RCPath
Cancer datasets – guiding care for the individual and the wider population

Reporting of lung cancer

Thursday 30th March 2017

Coin Street Conference Centre
London

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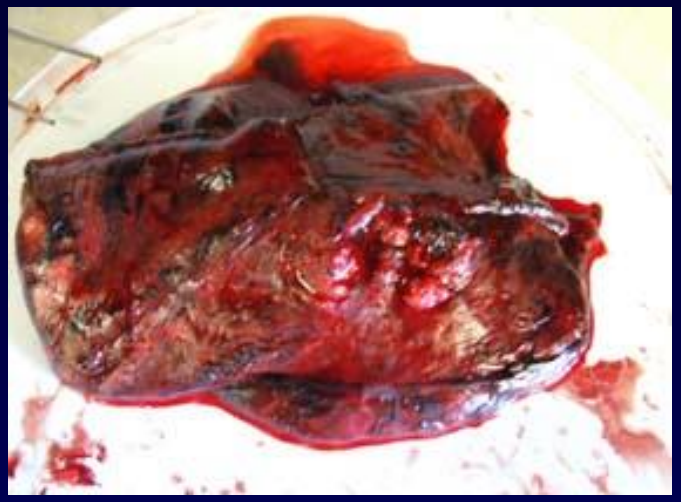
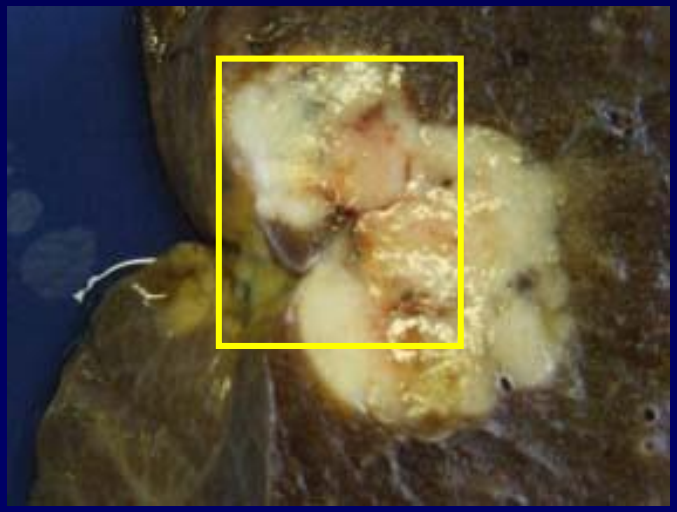
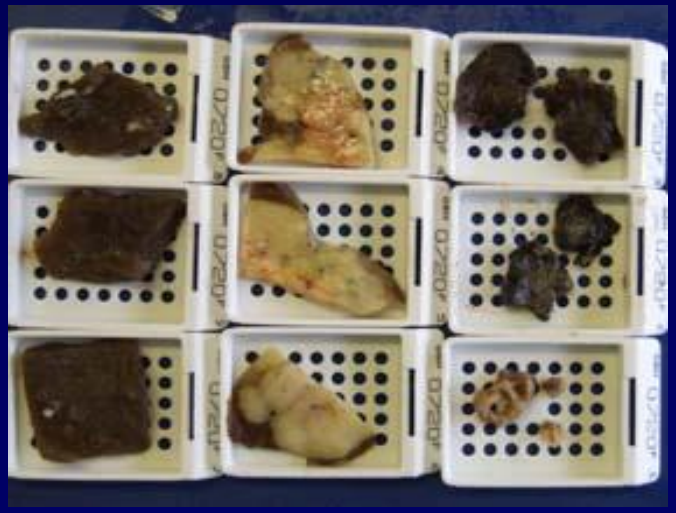
Purpose of the dataset….







CLINICAL DETAILS
Adenocarcinoma in right lower lobe.

Specimen:
A Right upper lobe
MACROSCOPIC DESCRIPTION
A piece of lung measuring 15x10x8mm. Cut surface shows an ill-defined firm area measuring 7x5x5mm.
Bisected & all embedded in A1 (2 pieces).
MICROSCOPIC EXAMINATION
Sections show a localised area of fibrosis and inflammation within which are several epithelioid granulomas with very focal central necrosis. Acid fast bacilli (AFB) are noted on ZN stain. Special stain for fungi (Grocott) is negative. The features are of granulomatous inflammation due to mycobacterial infection. There is no evidence of malignancy.

B 10i C 11i; D 7; E 9
MACROSCOPIC DESCRIPTION
Lymph nodes
All embedded in B1 (3 pieces); B2 (3 pieces); C1 (1 piece);
D1 (2 pieces); E1 (2 pieces) and E2 (3 pieces.)
MICROSCOPIC EXAMINATION
All lymph nodes showing no granuloma formation or evidence of malignancy.

F Right lower lobe of lung
MACROSCOPIC DESCRIPTION
Right lower lobe measuring 160x160x75mm in the inflated state. At the base of the lobe, there is a circumscribed tumour measuring 42x28mm x approximately 35mm, which abuts the visceral pleura. The tumour lies 75mm from the bronchial resection margin. The remaining lung is unremarkable.
F1: bronchial & vascular resection margin (3 pieces); F2-F3: hilar lymph nodes (2 pieces in each); F4-F6: tumour (1 piece in each); F6-F8: random lung (1 piece in each). Tissue remains.
MICROSCOPIC EXAMINATION
Sections show a non-mucinous adenocaricnoma with mainly acinar (90%) pattern other than an occasional microscopic focus of micropapillary change (10%). The tumour breaches the visceral pleura, confirmed on EVG stain., but does not reach the surface The resection margins are free of atypia and malignancy. The adjacent lung is unremarkable. The hilar lymph node shows no granuloma formation or evidence of malignancy. The adjacent lung is unremarkable.

G 11s; H right 2; J 12m; K Highest
L 12L; M 10s N Right 4
MACROSCOPIC DESCRIPTION
Lymph nodes.
G1 (2 pieces); H1 (4 pieces); J1 (4 pieces); K1 (4 pieces); L1: (2 pieces); M1 (1 piece); N1 (2 pieces); N2 (1 piece) & N3 (1 piece). All tissue embedded.
MICROSCOPIC EXAMINATION
All lymph nodes showing no granuloma formation or evidence of malignancy.

Right lower lobe of lung – Non-mucinous adenocarcinoma, acinar pattern, predominant. (pT2a N0 PL1, R0)
Right uppler lobe of lung - Granulomatous inflammation due to mycobacterial infection.

Table A.1 A protocol for reporting lung tissue resected in the treatment of lung cancer

Specimen Type

☐ Right	☐ Left
☐ VATS segmentectomy	☐ VATS lobectomy
☐ Open segmentectomy	☐ Open lobectomy/bi-lobectomy
☐ Pneumonectomy (extra-pericardial)	☐ Pneumonectomy (intra-pericardial)
☐ Sleeve	☐ Wedge resection
☐ Other, e.g. chest wall	

Gross description

Location of Tumour

- ☐ Main bronchus within 20 mm of carina (T3) – this will require clinical information
- ☐ Main bronchus more than 20 mm from carina (T2)
- ☐ Non-assessable
- ☐ Right upper lobe ☐ Right middle lobe ☐ Right lower lobe
- ☐ Left upper lobe ☐ Left lower lobe

Tumour size ... mm (T1 ≤30 mm or superficial tumours confined to bronchial wall, T2 > 30 mm)

Distance from bronchial or medial resection margin . . . mm

Extent of atelectasis/obstructive pneumonitis:
- ☐ None
- ☐ Involving hilar region but not whole lung (T2)
- ☐ Involving whole lung (T3)

Histology

Histological type

- ☐ Squamous cell carcinoma ☐ Adenocarcinoma ☐ Bronchoalveolar cell carcinoma
- ☐ Large cell undifferentiated ☐ Small cell carcinoma
- ☐ Mixed tumours (please specify: .....)
- ☐ Other tumour (please specify, e.g. carcinoid, etc.: .....)

Local invasion

- ☐ Visceral pleura (T2) ☐ Parietal pleura/chest wall (T3) ☐ Mediastinal pleura (T3)
- ☐ Pericardium (T3) ☐ Diaphragm (T3)
- ☐ Great vessel (aorta, central pulmonary artery or vein) (T4) ☐ Atrium, heart (T4)
- ☐ Malignant pleural effusion (T4) ☐ Separate tumour nodules in same lobe (T4)

Lymph node spread

Ipsilateral hilar/intrapulmonary (node stations 10–14)	☐ Submitted	☐ Involved (N1)
Ipsilateral mediastinal (node stations 1–9)	☐ Submitted	☐ Involved (N2)
Contralateral mediastinal, hilar, ipsilateral or contralateral scalene, supraclavicular	☐ Submitted	☐ Involved (N3)

Margins

Bronchial	☐ Clear	☐ Involved
Mediastinal	☐ Clear	☐ Involved
Vascular	☐ Clear	☐ Involved
Chest wall	☐ Clear	☐ Involved

Other Pathology

- ☐ Emphysema (moderate/severe degree) ☐ Interstitial fibrosis; State cause (if known): .....
- ☐ Other (please state: .....)

Metastases

- ☐ Unknown (MX) ☐ Absent (M0)
- ☐ Present (M1) including tumour nodules in different lobes. (please state: .....)

Pathological staging

- ☐ T ☐ N ☐ M (select highest stage from above data)
- Complete resection at all margins ☐ Yes ☐ No

Copies can be downloaded from the Royal College of Pathologists website: www.rcpath.org/resources/worddocs/dataset_lung_cancer_form_v2002.doc

Provides data points for

- *Pathology diagnosis*
- *Clinical practice*
- *Cancer registration*
- *Epidemiologic studies*
- *Clinical trials*
- *Cancer research*

AIMS OF PRESENTATION

- Updated staging
  - Discuss changes to T, N, M staging categories in the 8th TNM
  - Discuss handling of multiple pulmonary tumour nodules
  - Dealing with in-situ components/subsolid nodules
- Present correct terminology for small biopsies and cytology specimens (2015 WHO classification)
- Discuss the lung dataset in relation to molecular testing

IASLC

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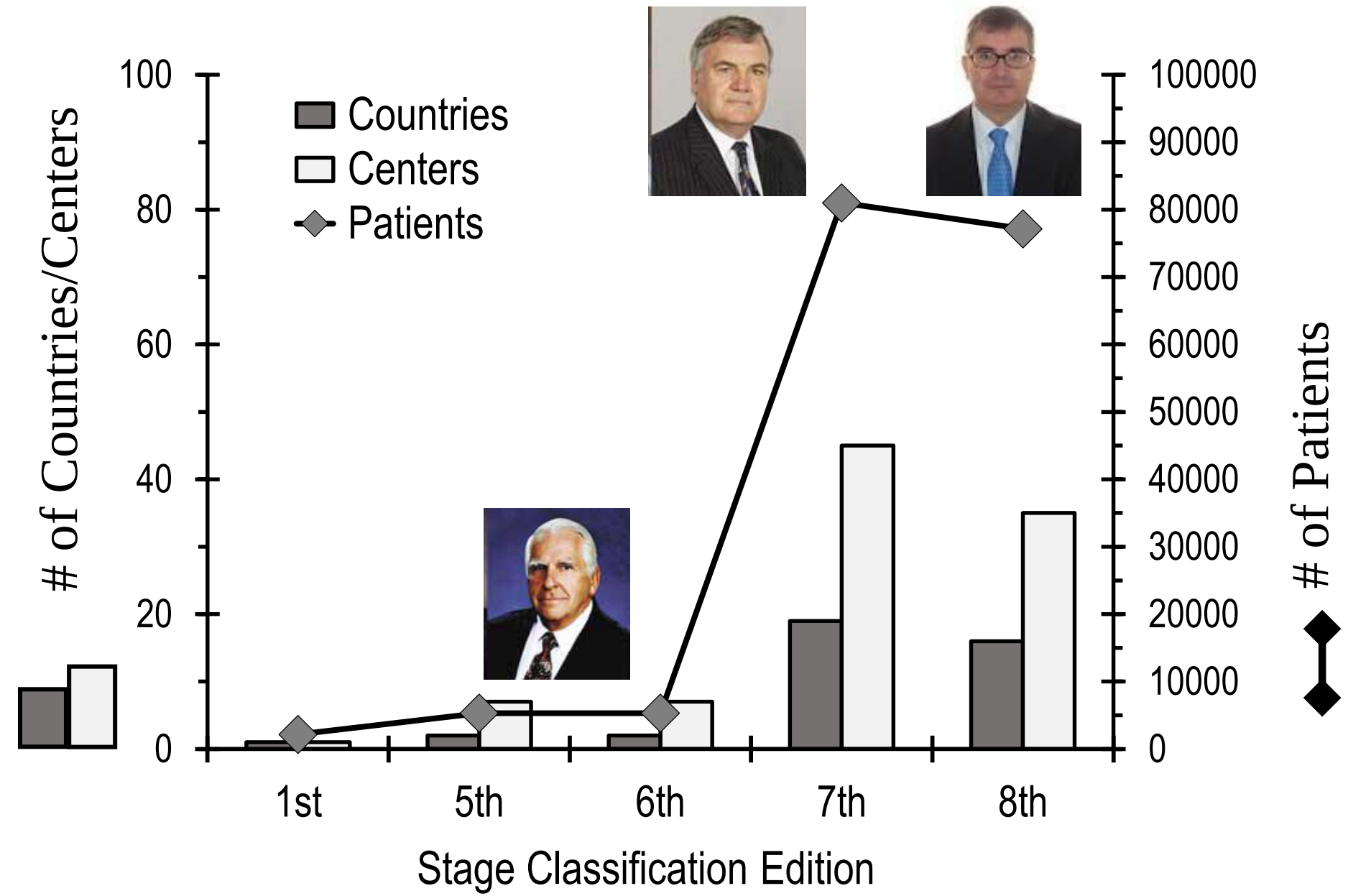
IASLC



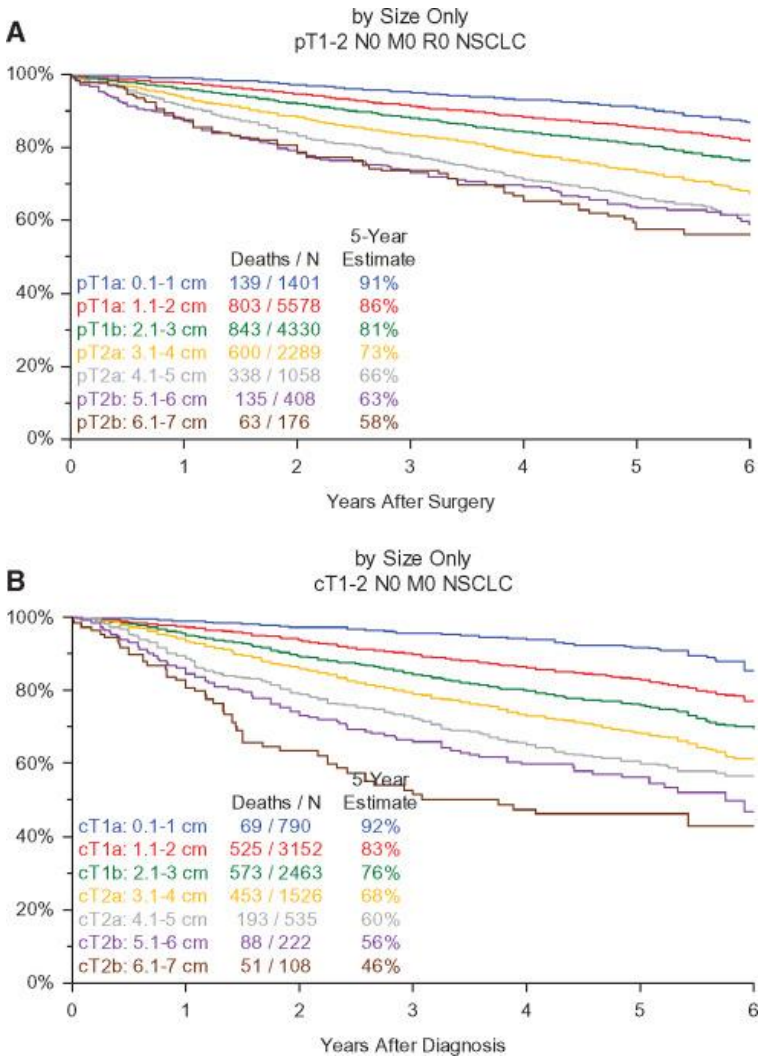
Courtesy of Frank Detterbeck: **The IASLC Lung Cancer Staging Project: Methodology and Validation Used in the Development of Proposals for Revision of the Stage Classification of Non-Small Cell Lung Cancer in the Forthcoming (Eighth) Edition of the TNM Classification of Lung Cancer. Submitted for publication**

T stage
Recommendations for changes

- to subclassify T1 into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm);
- to subclassify T2 into T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm);
- to reclassify tumors greater than 5 to less than or equal to 7 cm as T3;
- to reclassify tumors greater than 7 cm as T4;
- to group involvement of main bronchus as T2 regardless of distance from carina;
- to group partial and total atelectasis/pneumonitis as T2;
- to reclassify diaphragm invasion as T4;
- to delete mediastinal pleura invasion as a T descriptor

Rami-Porta R et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015 Jul;10(7):990-1003.

A, Survival of pathologically staged T1–T2 N0R0 tumours according to size only, at 1-cm intervals. *B*, Survival of clinically staged T1–T2 N0 tumours according to size only, at 1-cm intervals.



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Survival Comparisons of Pathologically Staged Tumours According to the T Categories of the 7th Edition and to the Proposed T Categories for the 8th Edition

7th Edition Categories					Proposed Categories				
Contrast	Estimate	Lower Limit	Upper Limit	*P* Value	Contrast	Estimate	Lower Limit	Upper Limit	*P* Value
T1a vs. T1b	1.3585	1.2353	1.4940	<0.0001	T1a vs. T1b	1.4899	1.2340	1.7988	<0.0001
T1b vs. T2a	1.4292	1.3162	1.5520	<0.0001	T1b vs. T1c	1.2767	1.1568	1.4090	<0.0001
T2a vs. T2b	1.2520	1.1191	1.4007	<0.0001	T1c vs. T2a	1.3647	1.2519	1.4873	<0.0001
T2b vs. T3	1.4486	1.2807	1.6384	<0.0001	T2a vs. T2b	1.2218	1.1022	1.3543	0.0001
T3 vs. T4	1.0045	0.7607	1.3264	0.9747	T2b vs. T3	1.2895	1.1553	1.4392	<0.0001
					T3 vs. T4	1.2997	1.1458	1.4742	<0.0001

Rami-Porta R et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015 Jul;10(7):990-1003.

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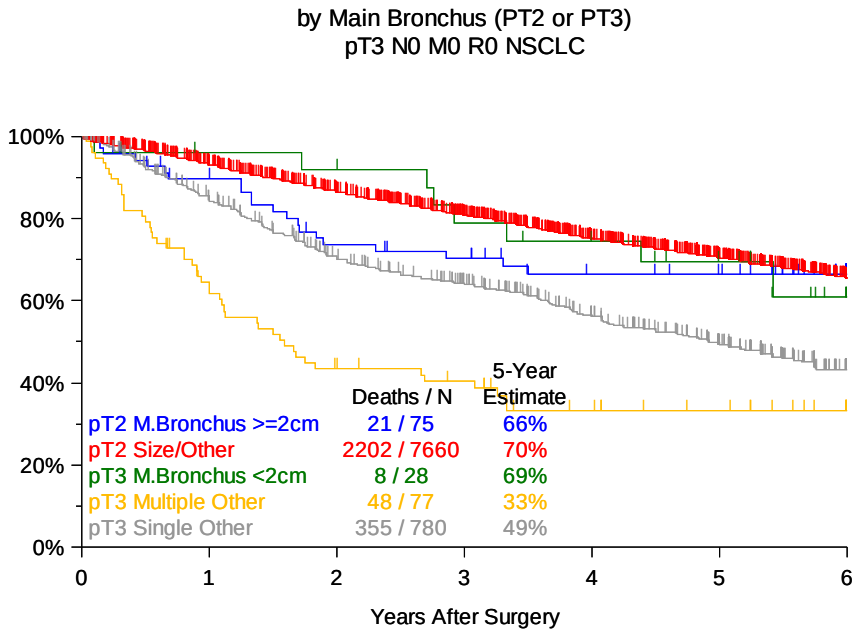
Survival of pathologically staged T2-T3 main bronchus N0 R0 tumors vs. others



Rami-Porta R et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015 Jul;10(7):990-1003.

Visceral pleural invasion

- Visceral pleural invasion is well positioned as a T2 descriptor and confers a worse prognosis even after adjusting for the current tumor size cutpoints.

- The extent of the visceral pleura invasion as currently defined (PL0: tumor within the subpleural lung parenchyma or invades superficially into the pleural connective tissue beneath the elastic layer; PL1: tumor invades beyond the elastic layer; and PL2: tumor invades to the pleural surface) appropriately distinguishes between risk groups and, while the prognosis PL1 and PL2 is worse than that of PL0.

- There are also significant differences between PL1 and PL2, the latter having a worse prognosis.

- Further analyses in pathologically and clinically staged tumors show that pathologically staged tumor of >3-4 cm with visceral pleura invasion have similar prognosis than those >4-5 cm; and that those of >4-5 cm with visceral pleura invasion have similar prognosis than those >5-7 cm.

Impact on VPI remains the same in 8th TNM

Recommendations for N and M changes

- **N STAGING**
- Current N descriptors adequately predict the prognosis and therefore should be maintained in the forthcoming staging system.
- Furthermore, we recommend that physicians record the number of metastatic lymph nodes (or stations) and to further classify the N category using new descriptors, such as N1a (single station), N1b (multi station), N2a1 (single/N1- (skip)), N2a2 (single/N1+) N2b (multi), and N3, for further testing
- **M STAGING**
- Cases with pleural/pericardial effusions, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or a combination of multiple of these parameters should continue to be grouped as M1a category.
- Single metastatic lesions in a single distant organ should be newly designated to the M1b category.
- Multiple lesions in a single organ or multiple lesions in multiple organs should be reclassified as M1c category.
- This new division can serve as a first step into providing rational definitions for an oligometastatic disease stage in non-small-cell lung cancer in the future.

Asamura H et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2015;10:1675-84
Eberhardt WE et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2015 Nov;10(11):1515-22.

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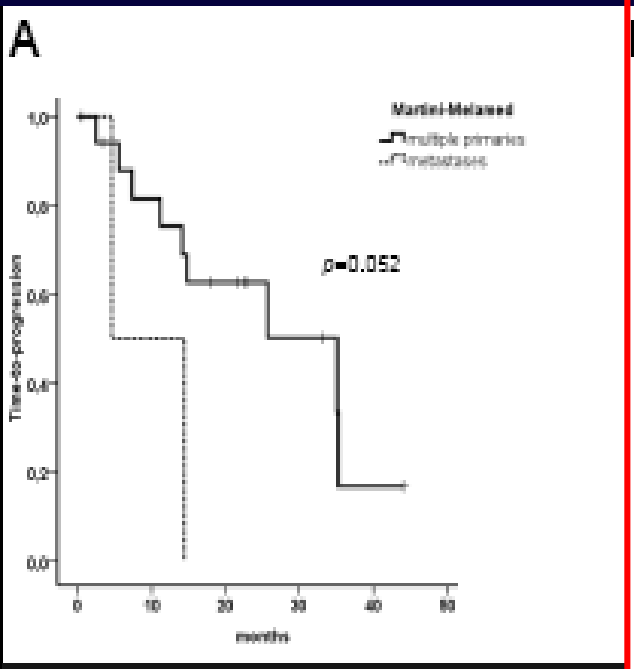
DISEASE FREE SURVIVAL COMPARING MARTINI MELAMED VS MOLECULAR VS SURGICAL PATHOLOGY

Martini Melamed

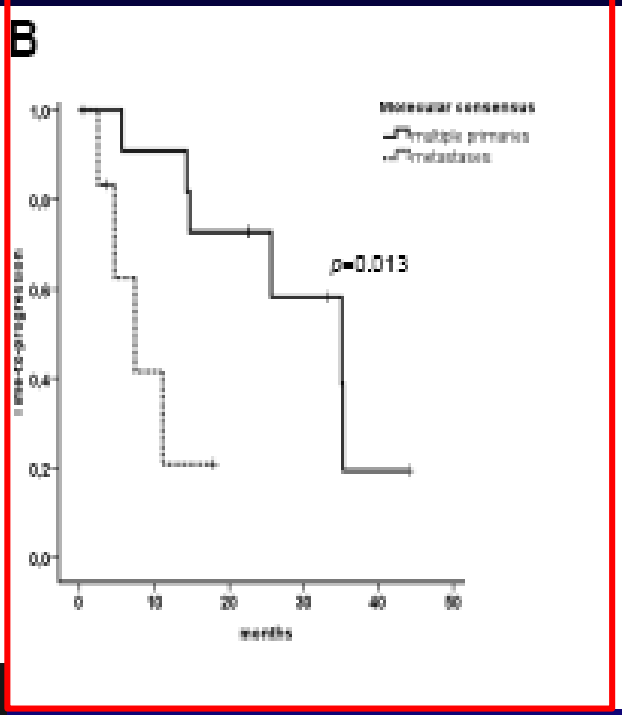
P=0.052



- different histology,
- different lobe
- time period of >2 yrs favoured second primary.

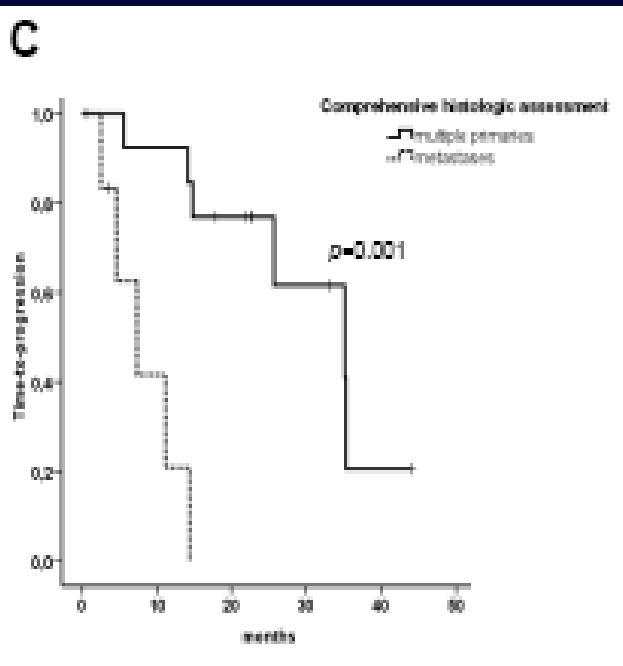
Molecular

P=0.013



Surgical Pathology

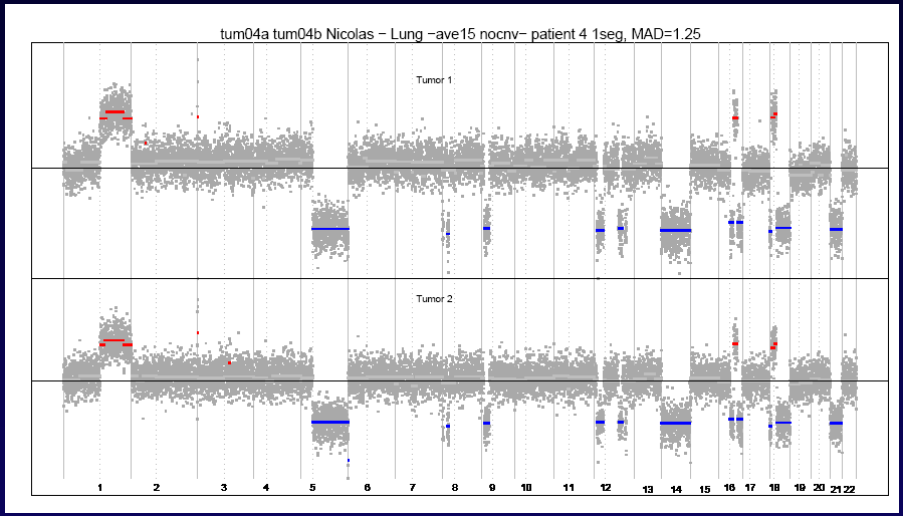
P=0.001



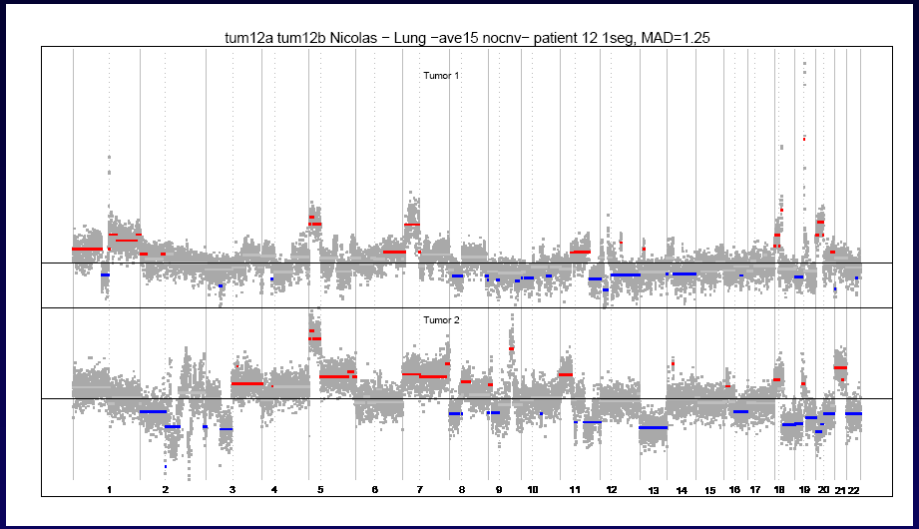
Girard, N, et al: Clin Ca Res 2009:15:5184-90

Courtesy of WD Travis

Genomic profiling: similar profile = metastases



Genomic profiling: different profile = multiple primary



42 tumors from 20 patients - 22 tumor pairs were evaluable by CGH.

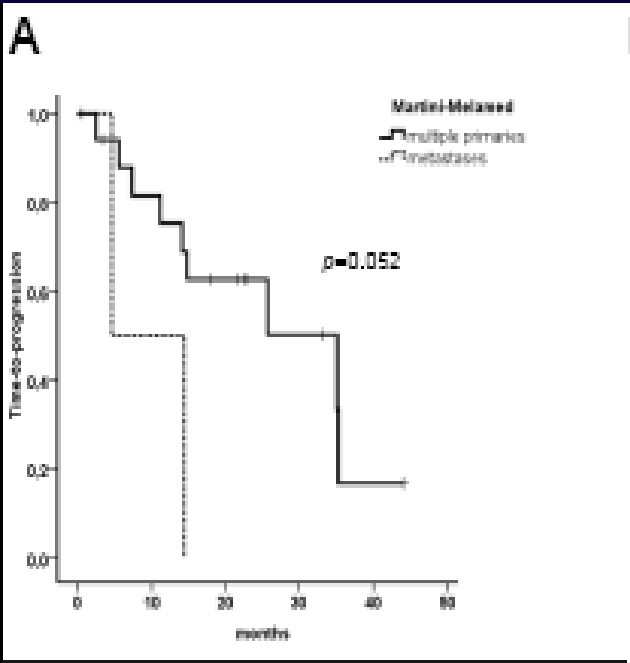
Classification based on genomic profiling contradicted the clinicopathologic diagnosis in 18% of cases

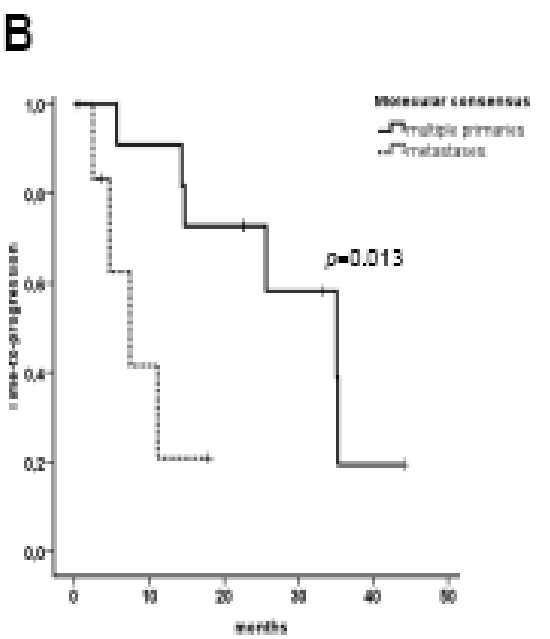
Conclusion: Genomic analysis can help distinguish clonal tumors from independent primaries. The development of rapid, inexpensive, and reliable molecular tools may allow for refinement of clinicopathologic criteria currently used in this setting

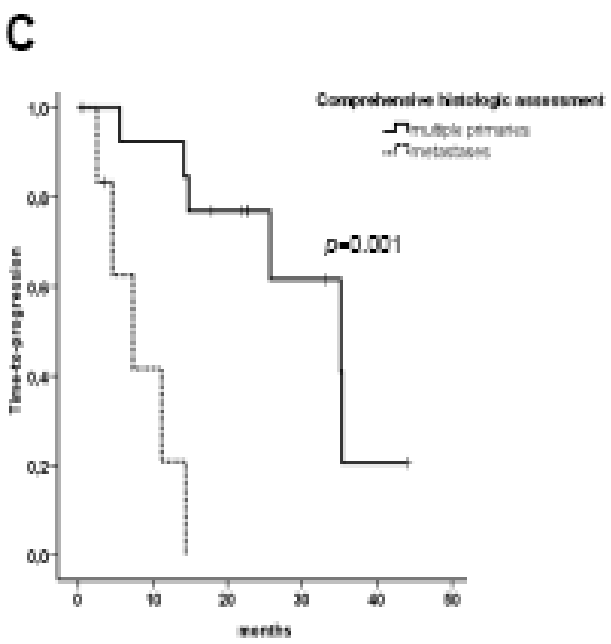
– Girard, N, et al: Clin Ca Res 2009:15:5184-90,

DISEASE FREE SURVIVAL COMPARING MARTINI MELAMED VS MOLECULAR VS SURGICAL PATHOLOGY

Martini Melamed	Molecular	Surgical Pathology
P=0.052	P=0.013	P=0.001







- different histology,
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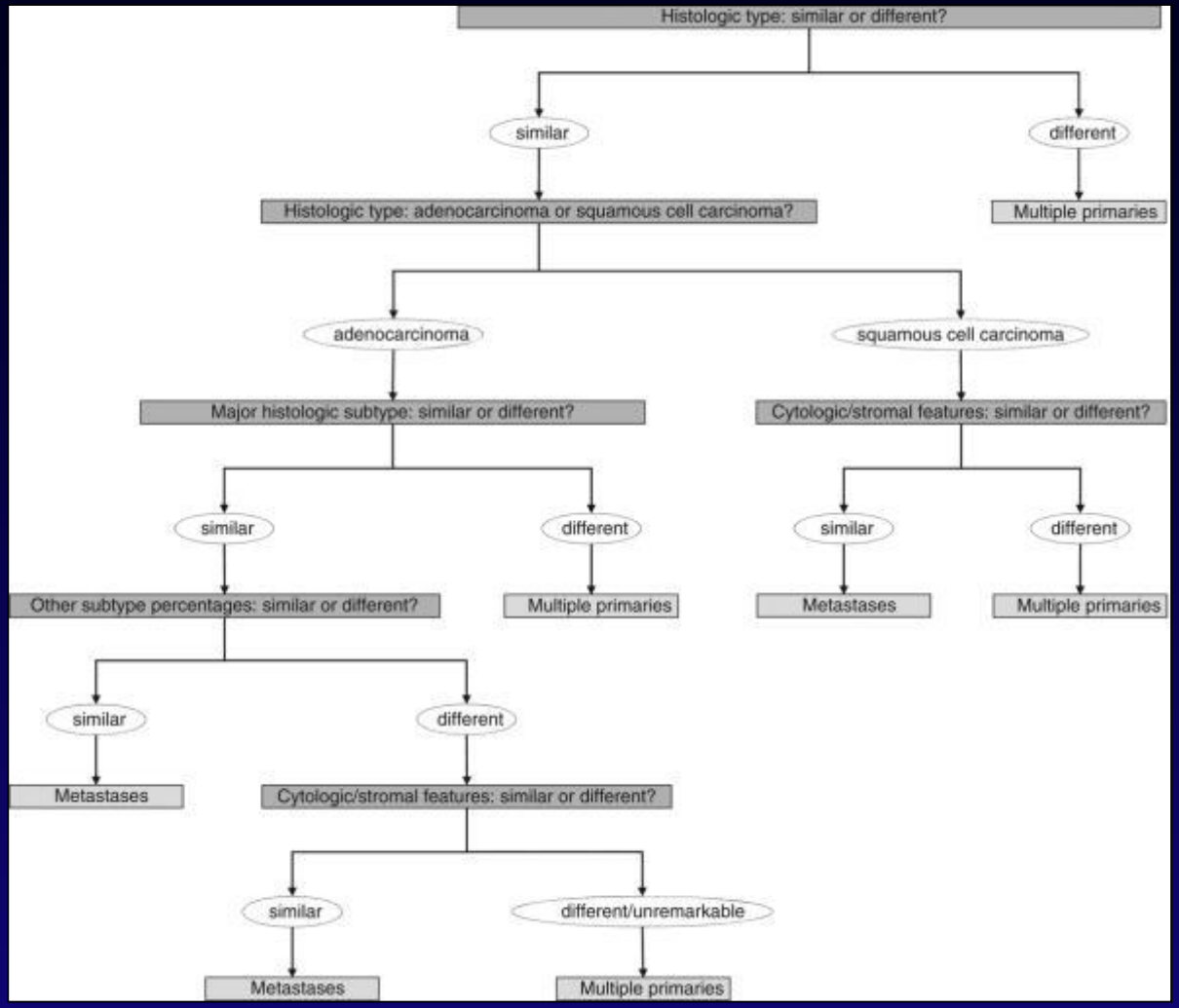
- time period of >2 yrs favoured second primary.

Girard, N, et al: AJSP 33: 1752-64, 2009

Courtesy of WD Travis

Comprehensive histologic assessment methodology for multiple nonsmall cell lung cancer.



Feature	P value Fisher Exact
Nuclear pleomorphism	0.0001
Cell size	0.0001
Gland Formation	0.0001
Nucleolar size	0.0001
Mitotic Rate	0.001
Nuclear inclusions	0.59
Intra-aveolar Clusters	0.003
Necrosis pattern	0.022
Lymphocytosis	0.07
Mucin content	1
Lepidic Growth	0.082
Vascular invasion	0.83
Macrophage response	0.224
Clear cell change	0.23
Acute inflammation	0.39
Keratinization	1
Emperipolesis	NA
Cytoplasmic granules	NA

Comprehensive Histologic Assessment Helps to Differentiate Multiple Lung Primary Nonsmall Cell Carcinomas From Metastases. Girard, Ni et al. American Journal of Surgical Pathology. 33(12):1752-1764,

Interobserver variation study on multiple nodules (separate primary tumour versus intrapulmonary metastasis)

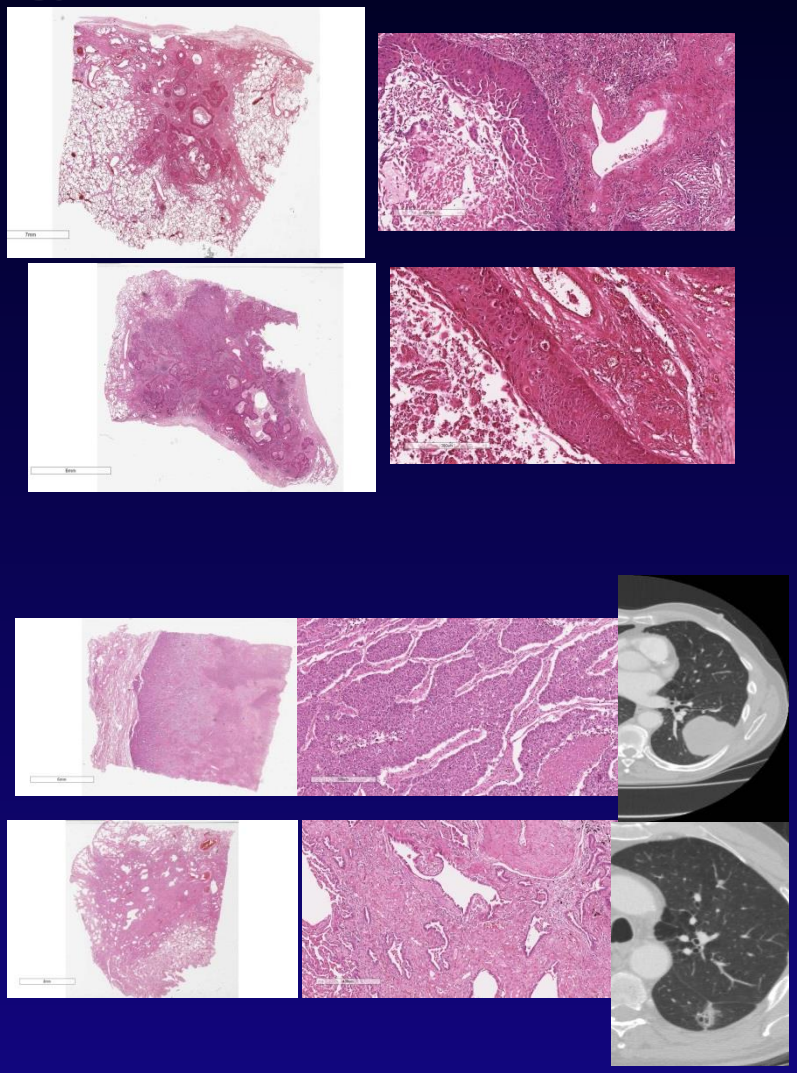
Undertaken by the IASLC Pathology Committee, Denver, 2015.

- PATHOLOGIST INTEROBSERVER AGREEMENT

- Kappa is 0.60
- This is on H&E only. IHC would likely increase this, ? molecular/MDT also.

- PATHOLOGY-IMAGING INTEROBSERVER AGREEMENT

- Of 12 cases where there was disagreement, only 3 were SPT and the majority were cases classified on pathology as IM.
- Kappa value of 0.42.



Unpublished data presented at World IASLC meeting, Denver 2015

	Second Primary Lung Cancer	Multifocal GG/L Nodules	Pneumonic-Type of Lung Cancer	Separate Tumor Nodule/ Intrapulmonary metastasis
Imaging Features	Two or more distinct masses with imaging characteristic of lung cancer (e.g. spiculated)	Multiple ground glass or part-solid nodules	Patchy areas of ground glass and consolidation	Typical lung cancer (e.g. solid, spiculated) with separate solid nodule
Pathologic Features	Different histotype or different morphology by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histology throughout (most often invasive mucinous adenocarcinoma)	Distinct masses with the same morphology by comprehensive histologic assessment
TNM Classi-fication	Separate cTNM and pTNM for each cancer	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size or T3 if in single lobe, T4 or M1a if in different ipsi- or contralateral lobes; single N and M	Location of separate nodule relative to primary site determines if T3, T4 or M1a; single N and M
Conceptual View	Unrelated tumors	Separate tumors, albeit with similarities	Single tumor, diffuse pulmonary involvement	Single tumor with intrapulmonary metastasis

The IASLC Lung Cancer Staging Project: Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification. Frank C. Detterbeck FC, Nicholson AG, Franklin WA, Marom EM et al. *Journal of Thoracic Oncology, in press*

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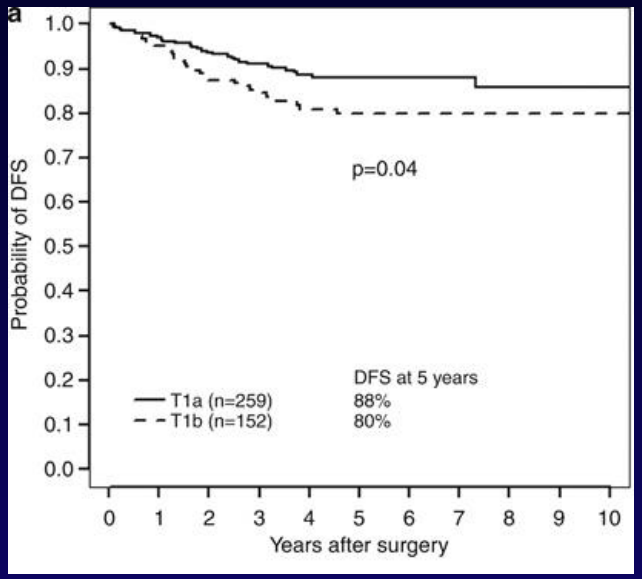
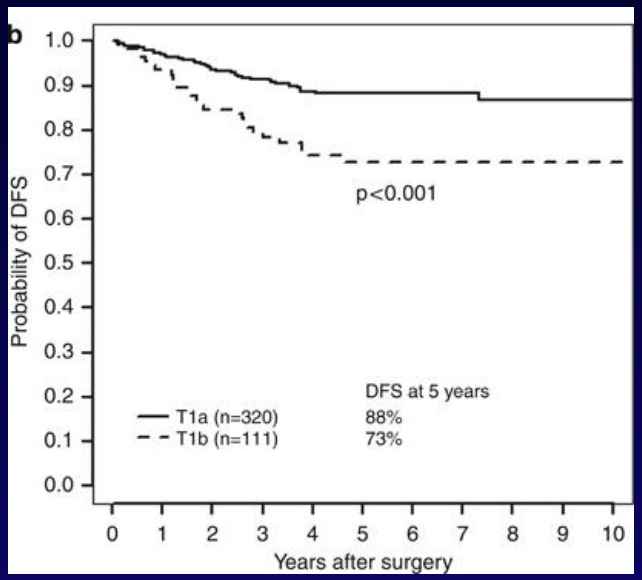
Should we only be measuring the invasive area……?

Disease-free survival (DFS) comparing T1a (≤2 cm) *versus* T1b (>2 cm or ≤3 cm).



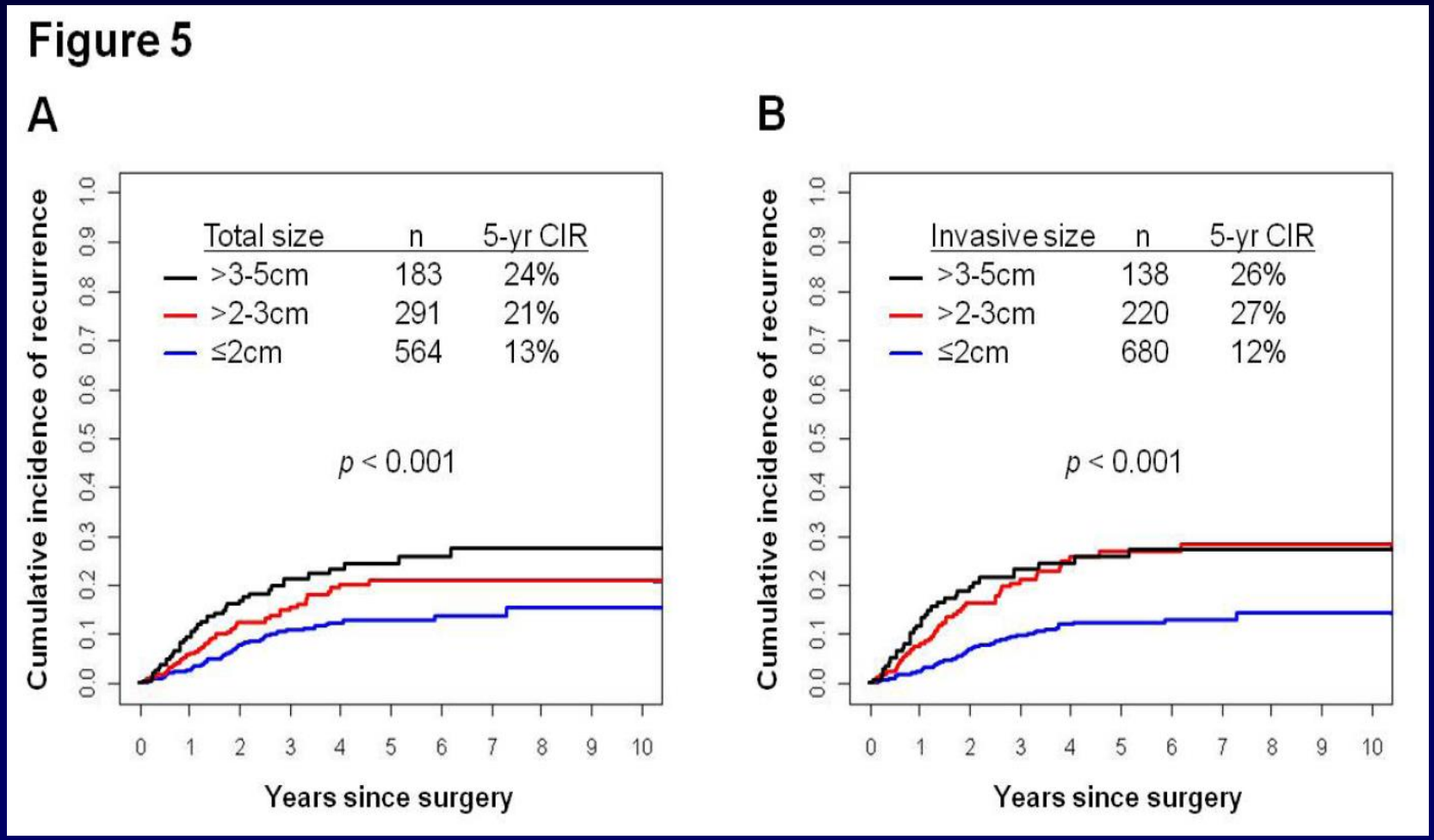
(a) T1a and T1b defined according to gross tumor size (*P*=0.04).



(**b**) T1a and T1b defined according to invasive size (*P*<0.001).

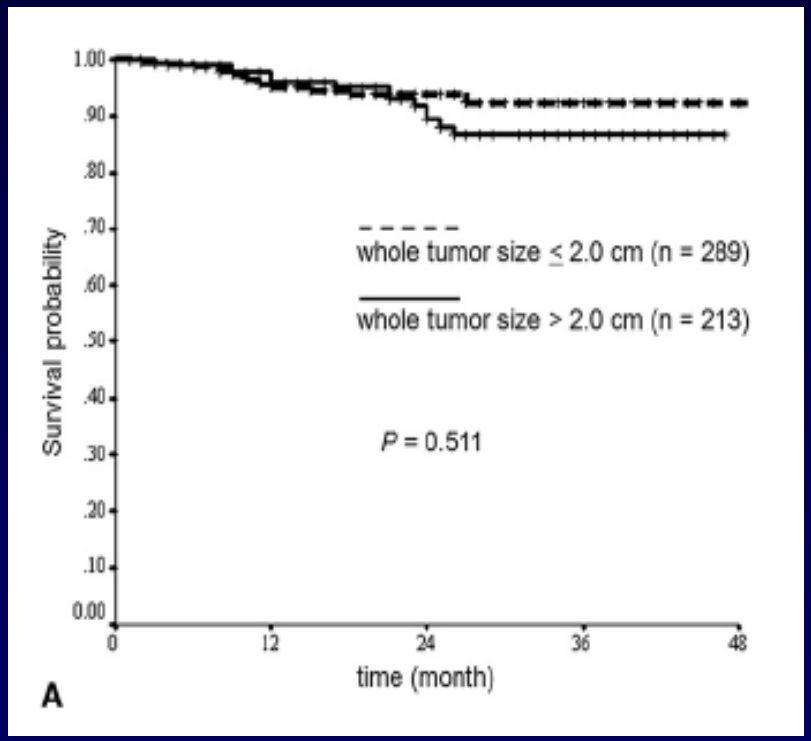
Yoshizawa A, et al Mod Pathol. 2011 May;24(5):653-64.

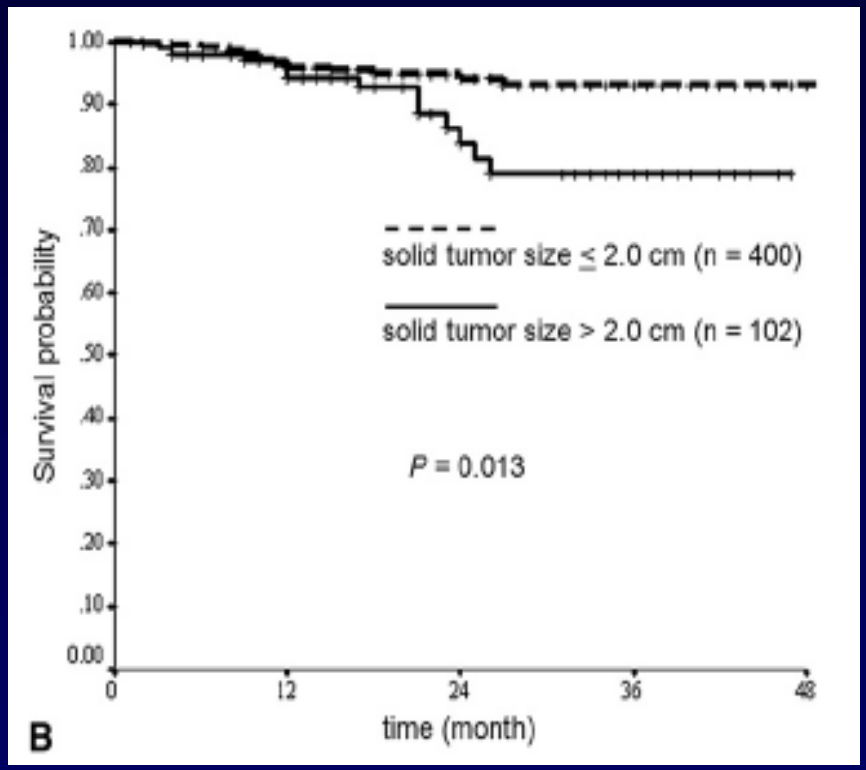
116 (40%) T1b (>2-3 cm) → T1a (≤2 cm)
45 (25%) T2a (>3-5 cm) → T1b (>2-3 cm)



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

Prognostic Significance of Solid vs Whole Tumor Size by HRCT 502 Stage IA Adenoca





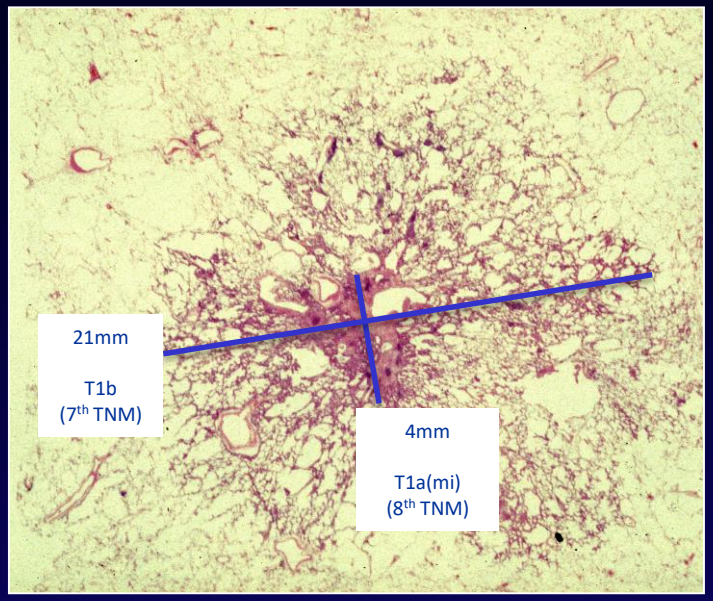
–DFS by HRCT A: 3 yr DFS 92.5% 2≤cm and 86.7 >2cm
B: 3 yr DFS 93.2% 2≤cm and 78.9 >2cm

–Solid size – independent predictor in multivariate analysis (HR 2.30; 95% CI 1.46-3.63)

Tsutani et al JTCVS 143:607-12, 2012

PROPOSAL FOR 8TH EDITION TNM

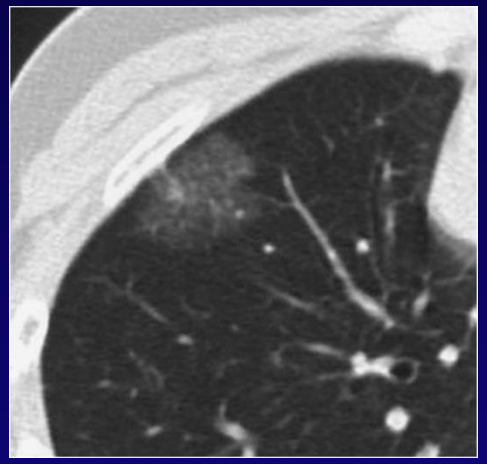
- *In situ* carcinoma
  - *Tis (AIS)*
  - *Tis (SCIS)*
- Minimally invasive adenocarcinoma
  - *T1a(mi)*
  - *If multiple – OK to use T1a(mi)(m)*

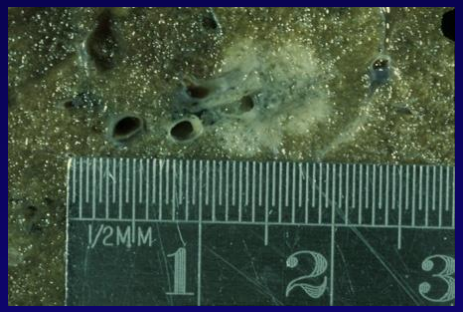


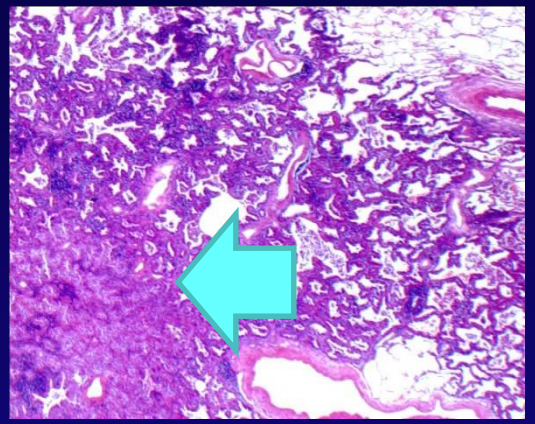
The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. Travis WD et al. *JTO, 2016*

Part solid nodules with small solid component

Small solid component within a subsolid nodule may indicate invasive adenocarcinoma….but not always







Adenocarcinoma in situ (Noguchi type B)

c/o Professor K Kerr

AIMS OF PRESENTATION

- Updated staging
  - Discuss changes to T, N, M staging categories in the 8th TNM
  - Discuss handling of multiple pulmonary tumour nodules
  - Dealing with in-situ components/subsolid nodules
- Present correct terminology for small biopsies and cytology specimens (2015 WHO classification)
- Discuss the lung dataset in relation to molecular testing

IASLC

2015 WHO CLASSIFICATION

- **1-1: Introduction**
  - 1-1A Lung cancer staging and grading
  - 1-1B Rationale for classification in small biopsies and cytology
  - 1-1C Terminology and criteria in non-resection specimens
  - 1-1D Molecular testing for treatment selection in lung cancer

- **1-2: Adenocarcinoma**
  - 1-2A Invasive adenocarcinoma
  - 1-2B Variants of invasive adenocarcinoma
  - 1-2C Minimally invasive adenocarcinoma
  - 1-2D Preinvasive lesions
    - 1-2D-i: Atypical adenomatous hyperplasia
    - 1-2D-ii: Adenocarcinoma in situ

- **1-3: Squamous cell carcinoma**
  - 1-3A: Keratinizing and nonkeratinizing squamous cell carcinoma
  - 1-3B: Basaloid carcinoma
  - 1-3C: Preinvasive lesion: Squamous carcinoma in situ

- **1-4: Neuroendocrine Tumours**
  - 1-4A: Small cell carcinoma
  - 1-4B: Large cell neuroendocrine carcinoma
  - 1-4C: Carcinoid tumors
  - 1-4D: Preinvasive lesion: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- **1-5: Large cell carcinoma**

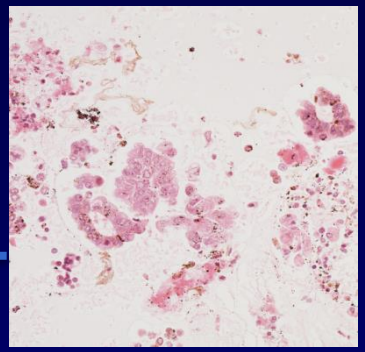
- **1-6: Adenosquamous carcinoma**

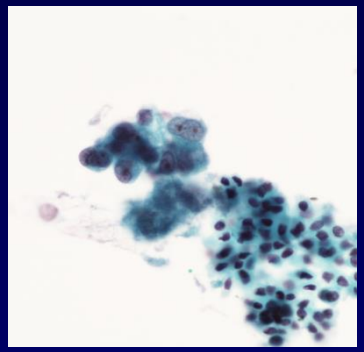
- **1-7: Sarcomatoid carcinoma**
  - 1-7A: Pleomorphic, spindle cell and giant cell carcinoma
  - 1-7B: Carcinosarcoma
  - 1-7C: Pulmonary blastoma

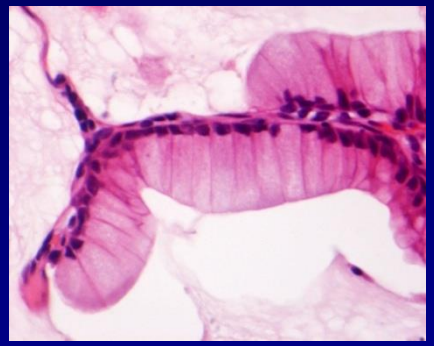
- **1-8: Other carcinomas**
  - 1-8A: Lymphoepithelioma-like carcinoma
  - 1-8B: NUT-carcinoma

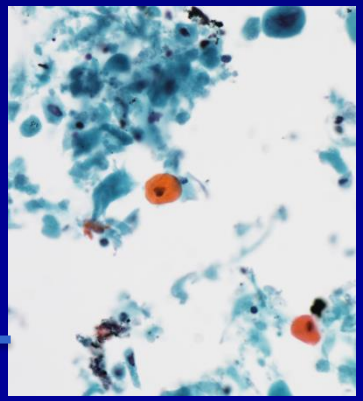
SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL **CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY†**

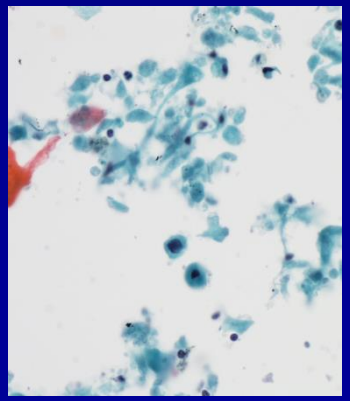
2015 WHO Classification in resection specimens	Morphology/Stains	New Small Biopsy/Cytology Terminology
ADENOCARCINOMA (Predominant pattern) **Acinar** **Papillary** **Solid** **Micropapillary**	Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma (describe identifiable patterns present)
Lepidic (nonmucinous)		Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
Invasive mucinous adenocarcinoma **Colloid adenocarcinoma** **Fetal adenocarcinoma** **Enteric adenocarcinoma**		Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern – see text) Adenocarcinoma with mucinous features Adenocarcinoma with fetal features Adenocarcinoma with enteric features ††
SQUAMOUS CELL CARCINOMA	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma







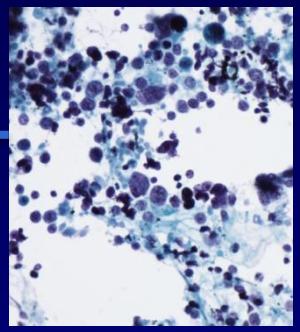


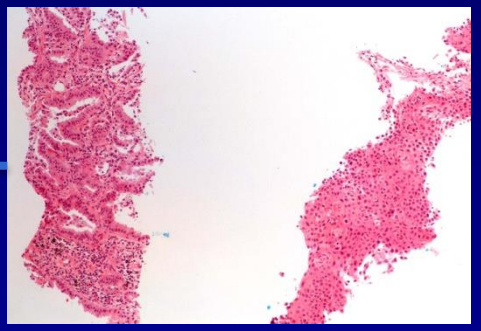


Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285

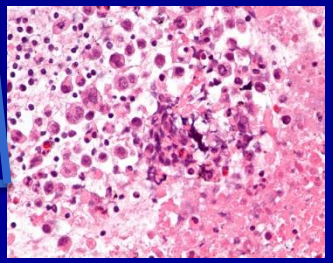
CLASSIFICATION FOR SMALL BIOPSIES/CYTOLOGY COMPARING 2015 WHO TERMS WITH NEW TERMS FOR SMALL CELL CARCINOMA, LARGE CELL NEUROENDOCRINE CARCINOMA, ADENOSQUAMOUS CARCINOMA AND SARCOMATOID CARCINOMA †

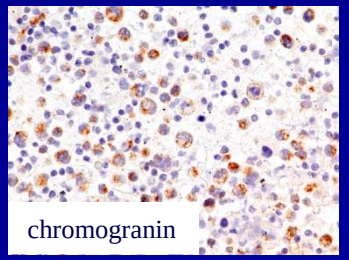
2015 WHO Classification	SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS
SMALL CELL CARCINOMA	Small cell carcinoma
LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)	Non-small cell carcinoma with neuroendocrine (NE) morphology and positive NE markers, possible LCNEC
ADENOSQUAMOUS CARCINOMA	Morphologic squamous cell and adenocarcinoma patterns present: Non-small cell carcinoma, NOS, (comment that adenocarcinoma and squamous components are present and this could represent adenosquamous carcinoma).
No counterpart in 2015 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.
Pleomorphic, spindle and/or giant cell carcinoma	NSCC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)





NSCC, NE marker +ve, ?LCNEC with pleomorphic features

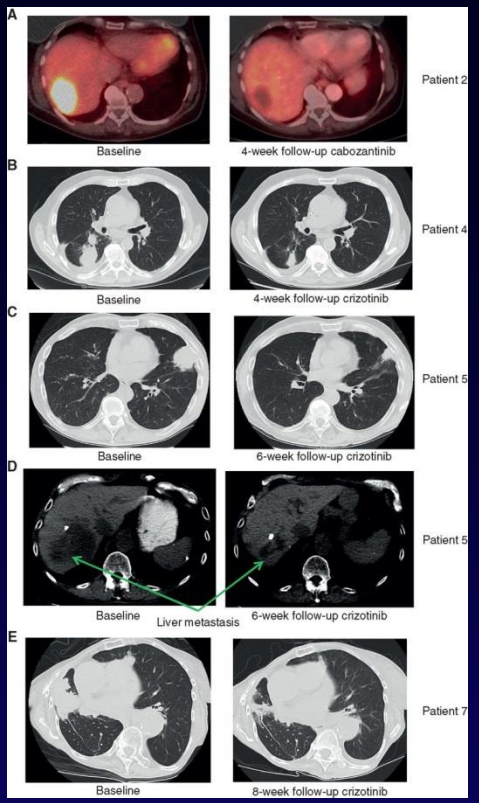




Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285

MET exon 14 skipping mutations: responses to cabozantinib

Paul K. Paik et al. Cancer Discovery 2015;5:842-849



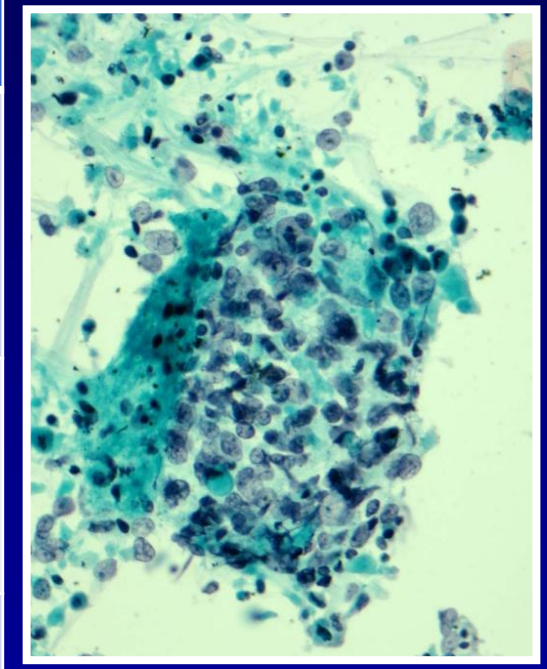
Programmed death-1 Ligand 1 (PD-L1) and 2 are highly expressed in pleomorphic carcinomas of the lung: Comparison of sarcomatous and carcinomatous areas. Kim S et al. Eur J Cancer. 2015;51:2698-707

High co-expression of PD-L1 and HIF-1α correlates with tumour necrosis in pulmonary pleomorphic carcinoma. Chang YL et al. Eur J Cancer. 2016 epub

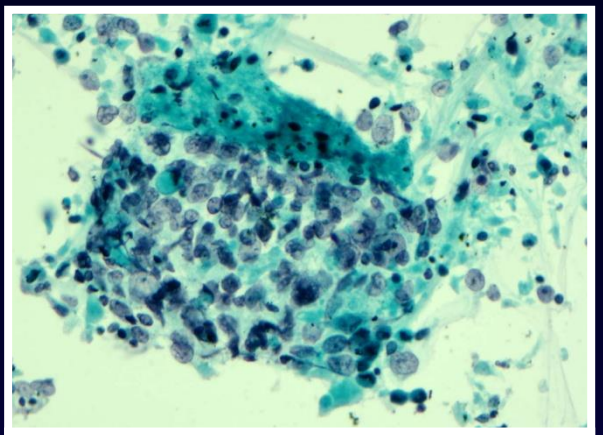
USE OF IMMUNOHISTOCHEMISTRY WHEN A TUMOUR SHOWS NON-SMALL CELL CARCINOMA-NOT OTHERWISE SPECIFIED (NOS) IN SMALL BIOPSIES AND CYTOLOGY

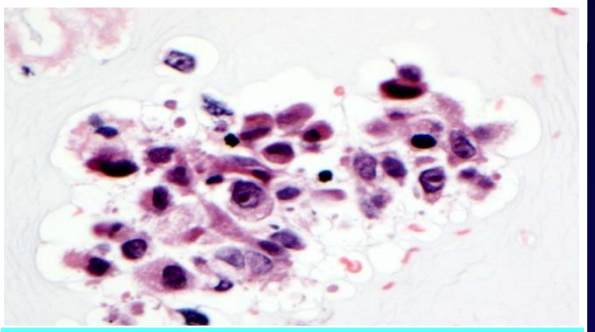
SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL **CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY †**

2015 WHO Classification in resection specimens	**Morphology/Stains**	**New Small Biopsy/Cytology Terminology**
Adenocarcinoma (solid pattern may be just one component of the tumor) ‡	Morphologic adenocarcinoma patterns not present, but supported by special stains, i.e. +TTF-1	Non-small cell carcinoma, favour adenocarcinoma using IHC
Squamous cell carcinoma, (nonkeratinizing pattern may be just one component of the tumor) ‡	Morphologic squamous cell patterns not present, but supported by stains i.e. +p40	Non-small cell carcinoma, favour squamous cell carcinoma using IHC
LARGE CELL CARCINOMA	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	Non-small cell carcinoma, not otherwise specified NSCLC-NOS using IHC

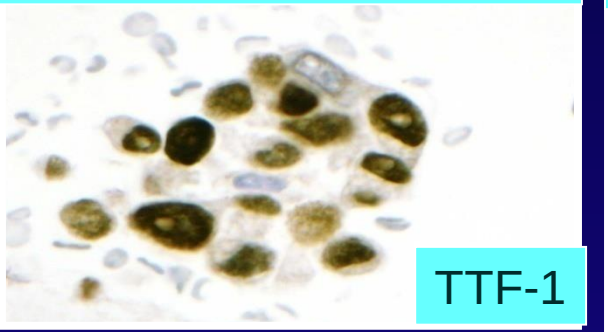


Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285

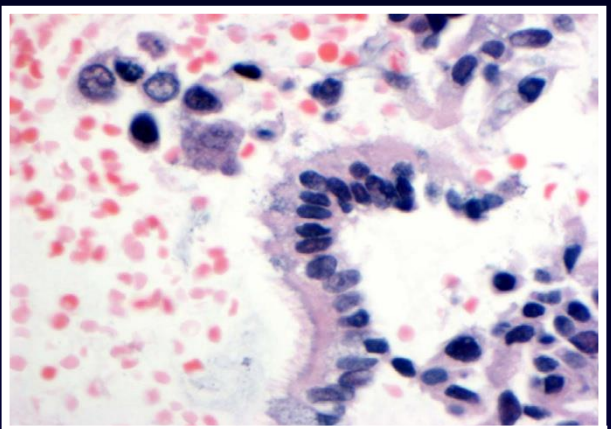




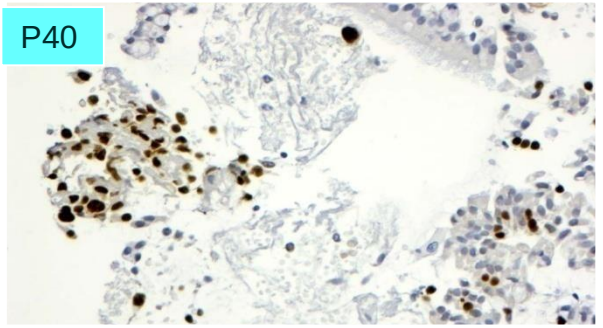
NSCLC, favouring ADC



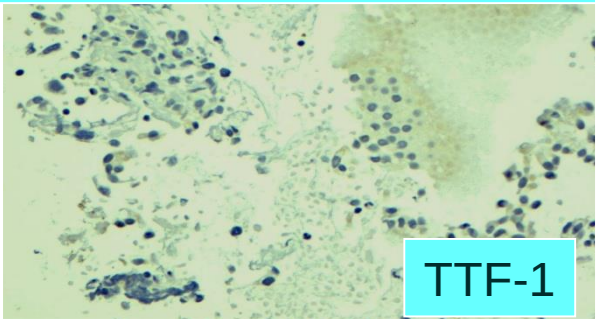
TTF-1



P40



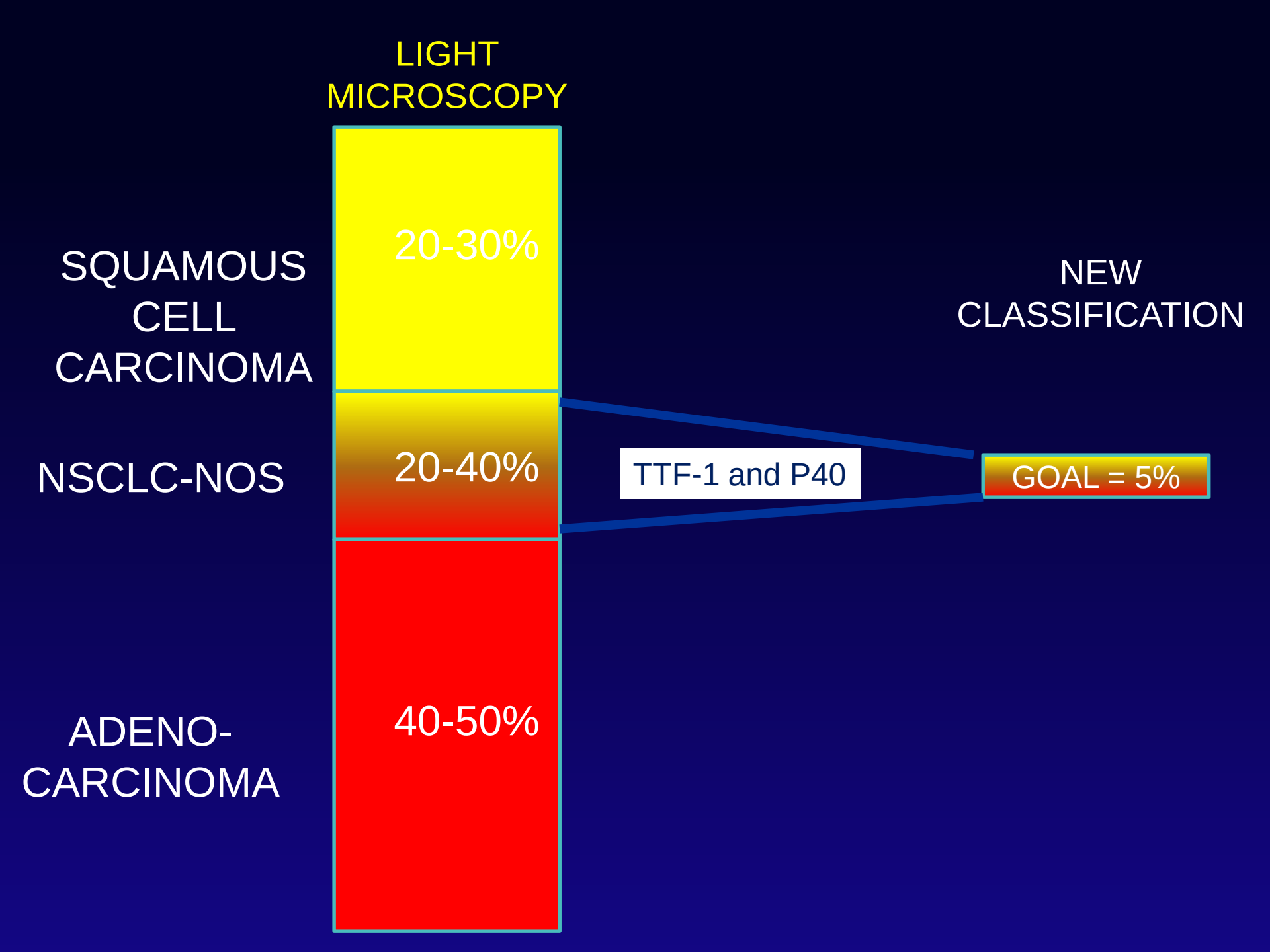
NSCLC, favouring SQCC



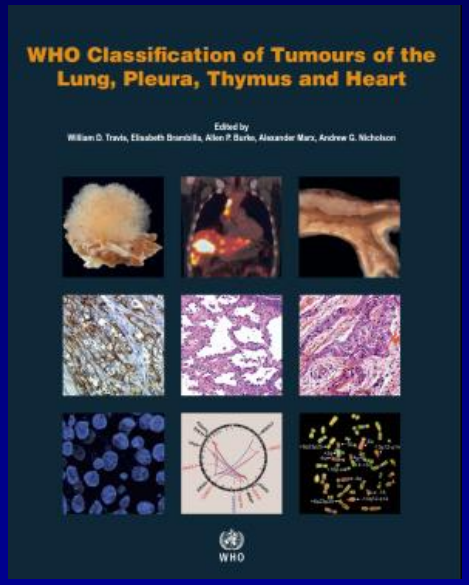
TTF-1

GENERAL PRINCIPLES

- Cut tissue block as sparingly as possible
- Obtain unstained slides for molecular at time of cutting block for IHC
- Minimize stains to maximize tissue for molecular testing by using a limited panel of IHC (i.e TTF-1 and P40)
- Further molecular testing, if clinically appropriate, can be performed on remaining tissue


LIGHT MICROSCOPY
SQUAMOUS CELL CARCINOMA
20-30%
NSCLC-NOS
20-40%
ADENO-CARCINOMA
40-50%
TTF-1 and P40
NEW CLASSIFICATION
GOAL = 5%

Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285



STEP 1

POSITIVE BIOPSY (FOB, TBBx, Core, SLBx)

POSITIVE CYTOLOGY (effusion, aspirate, washings, brushings)

NE morphology, large cells, NE IHC+ → **NSCLC, ?LCNEC**

NE morphology, small cells, no nucleoli, NE IHC+, TTF-1 +/-, CK + → **SCLC**

Keratinization, pearls and/or intercellular bridges → **Classic Morphology: SQCC**

Histology: Lepidic, papillary, micropapillary and/or acinar architecture(s)
Cytology: 3-D arrangements, delicate foamy/ vacuolated (translucent) cytoplasm, Fine nuclear chromatin and often prominent nucleoli
Nuclei are often eccentrically situated

No clear ADC or SQCC morphology: NSCLC-NOS

NSCLC, favor SQCC

Classic morphology: ADC

SQCC marker +ve
ADC marker -ve/or Mucin -ve

ADC marker and/or Mucin +ve; SQCC marker –ve (or weak in same cells)

STEP 2

Apply ancillary panel of one SQCC and one ADC marker +/or Mucin

IHC –ve and Mucin -ve

ADC marker or Mucin +ve; as well as SQCC marker +ve in different cells

NSCLC, favor ADC

NSCLC NOS

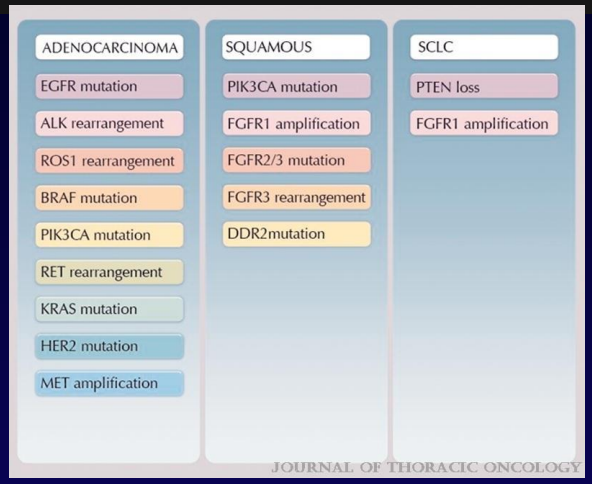
Molecular analysis: e.g. EGFR mutation, ALK rearrangement†

NSCLC, NOS, possible adenosquamous ca

STEP 3

If tumor tissue inadequate for molecular testing, discuss need for further sampling - back to Step 1

Adapted from: Travis WD et al. IASLC/ATS/ERS classification of ADCs *J Thor Oncol* 2011;6:244-285



Morgensztern, D-C et al. Journal of Thoracic Oncology. 10:S1-S63, January 2015

NEXT GENERATION SEQUENCING

IMMUNOMODULATORY THERAPY (e.g. PD-L1)

STEP 1

POSITIVE BIOPSY (FOB, TBBx, Core, SLBx)

POSITIVE CYTOLOGY (effusion, aspirate, washings, brushings)

NE morphology, large cells, NE IHC+ → NSCLC, ?LCNEC

NE morphology, small cells, no nucleoli, NE IHC+, TTF-1 +/-, CK + → SCLC

Keratinization, pearls and/or intercellular bridges → Classic Morphology: SQCC

Histology: Lepidic, papillary, micropapillary and/or acinar architecture(s)
Cytology: 3-D arrangements, delicate foamy/ vacuolated (translucent) cytoplasm, Fine nuclear chromatin and often prominent nucleoli
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Classic morphology: ADC

No clear ADC or SQCC morphology: NSCLC-NOS

NSCLC, favor SQCC

SQCC marker +ve
ADC marker -ve/or Mucin -ve

STEP 2

Apply ancillary panel of one SQCC and one ADC marker +/or Mucin

ADC marker and/or Mucin +ve; SQCC marker –ve (or weak in same cells)

NSCLC, favor ADC

IHC –ve and Mucin -ve

NSCLC NOS

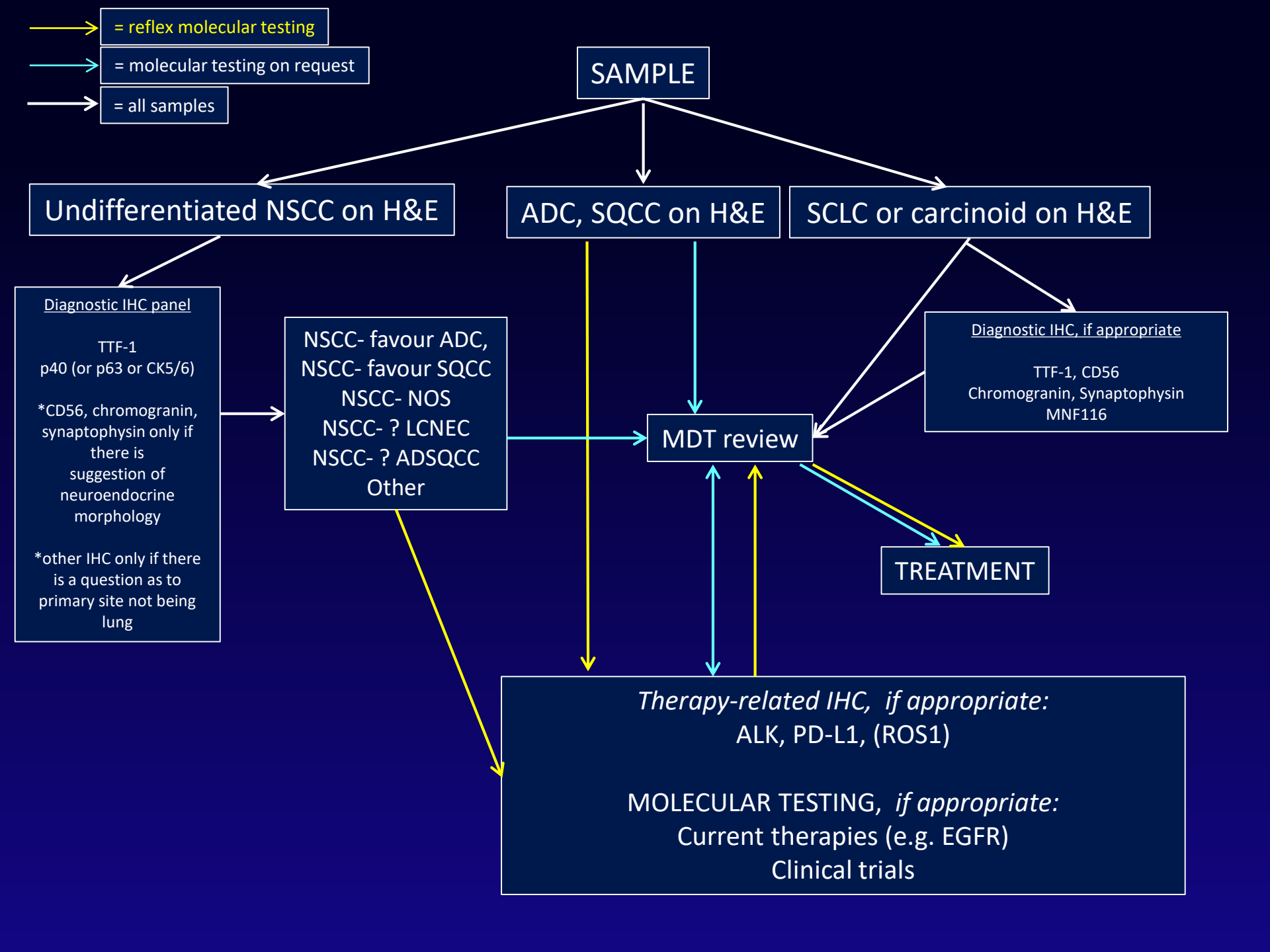
ADC marker or Mucin +ve; as well as SQCC marker +ve in different cells

NSCLC, NOS, possible adenosquamous ca

Molecular analysis: e.g. EGFR mutation, ALK rearrangement†

STEP 3

If tumor tissue inadequate for molecular testing, discuss need for further sampling - back to Step 1


= reflex molecular testing
= molecular testing on request
= all samples
SAMPLE
Undifferentiated NSCC on H&E
ADC, SQCC on H&E
SCLC or carcinoid on H&E
Diagnostic IHC panel
TTF-1
p40 (or p63 or CK5/6)
*CD56, chromogranin, synaptophysin only if there is suggestion of neuroendocrine morphology
*other IHC only if there is a question as to primary site not being lung
NSCC- favour ADC,
NSCC- favour SQCC
NSCC- NOS
NSCC- ? LCNEC
NSCC- ? ADSQCC
Other
Diagnostic IHC, if appropriate
TTF-1, CD56
Chromogranin, Synaptophysin
MNF116
MDT review
TREATMENT
Therapy-related IHC, if appropriate:
ALK, PD-L1, (ROS1)
MOLECULAR TESTING, if appropriate:
Current therapies (e.g. EGFR)
Clinical trials

AIMS OF PRESENTATION

- Updated staging
  - Discuss changes to T, N, M staging categories in the 8th TNM
  - Discuss handling of multiple pulmonary tumour nodules
  - Dealing with in-situ components/subsolid nodules
- Present correct terminology for small biopsies and cytology specimens (2015 WHO classification)
- Discuss the lung dataset in relation to molecular testing

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MOLECULAR ISSUES

- Come to recognise the increasing importance of immunohistochemistry and genetics in the diagnosis of lung tumours.
- TREATMENT OPTIONS….. will drive changes in classification and pathology practice
  - Conventional chemotherapy
    - Pemetrexed (non-squamous NSCLC),
    - Bevacizumab (non-squamous NSCLC)
  - Targeted agents
    - EGFR mutations: Gefitinib, Erlotinib, Afatinib (T790M mutation)
    - ALK translocations: Crizotinib, Alectinib
    - ROS translocations: Crizotinib
  - Immunomodulatory drugs
  - Therapeutic vaccines priming the immune response
    - e.g., MAGE-A3 (vaccine targeting MAGE-A3)[3], TG4010 (vaccine encoding MUC-1 and IL-2)[4], IMA901 (peptide vaccine)[5], racotumomab (anti-idiotype vaccine)[6], sipuleucel-T (Provenge, cellular therapeutic vaccine)[7], nelipepimut-S (E75/NeuVax, peptide vaccine)[8]
  - Agents targeting T-cell checkpoint dysregulation[2]
    - e.g., nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), MPDL3280A (anti-PD-L1), MEDI4736 (anti-PD-L1), ipilimumab (anti-CTLA-4), tremelimumab (anti-CTLA-4)

IASLC

Evolution and importance of biomarker use in NSCLC

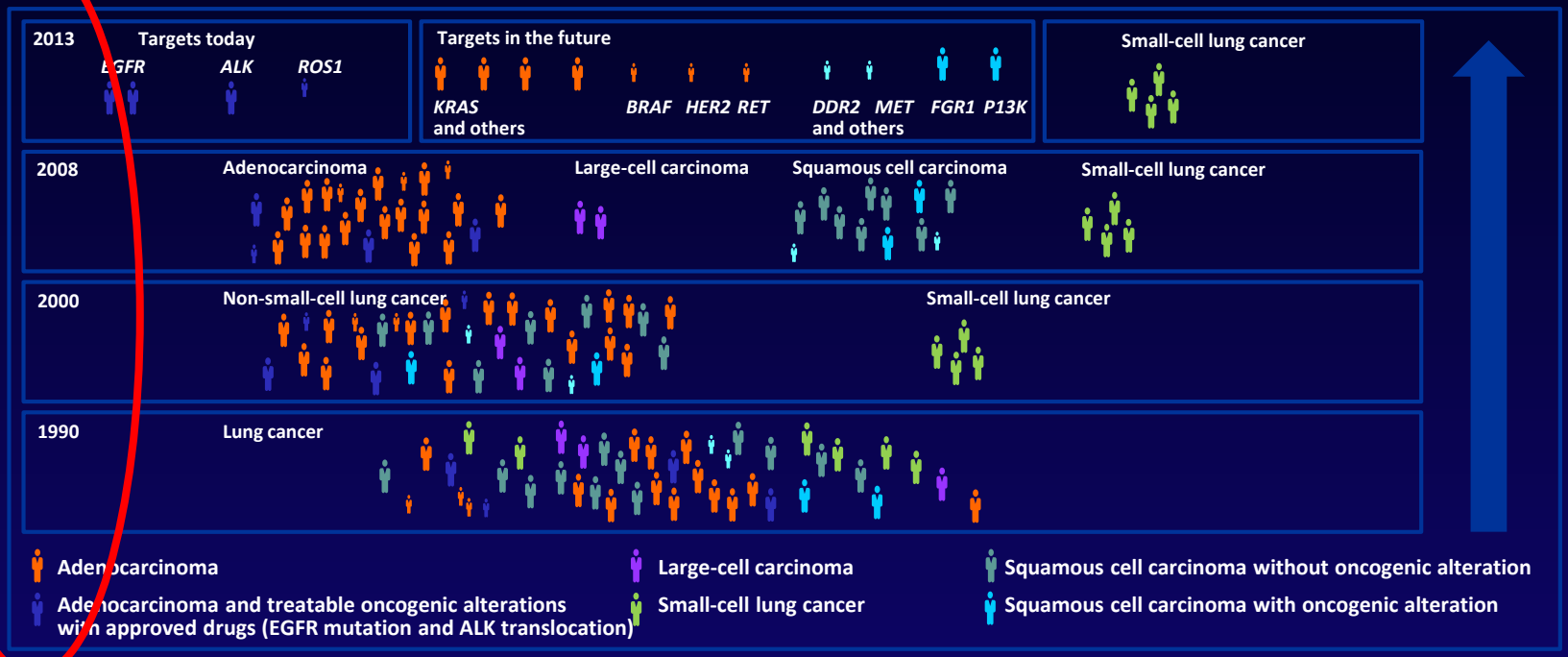


Figure adapted from Reck M, et al. *Lancet* 2013;383:709–19.[1]

- Evolution of biomarkers has driven guideline development
- Patient selection expedites clinical trials and drug approvals
- The resultant increase in complexity of therapy is also reflected in guidelines

Courtesy of Prof Keith Kerr, Aberdeen

Table A.1 A protocol for reporting lung tissue resected in the treatment of lung cancer

Specimen Type

☐ Right

- ☐ VATS segmentectomy
- ☐ Open segmentectomy
- ☐ Pneumonectomy (extra-pericardial)
- ☐ Sleeve
- ☐ Other, e.g. chest wall

☐ Left

- ☐ VATS lobectomy
- ☐ Open lobectomy/bi-lobectomy
- ☐ Pneumonectomy (intra-pericardial)
- ☐ Wedge resection

Gross description

Location of Tumour

- ☐ Main bronchus within 20 mm of carina (T3) – this will require clinical information
- ☐ Main bronchus more than 20 mm from carina (T2)
- ☐ Non-assessable
- ☐ Right upper lobe ☐ Right middle lobe ☐ Right lower lobe
- ☐ Left upper lobe ☐ Left lower lobe

Tumour size ... mm (T1 ≤30 mm or superficial tumours confined to bronchial wall, T2 > 30 mm)

Distance from bronchial or medial resection margin . . . mm

Extent of atelectasis/obstructive pneumonitis:

- ☐ None
- ☐ Involving hilar region but not whole lung (T2)
- ☐ Involving whole lung (T3)

Histology

Histological type

- ☐ Squamous cell carcinoma ☐ Adenocarcinoma ☐ Bronchoalveolar cell carcinoma
- ☐ Large cell undifferentiated ☐ Small cell carcinoma
- ☐ Mixed tumours (please specify: .....)
- ☐ Other tumour (please specify, e.g. carcinoid, etc.: .....)

Local invasion

- ☐ Visceral pleura (T2) ☐ Parietal pleura/chest wall (T3) ☐ Mediastinal pleura (T3)
- ☐ Pericardium (T3) ☐ Diaphragm (T3)
- ☐ Great vessel (aorta, central pulmonary artery or vein) (T4) ☐ Atrium, heart (T4)
- ☐ Malignant pleural effusion (T4) ☐ Separate tumour nodules in same lobe (T4)

Lymph node spread

Ipsilateral hilar/intrapulmonary (node stations 10–14)	☐ Submitted	☐ Involved (N1)
Ipsilateral mediastinal (node stations 1–9)	☐ Submitted	☐ Involved (N2)
Contralateral mediastinal, hilar, ipsilateral or contralateral scalene, supraclavicular	☐ Submitted	☐ Involved (N3)

Margins

Bronchial	☐ Clear	☐ Involved
Mediastinal	☐ Clear	☐ Involved
Vascular	☐ Clear	☐ Involved
Chest wall	☐ Clear	☐ Involved

Other Pathology

- ☐ Emphysema (moderate/severe degree) ☐ Interstitial fibrosis; State cause (if known): .....
- ☐ Other (please state: .....)

Metastases

- ☐ Unknown (MX) ☐ Absent (M0)
- ☐ Present (M1) including tumour nodules in different lobes. (please state: .....)

Pathological staging

- ☐ T ☐ N ☐ M (select highest stage from above data)
- Complete resection at all margins ☐ Yes ☐ No

Copies can be downloaded from the Royal College of Pathologists website: www.rcpath.org/resources/worddocs/dataset_lung_cancer_form_v2_02.doc

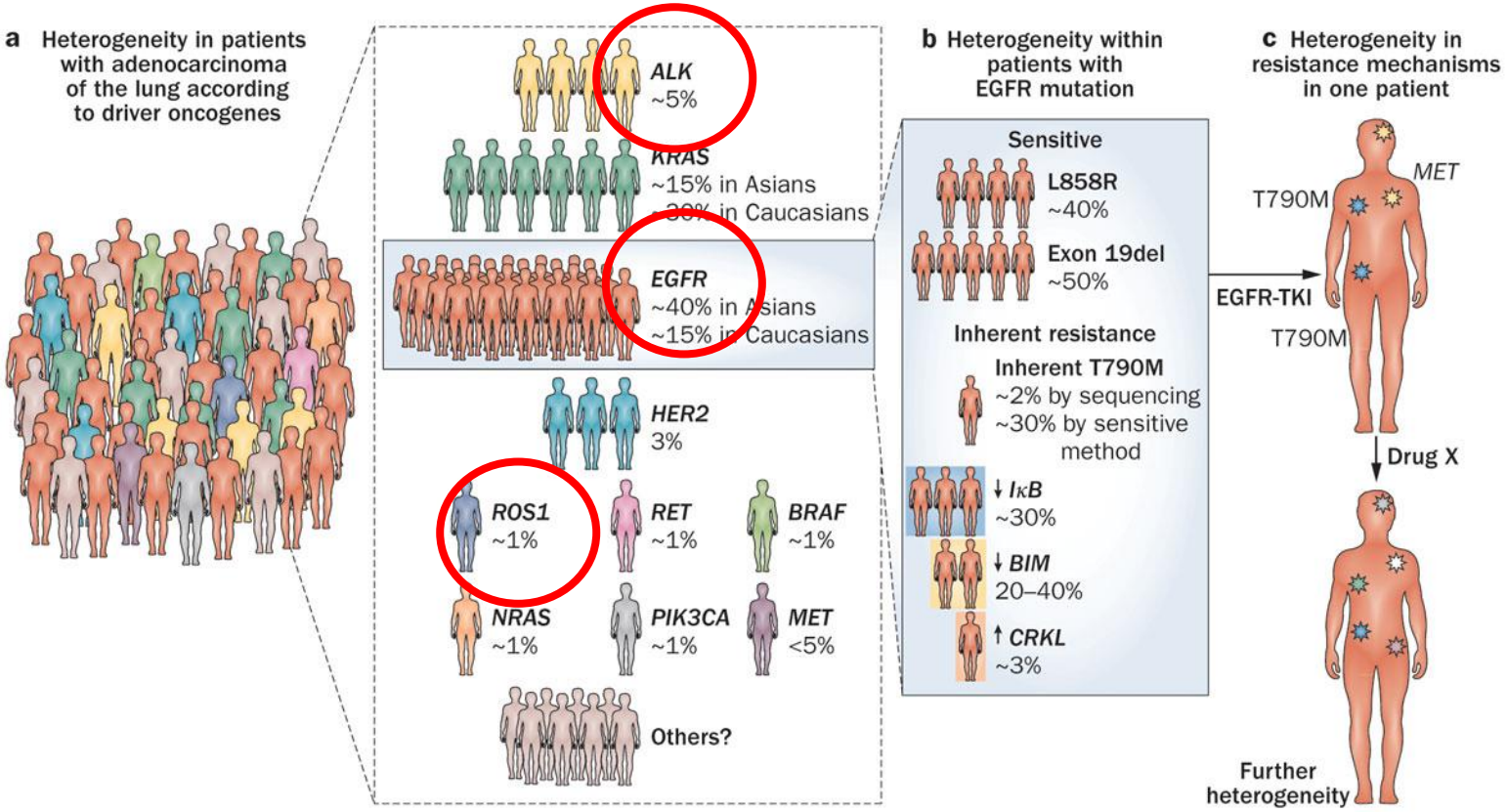
2017/8

2015/6

2014

2011

Molecular targeted therapy has proven benefits



Mitsudomi, T. *et al. Nat. Rev. Clin. Oncol.* **10**, 235–244 (2013);

Molecular Testing Guideline for Selection of Lung Cancer Patients – Revision

Yasushi Yatabe, MD, PhD

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Expertise that advances patient care through education, innovation, and advocacy.

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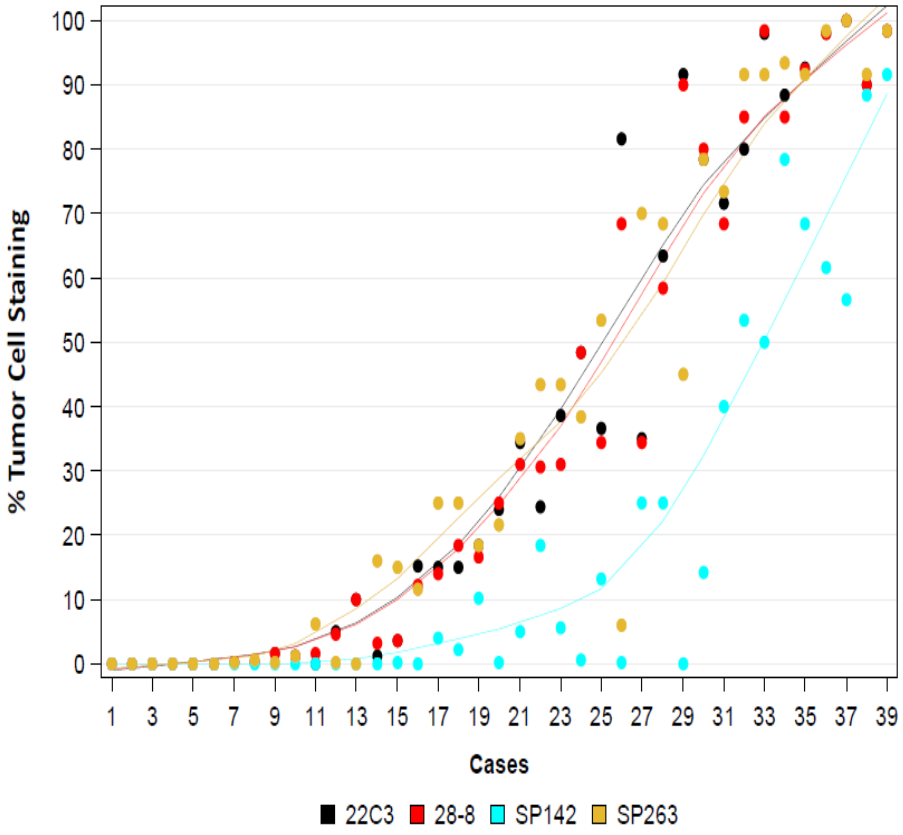
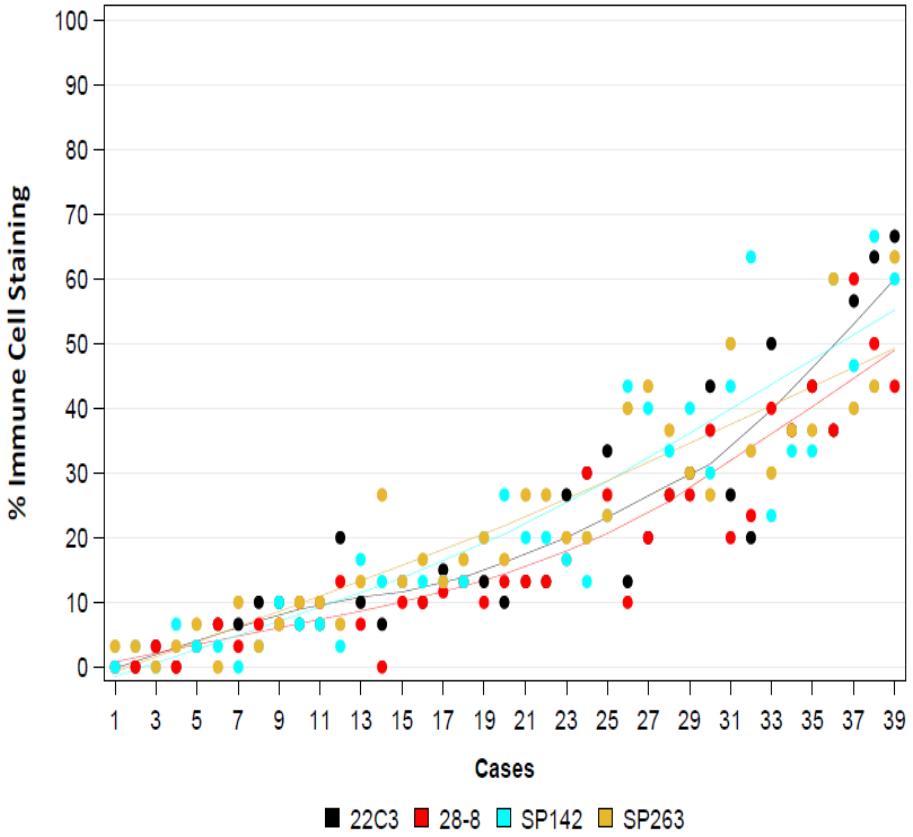
PD-1 and PD-Ll - Drugs and assays

Methodology	Kit assay	Automated Platform	Checkpoint inhibitors	APPROVAL FOR LUNG CANCER TREATEMENT (as of Nov 15) – All second line		
Kit based Assay	Dako 22C3 pharmDX	Dako Autostainer Link 48	Pembrolizumab (PD-1) "Keytruda" (MSD)	All NSCLCs (FDA and UK/EU)	COMPANION DIAGNOSTIC	Tumour cells ? 1%, ? 50%
	Dako PD-L1 IHC 28-8 pharmDX	Dako Autostainer Link 48	Nivolumab (PD-1) (BMS) "Opdivo"	Squamous NSCLC (FDA and UK/EU) All NSCLC (FDA)	COMPLEMENTARY DIAGNOSTIC	Tumour cells 1%, 5%, 10%
	SP142: Kit form TBC	Ventana: TBC	Atezolizumab (PD-L1) (Roche)	Not yet licensed	COMPANION DIAGNOSTIC	Tumour cells (1%, 5%, 50%) TILs (%age of surface area infiltrated by positive TILs) (1%, 5%, 10%)
	SP263: Kit form TBC	Ventana Ultra, XT and GX platforms	Durvalumab (PD-L1) (AZ/Medimmune)	Not yet licensed	COMPANION DIAGNOSTIC	Tumour cells ? 25%
	73-10		Avulumab (PD-1) (Merck Serono)			1% (and ? 80%)
Stand alone PD-L1 antibodies	• 28-8 (RabMab): BMS clone available from Abcam • E1L3N (RabMab): Cell Signaling • SP142 (RabMab): Spring Bioscience					

Updated from Kerr K et al. JTO 2015.

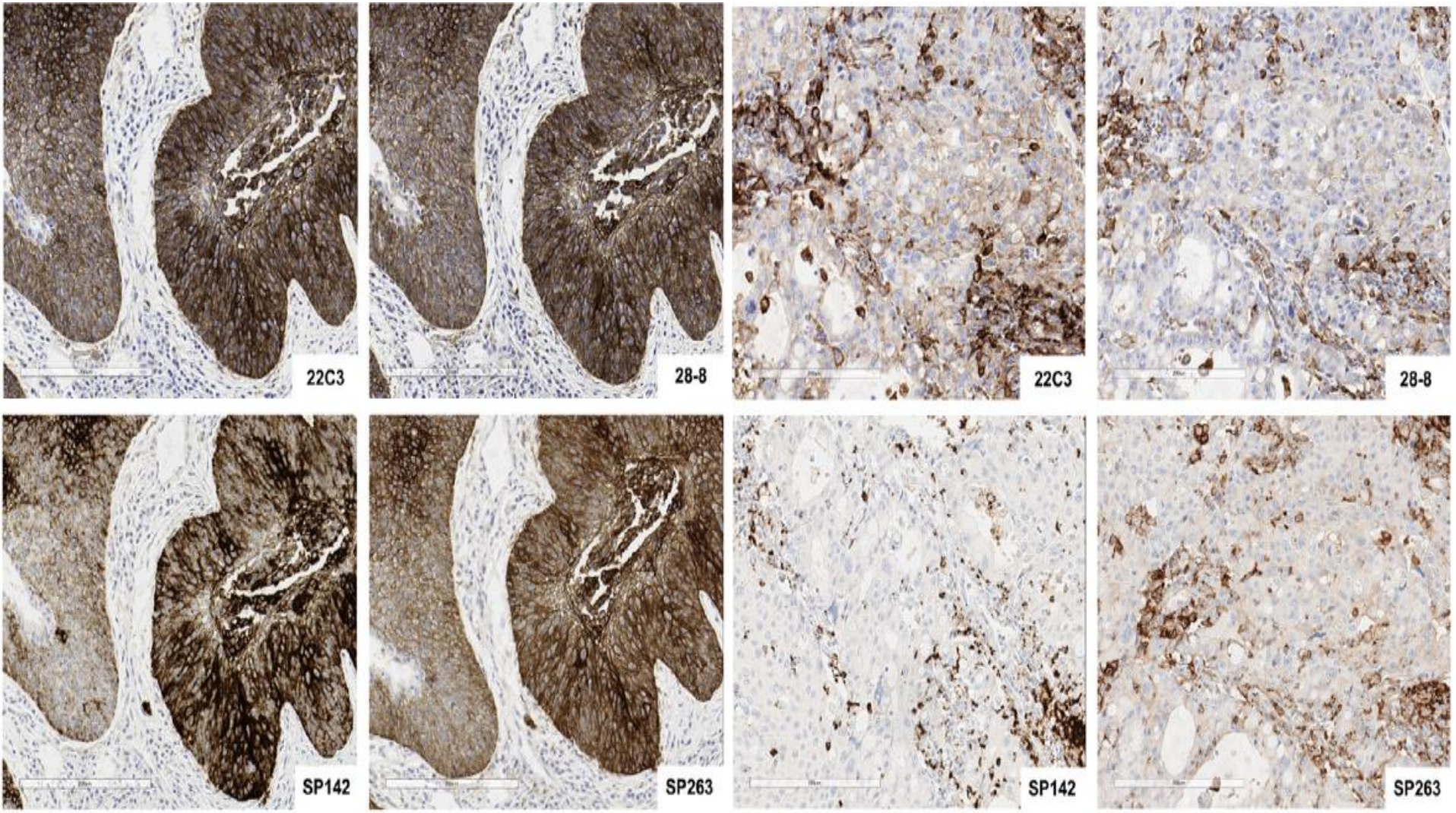
Analytical Comparison of Tumor cell/Immune Cell Staining





Each dot represents the mean score of 3 pathologists

Variability in Tumor Cells Staining between Assays



Strong staining tumor

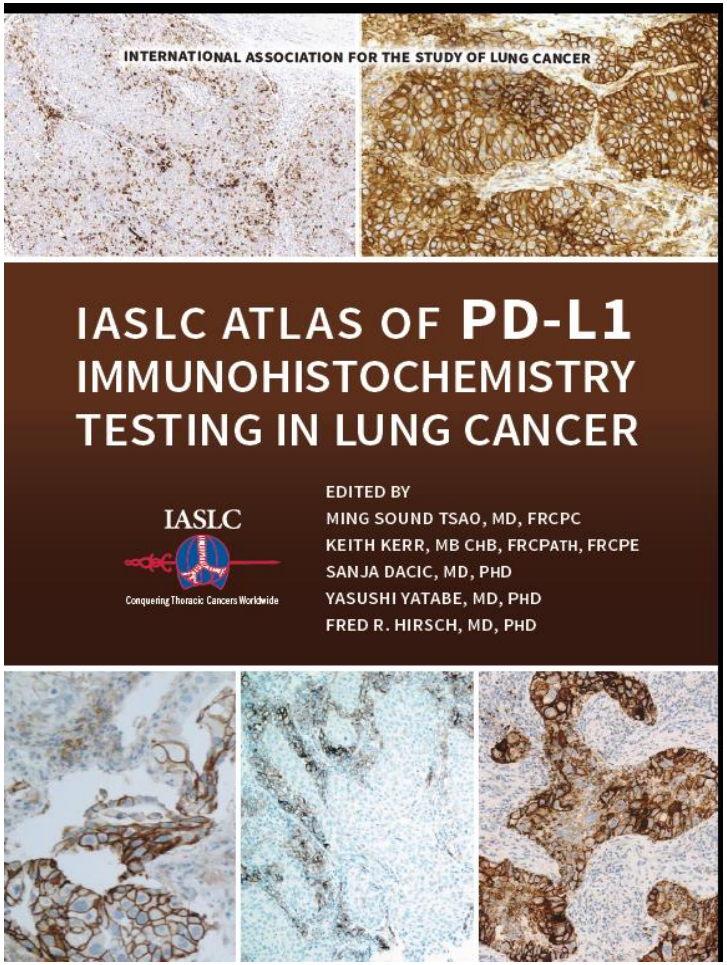
Weak staining tumor

Conclusion of Blueprint 1 Project

- Three of the four assays were closely aligned on tumor cell staining whereas the fourth showed consistently fewer tumor cells stained.
- All of the assays demonstrated immune cell staining, but with greater variability than with tumor cell staining.
- Despite similar analytical performance of PD-L1 expression for three assays, interchanging **assays (with cut-offs)** would lead to “misclassification” of PD-L1 status for some patients.
- However, using drug-specified cut-off, the use of 3 assays (22C3, 28-8 and SP263) may potentially be harmonized.

Blueprint phase 2 - Goals

- **Validation** of Blueprint phase 1 results using different types of clinical samples (resection, small biopsy, cytology cell block)
- **Comparability and heterogeneity** of PD-L1 assay results in surgical tumor resection, core needle and FNA samples prepared from same tumor.
- **Inter-observers concordance** among larger panel of pulmonary pathologists
- **Concordance** of PD-L1 scoring using standard light microscopy vs. digital images accessed by web-based system.



Available later this year

CONCLUSIONS
Reporting of lung cancer - classification

- 1967 – Histologic Typing of Lung Tumours
- 1981 – Histologic Typing of Lung Tumours
- 1999 – Histologic Typing of Tumours of the Lung and Pleura
- 2004 – Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart
- 2015 - Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart

INCREASING COMPLEXITY

New treatment options, Increasing molecular data

New sampling techniques, New investigative methods

IASLC

CONCLUSION
Major Changes in Classification that Impact Diagnosis of Surgically Resected Patients

- Main advances in lung adenocarcinoma: adopted the 2011 IASLC/ATS/ERS Lung Adenocarcinoma classification.
  - Improved prognostic significance.
  - Proposed changes to TNM staging.

- Restrict large cell carcinoma to tumors lacking clear differentiation by both IHC and morphology

- Reclassify squamous ca: keratinizing, need IHC (i.e. p40) for nonkeratinizing and basaloid

- Group NE tumors together (TC, AC, LCNEC, SCLC)

IASLC

CONCLUSION
2015 Classification: Impact on Management of Advanced Lung Cancer Patients

- Criteria/terminology for small bx/cytology
  - More accurate histologic subtyping
  - Strategic management of small tissues
- Streamlining workflow for molecular testing
- Need for local multidisciplinary team

IASLC

CONCLUSION

Reporting of lung cancer – Molecular testing

- Future classification
  - Balance of morphology and molecular data needs to be maintained
  - How to select core items. ? based on availability on treatments in the NHS

- Guidance on ensuring that tissue is handled as efficiently as possible to ensure optimal patient management.
  - Pre-examination phase
  - Examination phase
  - Post-examination phase
  - Research/clinical trials

IASLC

Acknowledgements: Bill Travis, USA Keith Kerr, UK; Lynette Sholl, USA; Yasushi Yatabe, Japan.