The Itracacies of Staging Patients with Suspected Lung Cancer

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Staging Lung Cancer is Critical

- Staging of cancer…
  - Dictates Treatment
  - Determines prognosis
  - Provides a common language for physicians to communicate while discussing patient care
  - Assures that patients and treatments are comparable across clinical trials

Physiologic stage

Anatomic stage

Anatomic	Resectable	Unresectable
I	Surgery	*Biopsy ➢SBRT ➢RFA ➢Other (Cryo, wedge/brachy)
II	Surgery ➢Adjuvant chemotherapy	
	PS 0~2	PS ~2-4
III	*Biopsy Definitive chemo-XRT	*Biopsy Palliative RT Chemo if feasible
IV	*Biopsy Palliative chemo CNS/skeletal XRT	*Biopsy Palliative… ➢"Chemotherapy" ➢Radiation

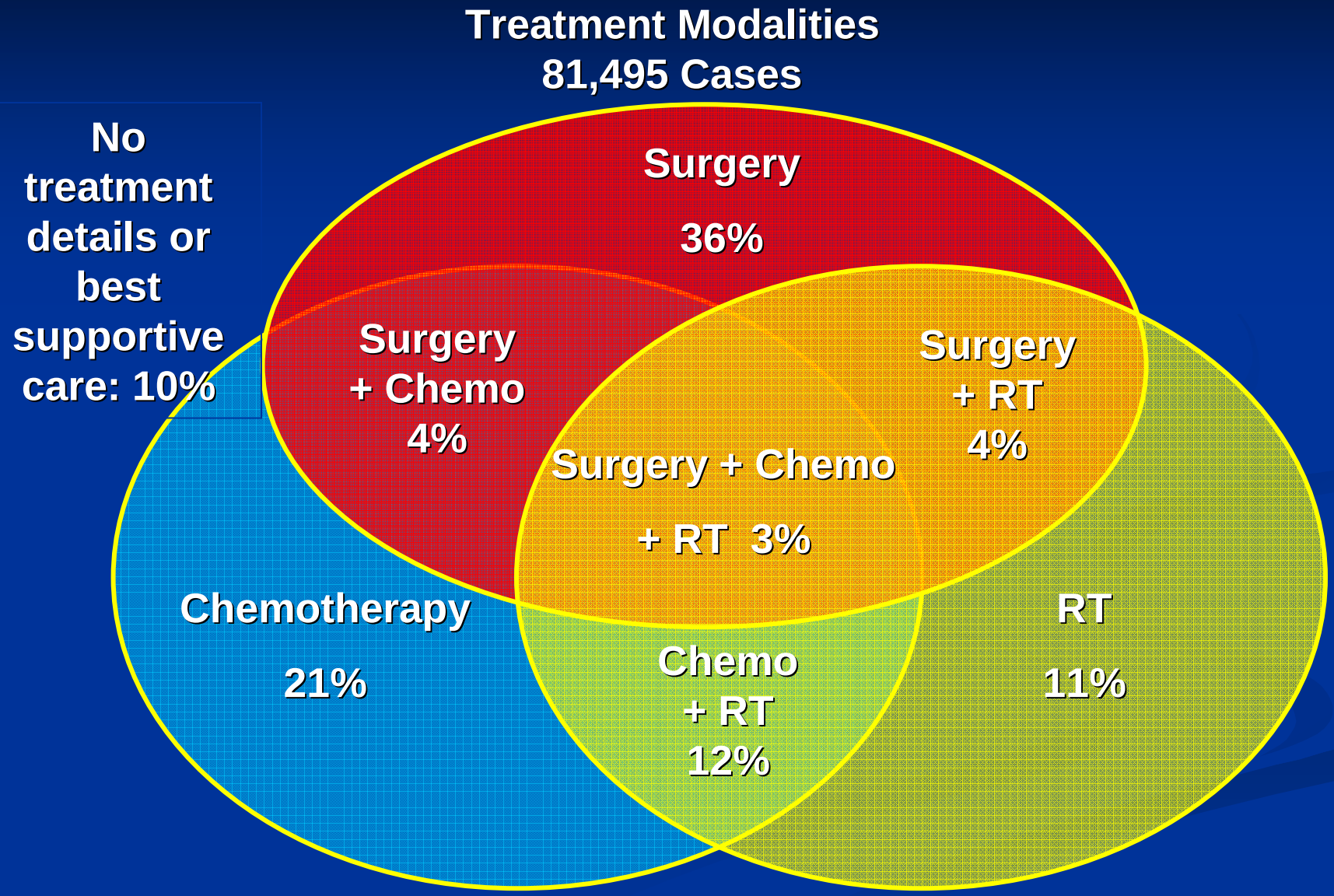
Curative intent

***Always biopsy the most "stage informative" lesion**

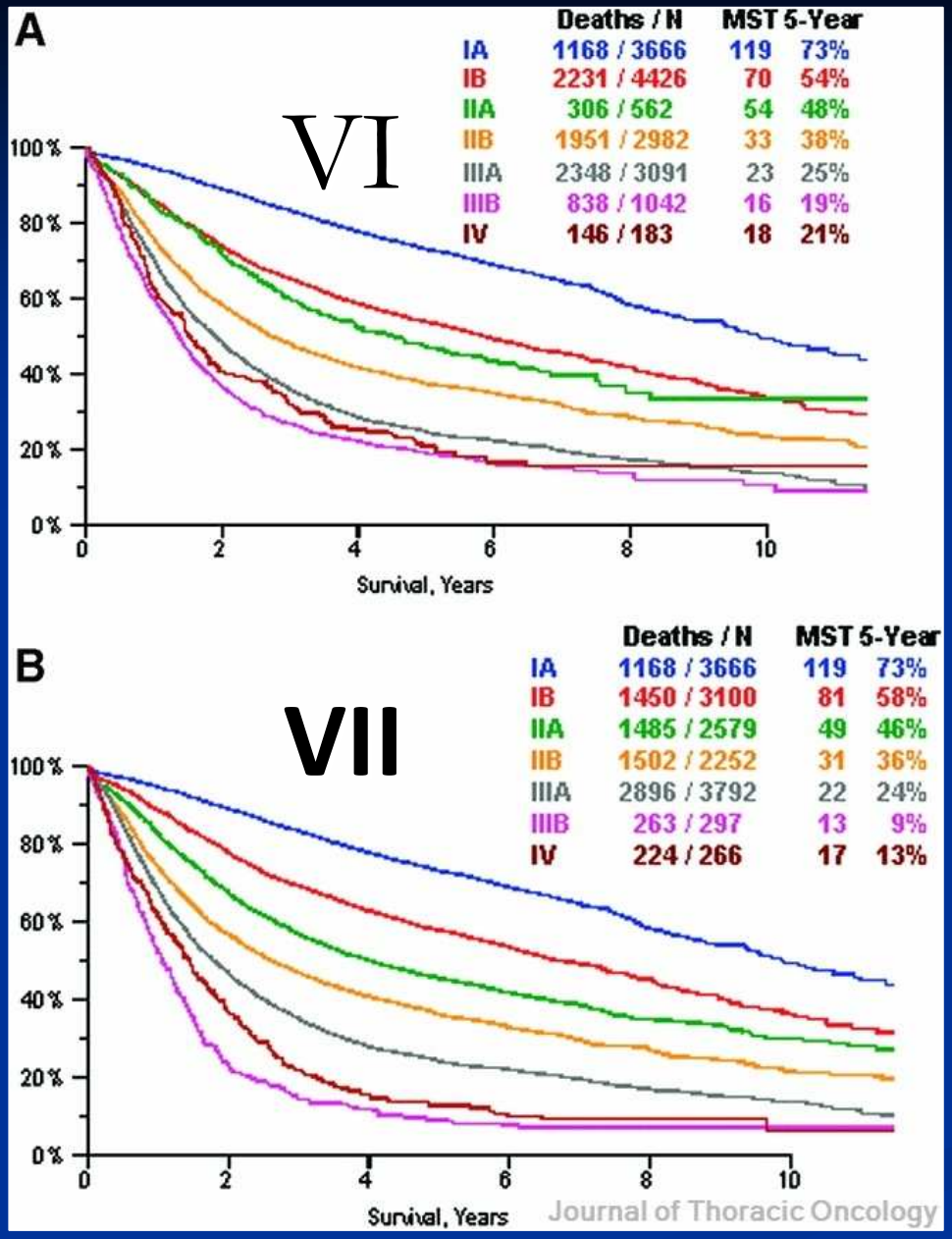
Why a *new* staging system?

- The sixth *TNM Classification of Malignant Tumors,* introduced in 2002, made no changes to the previous edition with regards to lung cancer.
- The 5th (1997) TNM system for lung cancer was based on a small database of 5319 cases accumulated since ~ 1975 (almost entirely surgical)
- Since 1975 there had been many refinements to the staging techniques.
  - **Principally the routine use of computed tomography and the addition of PET**

The IASLC Lung Cancer Database



Goldstraw P, Crowley JJ. J Thorac Oncol 2006; 1: 281-286.



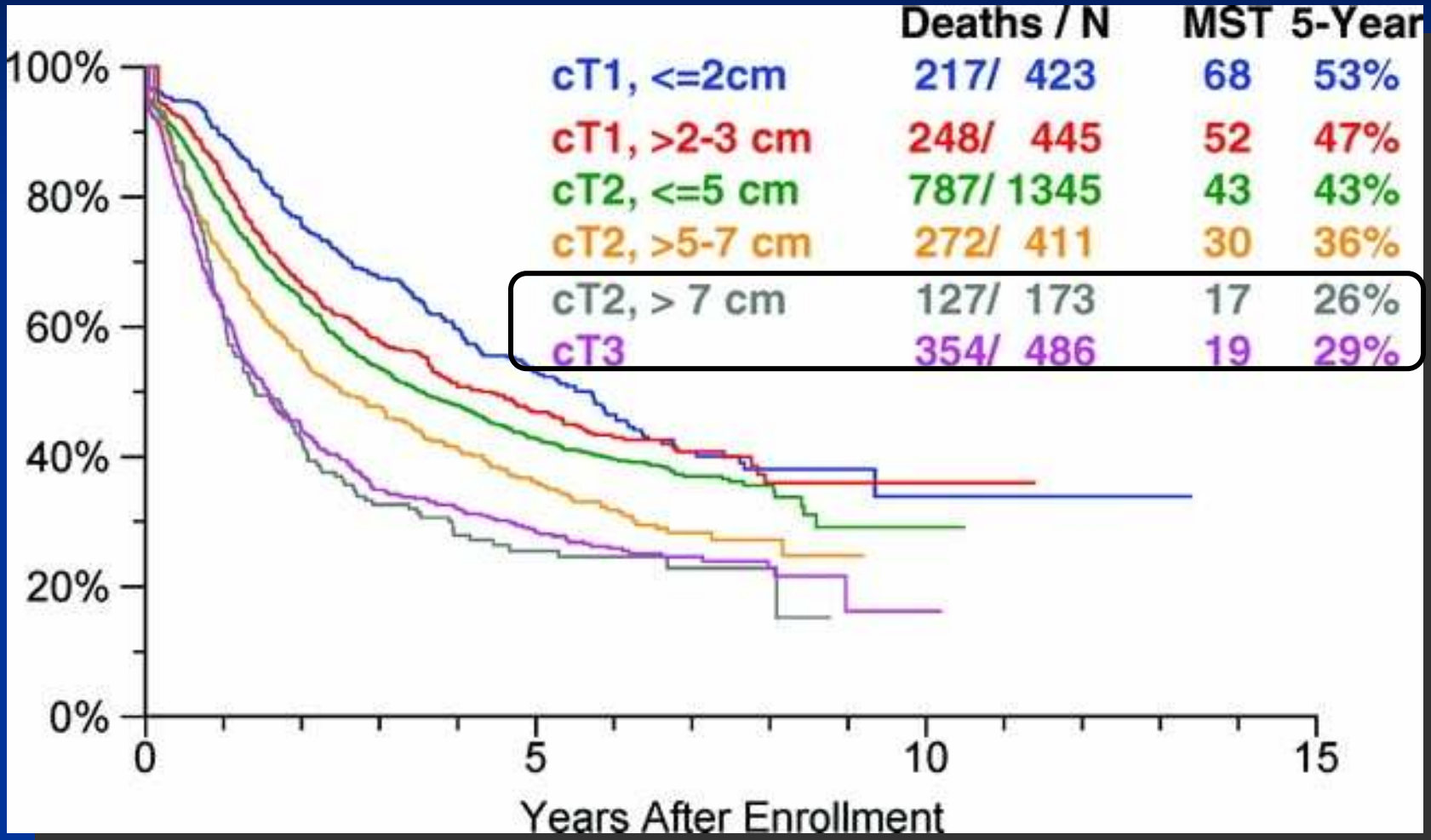
The IASLC Lung Cancer Staging Project:
JTO 2009; 2(8):706-714.

T descriptors: What changed?

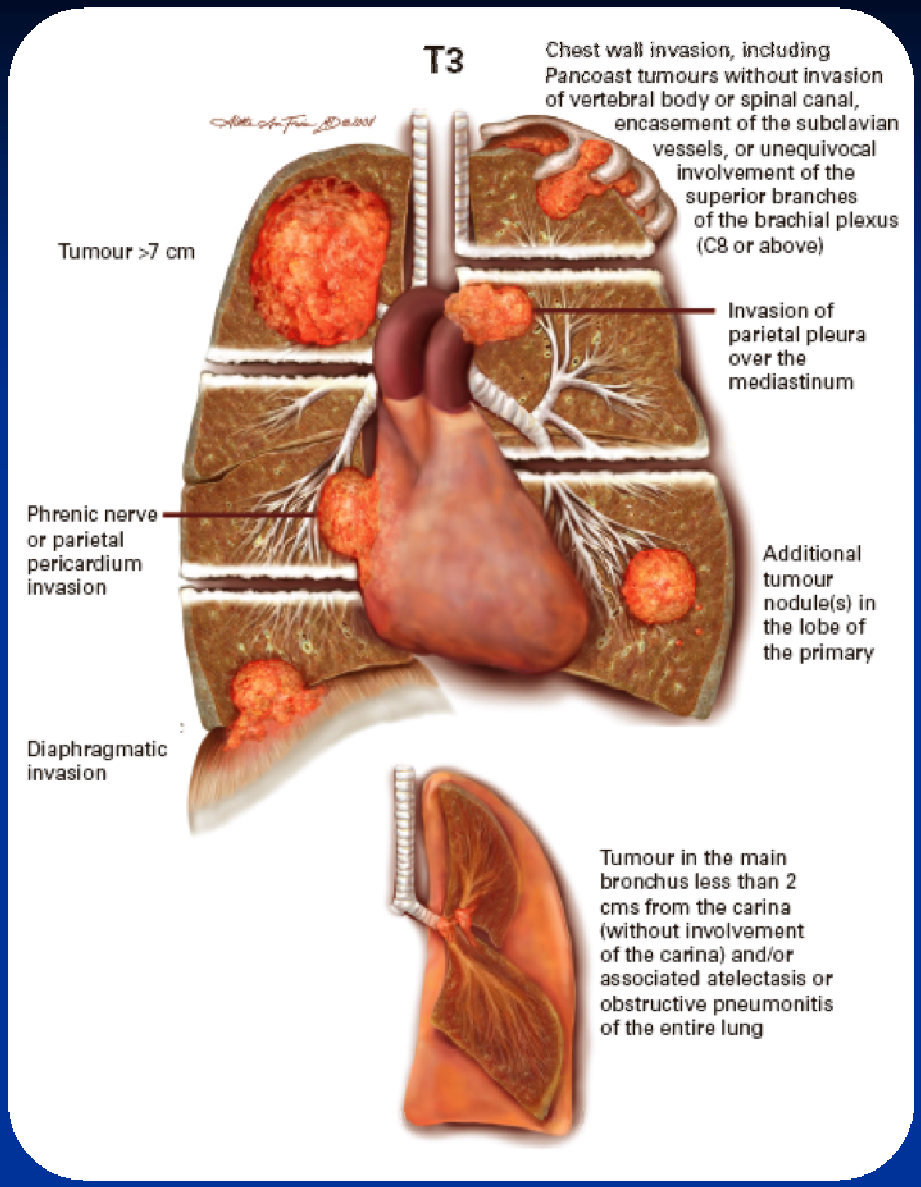
6th edition TNM	7th edition TNM
T1 (<=2cm)	T1a
T1 (>2 – 3 cm)	T1b
T2(<=5cm)	T2a
T2 (>5-7cm)	T2b
T2 (>7cm)	T3
T3 invasion	
T4 (same lobe nodules)	
T4 (extension)	T4
M1 (ipsilateral lung)	
T4 (pleural effusion)	M1a
M1 (contralateral lung)	
M1 (distant)	M1b

- Further subdivide T1 and T2 tumors
- Recognized the poorer prognosis for very large primaries (>7 cm)
- Recognize the better prognosis for ipsilateral lung nodules
- Recognize the poor prognosis associated with malignant pleural effusions

Primary tumor size in NSCLC



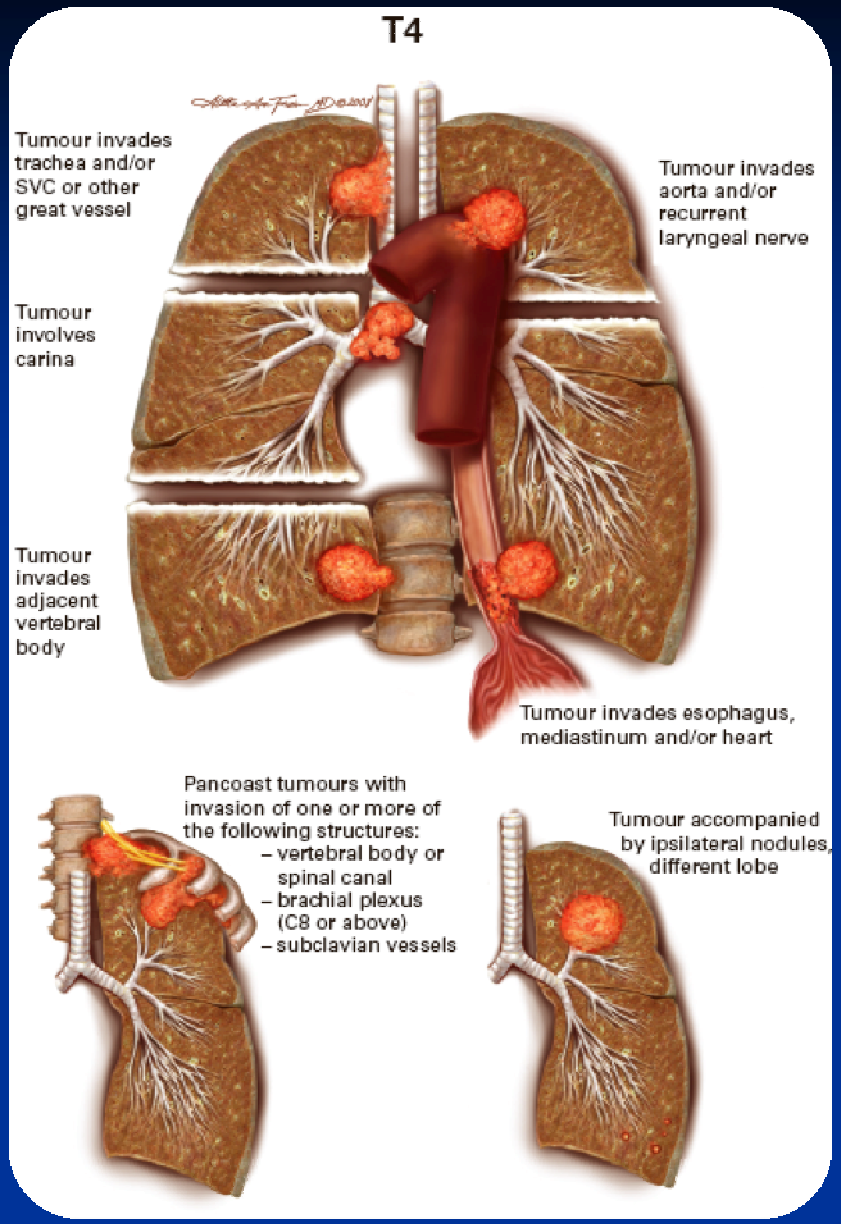
Overall survival by tumor size using UICC6 classification.



How to make a T3 tumor

- Be very large (>7 cm)
- Invade something
  - Not lung
  - Not essential
- **Have a second tumor in the same lobe**
- Cause atelectasis of a whole lung

IASLC Staging Handbook in Thoracic Oncology

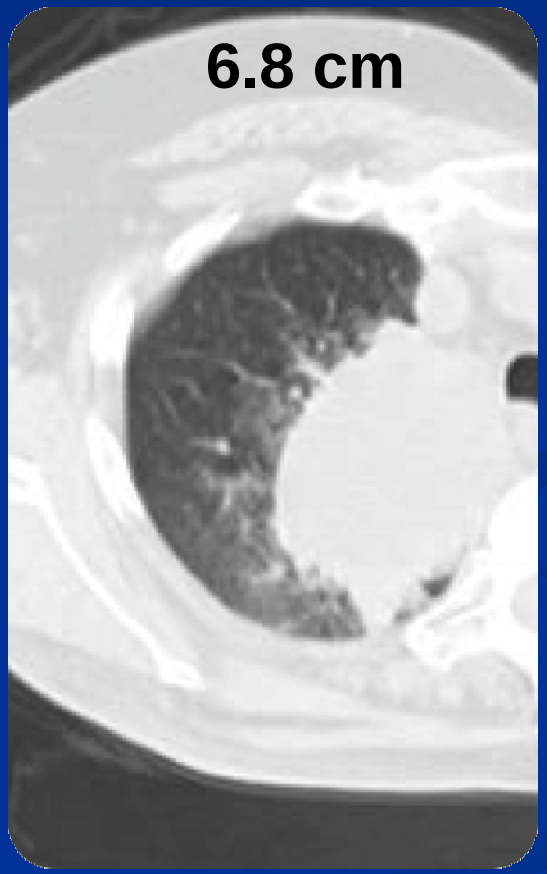


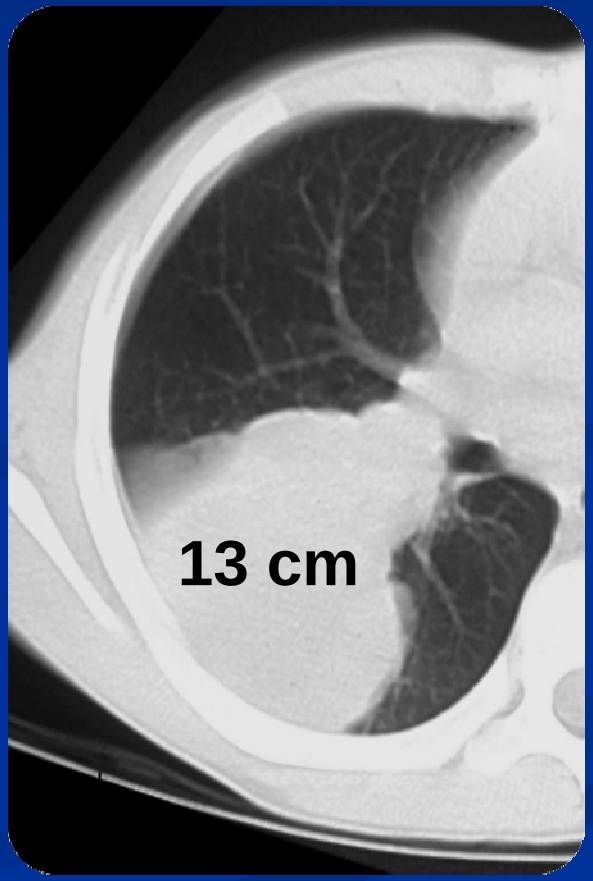
How to make a T4 tumor

- Invade something that surgeons can't or don't want to remove
- Get a second tumor
  - Ipsilateral lung
  - Different lobe

IASLC Staging Handbook in Thoracic Oncology

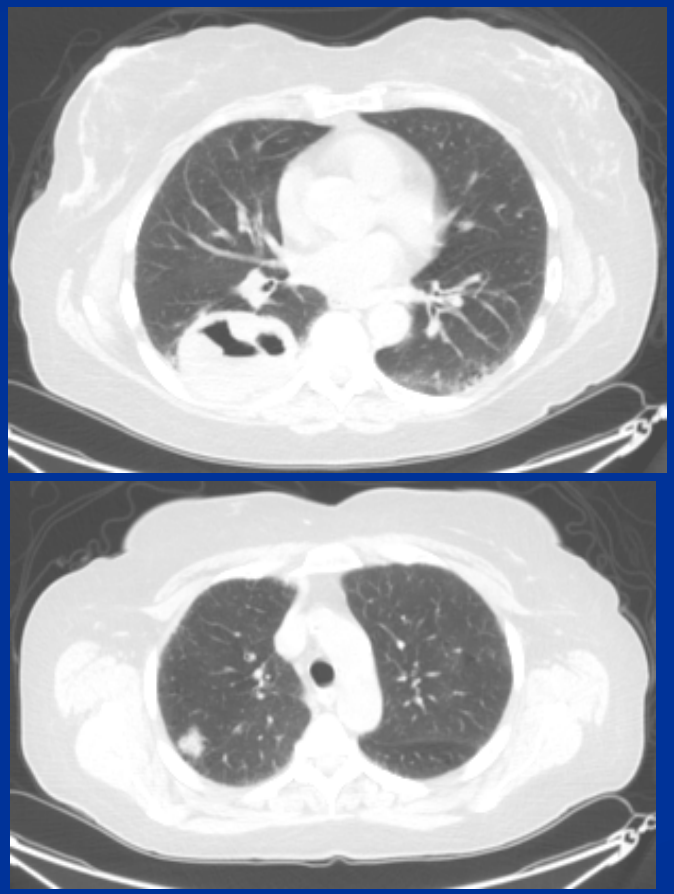
Old	T2	T2	T2
New	T2	T2b	T3



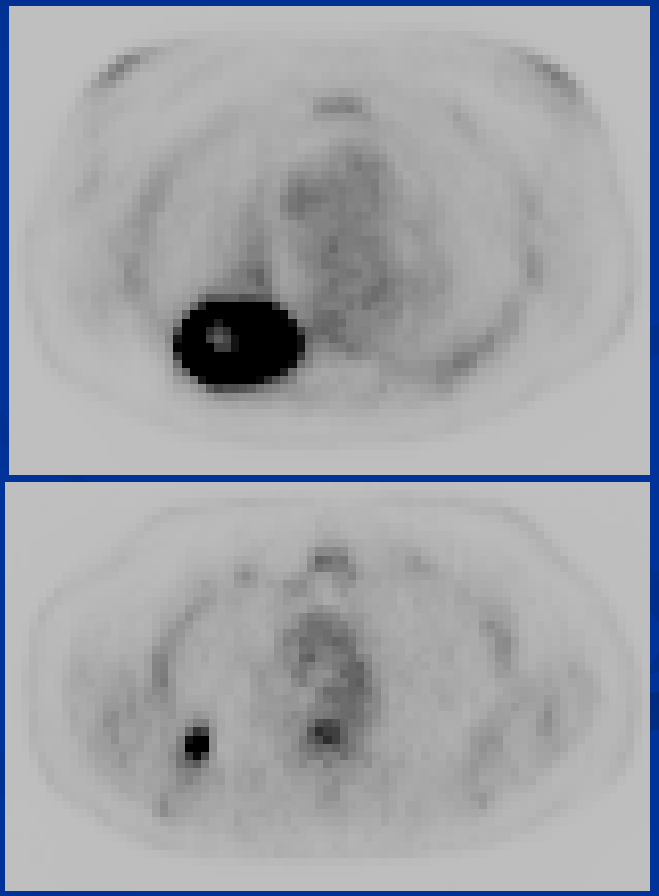


Ipsilateral primaries: Different lobe

Old: T4



New: T3



N descriptors

- No change, BUT…
- New lymph node map combining features of the Mountain-Dressler classification and Naruke lymph node map
- Nodal "zones"
  - Precisely defined
  - Relevant to bulky nodal masses that cross the boundaries of individual nodal "stations"

M descriptors
What has changed?

- Recognition that…
  - Not all metastases are created equal
    - Metastases to distant organs carry a worse prognosis than to the contralateral lung
  - Malignant pleural effusions confer a prognosis that is as poor as metastatic disease

T and M		N0	N1	N2	N3
6th edition TNM	7th edition TNM	Stg	Stg	Stg	Stg
T1 (<=2cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 – 3 cm)	T1b	IA	IIA	IIIA	IIIB
T2(<=5cm)	T2a	IB	IIA (IB)	IIIA	IIIB
T2 (>5-7cm)	T2b	IIA (IB)	IIB	IIIA	IIIB
T2 (>7cm)	T3	IIB (IB)	IIIA (IB)	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIB (IIIB)	IIIA (IIIB)	IIIA (IIIB)	IIIB
T4 (extension)	T4	IIIA (IIIB)	IIIA (IIIB)	IIIB	IIIB
M1 (ipsilateral lung)		IIIA (IV)	IIIA (IV)	IIIB (IV)	IIIB (IV)
T4 (pleural effusion)	M1a	IV (IIIB)	IV (IIIB)	IV (IIIB)	IV (IIIB)
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

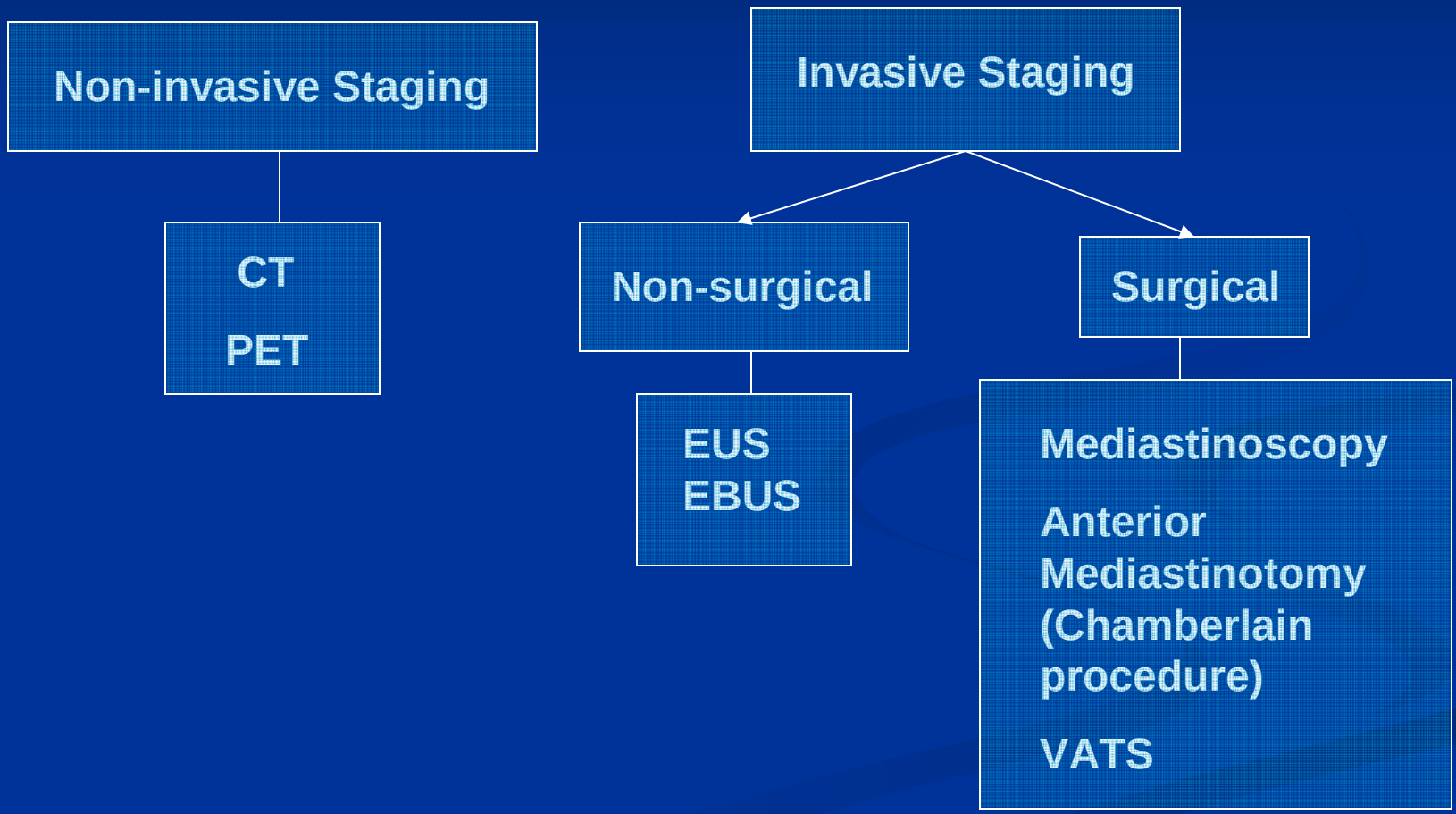
Summary

- OLD: 3 cm cut point between T1 and T2 tumors
- NEW: 2, 3, 5, and 7 cm cut points now separate additional descriptors of T1a, T1b, T2a, T2b, T3
- OLD: 2 nodules in the same lobe were T4, those in the other ipsilateral lobe(s) were M1
- NEW: Tumor nodules in the same lobe are T3, those in the other ipsilateral lobe(s) are T4
- OLD: Malignant effusions were T4
- NEW: Malignant effusions are now M1a

Summary

- M1 disease due to distant metastases has been reclassified as M1b
- The utility of the TNM classification in small-cell lung cancer has been validated across all treatment modalities
- The validity of TNM in Carcinoid tumors has been shown and these are now included
- A new IASLC nodal chart reconciles the previous differences between the Japanese and Mountain-Dresler charts

Staging for Lung Cancer



Why do Invasive Staging?

Isn't CT, PET good enough?

Accuracy of CT and PET Staging Mediastinal Lymph Nodes

Summary of 35 (CT) and 44 (PET) trials

	Sensitivity	Specificity
CT N=5,111	51%	86%
PET N=2,865	74%	85%

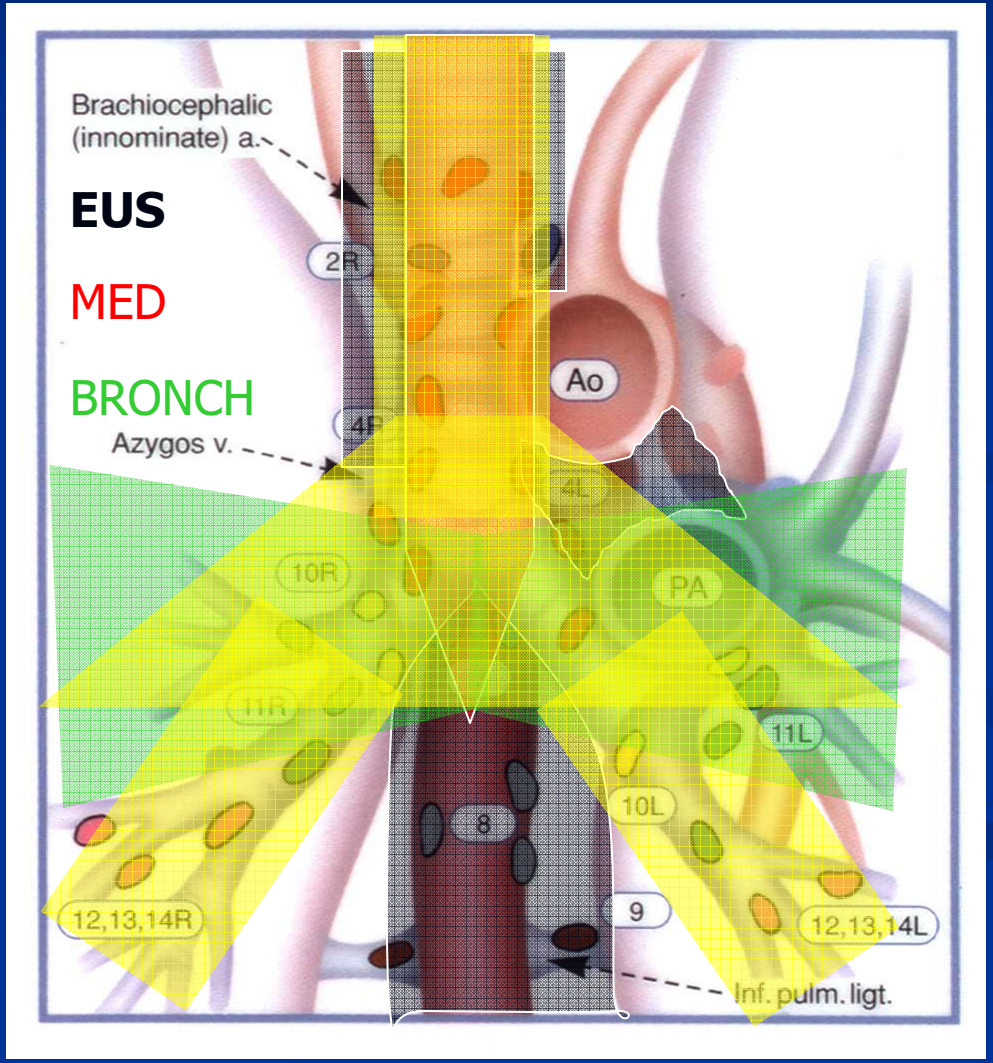
Silvestri et al. Chest 2007;132:178s

Methods of Obtaining Tissue

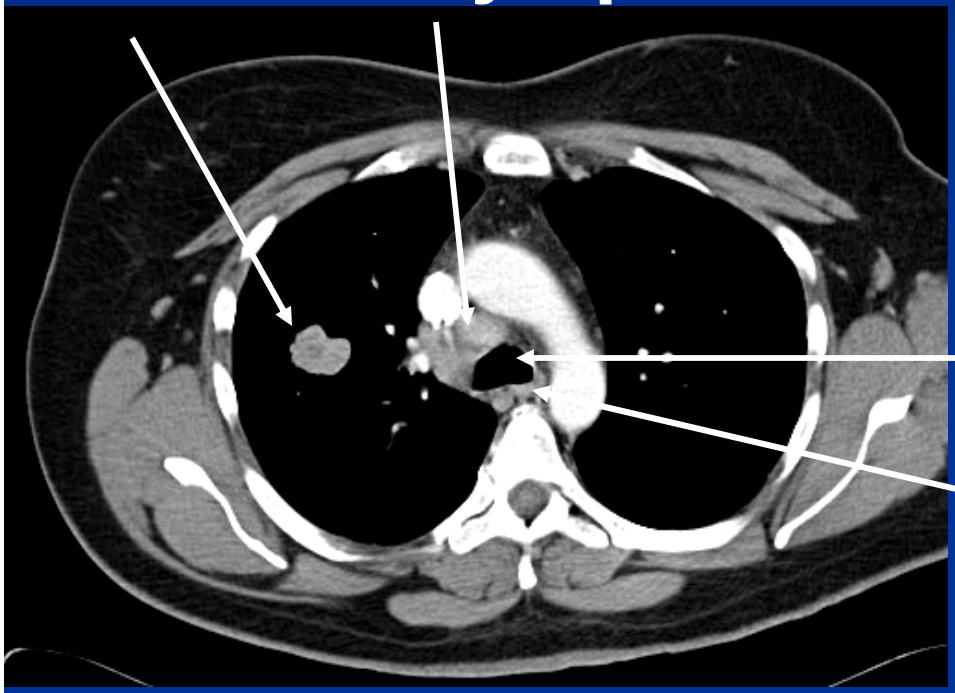
- Mediastinoscopy
- Mediastinotomy
- Thoracoscopy
- Trans bronchial needle aspirate
- EUS with FNA
- EBUS with FNA

Complementary Access to Mediastinum

- Complementary Access of
  - EUS
  - Mediastinoscopy
  - Bronchoscopy
  - EBUS

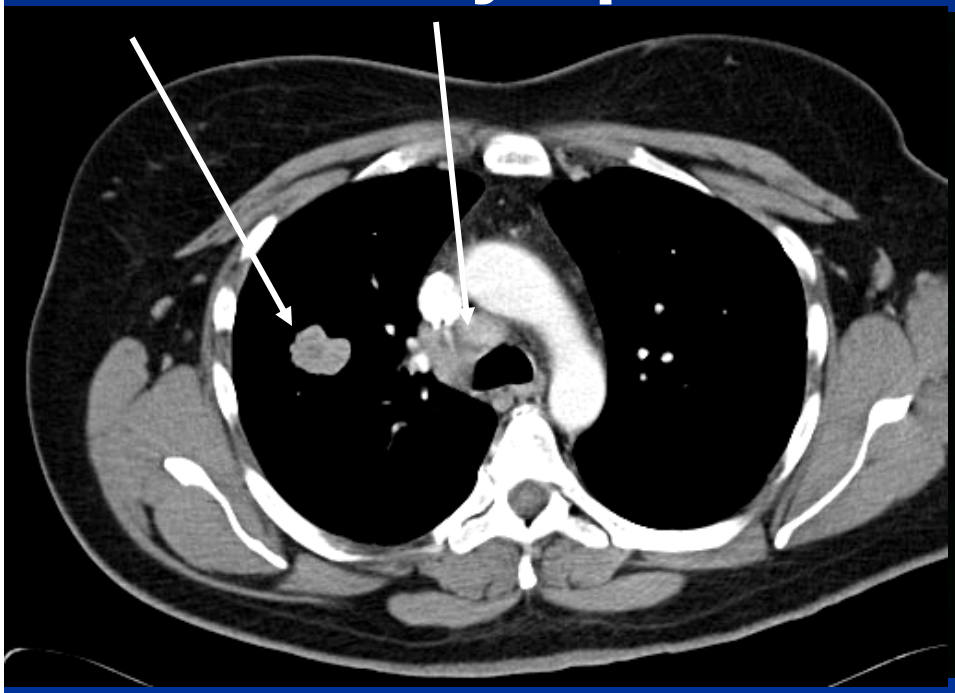


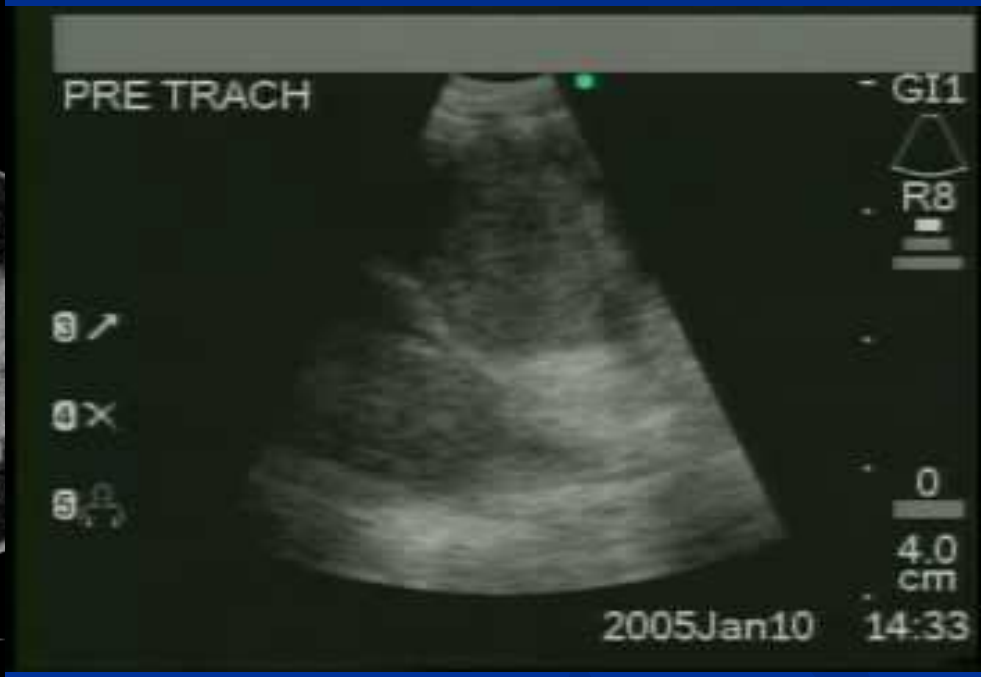
EBUS



EBUS

Mass **Lymph node**





Real-Time Endobronchial Ultrasound-Guided Transbronchial Lymph Node Aspiration

Brad D. Vincent, MD, Ezzat El-Bayoumi, MD, Brenda Hoffman, MD, Peter Doelken, MD, John DeRosimo, MD, Carolyn Reed, MD, and Gerard A. Silvestri, MD, MS

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Real-Time EBUS TBNA

- Retrospective analysis of 152 patients
- Cancer was identified in 113 patients
  - NSCLC 59% cases
- 20 underwent surgical resection
- Compared with radiologic staging EBUS-TBNA
  - Down-staged 18 of 113 (15.9%)
  - Up-staged 11 (9.7%)
- Sensitivity 98.7%
- Specificity 100%

Vincent BD, et al. Ann Thorac Surg 2008;85:224 –30

EBUS ACCURACY

Author (year)	N	Sensitivity	Specificity
Vincent/2008	152	99	100
Herth/2008	100	89	100
Bauwens/2008	106	95	97
Koh/2008	16	83	100
Herth/2006	502	94	100
Herth/2006	100	94	100
Plat/2006	33	93	100
Yasufuku/2005	108	95	100
Vilman/2005	31	85	100
Rintoul/2005	20	79	100
Kanoh/2005	54	86	100
Yasufuku/2004	70	95	100
Summary	1292	93	100

Preoperative Staging of Lung Cancer with Combined PET–CT

- Prospective randomized trial of conventional staging (H&P, Labs, Contrast CT of chest/abdomen, Bronchoscopy) or Conventional Plus PET-CT
- Endpoint – avoidance of futile thoracotomy defined as any one of the following:
  - Path confirmed mediastinal lymph nodes
  - Stage 4 disease
  - Benign lesion
  - Exploratory thoracotomy
  - Recurrence or death within one year
- **Fischer B, Lassen U, Mortensen J, et al. NEJM 2009;361:32**

Table 3. Distribution of Futile Thoracotomies.*

Characteristic	PET–CT	Conventional Staging	Total
		number (percent)	
Futile thoracotomy			
No	39 (65)	35 (48)	74 (56)
Yes†	21 (35)	38 (52)	59 (44)
Total	60 (100)	73 (100)	133 (100)
Reason that thoracotomy was considered futile			
Exploratory thoracotomy	5 (24)	4 (11)	9 (15)
Benign lung lesion	0	3 (8)	3 (5)
Stage IV disease	3 (14)	0	3 (5)
Stage IIIB disease	4 (19)	8 (21)	12 (20)
Stage IIIA (N2) disease	5 (24)	6 (16)	11 (19)
Recurrence within 12 mo	3 (14)	13 (34)	16 (27)
Death within 12 mo	1 (5)	4 (11)	5 (8)
Total	21 (100)	38 (100)	59 (100)

* PET–CT denotes combination positron-emission tomography and computed tomography. Percentages may not total 100 because of rounding.
† P=0.05 for the comparison between the two groups.

Additional Findings

- 38 inoperable after PET-CT vs. 18 in conventional staging alone
- Number of justified thoracotomies similar in each group
- Mediastinoscopy in 89% of PET-CT group and 97% of conventional group.
- 21 (21%) in PET-CT and 38 (42%) in conventional underwent a futile thoracotomy
- For every 5 PET-CT scans 1 futile thoracotomy was avoided
- Diagnostic accuracy/sensitivity PET – CT 79%/64% vs 60%/32% for conventional stage.

Mediastinoscopy vs EBUS/EUS for mediastinal nodal staging of lung cancer: a RCT

- Prospective randomized multicenter trial for presumed resectable NSCLC
- Patients enrolled consecutive to either
  - Group 1 - ES (EBUS/EUS) + SS (mediastinoscopy, mediastinotomy, VATS)
  - Group 2 - SS
  - Both had thoracotomy with lymph node dissection if negative mediastinum
    - **Annema JT, JAMA. 2010 Nov 24;304(20):2245-52**

Mediastinoscopy vs EBUS/EUS for mediastinal nodal staging of lung cancer: a RCT

- Results
  - 241 patients
  - Group 1 - 123 patients Group 2 - 118 patients
  - Sensitivity
    - Group 1 (ES+SS) 94%
    - Group 2 (SS) - 80%
    - (p=0.042)

Mediastinoscopy vs EBUS/EUS for mediastinal nodal staging of lung cancer: a RCT

- Result (cont)
  - Futile thoracotomy
    - Group 1 (ES+SS) 8 patients (7%)
    - Group 2 (SS) 21 (18%)
    - (p=0.009)
  - Complications similar both arms (6 vs. 7) 12/13 due to surgical procedure

- Conclusions
  - Starting mediastinal staging with endosonography in resectable NSCLC
    - 1) improves the detection of nodal metastasis
    - 2) reduces futile thoracotomies

Multi-Modality Mediastinal Staging For Lung Cancer Among Medicare Beneficiaries

Farjah F, Flum D, Ramsey S, et al.
J Thorac Oncol, 2009;4:355

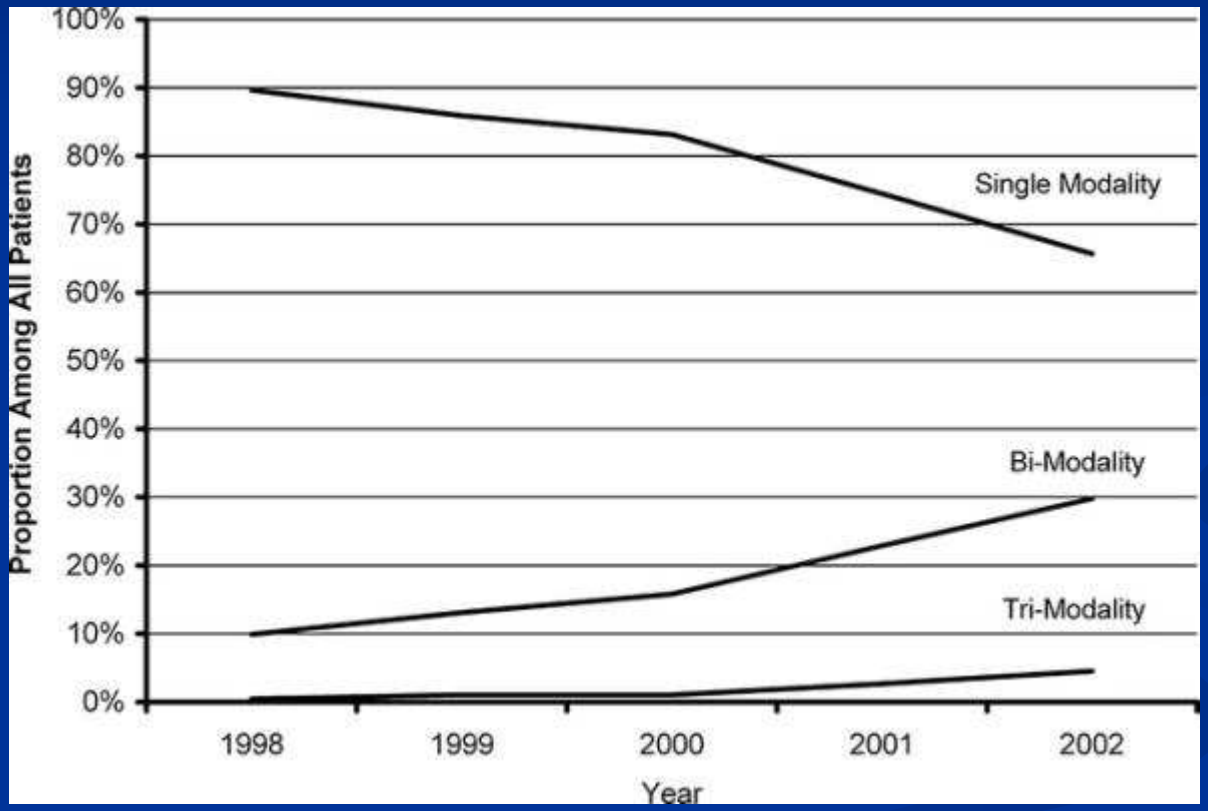
Multi-modality Mediastinal Staging for Lung Cancer

- Use of non-invasive and invasive tests improves accuracy of mediastinal staging
- Unknown how frequently it is used and whether it improves health outcomes
- Cohort study using SEER data (1998-2005)
- Categorized as staged by
  - Single modality (**CT**)
  - Bimodality (**CT & PET**)
  - Trimodality (**CT & PET & invasive staging**)

Findings

- 42,912 patients
- Median age 75
- Overall survival over 5 years – 13%
- 77% single modality
- 21% bi- modality
- 2% tri modality
- Over time PET increased, single mode decreased and invasive staging stayed about the same

Change over time in Multi-Modality Mediastinal Staging



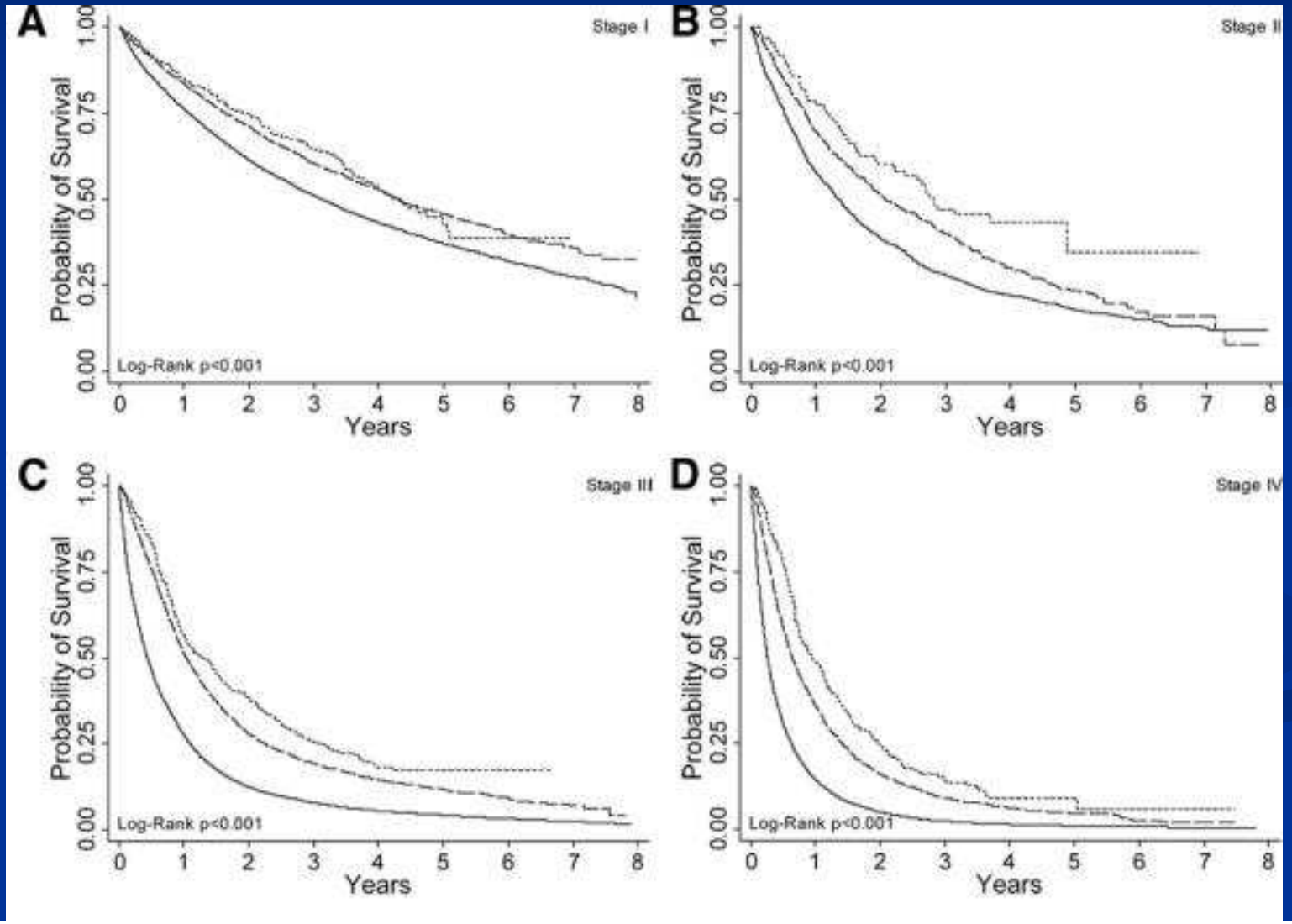
Factors Associated With the Receipt of Multi-Modality Staging

TABLE 3. Factors Associated With the Receipt of Multi-Modality Staging

	Odds ratio	(99% CI)
Age	0.97	(0.96–0.97)
Male	0.79	(0.74–0.84)
Race		
White	Referent	
Black	0.63	(0.55–0.72)
Other	0.85	(0.74–0.98)
Low income	0.84	(0.77–0.93)
Low education	0.89	(0.81–0.97)
Unmarried	0.76	(0.72–0.82)
Geography		
West	Referent	
East	0.98	(0.90–1.07)
Midwest	0.68	(0.62–0.74)
South	1.07	(0.98–1.17)
Residence		
Metro	Referent	
Urban	0.90	(0.79–1.03)
Rural	0.80	(0.71–0.91)
Prior malignancy	1.13	(1.05–1.21)
Comorbidity index	1.00	(0.97–1.03)

CI, confidence interval.

Stage-Based Overall Survival by Number of Staging Modalities



Relationship Between Mediastinal Staging and Survival

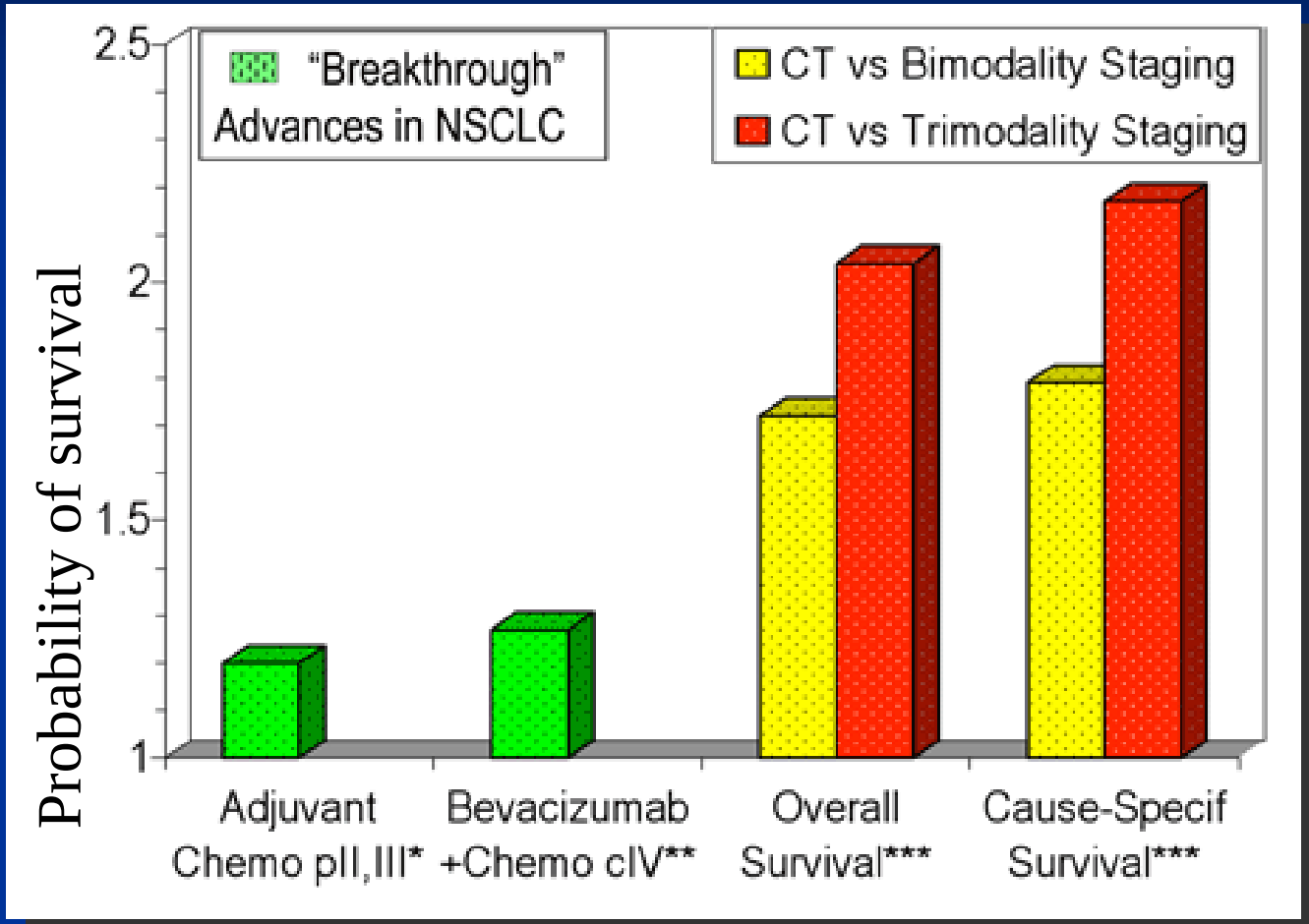
TABLE 4. Relationship Between Mediastinal Staging and Survival

	Overall survival Hazard ratio[a] (99% CI)	Lung cancer cause-specific survival Hazard ratio[a] (99% CI)
Bi- vs. single modality	0.58 (0.56–0.60)	0.56 (0.54–0.58)
Tri- vs. single modality	0.49 (0.45–0.54)	0.46 (0.42–0.52)
Tri- vs. bi-modality	0.85 (0.77–0.93)	0.83 (0.74–0.93)

[a] Adjusted for age, sex, race, income, education, marital status, geography, area of residence, history of prior malignancy, and comorbidity index.

CI, confidence interval.

Comparing the magnitude of survival benefit…



* LACE Clin Oncol (Meeting Abstracts) 2006; 24:7008

** ECOG 4599 Sandler A, NEJM 2006; 355:2542-2550

*** Data taken from a SEER-Medicare (1998-2005) analysis. Results are adjusted for all significant factors.6

What's Next?

- Aligning the T descriptors with that used for sub-groups from adjuvant trials?
  - **For example – tumors greater than 7 cm are now stage 2 – are they candidates for adjuvant chemotherapy?**
- Addition of biological or molecular markers to the staging system? – EGFR, KRAS, EML4 Alk

  e.g. T3N2M1a adenocarcinma, EGFR+
- Staging as a quality indicator?

"Oh well, another day's digging shot to hell."