

# 2018KOPANA 17<sup>th</sup> Spring Seminar

Critical Review and Appraisal of the Latest AJCC Systems and/or WHO Classifications

The Sutton Place Hotel, Vancouver, Canada

17 March, 2018

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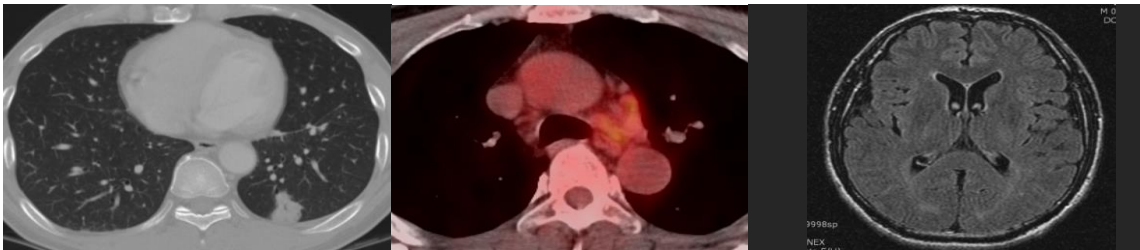
Jin-Haeng Chung, MD

Seoul National University Bundang Hospital

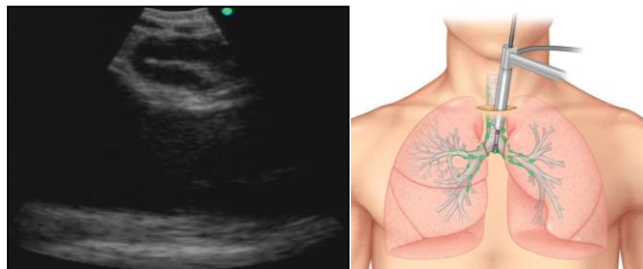
# TNM staging of the Lung Tumours Pathologist's Perspective

# Lung Cancer Staging Methods

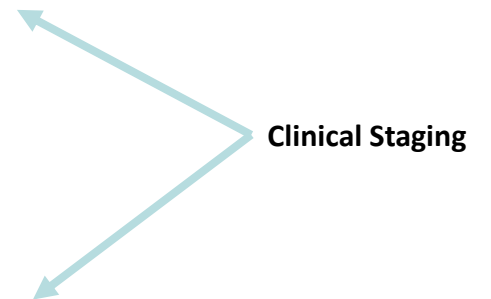
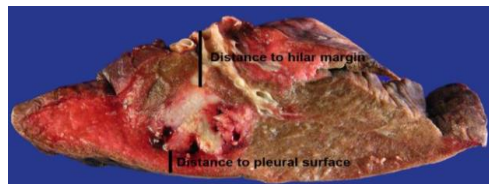
- Imaging Studies



- Preoperative Work-up



- Surgical



# Lung Cancer Stage Classification; Brief History

- First Edition; UICC 1968

T0	No tumor
T1	Segmental bronchus or segment
T2	Lobar bronchus or one lobe
T3	Main bronchus or more than one lobe
T4	Extending beyond the lung
N1	N1; enlargement of intrathoracic lymph nodes

# Evolution of TNM of Lung Cancer ; UICC

	Year	Data	Main Changes	
1st	1968		"the Livre de Poche"	1 <sup>st</sup> edition
2nd	1974	N=2,155	Mountain proposal 1973	T2 > 3cm, stage I-III
3rd	1978		Minimal change	Stage IV
4th	1987	N=3,753	UICC +AJCC Mountain proposal 1986	Stage IIIA/B ; N3 concept
5th	1997	N=5,319	Last Mountain revision	Stage IA/IB, Stage IIA/IIB
6th	2002		No change	
7th	2009	Yr. 1990-2000 N=100,869	IASLC  Quantum Leap ?	New LN map T3 > 7cm New definition; add. nodule Pleural effusion;M1a T2bN0 → IIA, T2aN1 → IIA, T4N0-1 → IIIA

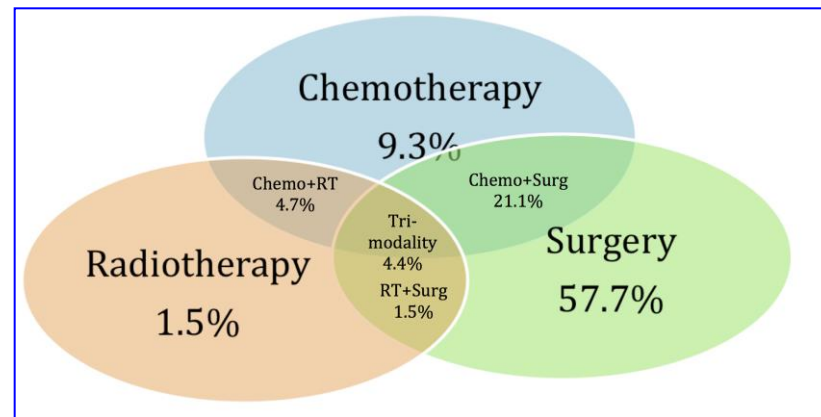
# Contents

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- ❖ Database used for the Eighth Edition Lung Cancer Stage Classification
- ❖ Changes in T, N, M descriptors in the Eighth Edition
- ❖ Stage Groupings in the Eighth Edition
- ❖ Summary

# Database for the 8th edition

Region	Number	%
Europe	46,560	49
Asia	41,705	44
North America	4,660	5
Australia	1,593	1.7
South America	190	0.3
<b>TOTAL</b>	<b>94,708</b>	<b>100</b>



Type of data	# of cases
Retrospective	73,251
Prospective	3,905
<b>TOTAL</b>	<b>77,156</b>

# Database for the Eighth Edition of TNM; Countries

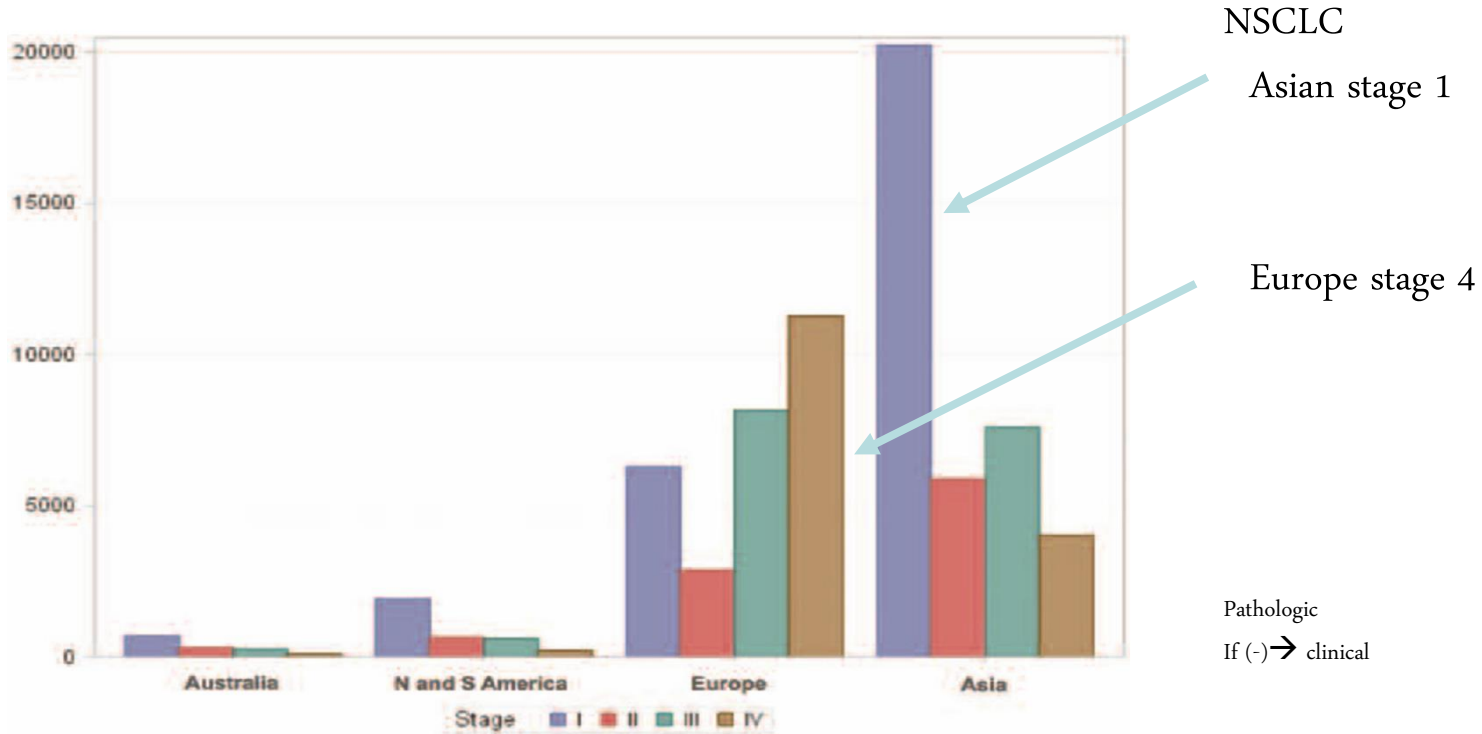
By Countries, comparing with 7<sup>th</sup> Edition, 35 sources from 16 countries

Element	Database for the seventh Edition	Database for the eighth Edition
Period of diagnosis	1990 to 2000	1999 to 2010
Total patients submitted	100,869	94,708
Geographical origin		
Europe	58,701 (58%)	46,560 (49%)
North America	21,130 (21%)	4,660 (5%)
Asia	11,622 (11.5%)	41,705 (44%)
Australia	9,416 (9.3%)	1,593 (1.7%)
South America	0	190 (0.3%)
Patients excluded	19,374 (19%)	17,552 (18%)

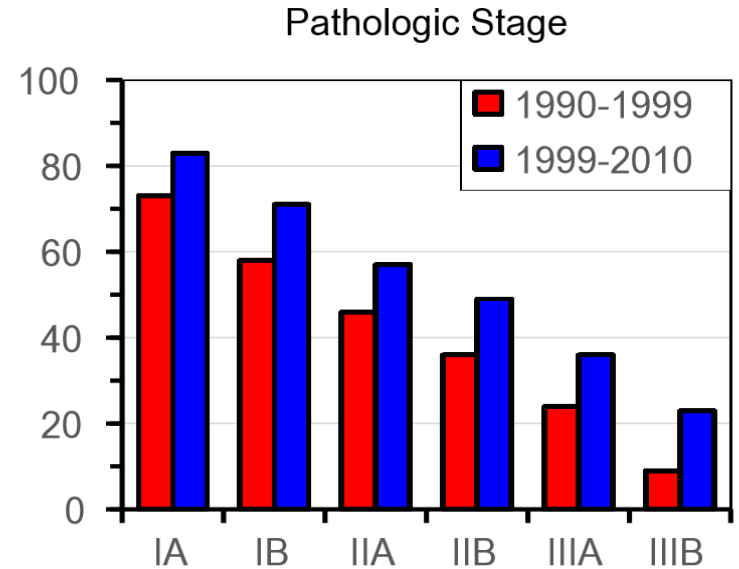
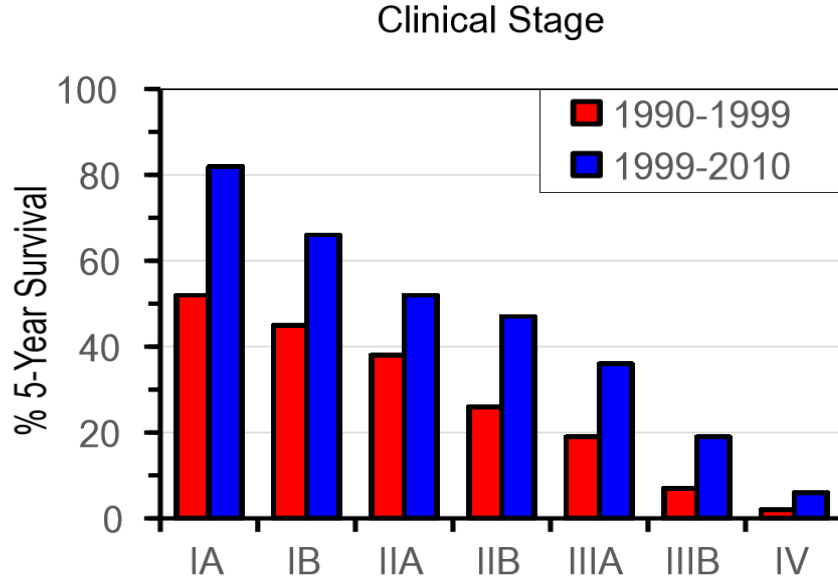
Increased Asia contribution



# Database for the Eighth Edition of TNM; Stage Distribution



# Comparison of survival in the 1990–1999 vs. 1999–2010 data sets



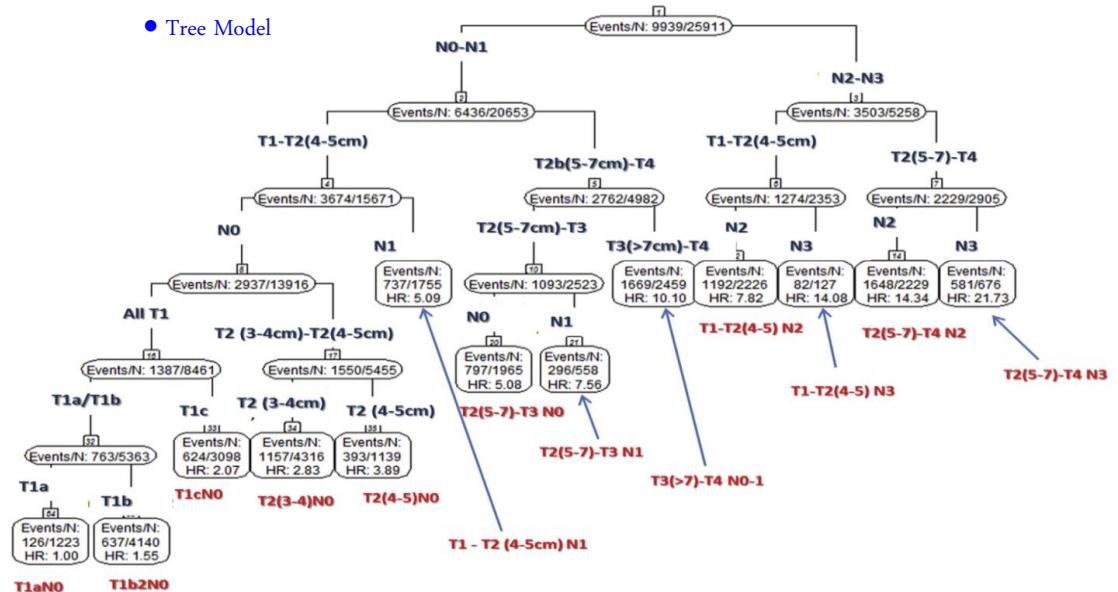
# Statistical Analysis

- Kaplan-Meier methods

Cox regression; baseline factors (age,sex, region, and cell type), proportional hazards regression

The recursive partitioning and amalgamation (RPA) analysis

- Tree Model



Database

The IASLC Lung Cancer Staging Project: The New Database to Inform the Eighth Edition of the TNM Classification of Lung Cancer



Methodology

The IASLC Lung Cancer Staging Project: Methodology and Validation Used in the Development of Proposals for Revision of the Stage Classification of NSCLC in the Forthcoming (Eighth) Edition of the TNM Classification of Lung Cancer

T descriptors

Subsolid T descriptors



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*

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

N descriptors

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*

M descriptors

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*

SCLC  
in a different article



Summary  
& Grouping

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Separate tumor nodules

The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Classification of Lung Cancer with Separate Tumor Nodules in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer

Separate primary or metastasis

The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer

Multiple GG/L, pneumonic type

The IASLC Lung Cancer Staging Project: Background Data and Proposals for the Application of TNM Staging Rules to Lung Cancer Presenting as Multiple Nodules with Ground Glass or Lepidic Features or a Pneumonic Type of Involvement in the Forthcoming Eighth Edition of the TNM Classification



Summary; multiple nodules

The IASLC Lung Cancer Staging Project: Summary of Proposals for Revisions of the Classification of Lung Cancers with Multiple Pulmonary Sites of Involvement in the Forthcoming Eighth Edition of the TNM Classification

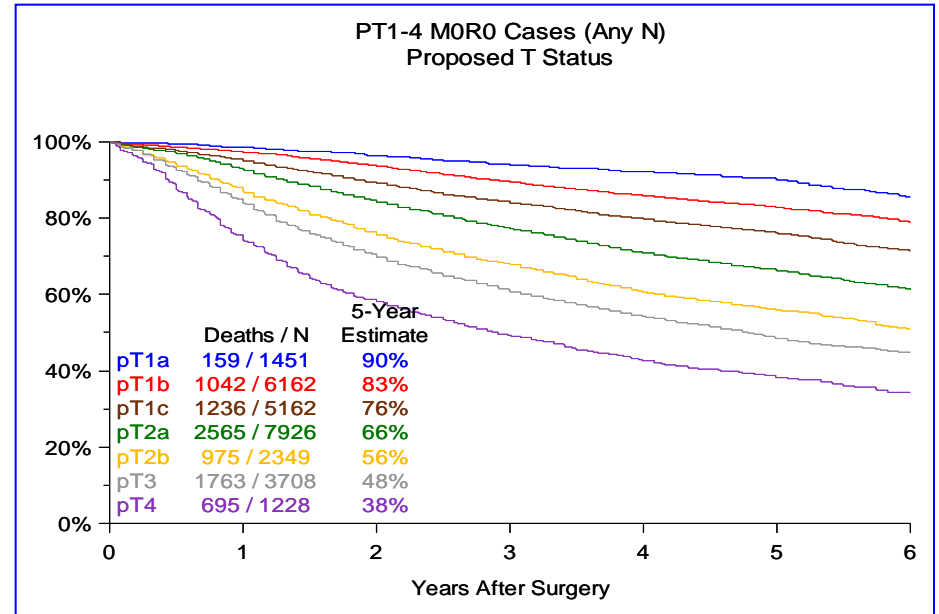
# Contents

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- ❖ Database used for the Eighth Edition Lung Cancer Stage Classification
- ❖ **Changes in T, N, M descriptors in the Eighth Edition**
- ❖ Stage Groupings in the Eighth Edition
- ❖ Summary

Descriptor	Category
</= 1 cm	T1a
>1-2 cm	T1b
>2-3 cm	T1c
>3-4 cm	T2a
>4-5 cm	T2b
>5-7 cm	T3
>7 cm	T4
Bronchus + < 2 cm	T2
Total atelectasis	T2
Diaphragm	T4

# The T component



# Changes in T stage

- Size
- Involvement of main bronchus
- Atelectasis/obstructive pneumonitis
- Visceral Pleural Invasion
- Diaphragm

More segmented, upward, more weighted

Descriptor in 7th edition		Proposed T/M
T1 <sup>a</sup> ≤ 1 cm	up	T1a
T1 <sup>a</sup> > 1-2 cm	→	T1b
T1 <sup>b</sup> > 2-3 cm	→	T1c
T2 <sup>a</sup> > 3-4 cm		T2a
T2 <sup>a</sup> > 4-5 cm	→	T2b
T2 <sup>b</sup> > 5-7 cm	→	T3
T3 structures		T3
T3 > 7 cm	→	T4



# Changes in T stage

Generally Downward

- Size
- **Involvement of main bronchus**
- Atelectasis/obstructive pneumonitis
- Visceral Pleural Invasion
- Diaphragm
- Others

	7 <sup>th</sup>		8 <sup>th</sup>
tumor in the main bronchus $\geq$ 2cm distal to the carina	T2	3-4cm	T2a
		4-5cm	<b>T2b</b>
		5-7cm	<b>T3</b>
tumor in the main bronchus < 2 cm distal to the carina	T3	3-4 cm	T2a
		4-5cm	T2b
		5-7cm	T3
Carina or trachea involve	T4		T4

**TABLE 5.** Multivariate Survival Analyses of Pathologically Staged pT2-3 Tumors Based on Their Endobronchial Location

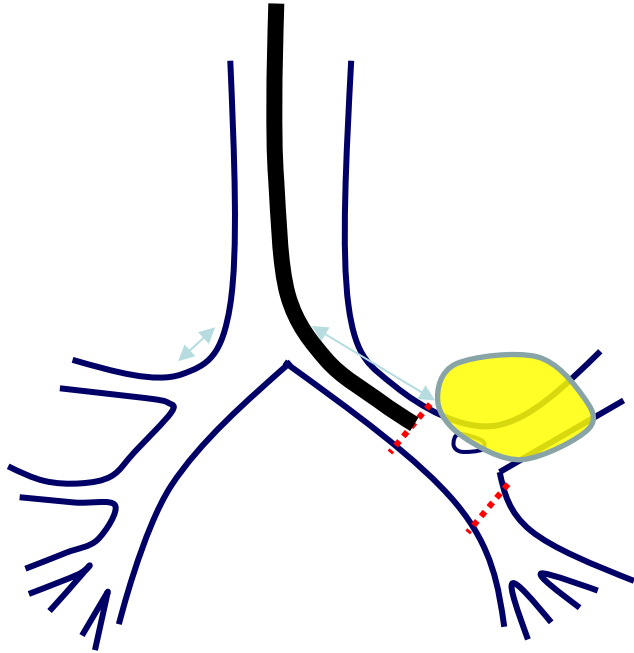
Multivariate Results Variable	n/N (%)	Survival from Surgery	
		HR (95% CI)	P Value
Other histology vs. adenocarcinoma	3725/8807 (42)	1.42 (1.26, 1.60)	<0.001
Squamous vs. other	2868/8807 (33)	0.88 (0.78, 1.00)	0.045
Age ≥ 60 vs. <60	7031/8807 (80)	1.96 (1.76, 2.20)	<0.001
Male vs. female	5807/8807 (66)	1.45 (1.33, 1.58)	<0.001
Americas vs. Asia	234/8807 (3)	1.74 (1.39, 2.18)	<0.001
Europe vs. Asia	1031/8807 (12)	1.98 (1.78, 2.21)	<0.001
Size >2 vs. ≤ 2 cm	7640/8807 (87)	1.28 (1.09, 1.50)	0.002
Size >3 vs. 2 to ≤3 cm	6230/8807 (71)	1.09 (0.97, 1.22)	0.133
Size >5 vs. 3 to ≤5 cm	1571/8807 (18)	1.33 (1.20, 1.48)	<0.001
Size >7 vs. 5 to ≤7 cm	467/8807 (5)	0.99 (0.83, 1.19)	0.953
pT2 main bronchus >2 cm from carina vs. pT2 without invasion	67/8807 (1)	1.08 (0.69, 1.69)	0.725
pT3 main bronchus <2 cm from carina vs. pT2 without invasion	24/8807 (0)	1.03 (0.51, 2.06)	0.937
pT3 other than main bronchus vs. pT2, pT3 with invasion of main bronchus	1304/8807 (15)	1.56 (1.39, 1.76)	<0.001

*p* value from Wald  $\chi^2$  test in Cox regression.

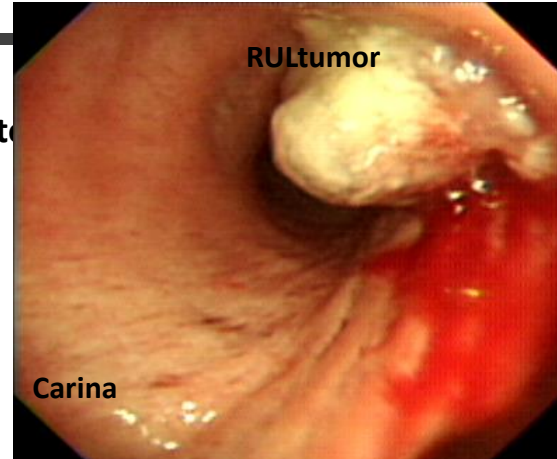
HR, hazard ratio; 95% CI, 95% confidence interval; n, number with descriptor; N, number evaluated; %, percent with descriptor.

# Main Bronchus Invasion

- Difficult Clinical-Pathologic Correlation



- Difficult to



- Difficult to



# Changes in T stage

- Size
- Involvement of main bronchus
- **Atelectasis/obstructive pneumonitis**
- Visceral Pleural Invasion
- Diaphragm
- Others

Generally Downward



	7 <sup>th</sup>		8 <sup>th</sup>
atelectasis or obstructive pneumonitis that extends to the hilar region but does <b>not involve the entire lung</b>	T2	3-4cm	T2a
		4-5cm	<b>T2b</b>
		5-7cm	<b>T3</b>
associated atelectasis or obstructive pneumonitis of <b>the entire lung</b>	T3	3-4 cm	<b>T2a</b>
		4-5cm	<b>T2b</b>
		5-7cm	T3

## Changes in T stage

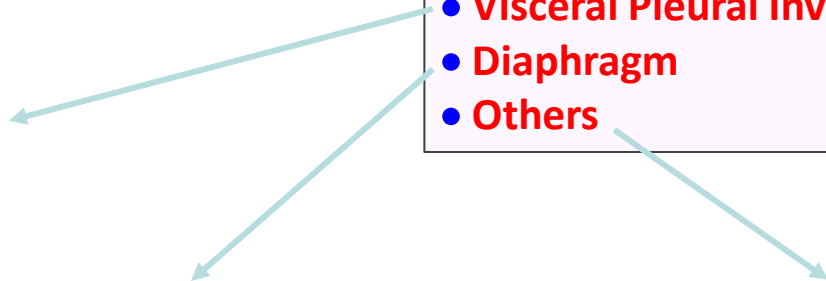
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- Size
- Involvement of main bronchus
- Atelectasis/obstructive pneumonitis
- **Visceral Pleural Invasion**
- **Diaphragm**
- **Others**

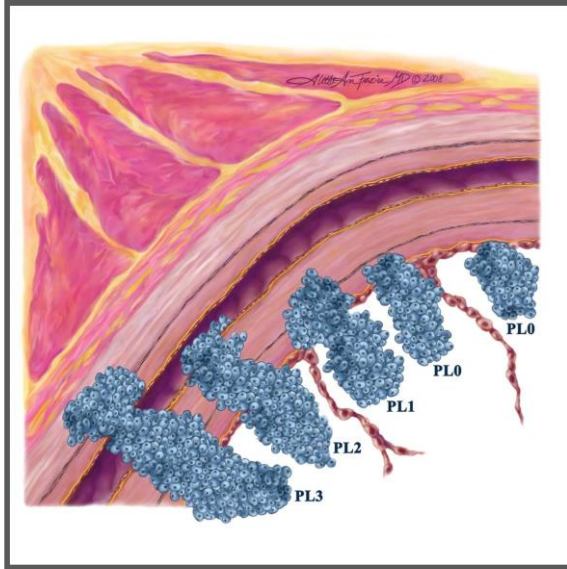
No change ; T2

T3 → T4

Elimination of mediastinal pleura



# Visceral pleura invasion




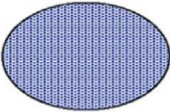

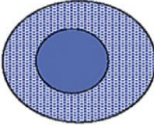
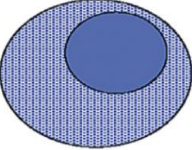
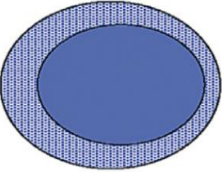
To clarify visceral pleura involvement, the use of **elastic stains** is recommended.

PL0:	----
PL1 / PL2:	T2
PL3:	T3

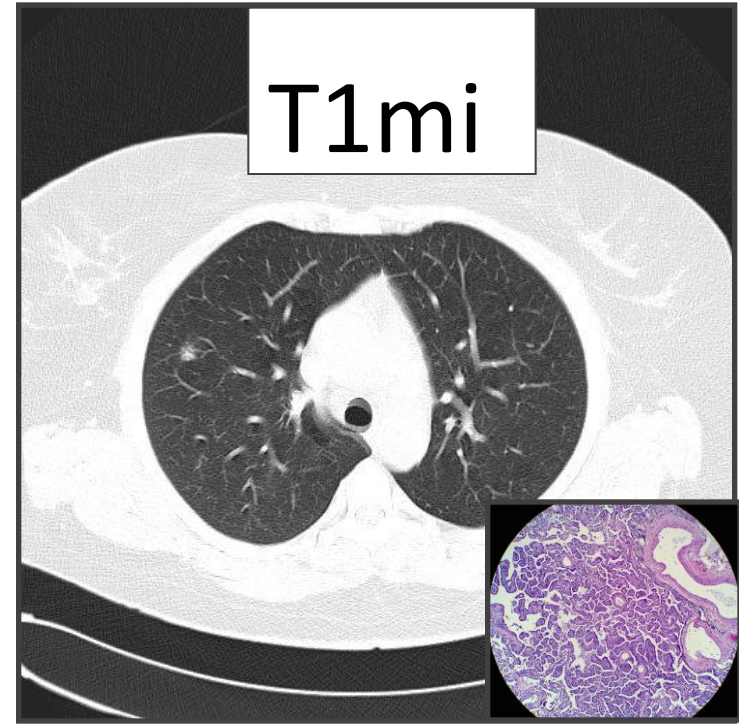
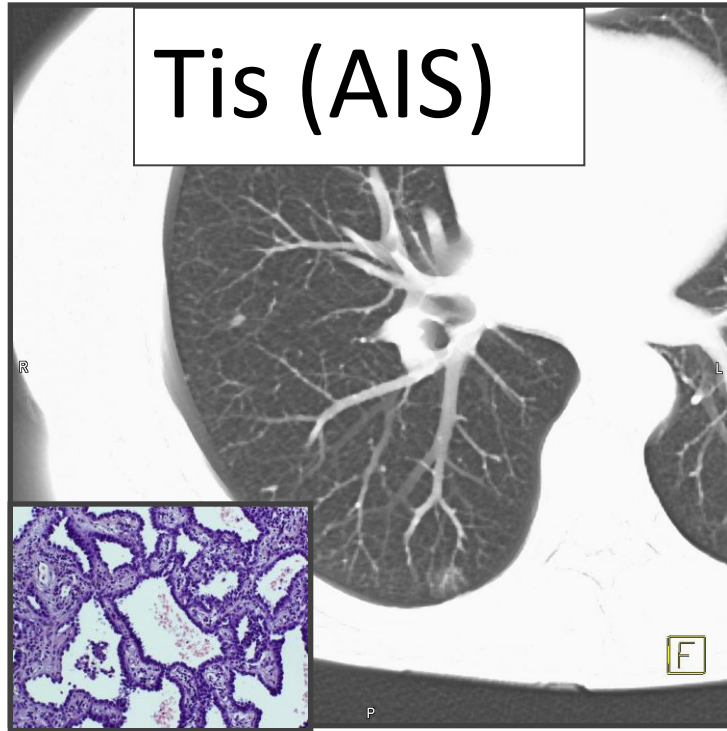
20% of presumed stage IA cancers can be understaged if elastic stains are not used

Taube JM et al.  
Am J Surg Pathol 2007; 31: 953

# Changes in T stage; subsolid nodules

cT*	CT image on HRCT						
	Solid part	0 cm	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm‡‡	≤3.0 cm‡‡	0.6-3.0 cm‡‡	1.1-3.0 cm‡‡	2.1-3.0 cm‡‡
	Pathologic Differential Diagnosis	AAH‡, AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
	<b>Clinical Stage*</b>		cTis‡‡	cT1mi‡‡	cT1a	cT1b	cT1c
pT	Invasive part	0 cm	0 cm	≤0.5 cm‡‡	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including lepidic growth part	Usually ≤0.5 cm‡	≤3.0 cm‡‡	≤3.0 cm‡‡	0.6-3.0 cm‡‡	1.1-3.0 cm‡‡	2.1-3.0 cm‡‡
	Pathology	AAH	AIS	MIA	Lepidic predominant AD or Invasive AD with lepidic component	Invasive AD with a lepidic component or lepidic predominant AD	Invasive AD with lepidic component
	<b>Pathologic Stage</b>		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c

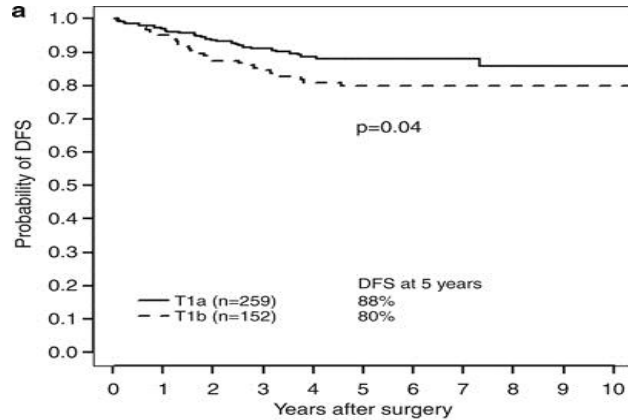
# Minimally invasive lesion



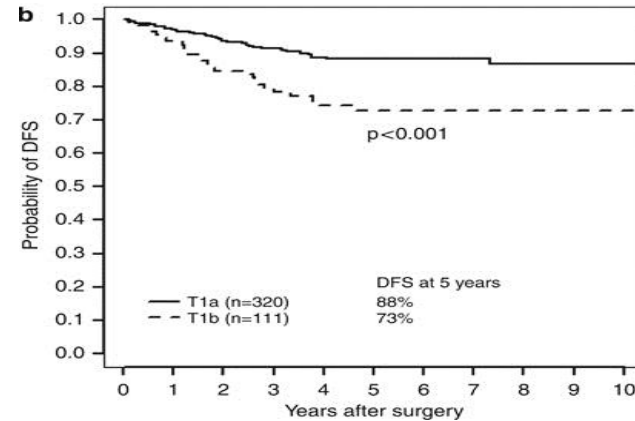


# Measuring the invasive area.....

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



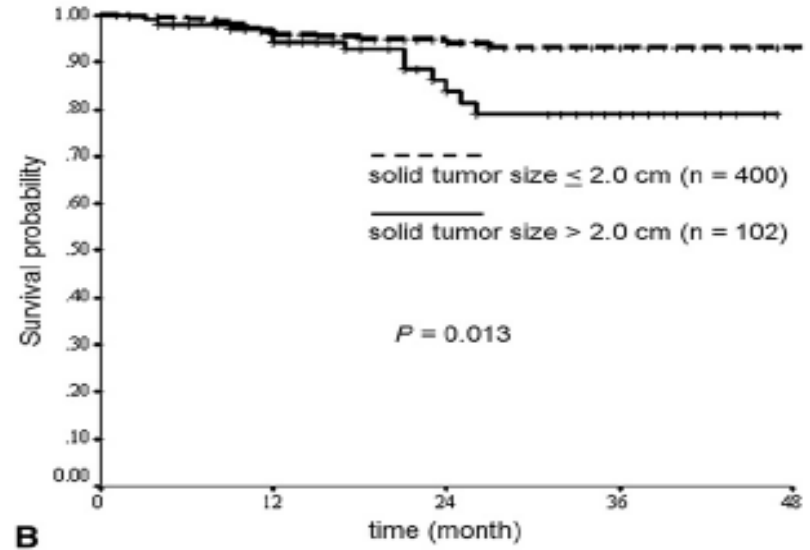
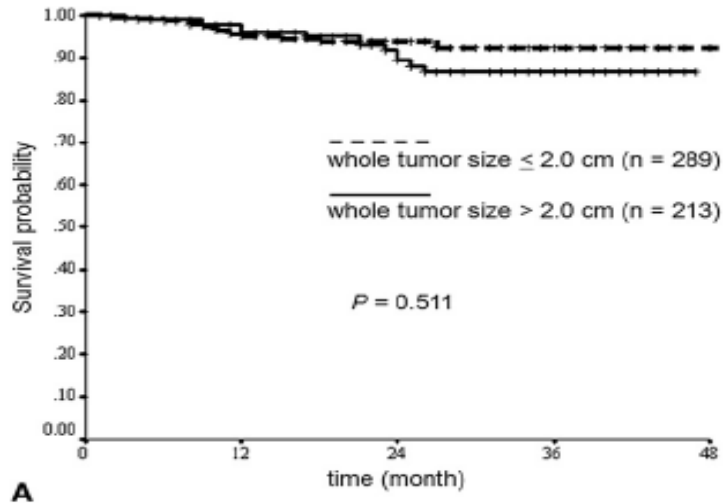
(a) T1a and T1b defined according to gross tumor size ( $P=0.04$ ).



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

# Prognostic Significance of Solid vs Whole Tumor Size by HRCT

## 502 Stage IA Adenocarcinoma



–DFS by HRCT A: 3 yr DFS 92.5%  $2 \leq$ cm and 86.7%  $>$ 2cm

B: 3 yr DFS 93.2%  $2 \leq$ cm and 78.9%  $>$ 2cm

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

# Size measurement in part-solid non-mucinous ADC

Clinical staging: solid part

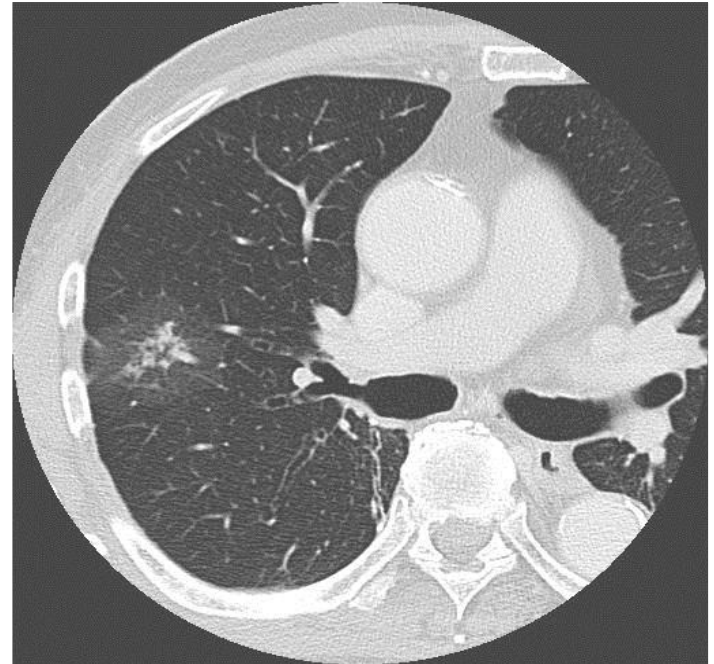
Pathologic staging: invasive part

Also measure total tumor size

**For all cell types**

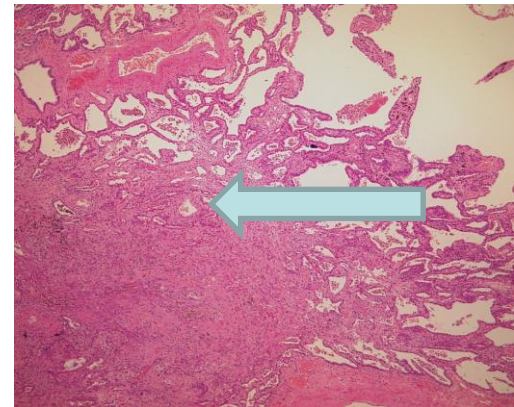
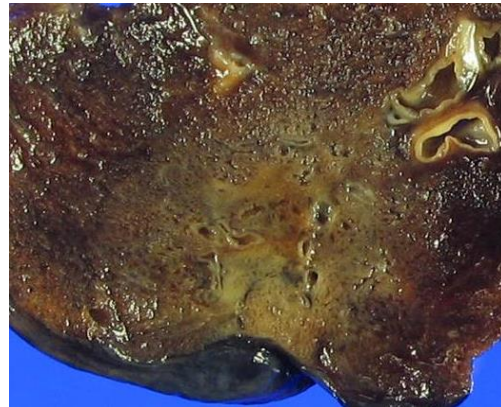
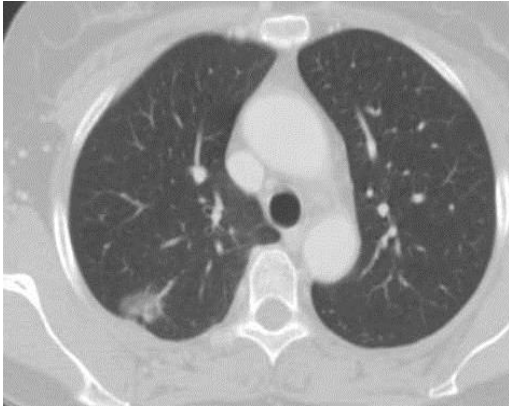
After induction (yp): size = % of viable cells x total size

Measure size with **LUNG WINDOW**

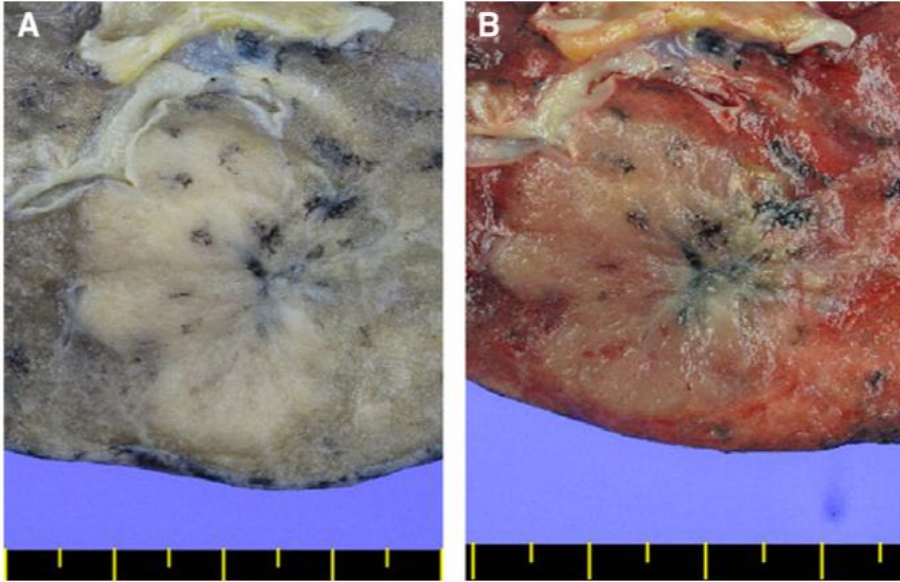


# Subsolid nodules with small solid component

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



# Size change after Formalin Fixation



- Size difference after fixation
- ✓ Stage shift after fixation : 3.17%
  - ✓ The risk of a > 10% change in size was increased in tumours with a lepidic pattern (subsolid nodule)
  - ✓ Longer ischemic time: tumor shrinkage

# Cancers with multiple lesions

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Multiple primary tumours:

**One TNM for each tumour**

Separate tumour nodules:

**T3, T4, M1a**

Multiple adenos with GGO/lepidic features:

**Highest T (#/m) N M**

Pneumonic type adenocarcinoma:

**T3, T4, M1a**

Detterbeck F et al.

J Thorac Oncol

2016; 11 (5):

639-650

651-665

666-680

681-692

# Multiple Nodules

	Tumor Site 1	Tumor Site 2	Tumor Site 1	Tumor Site 2	TNM Classification
<b>A</b>					
Second Primary Cancer					Separate T, N and M for each tumor
<b>B</b>					
Separate Tumor Nodules					T3 if in same lobe T4 if same side (other lobe) M1a if different lobe, Single N and M for all
<b>C</b>					
Multifocal GG/L Nodules					T according to highest T lesion, single N and M for all lesions collectively, (#/m) indicates multiplicity
<b>D</b>					
Diffuse Pneumonic-Type					T3 if in same lobe T4 if same side (other lobe) M1a if different lobe, Single N and M for all

# Implications for clinical practice: T

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Every cm counts; careful follow-up

Accurate tumour size measurement, important BUT...

Rules to measure tumour size

Rules to measure part-solid non-mucinous ADC

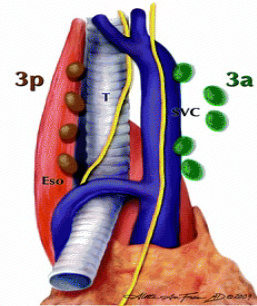
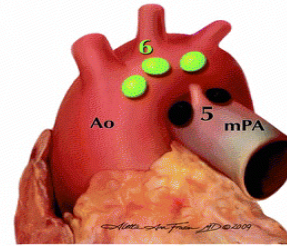
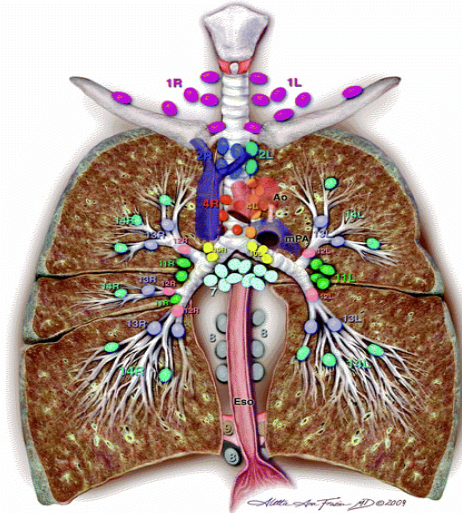
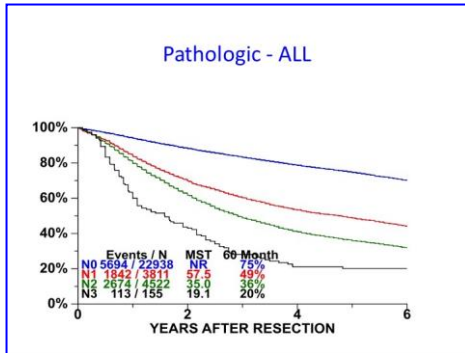
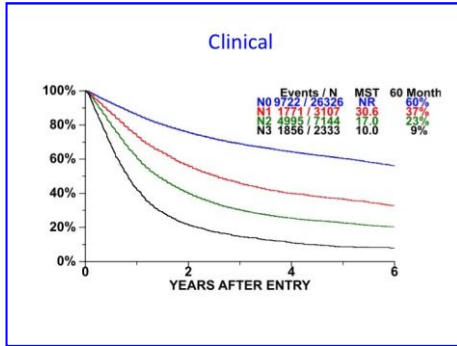
Elastic stains for visceral pleura invasion

Prognosis refinement

Better stratification for clinical trials



# The N component



**Supraclavicular zone**  
 1 Low cervical, supraclavicular, and sternal notch nodes

**SUPERIOR MEDIASTINAL NODES**  
*Upper zone*  
 2R Upper Paratracheal (right)  
 2L Upper Paratracheal (left)  
 3a Prevascular  
 3p Retrotracheal  
 4R Lower Paratracheal (right)  
 4L Lower Paratracheal (left)

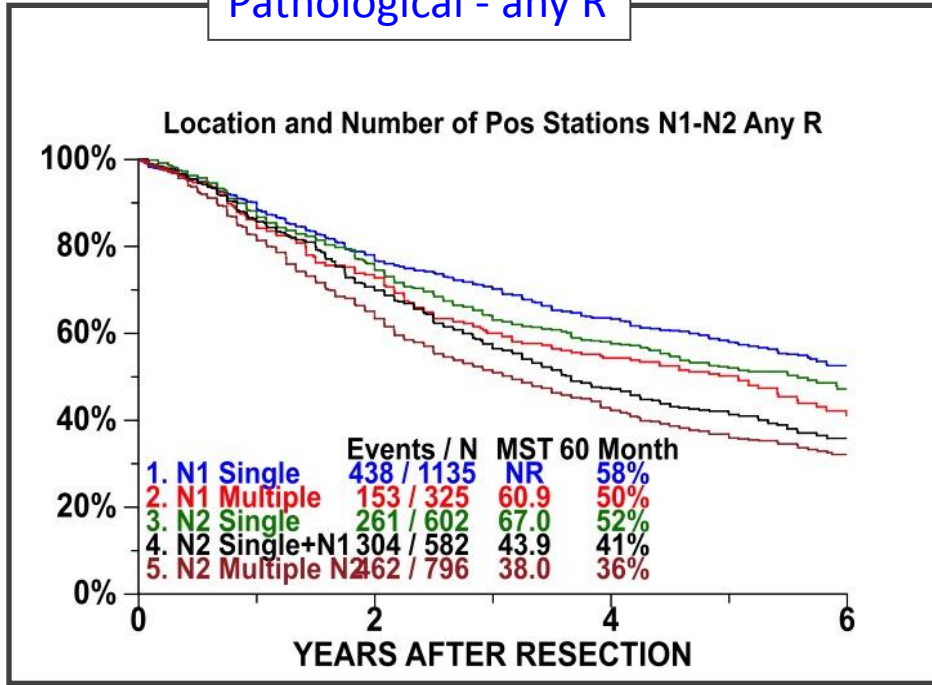
**AORTIC NODES**  
*AP zone*  
 5 Subaortic  
 6 Para-aortic (ascending aorta or phrenic)

**INFERIOR MEDIASTINAL NODES**  
*Subcarinal zone*  
 7 Subcarinal  
*Lower zone*  
 8 Paraesophageal (below carina)  
 9 Pulmonary ligament

**N1 NODES**  
*Hilar/Interlobar zone*  
 10 Hilar  
 11 Interlobar  
*Peripheral zone*  
 12 Lobar  
 13 Segmental  
 14 Subsegmental

# Changes in N stage; No changes but recommendations

Pathological - any R



## Quantification of nodal disease

N1 Single = N1a

N1 Multiple = N1b

N2 Single N2 ("skip mets") = N2a1

N2 Single N2 + N1 = N2a2

N2 Multiple N2 = N2b

# Limitations of Database for N staging; Pathologic

**TABLE 2.** Origin of the Data for Pathological Nodal (pN) Categories

Data Source	Pathological N				Total	Follow-up (mo)		
	N0	N1	N2	N3		Min	Median	Max
Belgrade	10	54	24	0	88	6	42	70
EDC	1002	218	189	21	1430	<1	23	125
Japan 1999	7717	1296	1855	100	10,968	1	66	83
Japan 2002	2994	386	401	11	3792	1	73	90
Japan 2004	6662	726	1296	19	8703	1	62	77
Korea	933	270	222	1	1426	60	87	139
MDACC	1233	260	212	0	1705	<1	42	120
MSKCC	451	74	60	1	586	1	79	110
Norway	1193	369	145	1	1708	8	55	96
Sydney	743	158	118	1	1020	<1	69	139
Total	22,938	3811	4522	155	31,426	<1	64	139

EDC, electronic data capture; MDACC, M. D. Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center.

- [Japan with Naruke map](#)

## Changes in N stage; No changes but recommendations

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### Quantification of nodal disease, recommended:

**N**

pN1a: involvement of single pN1 nodal station

pN1b: involvement of multiple pN1 nodal stations

pN2a1: involvement of single pN2 nodal station without pN1 (skip pN2)

pN2a2: involvement of single pN2 nodal station with pN1

pN2b: involvement of multiple pN2 nodal stations

pN3: as it is

# Implications for clinical practice: N

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The amount of nodal disease has prognostic impact

Important to quantify nodal disease both at clinical and pathologic staging

Upfront resection for single station cN2 will be discussed

Prognosis refinement

Better stratification

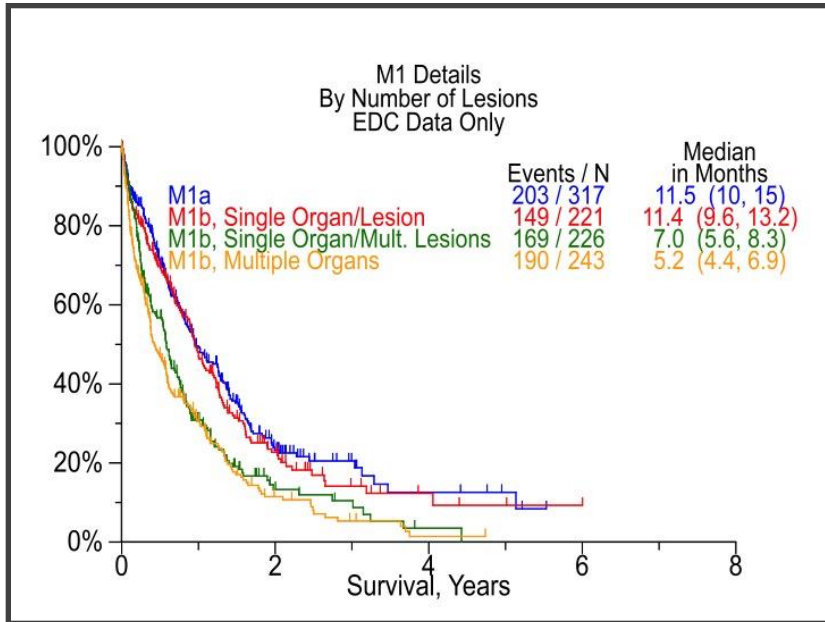
# Changes in M stage

**TABLE 3.** Prognostic Impact of Single and Multiple Metastatic Lesions in a Single Organ versus Multiple Metastatic Sites

Proposed Category	Variable	Overall Survival		
		n/N (%)	HR (95% CI)	P Value
M1a	M1a	324/1025 (32)	Reference level	
M1b	M1b, single organ/lesion	225/1025 (22)	1.11 (0.91, 1.36)	0.308
M1c	M1b, single organ/multiple lesions	229/1025 (22)	1.63 (1.34, 1.99)	<0.001
	M1b, multiple organs	247/1025 (24)	1.85 (1.52, 2.24)	<0.001

*J Thorac Oncol.* 2015;10: 1515–1522

# The M component: M1b



M1a: no change

M1b: single extrathoracic M1

M1c: multiple extrathoracic M1s in one organ

M1c: multiple extrathoracic M1s in several organs

# Implications for clinical practice: M

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Number of M1s is more important than their location

M1b: baseline definition of oligometastases

Prognosis refinement

Better stratification



# Contents

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- ❖ Database used for the Eighth Edition Lung Cancer Stage Classification
- ❖ Changes in T, N, M descriptors in the Eighth Edition
- ❖ **Stage Groupings in the Eighth Edition**
- ❖ Summary

# The Eighth Edition; Grouping

7th

T/M	Subgroup	N0	N1	N2	N3
T1	T1a <2	Ia	Ila	IIla	IIlb
	T1b >3	Ia	Ila	IIla	IIlb
T2	T2a >3-5	Ib	Ila	IIla	IIlb
	T2b >5-7	Ila	IIb	IIla	IIlb
T3	T3 >7	IIb	IIla	IIla	IIlb
	T3 <i>Inv</i>	IIb	IIla	IIla	IIlb
	T3 <i>Satell</i>	IIb	IIla	IIla	IIlb
T4	T4 <i>Inv</i>	IIla	IIla	IIlb	IIlb
	T4 <i>Ipsi Nod</i>	IIla	IIla	IIlb	IIlb
M1	M1a <i>Contra Nod</i>	IV	IV	IV	IV
	M1a <i>Pl Dissem</i>	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

**TABLE 5 ] Lung Cancer Stage Grouping (Eighth Edition)**

T/M	Label	N0	N1	N2	N3
T1	T1a $\leq 1$	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a <i>Cent, Yisc Pl</i>	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 <i>Inv</i>	IIB	IIIA	IIIB	IIIC
	T3 <i>Satell</i>	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 <i>Inv</i>	IIIA	IIIA	IIIB	IIIC
	T4 <i>Ipsi Nod</i>	IIIA	IIIA	IIIB	IIIC
M1	M1a <i>Contr Nod</i>	IVA	IVA	IVA	IVA
	M1a <i>Pl Dissem</i>	IVA	IVA	IVA	IVA
	M1b <i>Single</i>	IVA	IVA	IVA	IVA
	M1c <i>Multi</i>	IVB	IVB	IVB	IVB

# Changes Summary

## More complex !!!!

- ✓ More emphasis in T stage by Size
- ✓ Main bronchus invasion & atelectasis; down grade
- ✓ Diaphragm invasion; T4
- ✓ Subsolid Tumor
- ✓ N staging; further suggestion
- ✓ M1b; single distant mets, M1c; multiple distant mets



- ✓ Stage group shift ; mainly due to tumor size
- ✓ New stage groups; IA1, 1A2, IA3, IIIC, IVB

## UICC second Edition

Second ed. (1974)	
Occult ca.	TXN0M0
Stage I	T1N0M0 T1N1M0 T2N0M0
Stage II	T2N1M0
Stage III	T3anyN/M N2anyT/M M1anyT/N

# Changes Summary

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More relevance to tumour size

Reclassification of some T descriptors

Validation of present N descriptors

Amount of nodal disease is prognostic

Three metastatic groups

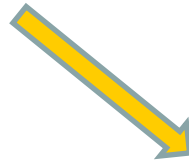
More stages for better prognostic stratification

# Limitations & Future Direction

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## Limitations

- Geographic distribution
- Surgical cases dominant
- Less information in clinical stage (N)



## Future

- More data contribution
- Non surgical cases
- Information in clinical stage (N)  
especially endoscopic staging

# Thank You

