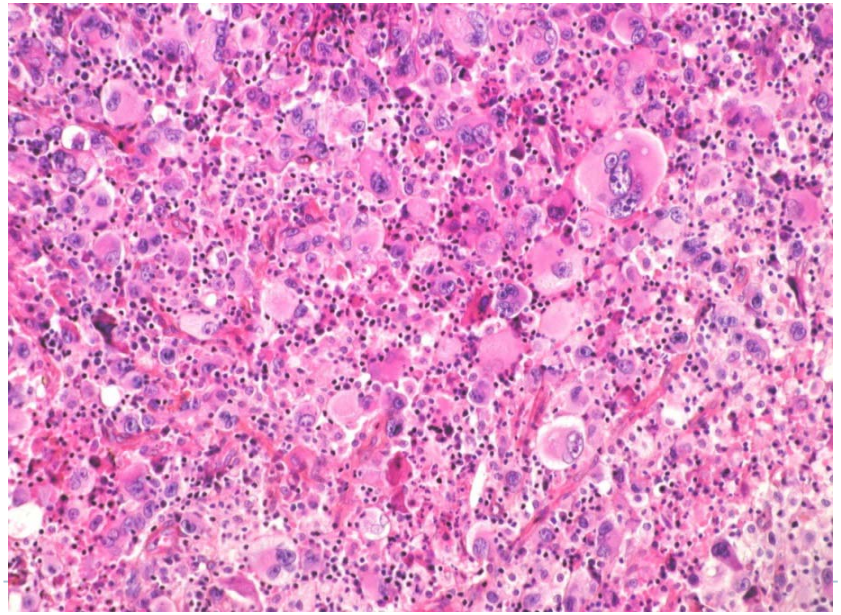


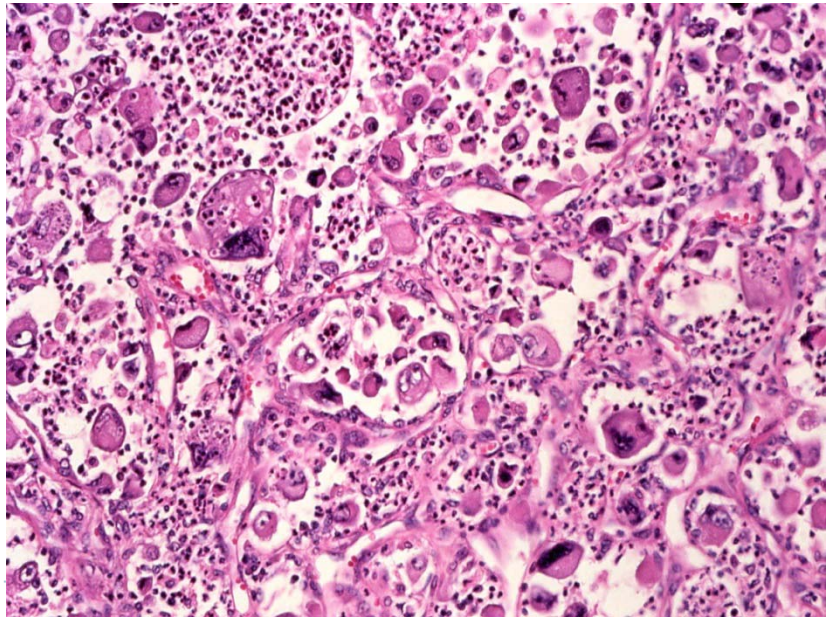
J Georges et al, submitted

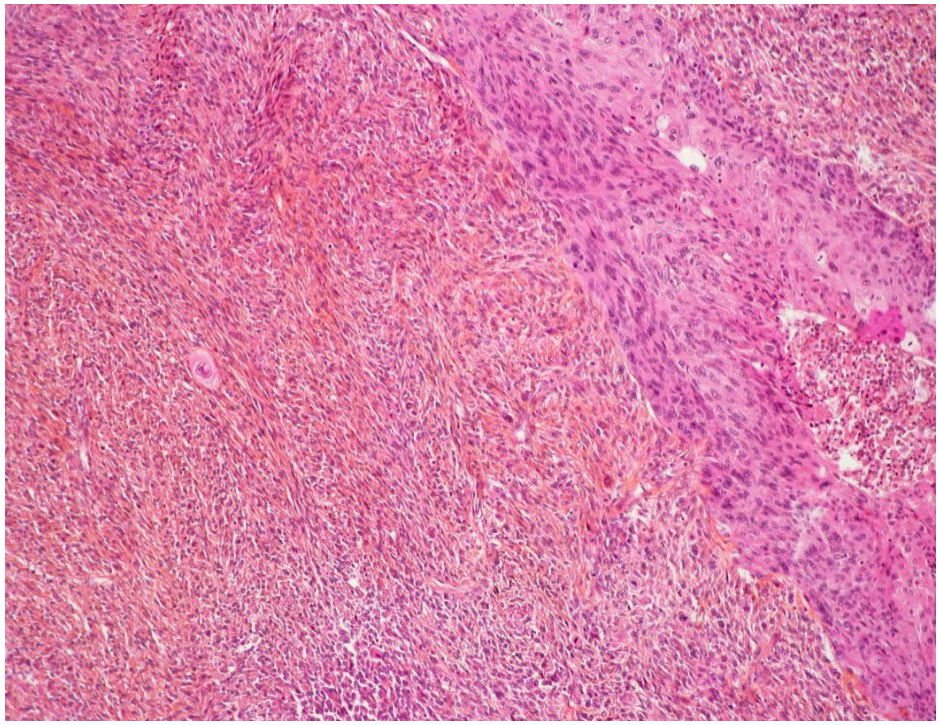
Carcinome pleiomorphe (Sarcomatoide)

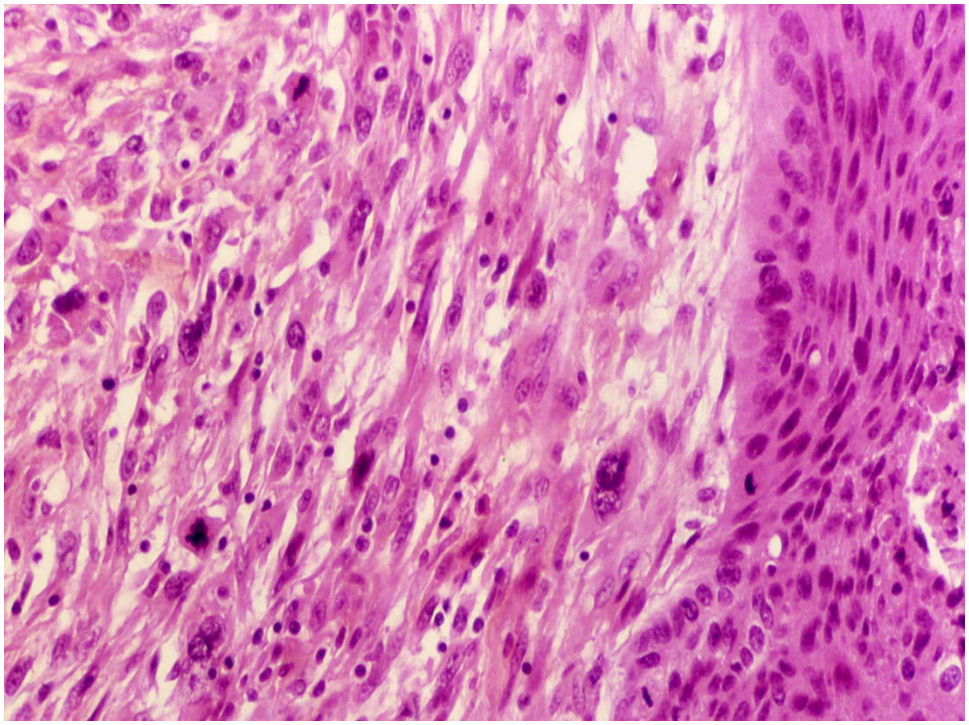


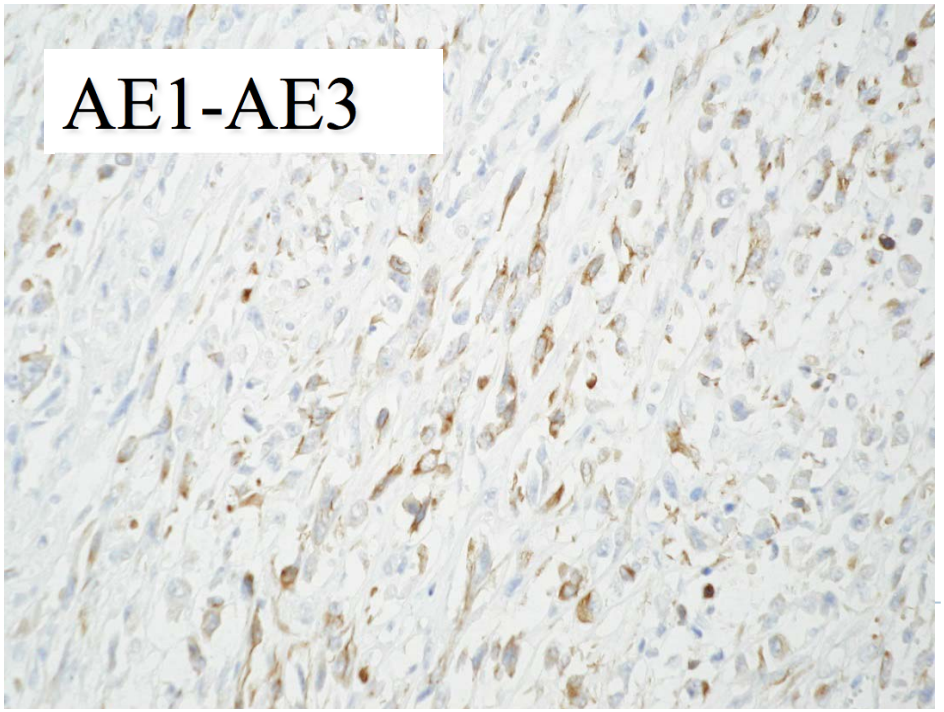


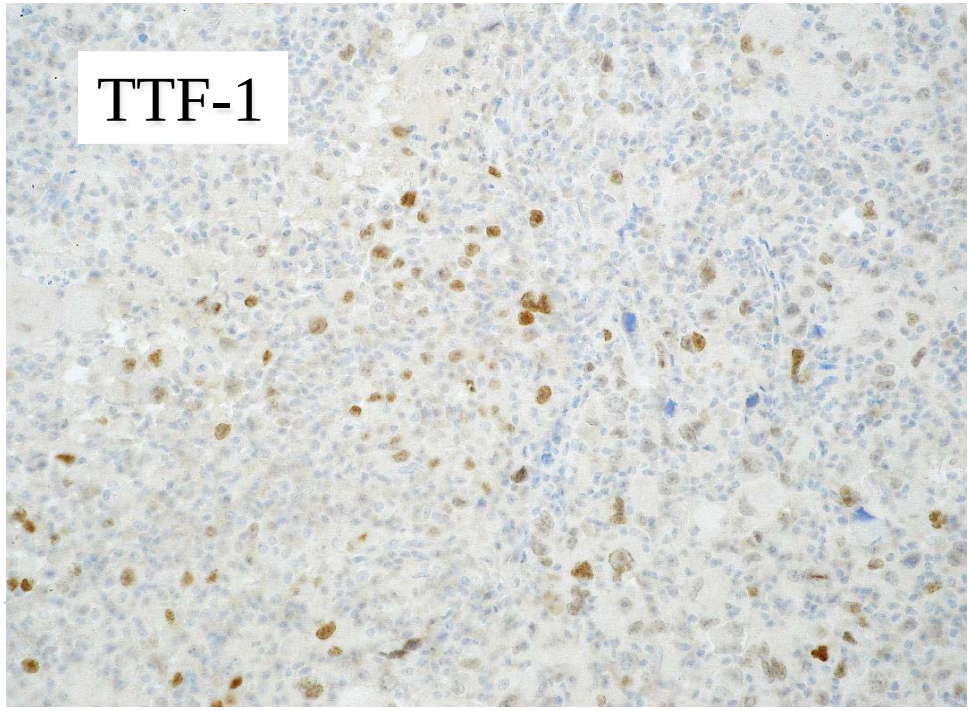









AE1-AE3

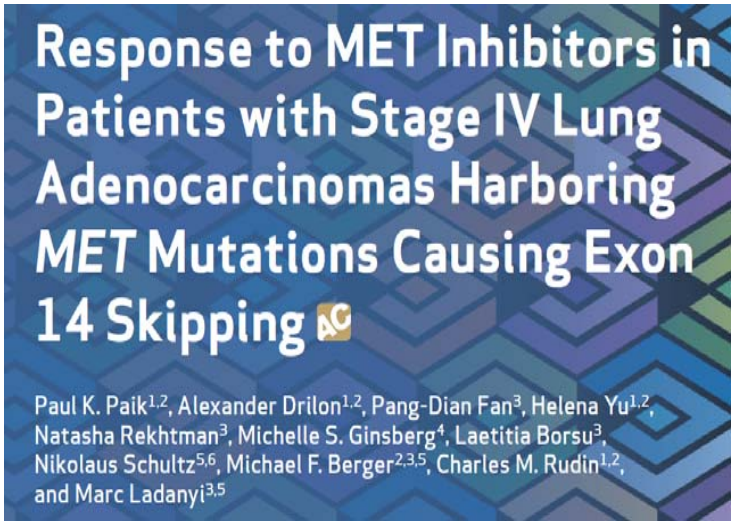

TTF-1

MET Exon 14 Splice Site Mutations

Next-Generation Sequencing of Pulmonary Sarcomatoid Carcinoma Reveals High Frequency of Actionable *MET* Gene Mutations

J Clin Oncol 2015; epub

Xuewen Liu, Yuxia Jia, Mark B. Stoopler, Yufeng Shen, Haiying Cheng, Jinli Chen, Mahesh Mansukhani, Sanjay Koul, Balazs Halmos , and Alain C. Borczuk



Cancer Discov 5:842-9, 2015

Lead to MET variants lacking the JM domain for Cbl ubiquitinilase binding
Occur in 4% of NSCLC
In up to 32% in SC ?

In PROFILE 1001 trial, patients were former / never smokers with ADC (71%). Crizotinib demonstrated antitumor activity in 10 out of 15 patients

J Clin Oncol 2016

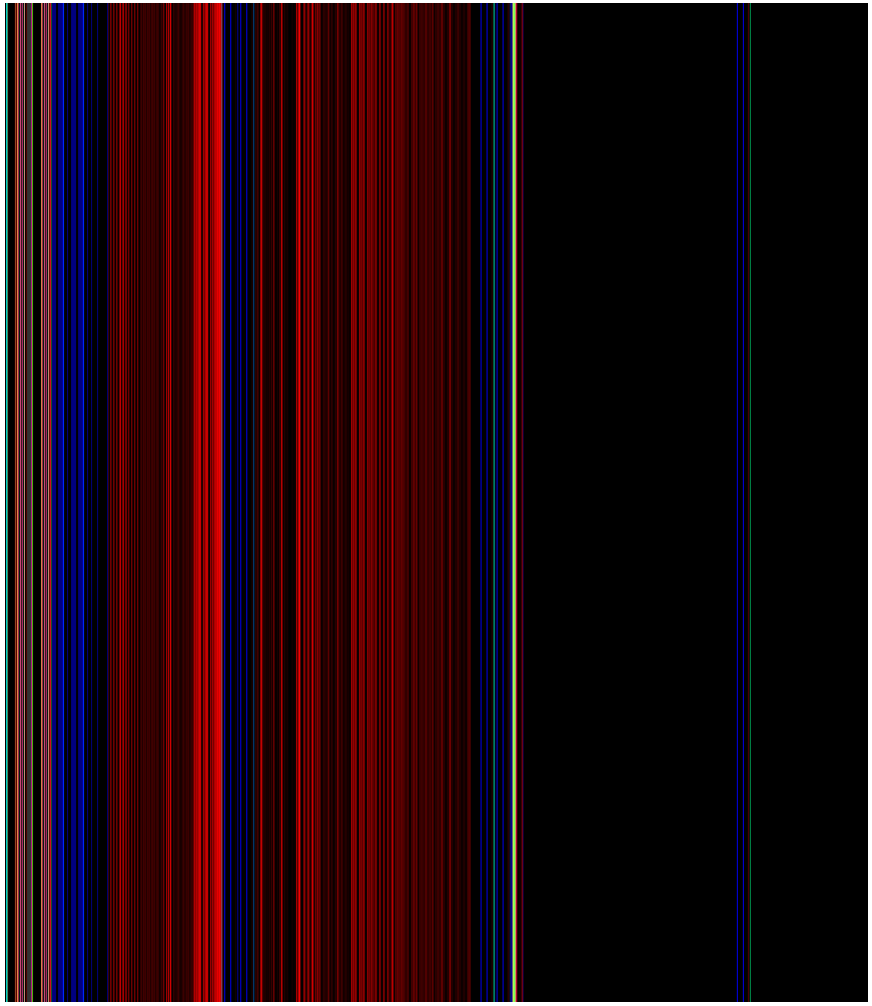
36 carcinomes pulmonaires sarcomatoïdes
22% mutations exon 14

Mut KRAS (27.2%), EGFR (22.2%), TP53 (22.2%), STK11 (7.4%), NOTCH1 (4.9%), NRAS (4.9%), PI3KCA (4.9%)
V Fallet et al Ann Oncol 2015

Signature moléculaire des carcinomes sarcomatoides pulmonaires (WES n=15)

Pécuchet et al Ann Oncol 2017

- Deux groupes principaux
  - Signature 4 (cluster 1):
    - Liée au tabagisme (C to A/G to T transversions)
    - Mutations voies MAPK-KRAS
    - PD-L1+ fortement exprimé
    - Survie globale 7,3 mois
  - Signatures 2-3-13 (cluster 2)
    - Déficit BRCA1/2 et activation protéines APOBEC
    - Alterations MET 5/11
    - Mutations EGFR, IDH1, amplification AKT3
    - + de femmes et + patients agés
    - OS et DFS un peu supérieures
  - Hétérogénité intratumorale limitée (ampli MET subclonale)



Bibiographie

nature genetics

SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas

Francois Le Loarer[1–3], Sarah Watson[4,5], Gaelle Pierron[6], Vincent Thomas de Montpreville[7], Stelly Ballet[6], Nelly Firmin[8], Aurelie Auguste[9], Daniel Pissaloux[2], Sandrine Boyault[10], Sandrine Paindavoine[2], Pierre Joseph Dechelotte[11], Benjamin Besse[12,13], Jean Michel Vignaud[14], Marie Brevet[3,15], Elie Fadel[13,16], Wilfrid Richer[4,17], Isabelle Treilleux[2], Julien Masliah-Planchon[5,6], Mojgan Devouassoux-Shisheboran[18], Gerard Zalcman[19,20], Yves Allory[21–23], Franck Bourdeaut[6,24], Francoise Thivolet-Beju[3,15], Dominique Ranchere-Vince[2], Nicolas Girard[3,25], Sylvie Lantuejoul[26,27], Francoise Galateau-Sallé[28,29], Jean Michel Coindre[30,31], Alexandra Leary[9,12], Olivier Delattre[4–6], Jean Yves Blay[1,3,32,33] & Franck Tirode[4,5,33]

Hommes, fumeurs- 41 ans (28-72 ans)

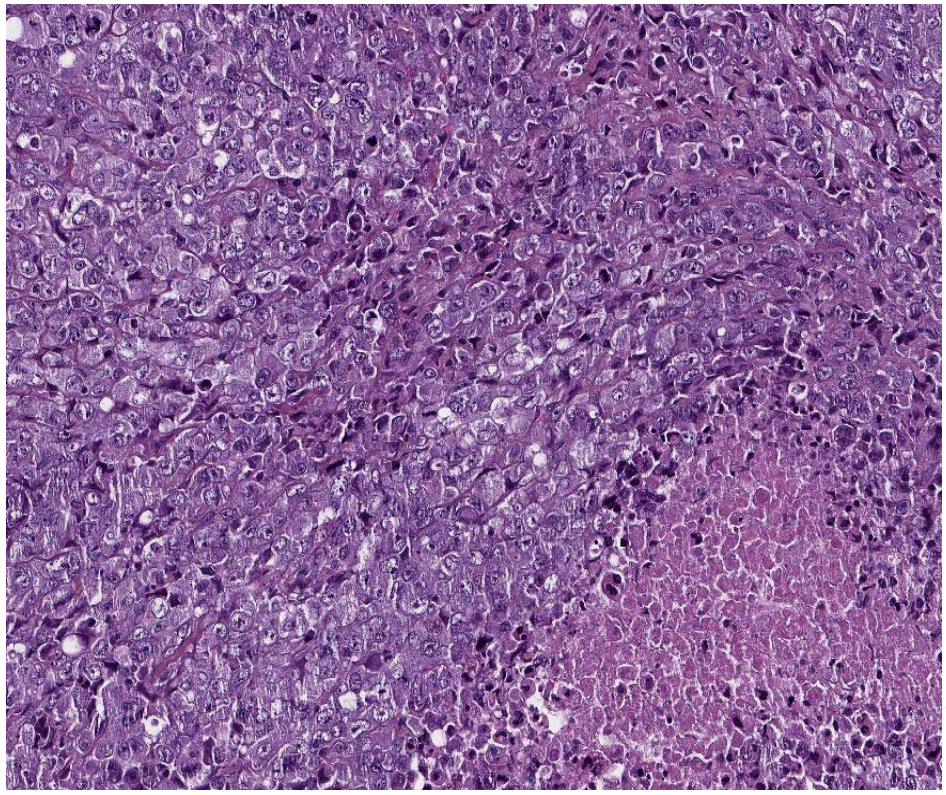
Volumineuse masse (130mm ; 35 à 210mm)

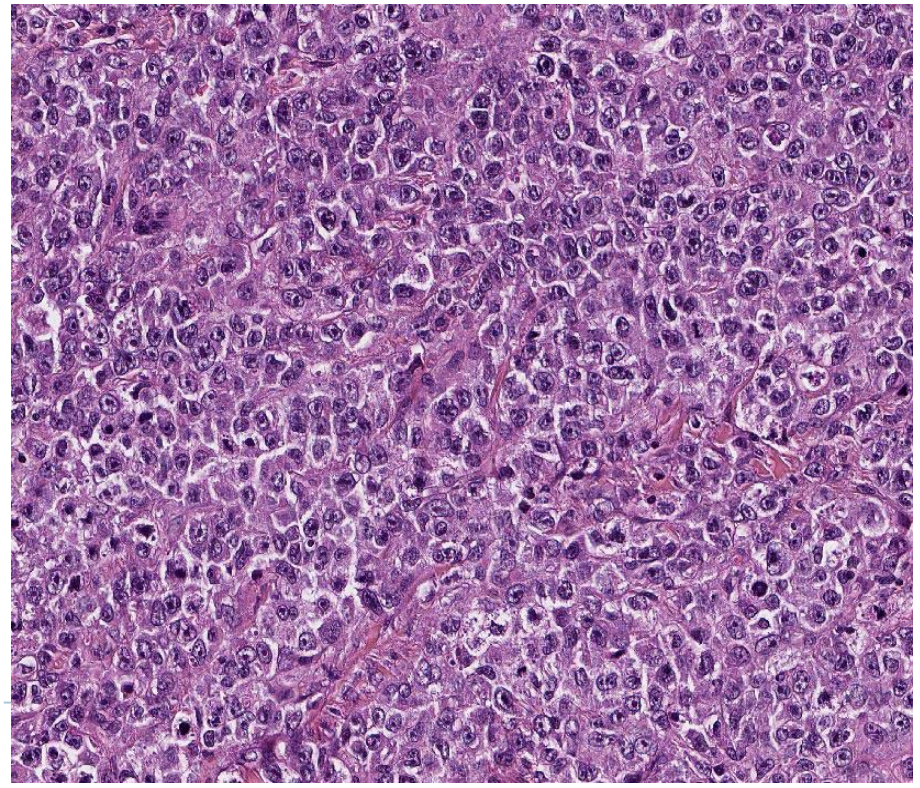
Localisation médiastinale, pleurale, pulmonaire, (péritonéale)

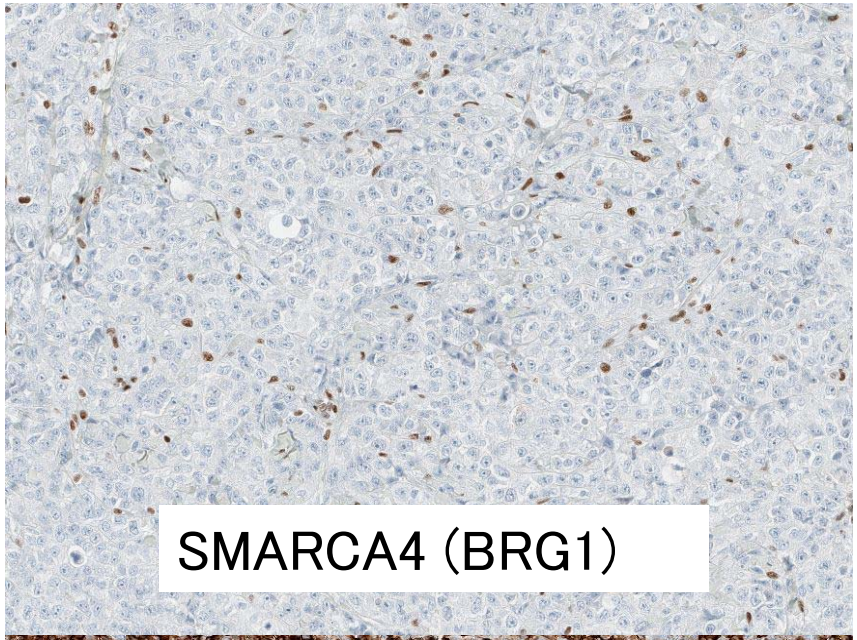
Évolution locale rapide en 1 mois (suspicion de LMNH ou de carcinome NUTM1 réarrangé)

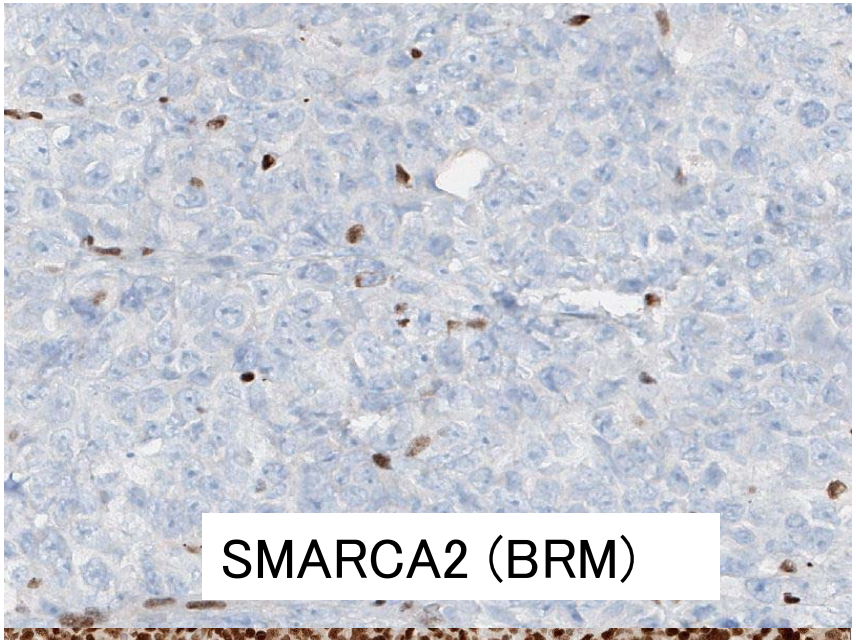
Réponse limitée à la chimiothérapie

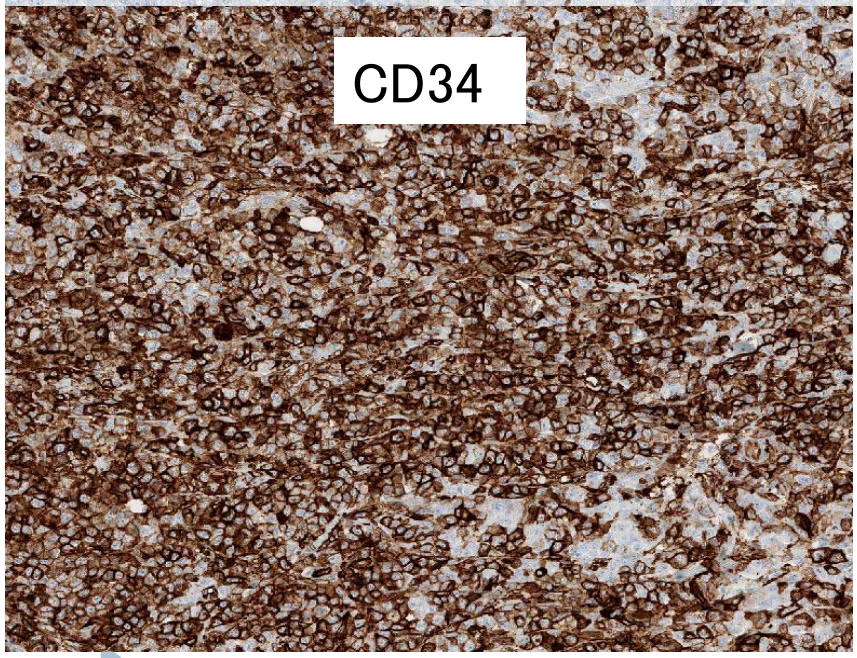
Survie médiane 7 mois

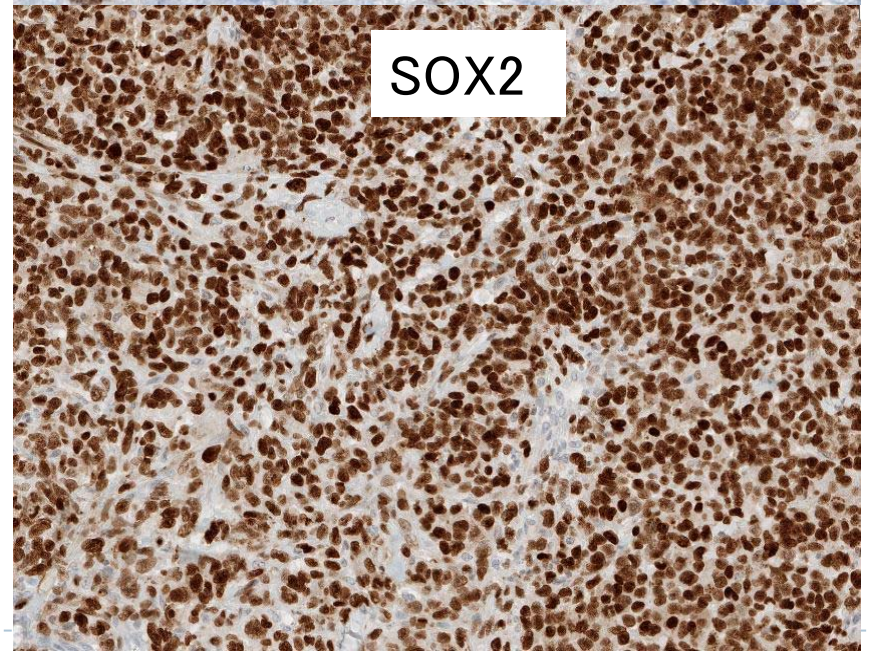





SMARCA4 (BRG1)


SMARCA2 (BRM)


CD34


SOX2

Génétique

- Famille des tumeurs SMARCA4 ou SMARCB1 déficientes

Tumeurs rhabdoïdes malignes, sarcomes épithélioïdes proximaux, Small Cell Carcinoma of the Ovary, Hypercalcemic Type SSCOHT (germline mut 50%)

- Mutations inactivatrices du gène SMARCA4 (famille BAF des gènes de la structure chromatinienne et de la transcription ; sous unités SMARCA4 et SMARB1)
  - Non sense, frameshift, **missense**, splice site
- + LOH et délétion en 19p13 (locus SMARCA4)
- Transcriptomique : CoExpression SOX2 (OCT4 et NANOG) et perte expression de SMARCA2

Diagnostic différentiel

- Carcinomes à grandes cellules ou adénocarcinomes pulmonaires
  - 10% sont mutés SMARCA4 (données TCGA)
  - Mauvais pronostic
  - SMARCA2 (BRM)+, SOX2-
- Lymphomes, mélanome, mésothéliome, autres sarcomes épithélioïdes, tumeurs germinales, ..

Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities

Yoshida A et al Mod Pathol 2016

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

UNICANCER

Inserm
Institut national de la santé et de la recherche médicale

GRENOBLE 1
UNIVERSITE JOSEPH FOURIER
SCIENCES TECHNOLOGIE MEDECINE