Advances in the Management of Early Stage Lung Cancer

"Sir, the following paradigm shifts occurred while you were out."

Frank Detterbeck MD

Thoracic Surgery, Yale University, Thoracic Oncology Program

Potential Conflicts of Interest

- Olympus – member of Data Safety Monitoring Board for study of endobronchial valves for emphysema
- Medela – research grant on chest drainage device
- Chair of ACCP Evidence-Based Lung Cancer Guidelines
- IASCLC Staging and Prognostic Factors Committee (Chair of several subcommittees)

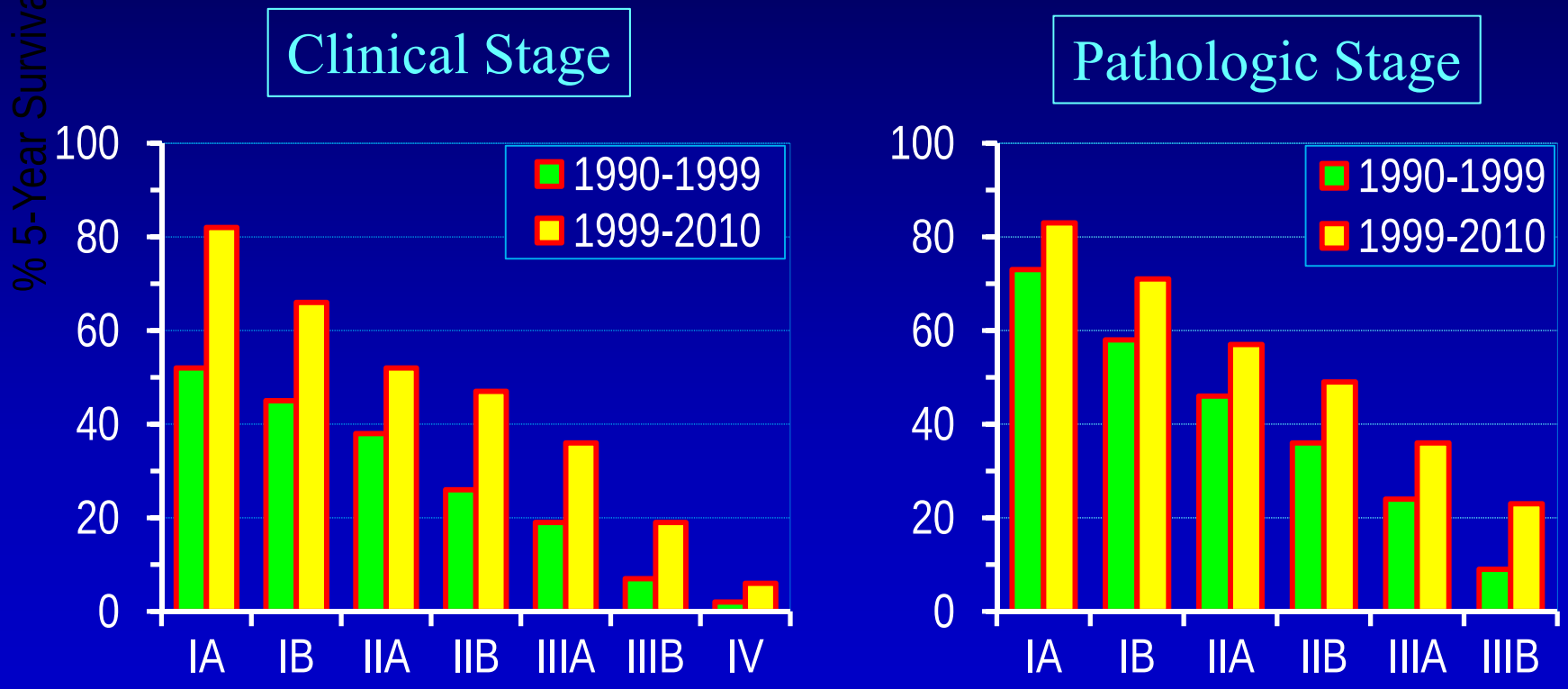
Overview

- Setting the Stage – How the world is changing
- The Nature of Early Stage Lung Cancer
- GGO – slow down and take a deep breath
- Advances in Surgery
- SBRT – a valuable addition
- Approach to the compromised patient

Setting the Stage:
How the world is changing

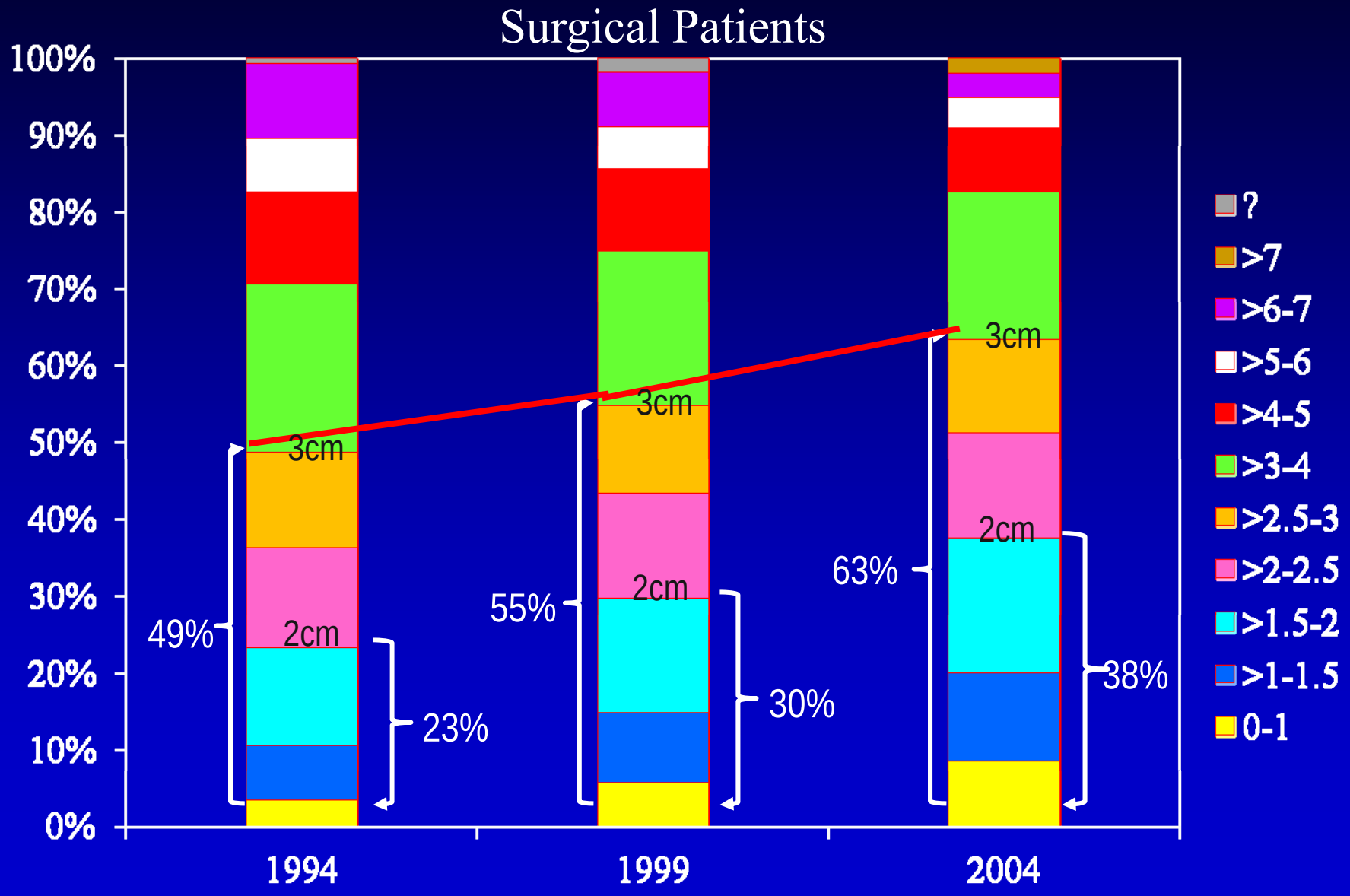
Improvement in Survival over Time

There has been a major improvement in Survival between the 1990-1999 and the 1999-2010 datasets

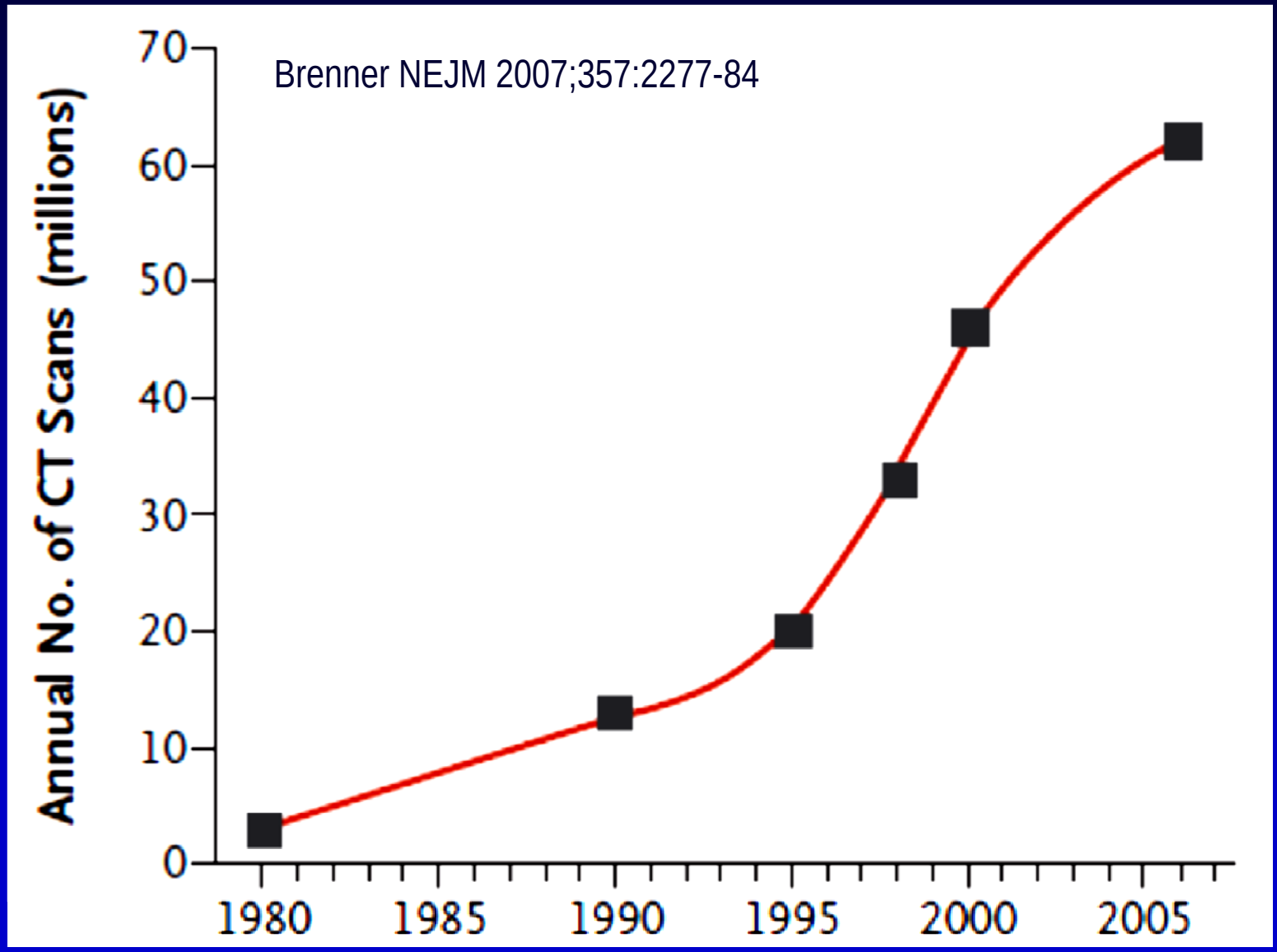


IASLC datasets, using the 7th edition classification in both

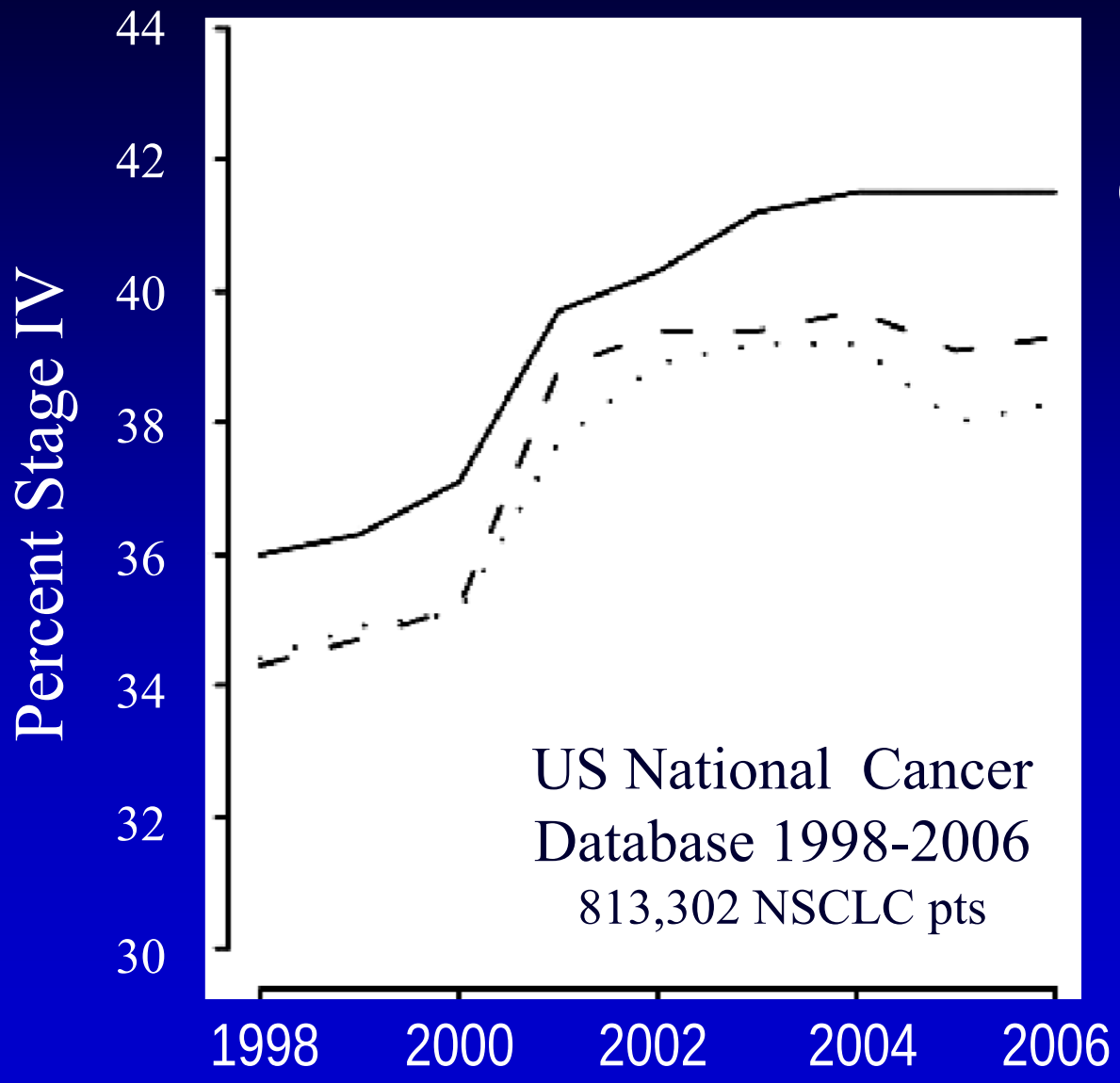
Changes in Size: Japan Registry



CT scans performed in US by Year



Change in Stage IV NSCLC: NCDB



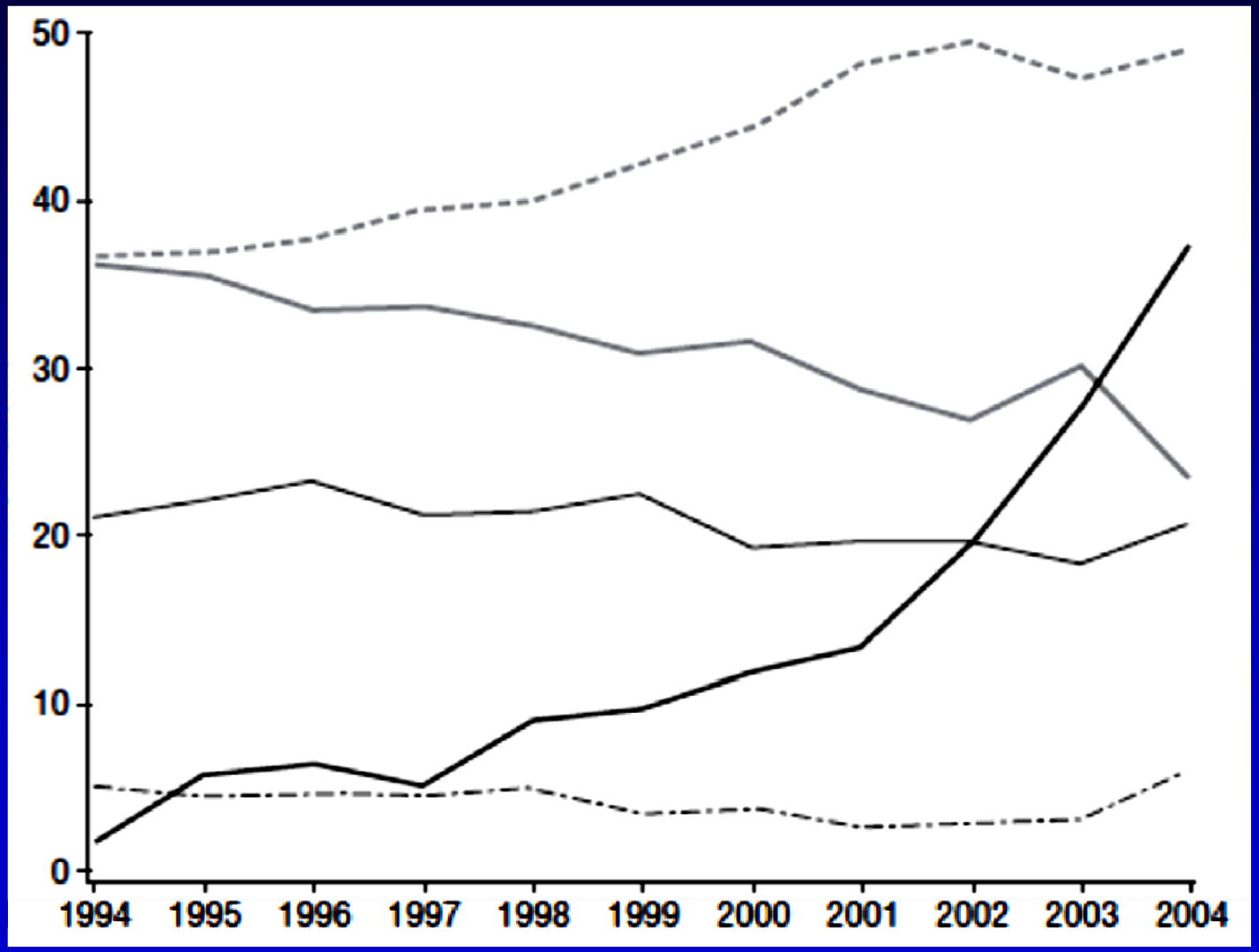
Community Hosp (100-649 Ca/Yr)

Community Hosp (>650 Ca/Yr)

Teaching Hosp Cancer Program

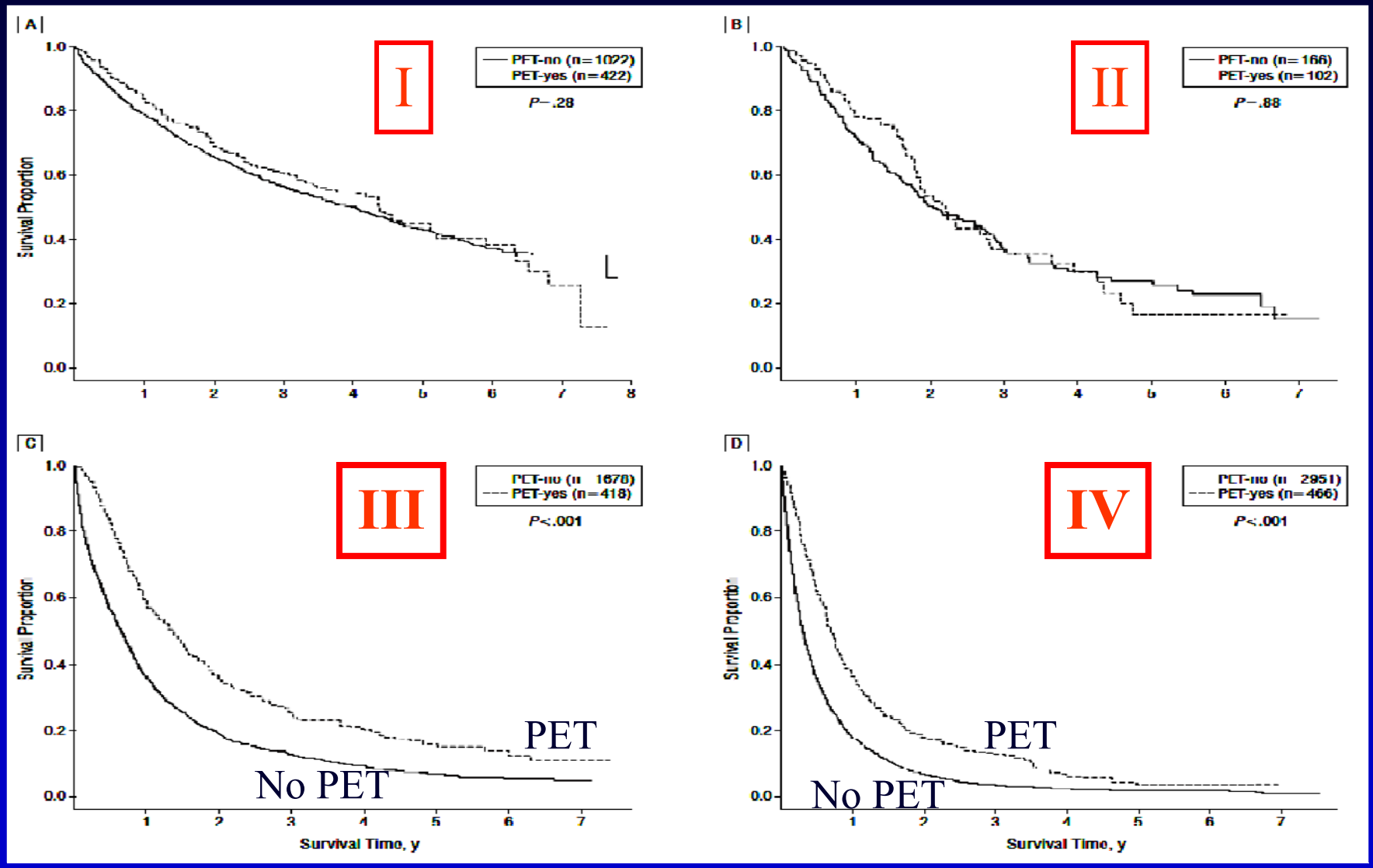
Ref: Morgensztern D et al
J Thor Onc.2010; 5(1):29-33

Trends in NSCLC (California Cancer Registry)



Ref: Chee Arch Int Med 2008;168:1541-9

Survival Trends in NSCLC (California Ca Regis)



Survival by PET vs No PET 1999-2004

Ref: Chee Arch Int Med 2008;168:1541-9

Changing Survival over Time

Why?

Reasons probably include:

- Earlier detection
- Changing spectrum of disease

  → Cohort includes more indolent tumors
- Better staging
- Better treatment modalities

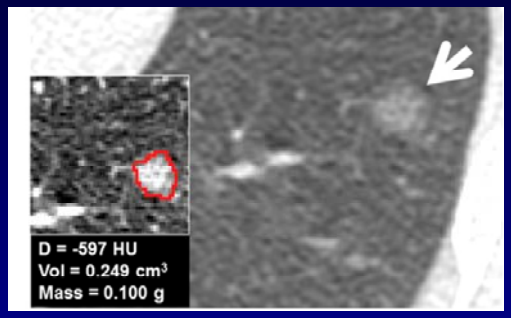
  → Higher cure rate, prolonged survival with incurable Ca
- ↓ inappropriate (or no) treatment
- ↓ competing causes of death

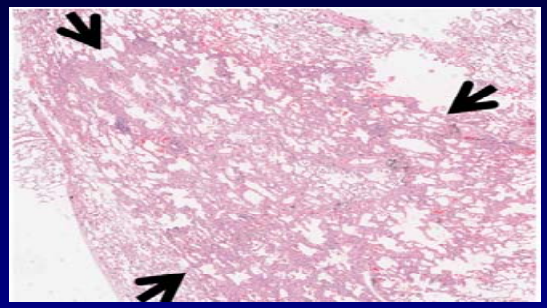
The Nature of Early Stage Lung Cancer

Adenocarcinoma Subclassification

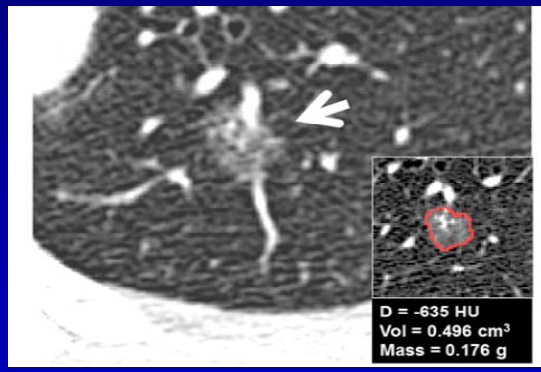
Atypical Adenomatous Hyperplasia (AAH) – (precancerous lesion)

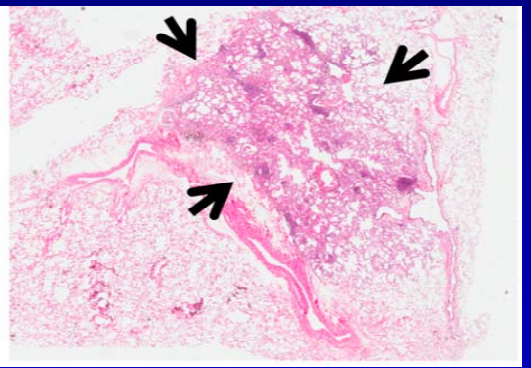
Adenocarcinoma in situ (AIS)



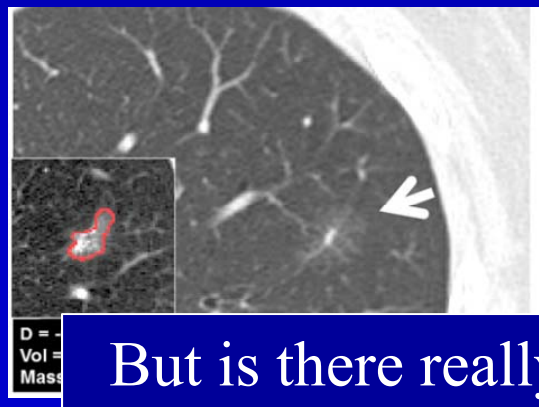


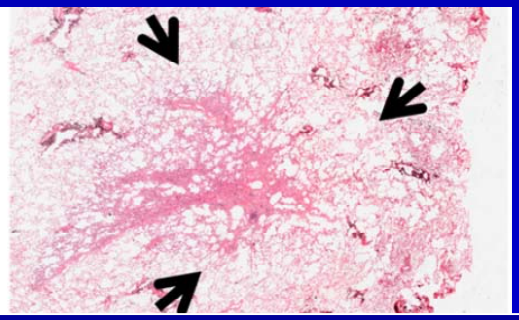
Minimally Invasive Adenocarcinoma (MIA)
(<5mm invasive component)





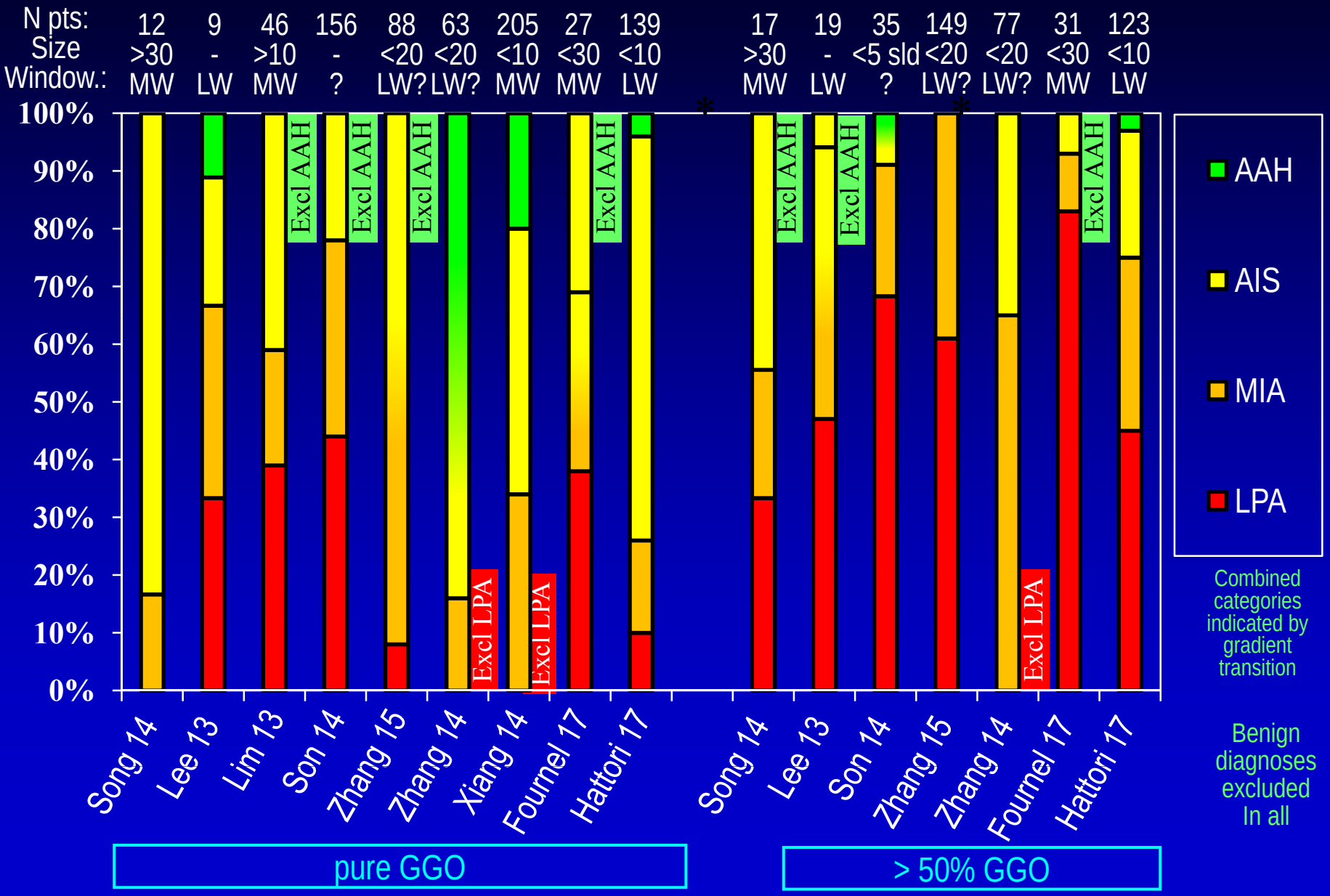
Invasive Adenocarcinoma
Lepidic, Acinar, Papillary, Micropapillary, Solid
(Usually mixed – shown is Acinar predominat)





But is there really a 1:1 correlation?

Correlation of CT & Pathology



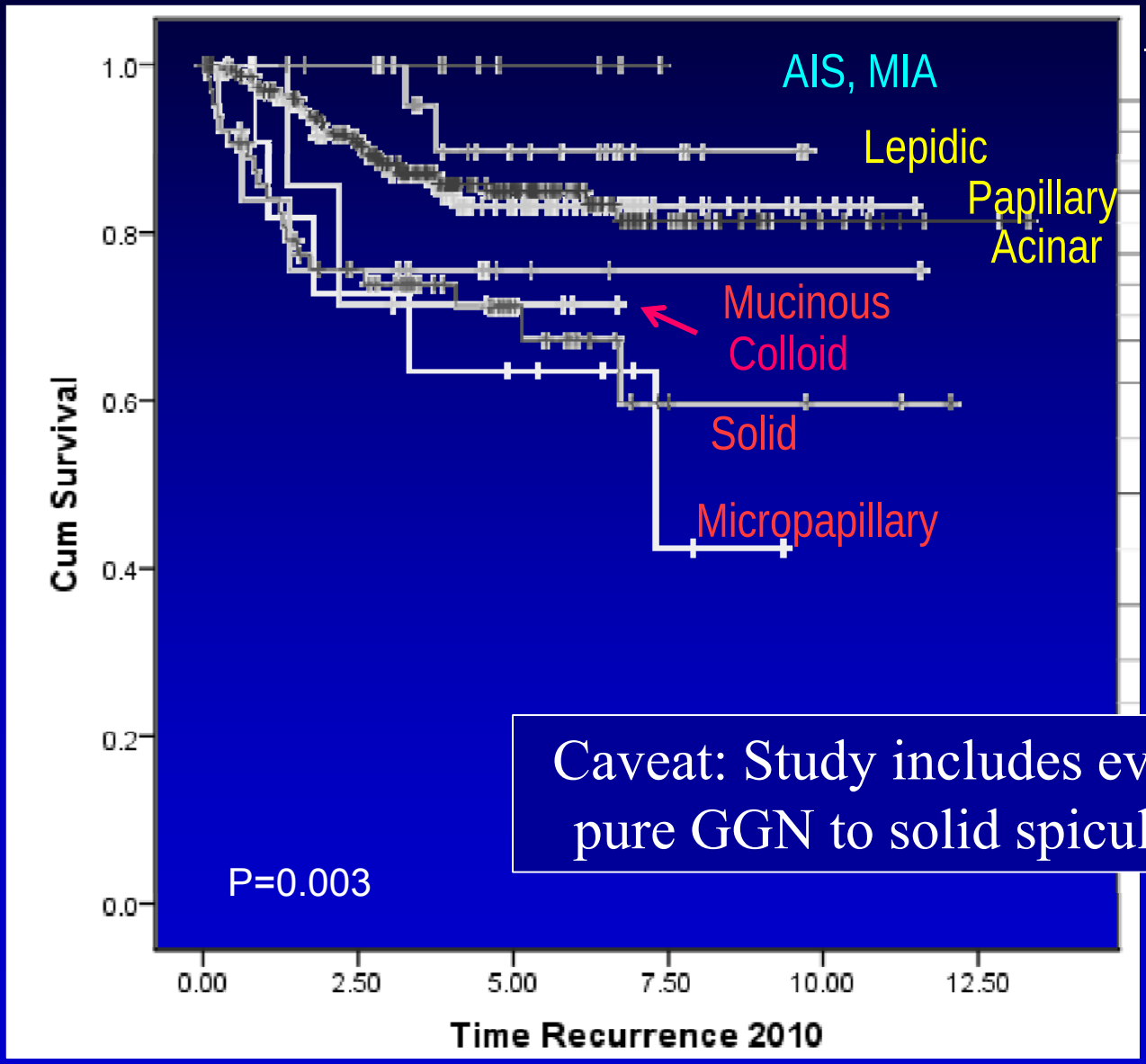
Prediction of Adeno Subtype

Study	N	Inclusion		Imaging		Multivariate Results					
		GGN type	Size (mm)	Slice Thick-ness (mm)	Window for Solid part	Total Size	Solid Size	Density	Mass	margin	Air Bronch
Adeno vs AIS / MIA											
Cohen 15	31	Part	-	≤2	MW	N	Y	N	N	-	N
Zhang 15	237	Both	<20	?	?	Y	Y	y	N	N	Y
Son 14	191	Pure + <5	-	≤1.5	MW	N	N	N	y	-	-
Lim 13	46	Pure	≥10	2.5	MW	y	-	N	y	N	N
MIA vs AAH / AIS											
Zhang 14	140	Both	<20	1	?	N	-	y	-	N	N
Xiang 14	205	Pure	≤10	≤2	MW	N	-	Y	-	N	N
AIS vs AAH											
Xiang 14	205	Pure	≤10	≤2	MW	Y	-	N	-	Y	N

N = Not Signif; Y = Stst signif by MVA; y = inconsistently signif in different models

STAGE pI ADENOCARCINOMA (N=514)

RECURRENCE-FREE SURVIVAL



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

Caveat: Study includes everything from pure GGN to solid spiculated leasions

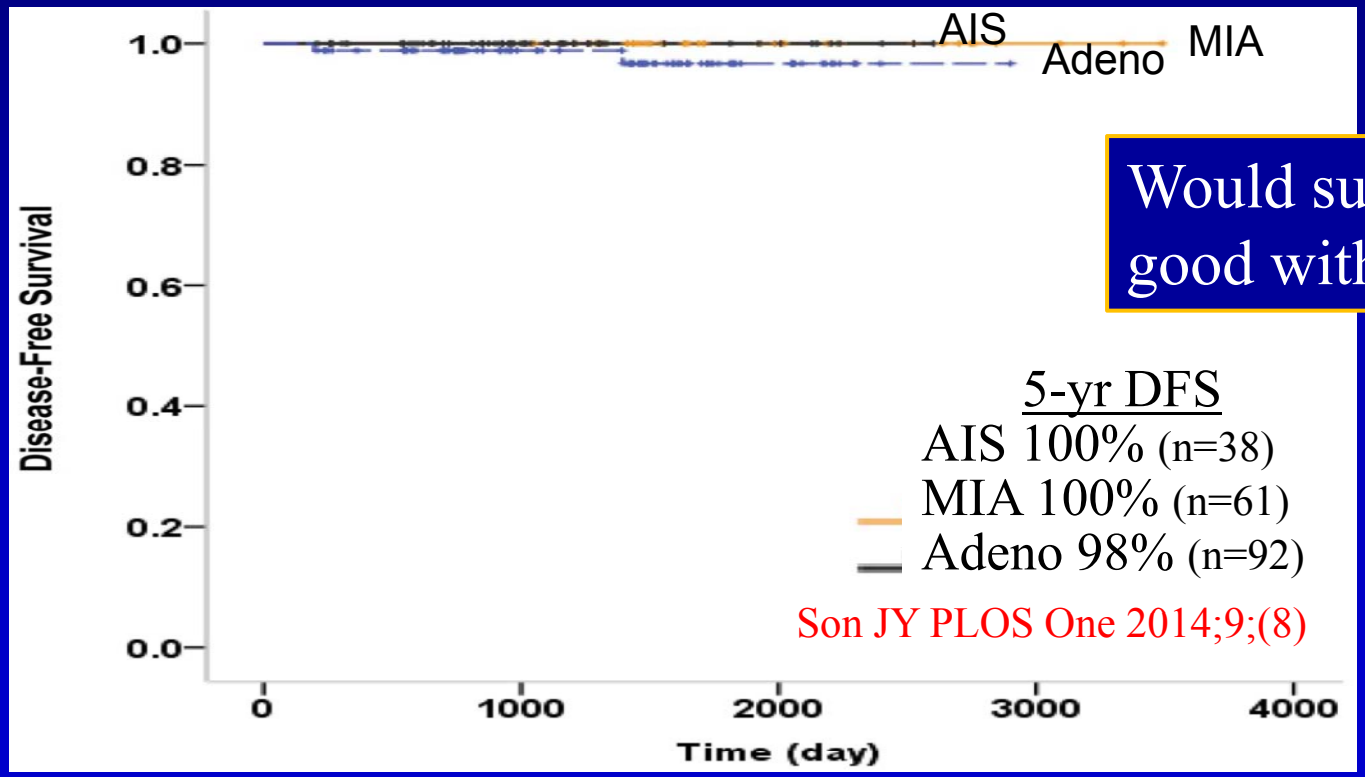
Outcomes of Adeno Subtypes

All studies show: AIS/MIA survival is consistently excellent

Most studies include the full spectrum from pure GGO to pure solid

Only study focused on mostly GGN shows that for these tumors the pathologic adenocarcinoma subtype doesn't matter

Pure GGN + <5mm solid portion



Would survival be just as good without resection?

5-yr DFS
AIS 100% (n=38)
MIA 100% (n=61)
Adeno 98% (n=92)

Son JY PLOS One 2014;9;(8)

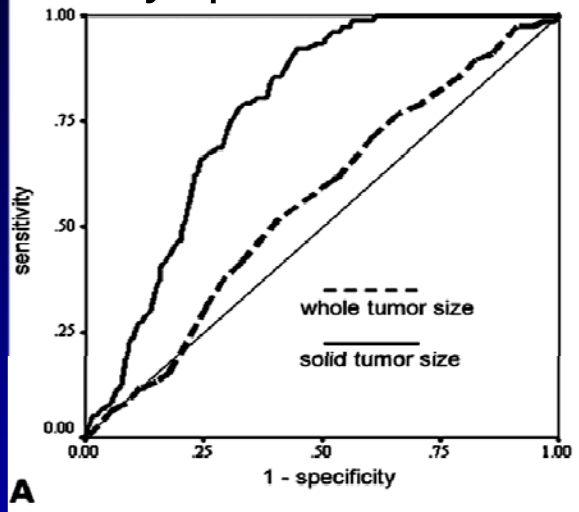
Whole vs Solid Tumor Size by CT

Whole tumor size 1.5 cm	Whole tumor size 2.8 cm	Whole tumor size 3.0 cm
Solid tumor size 1.5 cm	Solid tumor size 1.0 cm	Solid tumor size 0 cm

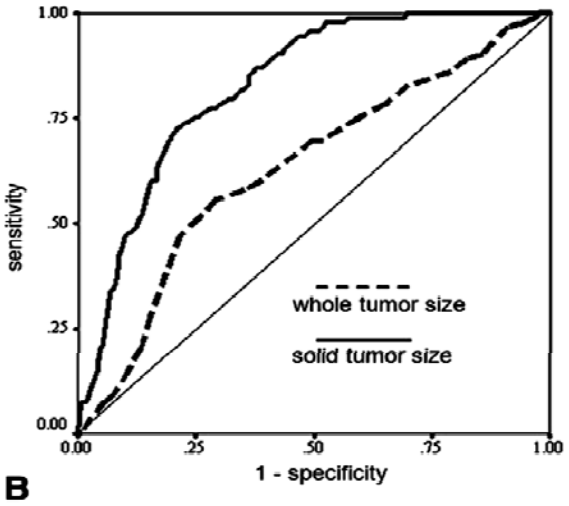
Tsutani JTCVS 143:607-12, 2012

Solid/Invasive Component is Key

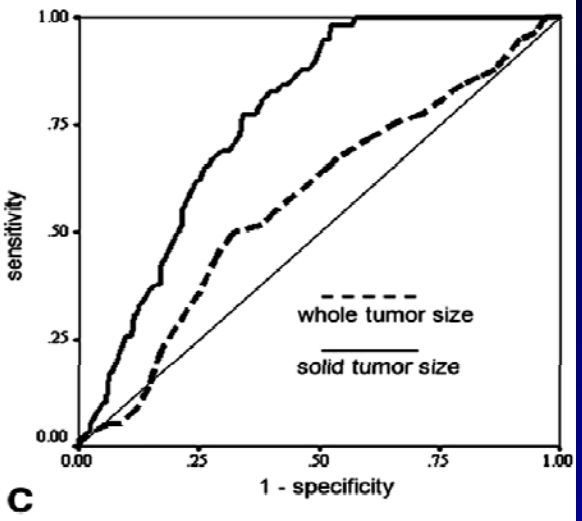
Lymphatic Invasion



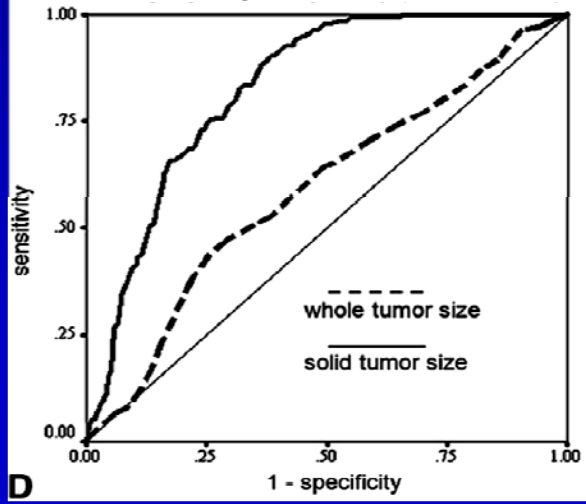
Vascular Invasion



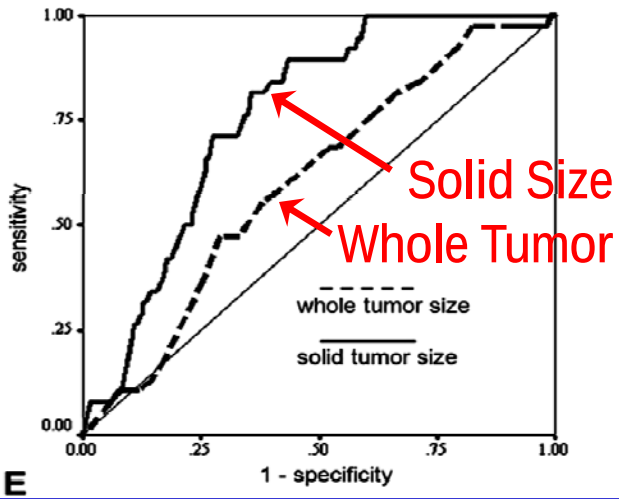
Pleural Invasion



Pathologic Invasiveness



Node Involvement



- 502 cla Adeno pts, R0
- CT 1-2mm thickness
- Solid part measured on lung windows, max ∅
- DFS predicted by solid size, PET, N+ (not whole size) in MV anal.

Tsutani JTCVS 2012;;143:607-12

Solid/Invasive Component is Key

Multiple multivariate analysis studies have shown that the size of the solid or invasive component is key

- Predicts Recurrence-Free Survival (RFS)[1,2,3,5,6]
- Predicts N+[1,4]
- Predicts Lymph, Vasc, Pleural invasion[1,3]

- Size of GGO component has no value[1,2,3,4,5,6]

- Maybe also of prognostic value: Pleur Inv[2]; PET[1,3,6]; N+[1]; CEA[2]; Ly Inv[3]; Air Bronchogram[4];

References: 1 Tsutani JTCVS 2012; 2 Murakawa EuJCTS 2013; 3 Tsutani JTCVS 2013; 4 Maeyashiki EuJCTS 2012; 5 Yanagawa JTO 2013; 6 Sawabata EuJCTS 2013

8th Edition Size Measurement

Clinical Size Measurement

- 8th Ed: cT determined by largest dimension of solid component
- long axis dimension. lung window setting, 1 mm slices

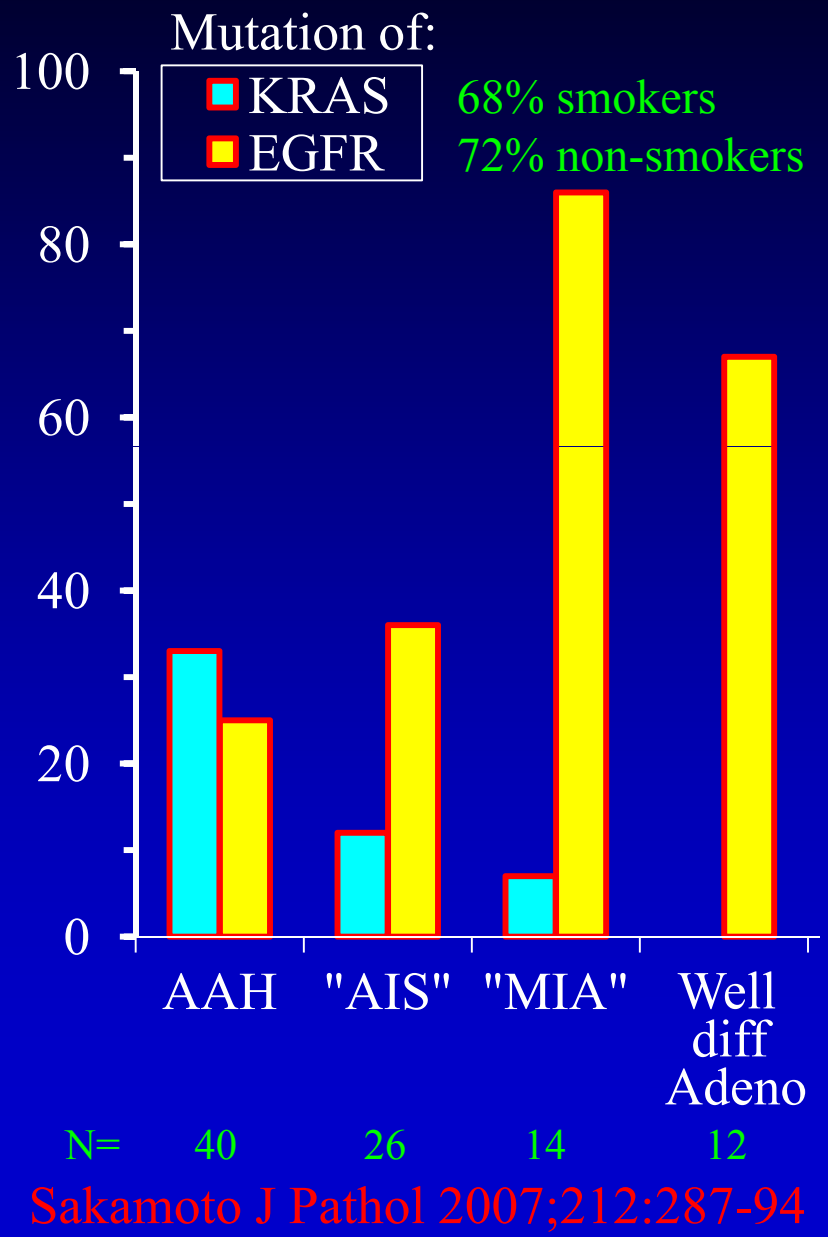
Pathologic Size Measurement

- 8th Ed: pT determined by largest dimension of invasive component (or the % that is invasive if several sites);
  also record largest dimension of lepidic component

If interspersed components, measure total size and % solid / invasive

Ground Glass Opacities:
Slow Down and
Take a Deep Breath

Genetic Features of Multifocal Adeno



Sakamoto J Pathol 2007;212:287-94

↓ rate of KRAS with de-differentiation suggests that AAH with KRAS mutation doesn't progress

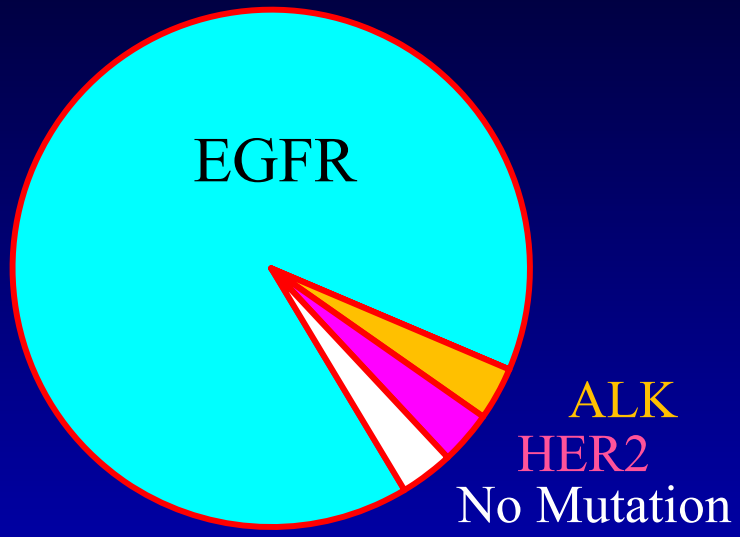
Opposite for EGFR mutation

Mutually exclusive KRAS & EGFR mutations suggests different pathways
Also correlation w smoking

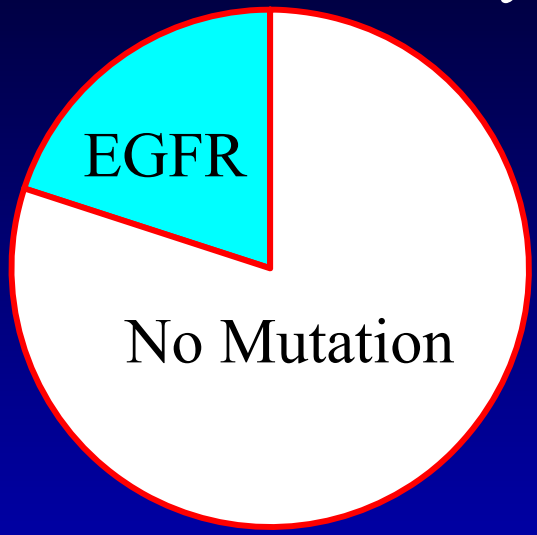
↑ rate of KRAS with Mod-Poorly differentiated Adeno suggests it doesn't develop from AAH
maybe different mechanism?

Genetic Features of Resected GGN

Growth



No Growth >2 yrs

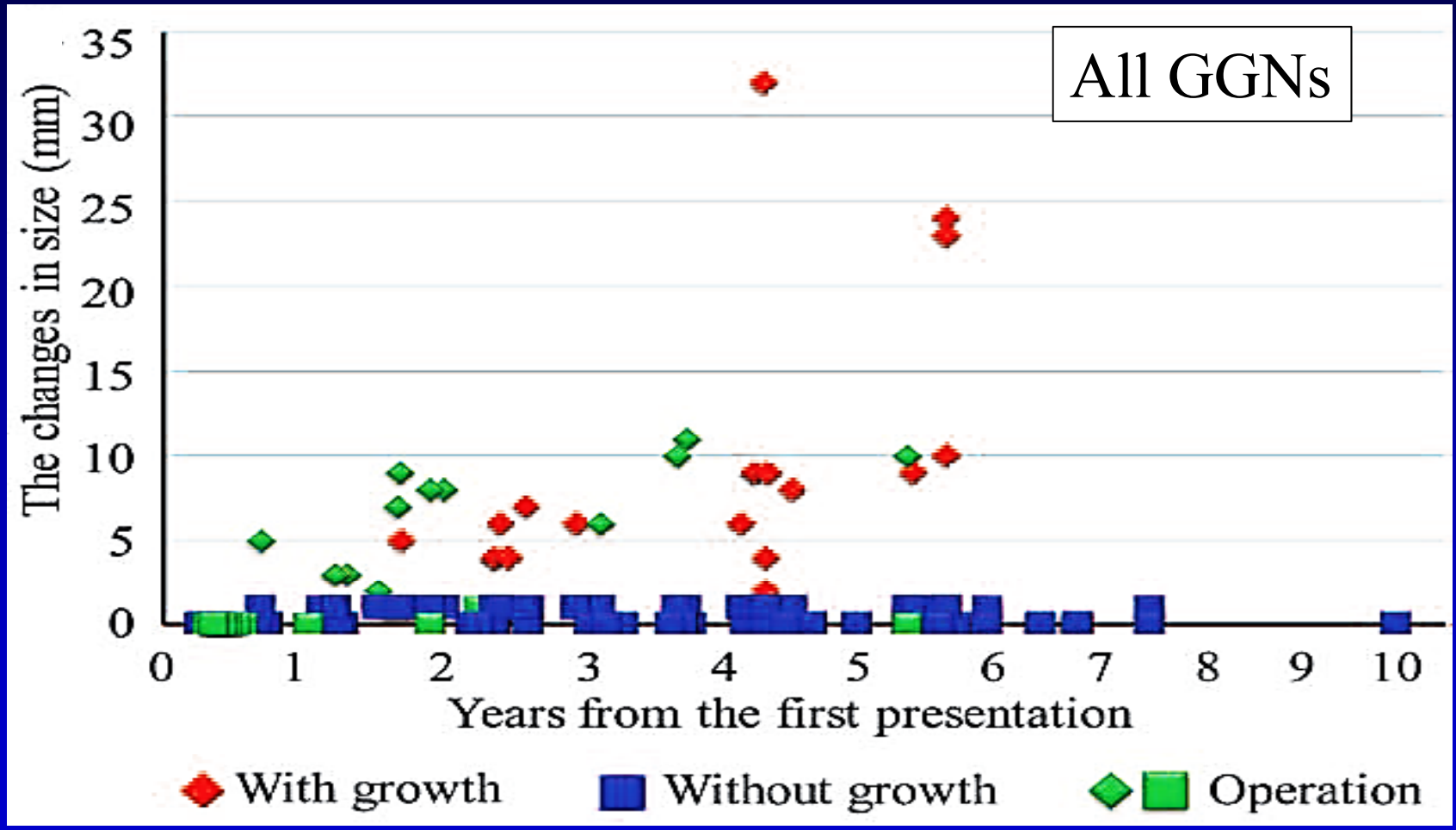


Ref: Kobayashi Annals Oncol 2015;26:156-61

There is evidence for different types of GGNs with different biologic behavior

Only Some GGNs Grow

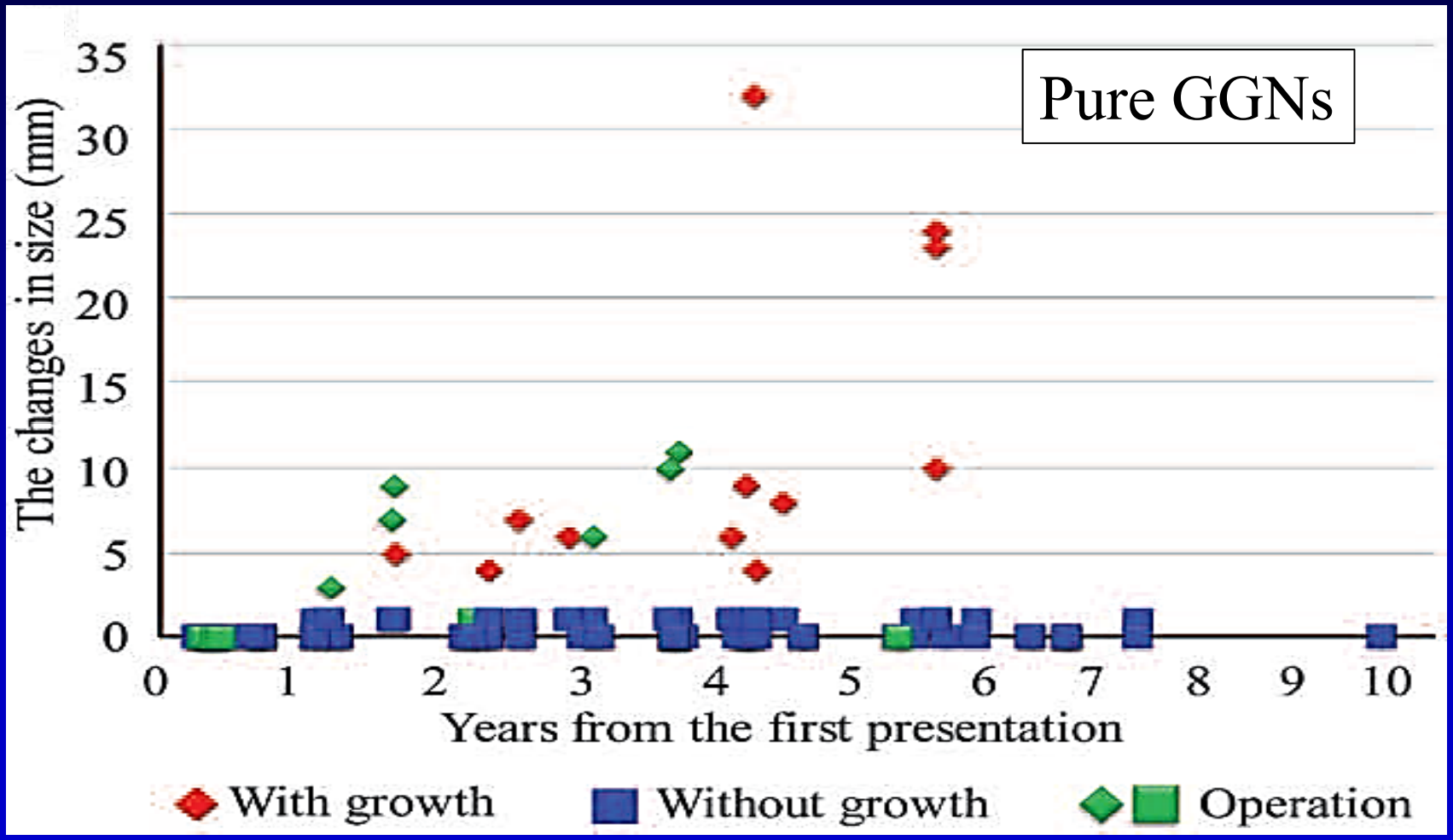
Patients with a Lung Cancer and additional sub-solid GGNs over time



Ref: Kobayashi J Thor Oncol 2013;8:309-14

Only Some GGNs Grow

Patients with a Lung Cancer and additional sub-solid GGNs over time



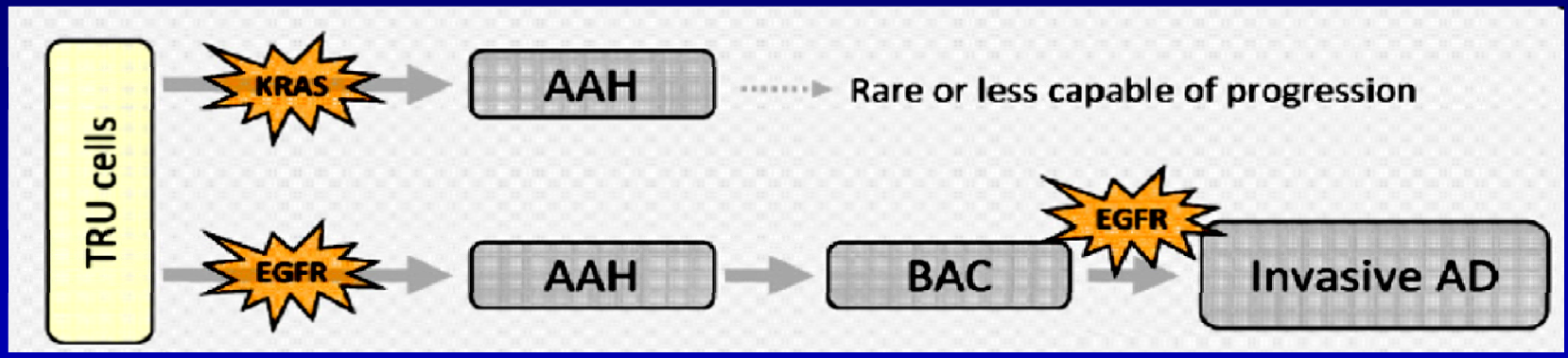
Ref: Kobayashi J Thor Oncol 2013;8:309-14

Do All GGNs Grow?

AAH w KRAS mutation: not destined to grow? (Associated with smoking?)

A manifestation of the ability of KRAS to induce senescence?

AAH w EGFR mutation: progression to lepidic Adeno No assoc w smoking?



How well can we determine growth?

Solid Nodules

Poor inter- & intra-observer consistency for differences of <1.5-2 mm

Bottom line:

- Use thin slices (1.25 mm)
- Don't trust changes <2 mm
- Don't compare apples to oranges
  (i.e. PET-CT to diagnostic CT,
  5 mm slices to 1.25 mm slices)

When in doubt, get another data point!

Challenges in Assessing Growth

How well can we determine growth?

- Ignore differences less than 2 mm
- Use thin slice CT (1.25mm)
- Compare like to like (type of scan, setting, slice thickness)
  - Don't trust diagnostic CT compared to PET/CT
  - Don't trust thick vs thin slices
  - Don't use MIP images, different window settings

Bottom line: when there is doubt, don't cut it out

➔ get more data points

Incidence of Progression by %GGO and Time

% of Resections	
AIS/MIA	Other
96%	4%
70%	30%
33%	67%
27%	73%

99.2% Stage Ia

Prospective, Long-Term Study

Patients followed for 10-15 years (accrued 2000-2005); Pure or part-solid GGO ≤ 3 cm
Progression defined as either growth or increased consolidation (usually ~2-3 mm ↑)
Proportion of consolidation assessed on lung windows

Sawada Chest 2016;

Progression of GGO (Prospective Study)

Prospective multicenter study 2009-11; median f/u 4.3 yrs
Patients with pure GGN or with ≤ 5mm solid component (n = 1253)
Defined as pure, heterogeneous (consolidated on lung window) or part-solid (mediastinal window) on 1.25 mm slice CT

Central expert radiology and pathology review (of changing or resected cases)

Growth was defined as:

- ↑ in max diam of ≥2mm of GG portion
- ↑ in max diam of ≥2mm of solid portion (either lung or mediast window)
- New solid portion (either lung or mediast window)

74% CT & 6% CXR screening, 17% incidental;
60% never-smoker; 31% multiple

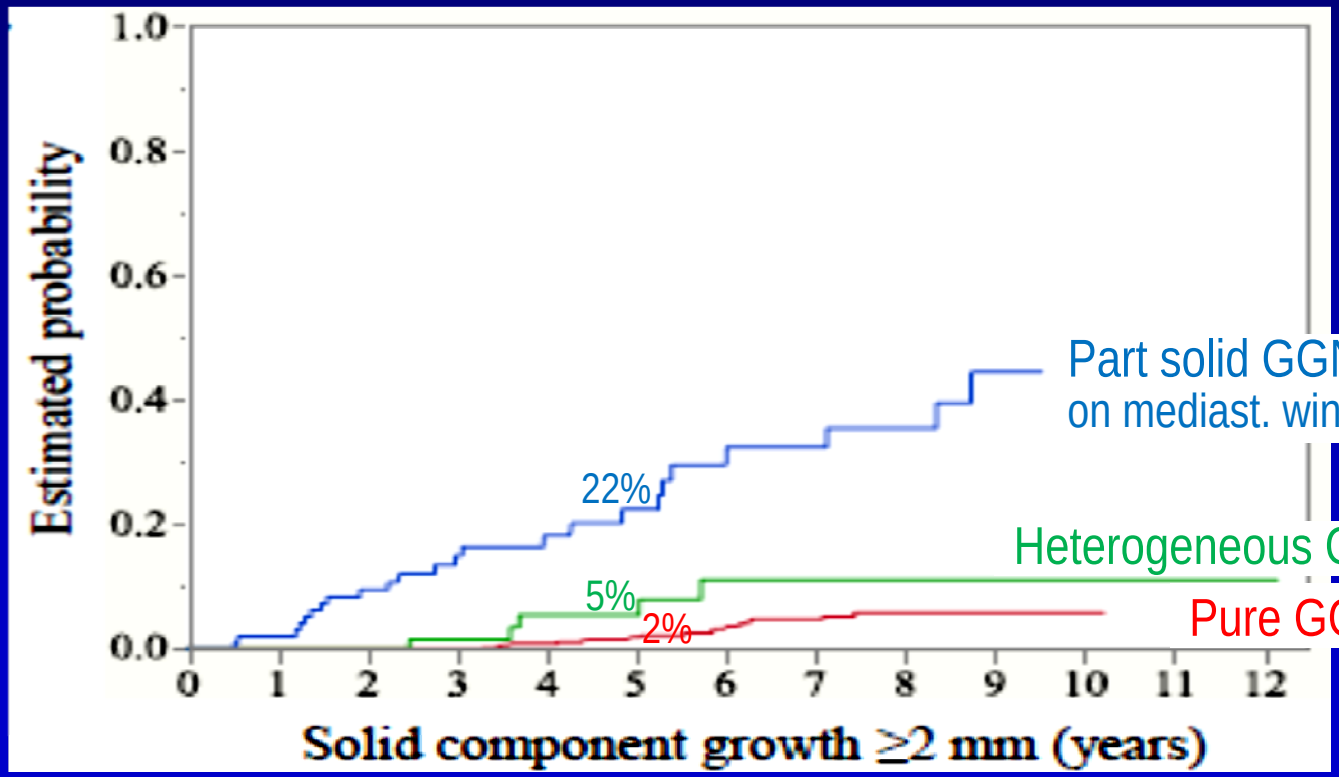
Kakinuma J Th Onc 2016;11:1012-28

Progression of GGO (Prospective Study)

Patients with pure GGN or with ≤ 5mm solid component (n = 1253)

Growth of max Size of Solid Component ≥ 2mm

Multivariate predictor:
Pure – initial size,
Hetero – none
part-solid – initial size



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Progression of GGO (Prospective Study)

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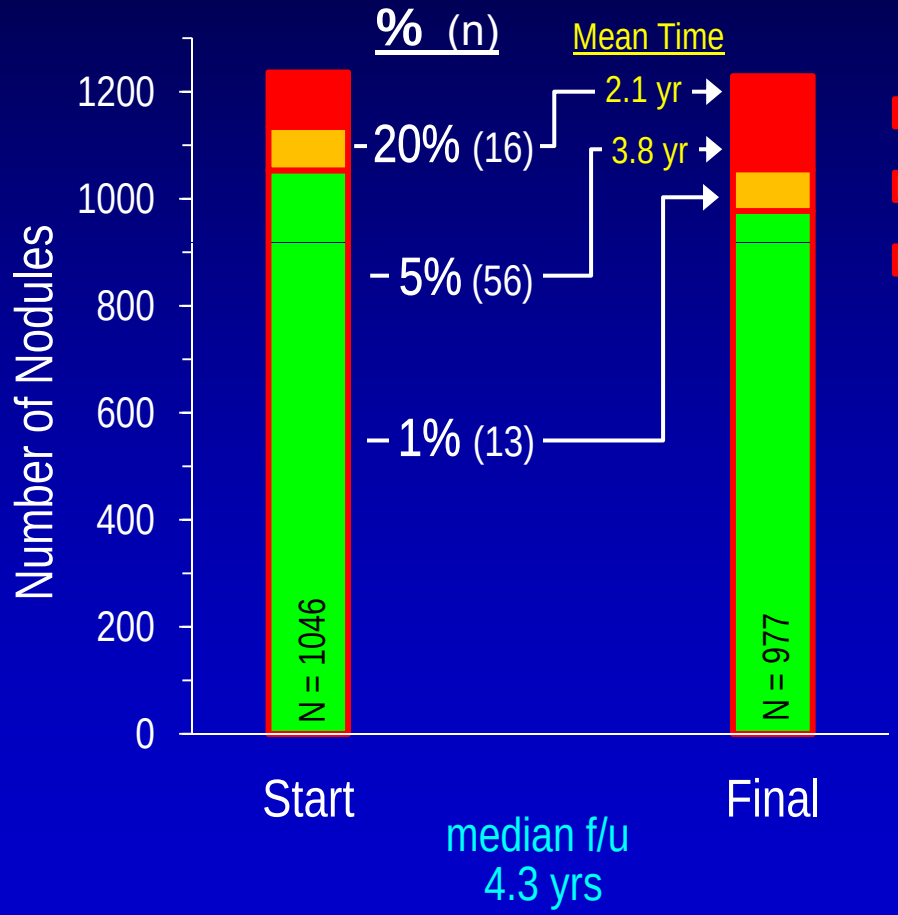


Part-solid (Mediast. Window)
Hetero (Lung Window)
Pure

Final Results (% of 1253 GGNs):

7.4% resected
1% Adeno; 3.3% MIA,
2.7% AIS, 0.5% AAH

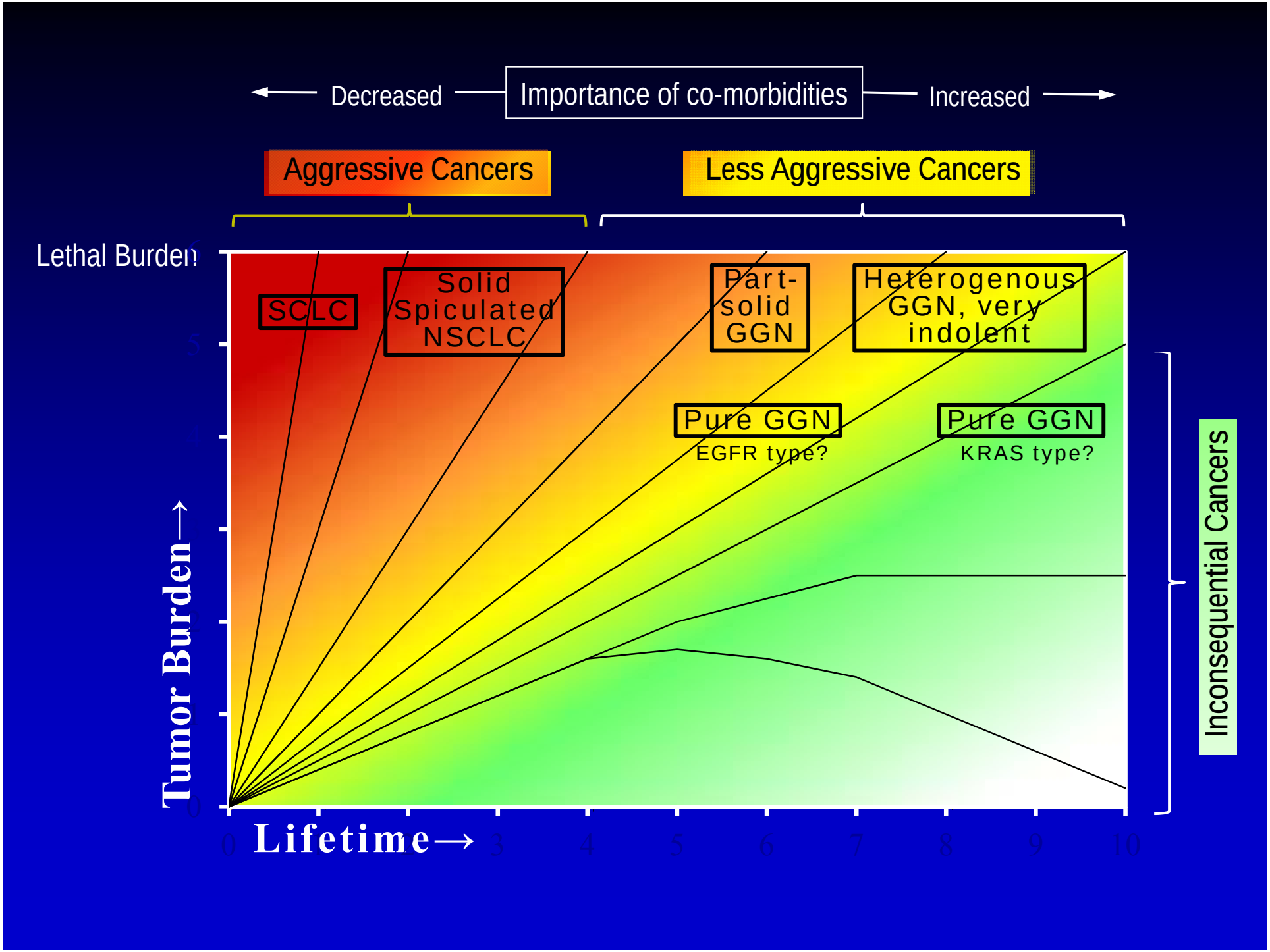
All Adeno were part-solid on CT

98% Stage Ia (2% stage Ib)

No recurrences (median f/u 3 yrs)

No new nodules developed

Kakinuma J Th Onc 2016;11:1012-28


Decreased
Importance of co-morbidities
Increased
Aggressive Cancers
Less Aggressive Cancers
Lethal Burden
SCLC
Solid Spiculated NSCLC
Part-solid GGN
Heterogenous GGN, very indolent
Pure GGN
EGFR type?
Pure GGN
KRAS type?
Tumor Burden→
Lifetime→
Inconsequential Cancers

GGN Management Recommendation

Triggers for Intervention

This is a moving target - my current recommendation:

GGN Type	Follow-Up Schedule
Pure GGN	LDCT q 12 mo
Heterogeneous	CT q 6 mo x 2 years; if stable revert to LDCT q 12 mo
Part-solid GGN (2-5 mm solid portion on MW)	CT q 3 mo x 1 year; if stable revert to CT q 6 mo

Note: CT should be done with 1.25 mm slice thickness

[a] Assuming no doubt about measurement (generally requires ≥2 interval scans)

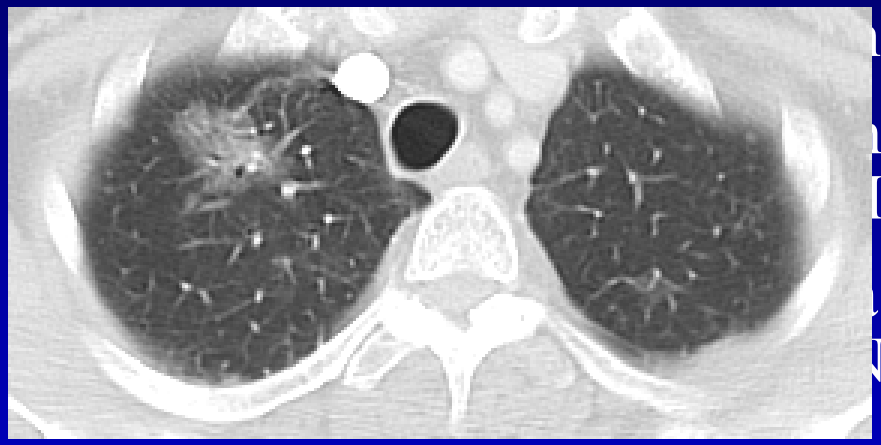
[b] speculative recommendation, based on limited data

Criteria for Multifocal GG/L Category

Clinical Criteria

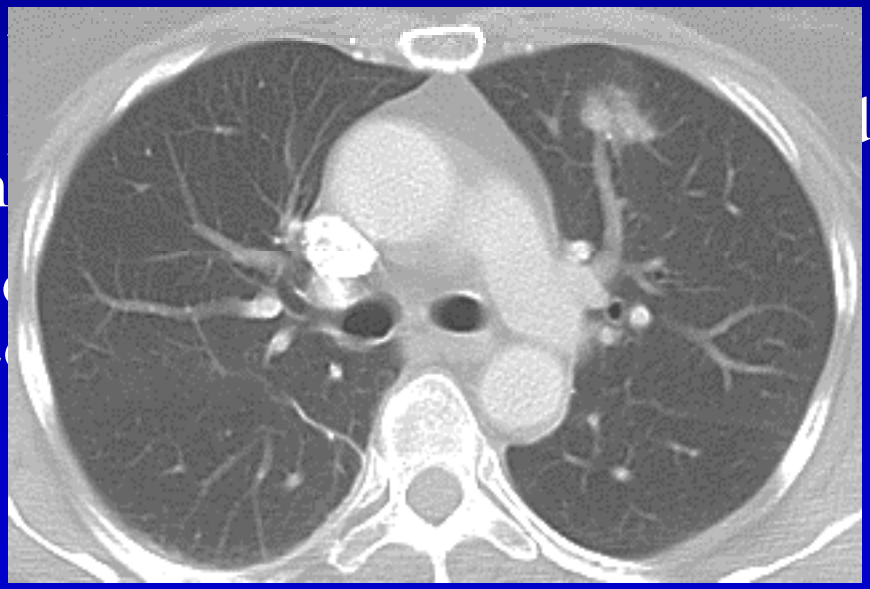
Tumors should be considered multifocal GG/L lung cancer if:

There are multiple sub-solid nodules (either pure ground glass or part-solid), with at least one suspected (or proven) to be cancer.



ot the nodules have been biopsied

odules(s) are suspected to be AIS, IIA or LPA



- GGN lesions <5mm or lesi

Multifocal GG/L Adenocarcinoma

Systematic Literature Review:

First Author	N	% pN2	% Re-sected	% Multi-focal	CT appearance (% ground glass)			% BAC[a] Histology		% 5-year Survival	
					<50%	>50%	Pure	Mixed	Pure	all	pN0
Ishikawa	93	8	100	87	26	51	22	-	-	87	93
Vazquez[b]	49	10[c]	100	100	42	23	34	74	12	-	100
Nakata	31	6	100	84	28	43	29	69[d]	31	93	-
Ebright	29[e]	3[c]	100	100	-	-	-	66	34	68	-
Mun[b]	27	0	100	93	0	-	-	14	86	100[f]	100[f]
Kim	23	0	100	100	0	0	100	0	69	100	100
Roberts	14	0	100	100	-	-	-	14	57	64	64
Average										**85**	**91**

Inclusion criteria: studies involving multifocal lung cancer and ≥10 patients from 1995-2015.

[a]bronchioloalveolar carcinoma (term was in use at the time these papers were written)

[b]involving primarily pts detected by CT screening for lung cancer [c]N1 and N2 combined

[d]Includes adenocarcinoma [e]pts with pneumonic (infiltrative) adenocarcinoma excluded

Multifocal GG/L: Recurrence Pattern

Systematic Literature Review:

1st Author	N	Type	Recurrence Type (%)				
			New 1º	Lung	N2,3	L+D	D
Ebright[u]	47	Pure GG	43	38		10	10
Mun[b]	27	Pure GG	100	0		0	0
Ebright[u]	21	>50% GG	50	30		10	10
Ebright[u]	32	<50% GG	62	23		0	15
Ishikawa	93	Multifocal	-[c]	(53)[c]	(29)[c]	-	(18)[c]
Regnard[a]	61	BAC[d]	-[c]	(55)[c]	(15)[c]	-	(30)[c]
Average[e]			**64**	**23**		**5**	**6**

Inclusion criteria: studies reporting recurrence patterns in multifocal lung cancer and ≥10 pts from 1995-2015.

[u]included pts with unifocal disease [b]involving primarily pts detected by CT screening

[c]data for new primary cancers not reported [d]pre-1999 definition

[e]excluding values in parentheses

Multifocal GG/L Tumors - Management

Less investigation needed to confirm clinical stage

Manage each nodule individually →

- Observe if it doesn't meet criteria for intervention
- Resect if meets criteria for intervention (prefer segmentectomy)

Rationale:

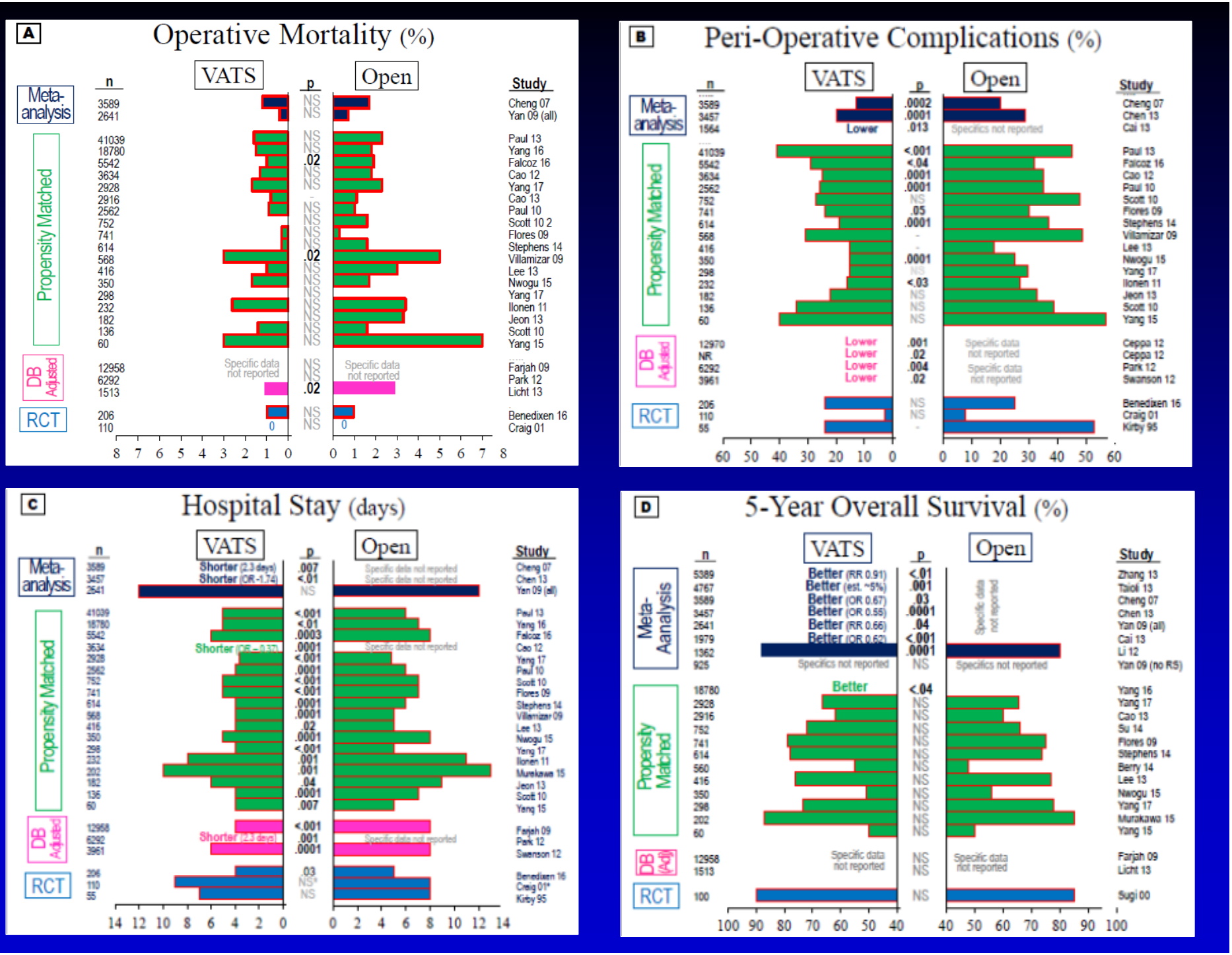
- often indolent, many do not progress
- low propensity for nodal or distant metastases,
- higher propensity for development of new lung cancers

Advances in Surgery

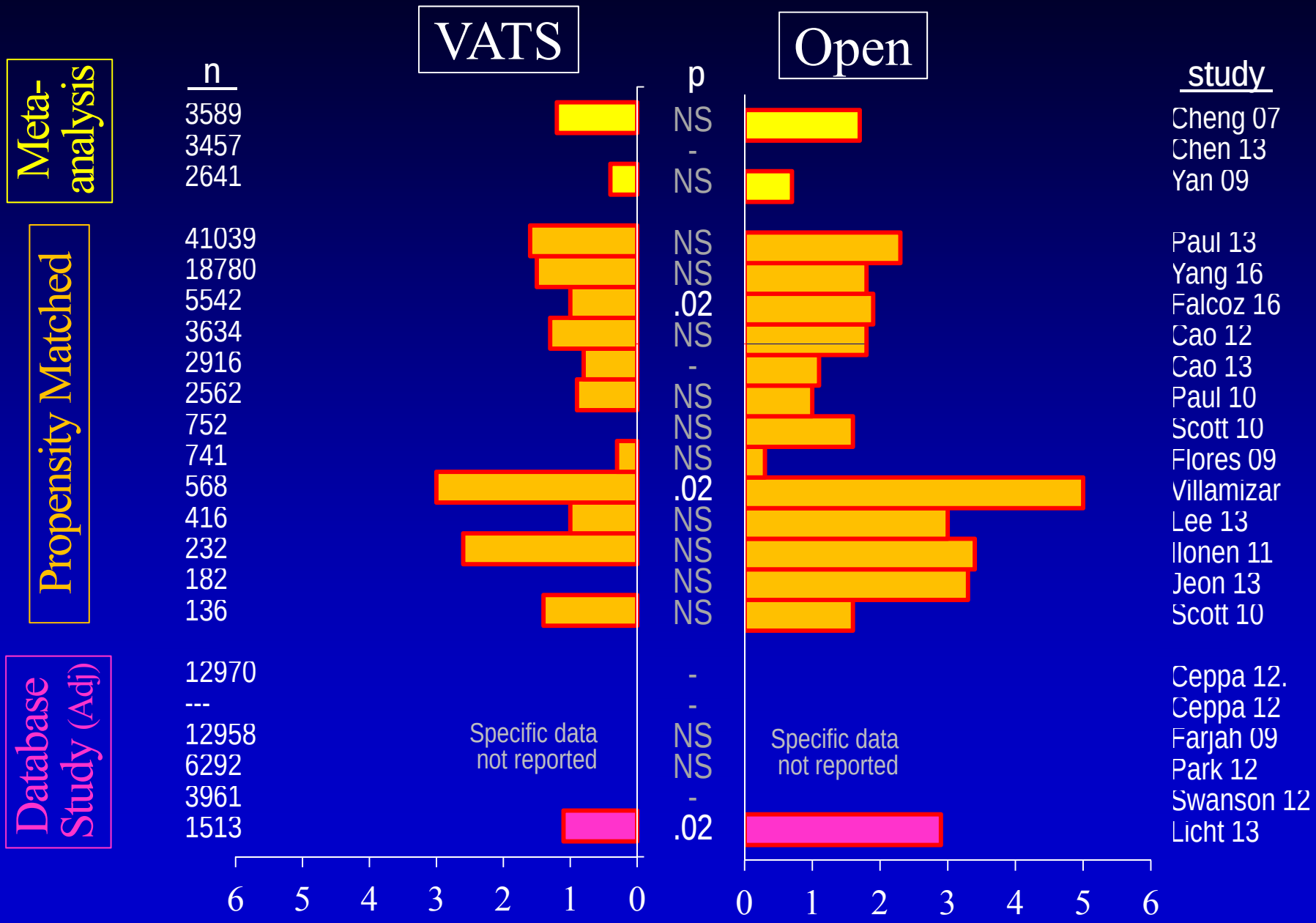
Minimally Invasive Surgery

5 cm incision
No rib spreading

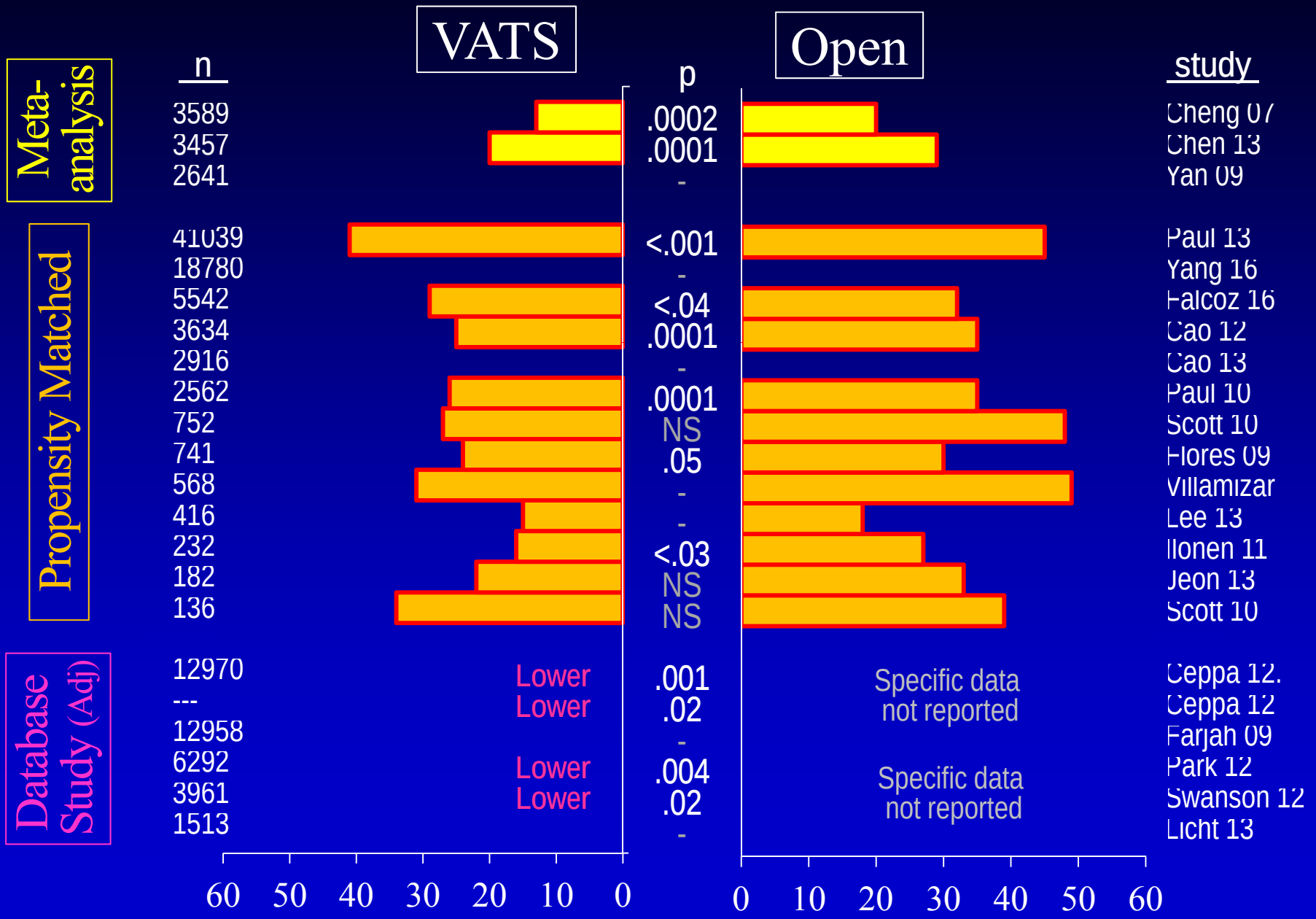
Additional
5 & 10 mm
incisions

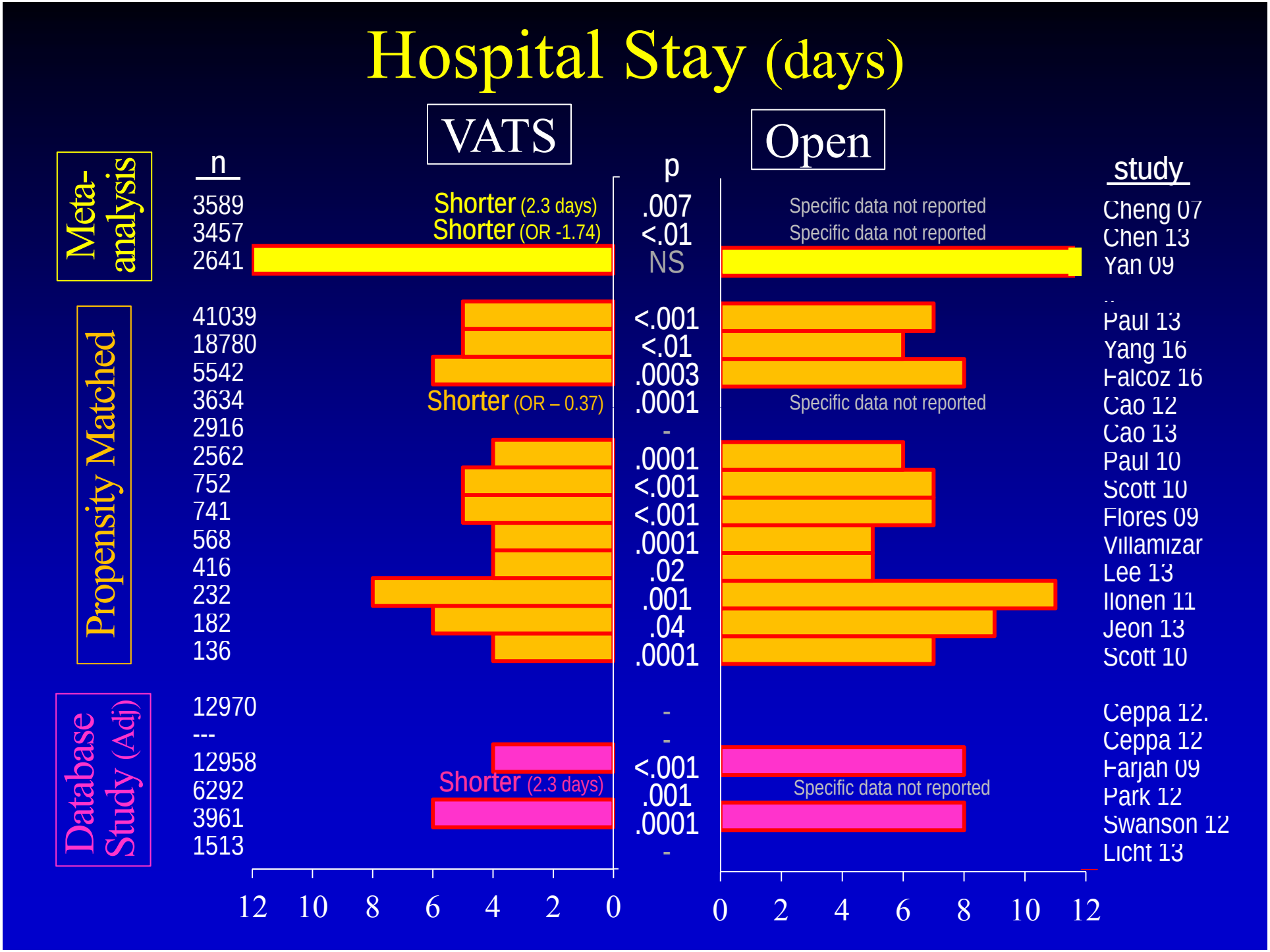

A
Operative Mortality (%)
VATS
Open
n
p
Study
Meta-analysis
Propensity Matched
DB Adjusted
RCT
Specific data not reported
Cheng 07
Yan 09 (all)
Paul 13
Yang 16
Falcoz 16
Cao 12
Yang 17
Cao 13
Paul 10
Scott 10 2
Flores 09
Stephens 14
Villamizar 09
Lee 13
Nwogu 15
Yang 17
Ilonen 11
Jeon 13
Scott 10
Yang 15
Farjah 09
Park 12
Licht 13
Benedixen 16
Craig 01
B
Peri-Operative Complications (%)
Lower
Specifics not reported
Specific data not reported
Ceppa 12
Ceppa 12
Park 12
Swanson 12
Chen 13
Cai 13
Ilonen 11
C
Hospital Stay (days)
Shorter (2.3 days)
Shorter (OR ~1.74)
Shorter (OR ~0.37)
Mureakawa 15
D
5-Year Overall Survival (%)
Better (RR 0.91)
Better (est. ~5%)
Better (OR 0.67)
Better (OR 0.55)
Better (RR 0.66)
Better (OR 0.62)
Better
Meta-Aanalysis
Zhang 13
Taioli 13
Cheng 07
Chen 13
Yan 09 (all)
Cai 13
Li 12
Yan 09 (no RS)
Yang 16
Yang 17
Cao 13
Su 14
Flores 09
Stephens 14
Berry 14
Lee 13
Nwogu 15
Yang 17
Murakawa 15
Yang 15
Farjah 09
Licht 13
Sugi 00

Operative Mortality (%)



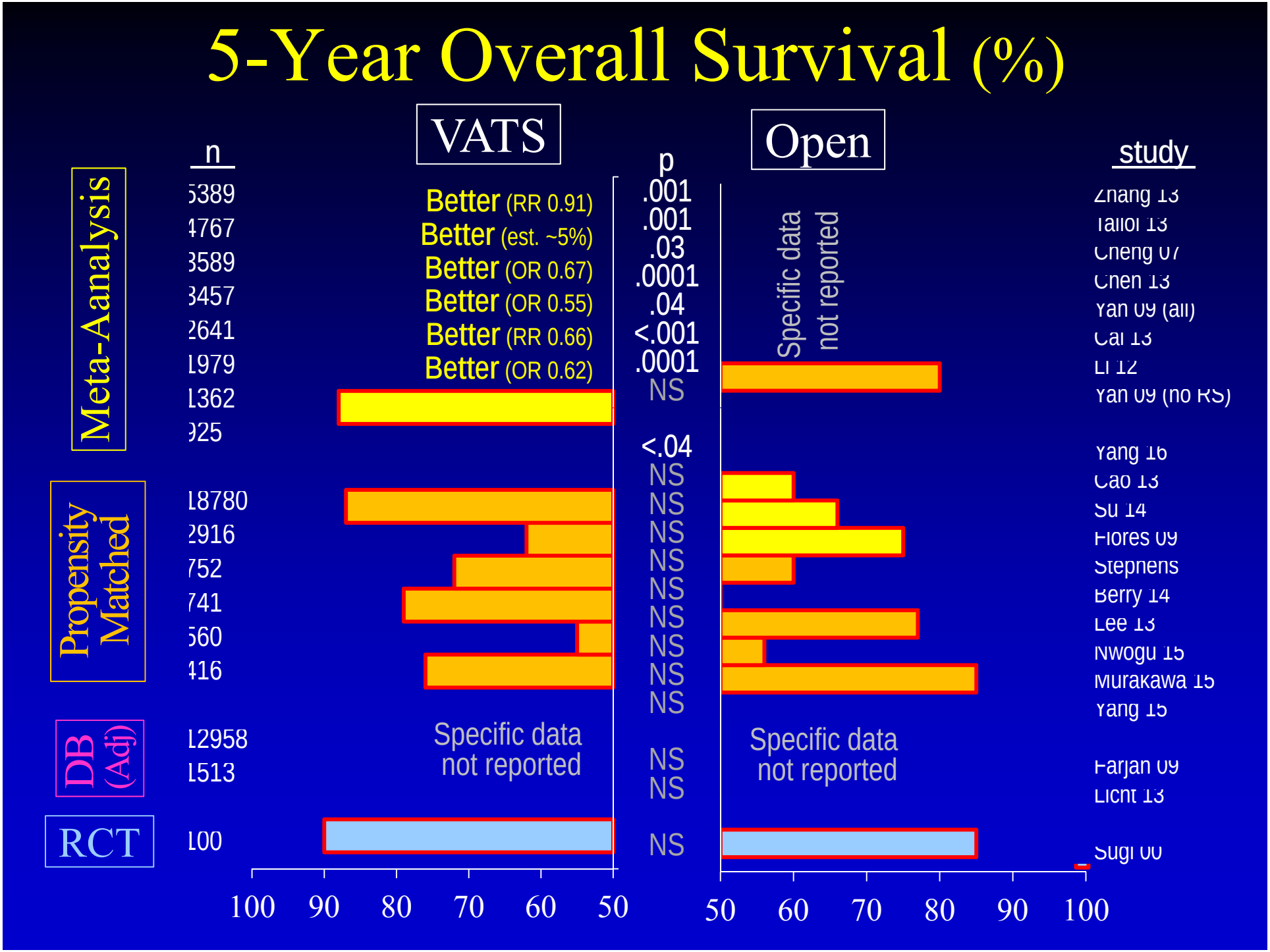
Peri-Operative Complications (%)




Hospital Stay (days)
VATS
Open
Meta-analysis
Propensity Matched
Database Study (Adj)
n
p
study
3589
3457
2641
Shorter (2.3 days)
Shorter (OR -1.74)
.007
<.01
NS
Specific data not reported
Specific data not reported
Cheng 07
Chen 13
Yan 09
41039
18780
5542
3634
2916
2562
752
741
568
416
232
182
136
<.001
<.01
.0003
.0001
-
.0001
<.001
<.001
.0001
.02
.001
.04
.0001
Shorter (OR – 0.37)
Specific data not reported
Paul 13
Yang 16
Falcoz 16
Cao 12
Cao 13
Paul 10
Scott 10
Flores 09
Villamizar
Lee 13
Ilonen 11
Jeon 13
Scott 10
12970

12958
6292
3961
1513
-
-
<.001
.001
.0001
-
Shorter (2.3 days)
Specific data not reported
Ceppa 12.
Ceppa 12
Farjah 09
Park 12
Swanson 12
Licht 13
12 10 8 6 4 2 0
0 2 4 6 8 10 12

5-Year Overall Survival (%)



Metaanalysis: VATS vs Open

36 Studies (3 randomized), 3384 patients, 1995-2007

Intraoperative Outcomes: **Safe**

6% conversion, no Δ transfusion, periop Mortality ~1%

↓ Bl loss (80 ml), ↑ OR time (16 min)

Peri-operative Complications: **Better**

↓ Complications, ↓ Hosp days

Postoperative Pain, Quality of Life: **Better**

↓ Pain (any measure x >3 mo.), ↑ FEV1

↑ return of function, trend to ↑ QOL

Oncologic Aspects: **Equal or Better**

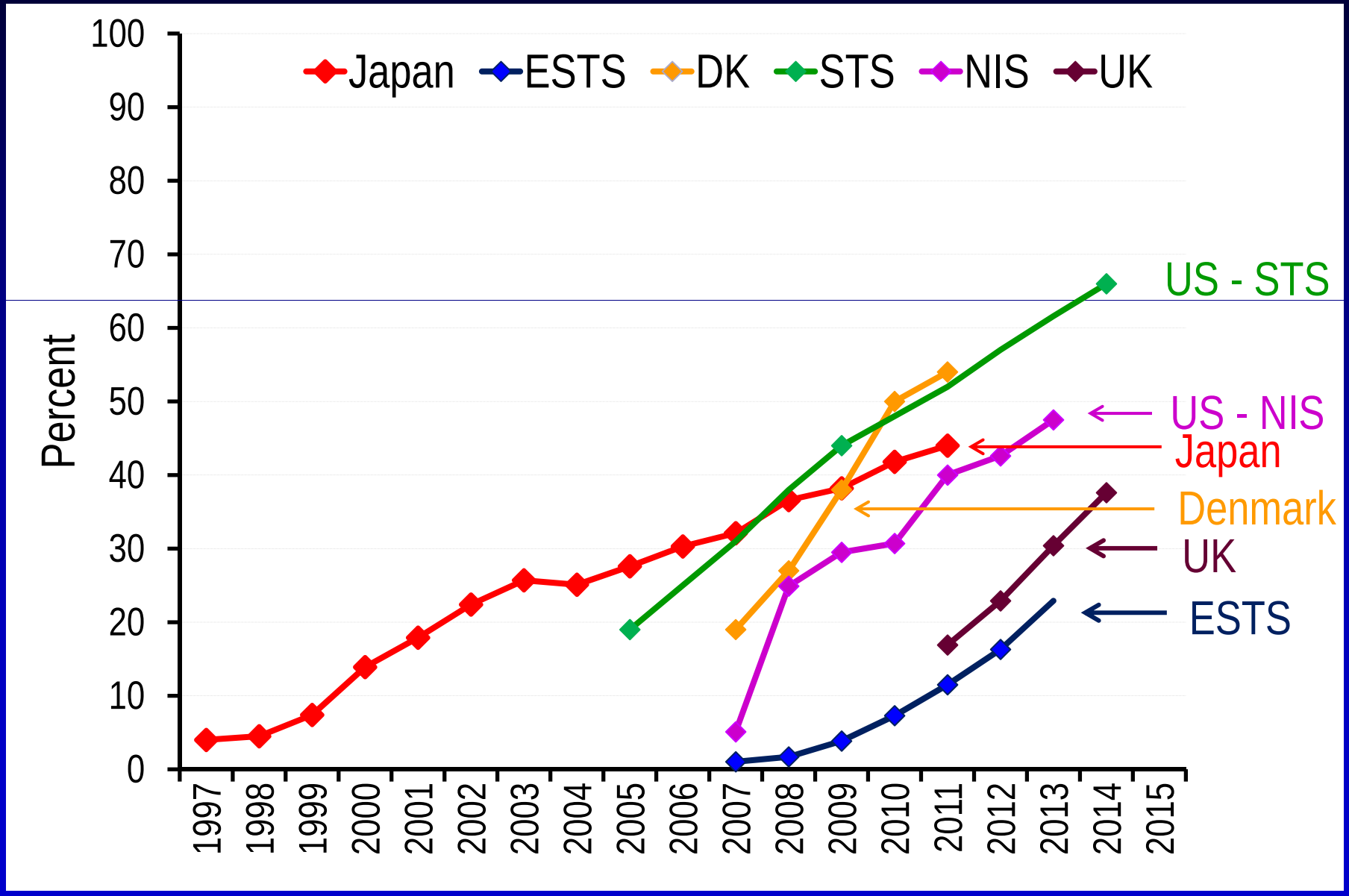
no Δ node staging, ↑ Delivery of adjuvant chemotherapy

Long-Term Outcomes: **Equal**

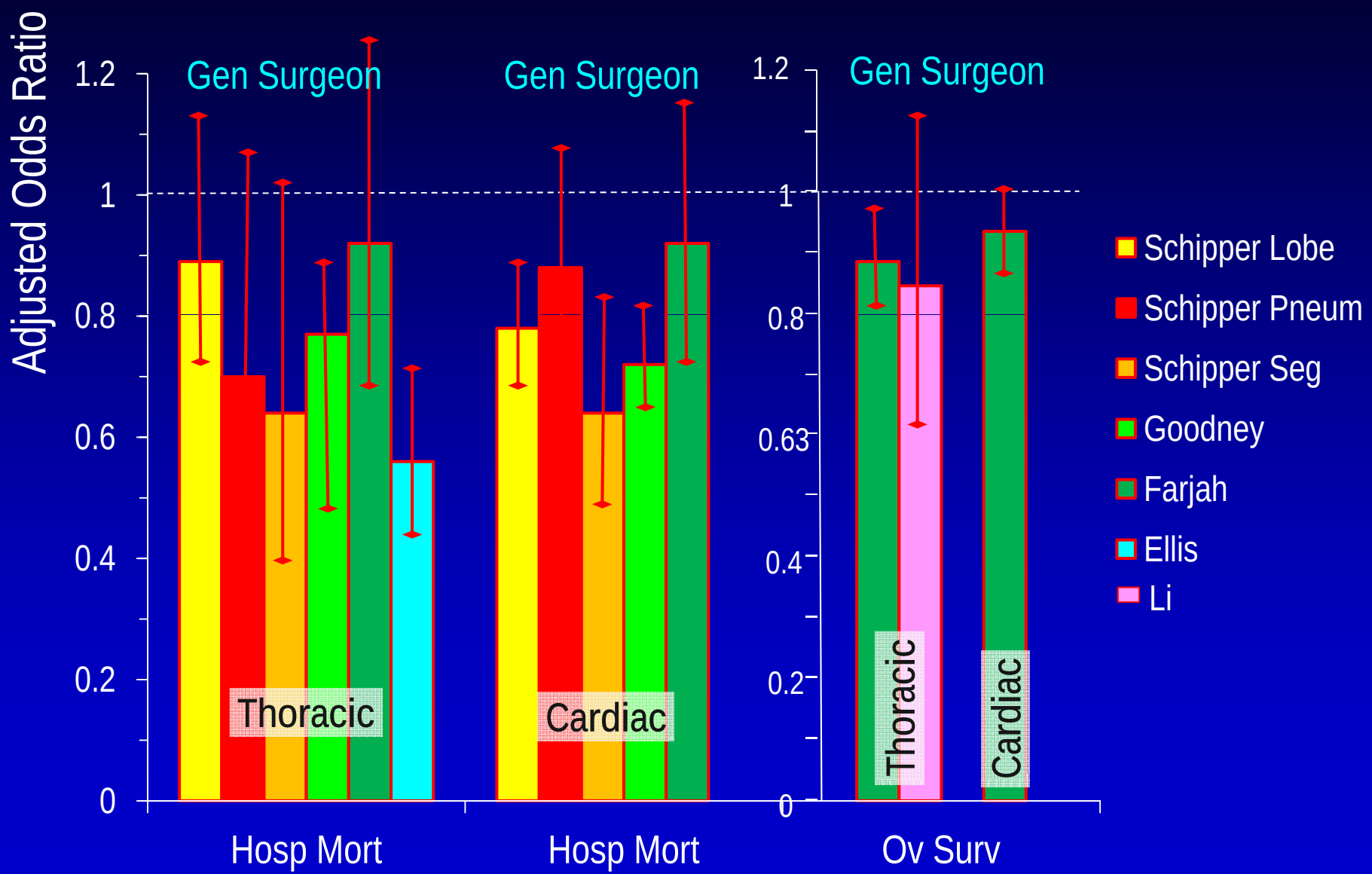
↑ long-term survival

Ref: Cheng. Innovations 2007;2:261-92

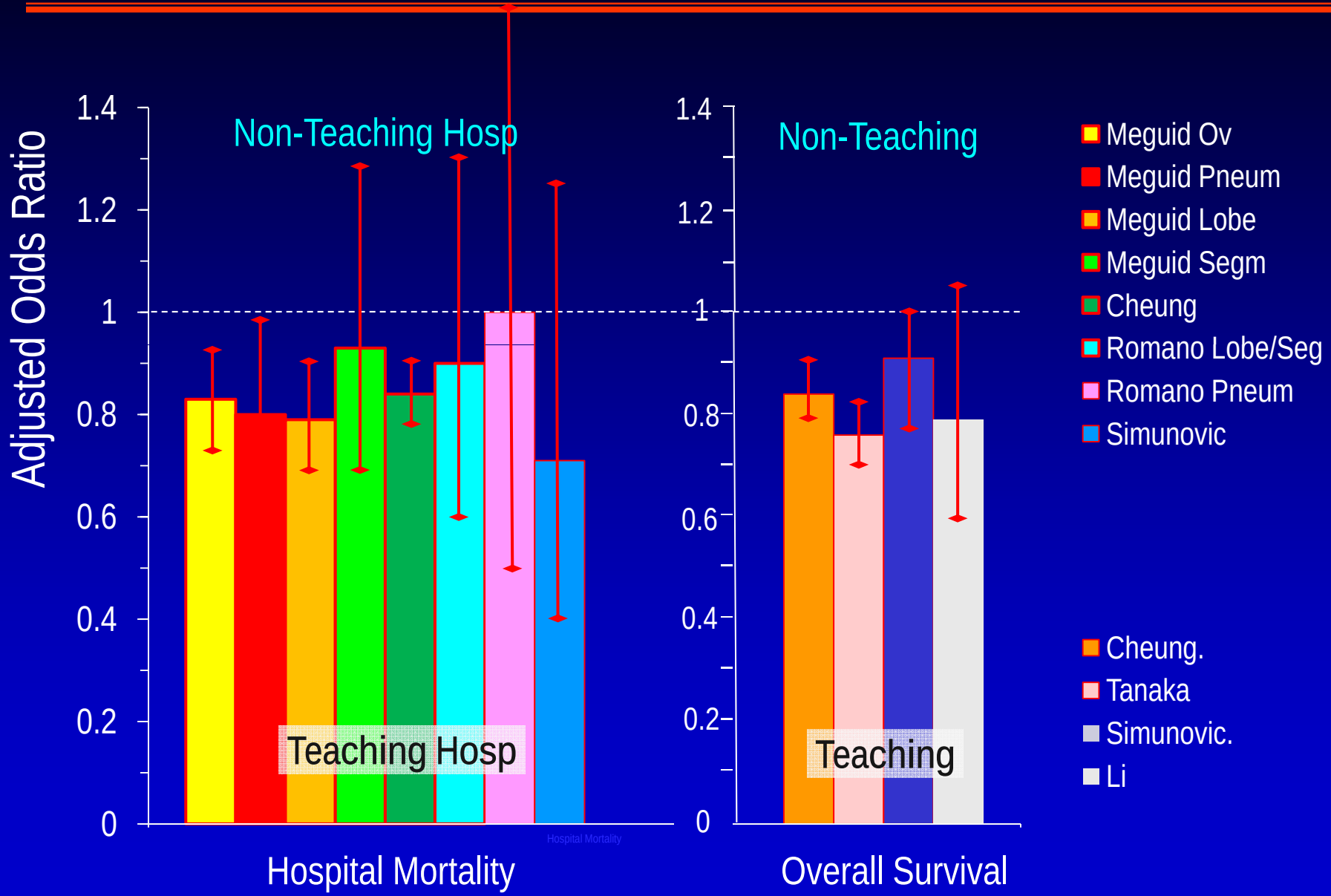
Approach Used for Lobectomy



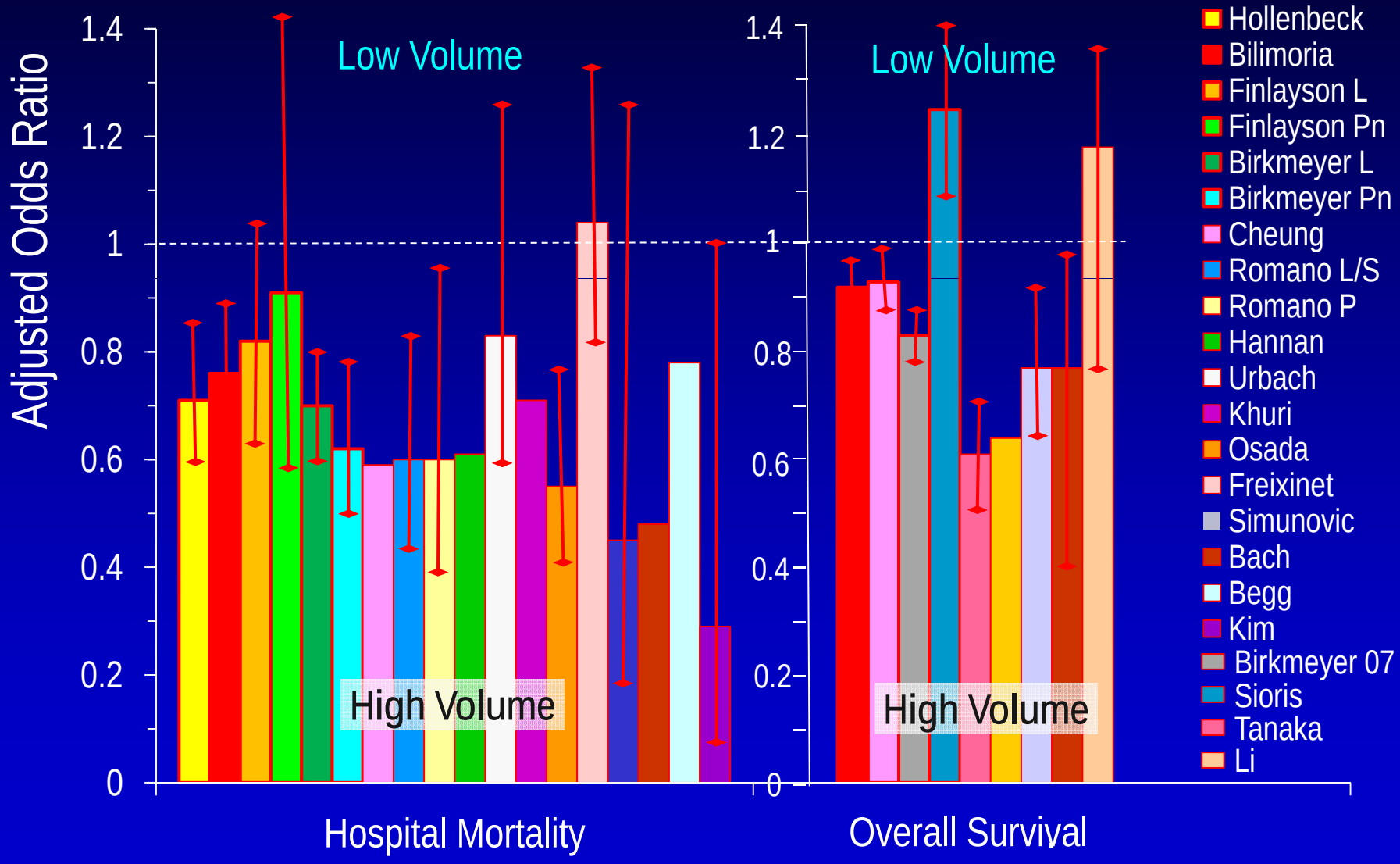
Outcomes according to Specialization



Outcomes according to Hospital Type



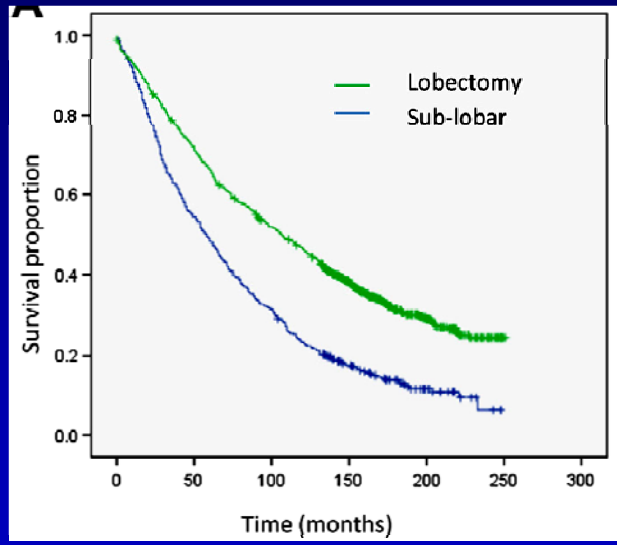
Outcomes according to Case Volume



Trends in SEER for pI ≤2cm NSCLC

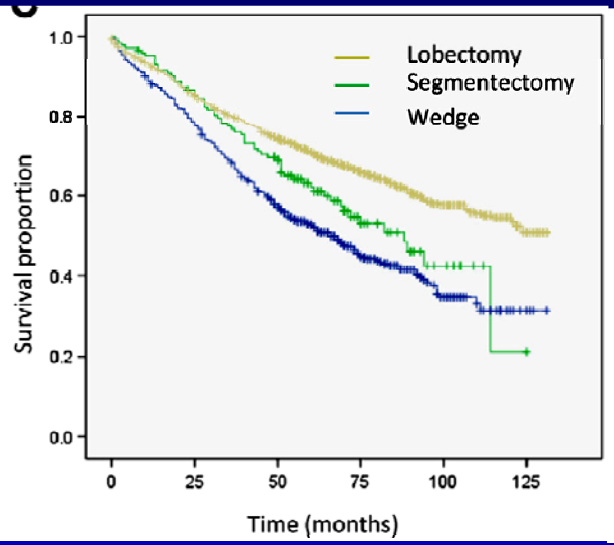
Segmentectomy may be appropriate for some patients

1987-97
n = 1961



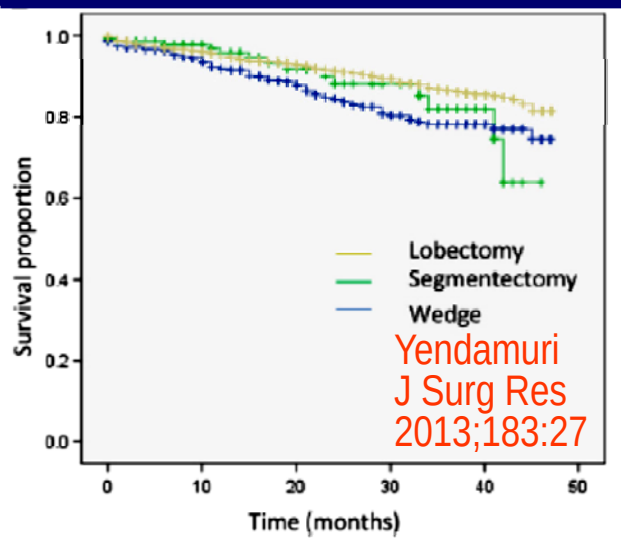
MVA: HR 1.41 (1.21-1.65)
Predates codes for W vs Seg

1998-2004
n = 3327



Wedge-HR 1.19 (1.01-1.41)
Seg – HR 1.04 (0.80-1.36)

2005-08
n = 3509



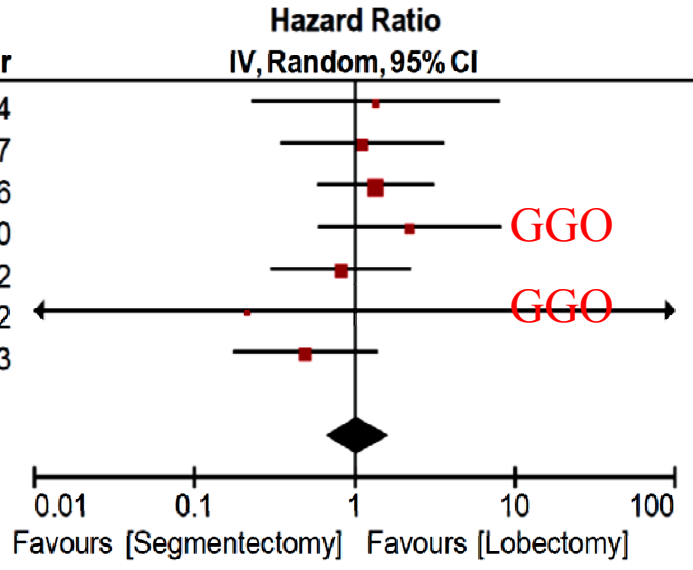
Wedge-HR 1.09 (0.79-1.50)
Seg – HR 0.83 (0.47-1.45)

Meta-analysis: Intentional Segment vs Lobe

Systematic Review (up to Dec 2013), metaanalysis
Subgroup of Intentional Segment vs Lobe for stage I
(7 studies, 1550 pts; > stage I in 5.8% Seg; 4.4% lobe;)
No Difference in OS or DFS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Warren	0.3	0.91	6.3%	1.35 [0.23, 8.03]	1994
Kodama 1997	0.11	0.6	14.6%	1.12 [0.34, 3.62]	1997
Okada	0.3	0.43	28.4%	1.35 [0.58, 3.14]	2006
Sugi	0.79	0.67	11.7%	2.20 [0.59, 8.19]	2010
Yamashita	-0.2	0.51	20.2%	0.82 [0.30, 2.22]	2012
Hamatake	-1.54	282.84	0.0%	0.21 [0.00, 1.216E240]	2012
Tsutani	-0.71	0.53	18.7%	0.49 [0.17, 1.39]	2013
Total (95% CI)			**100.0%**	**1.04 [0.66, 1.63]**	

Heterogeneity: Tau² =0.00; Chi² =3.94, df =6 (P=0.69); I²=0%
Test for overall effect: Z=0.17 (P=0.86)



Overall Survival – HR 1.04 (0.66-1.63)

Ref: Cao Ann CardioThor Surg 2014;3:134-41

Meta-analysis: Intentional Sublobar vs Lobe

Systematic Review, metaanalysis (12 studies, 2745 pts)

Intentional Wedge/Seg for stage I (> stage I in 3% SL; 6% lobe)

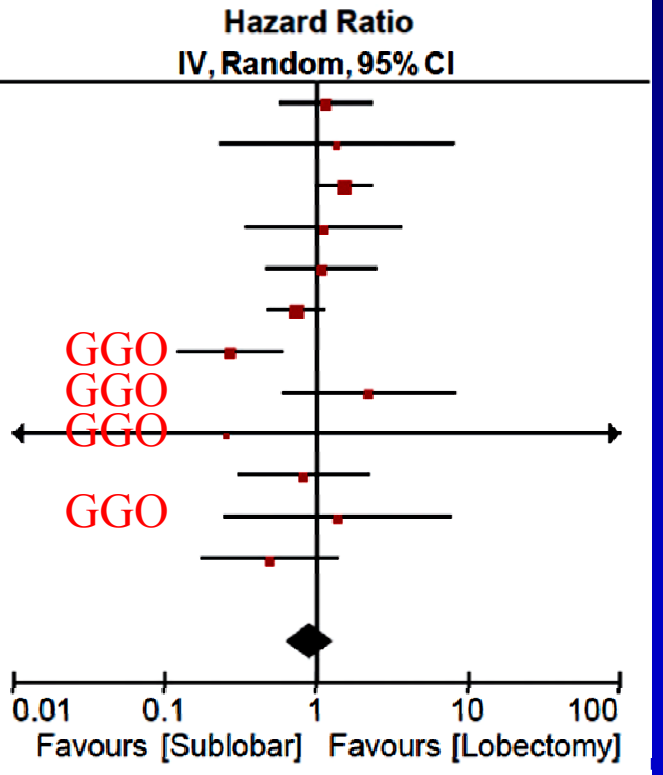
No Difference in OS or DFS

Size ~ 6mm smaller in wedge/Seg (~ 16 vs 22 mm)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Read	0.14	0.36	11.8%	1.15 [0.57, 2.33]	1990
Warren	0.3	0.91	3.3%	1.35 [0.23, 8.03]	1994
Ginsberg	0.42	0.22	17.1%	1.52 [0.99, 2.34]	1995
Kodama 1997	0.11	0.6	6.3%	1.12 [0.34, 3.62]	1997
Koike	0.08	0.43	9.8%	1.08 [0.47, 2.52]	2003
Okada	−0.31	0.22	17.1%	0.73 [0.48, 1.13]	2006
Kodama 2008	−1.31	0.41	10.3%	0.27 [0.12, 0.60]	2008
Sugi	0.79	0.67	5.4%	2.20 [0.59, 8.19]	2010
Ichiki	−1.37	294.88	0.0%	0.25 [0.00, 2.555E250]	2011
Yamashita	-0.2	0.51	7.9%	0.82 [0.30, 2.22]	2012
Hamatake	0.32	0.88	3.5%	1.38 [0.25, 7.73]	2012
Tsutani	−0.71	0.53	7.5%	0.49 [0.17, 1.39]	2013
Total (95% CI)			**100.0%**	**0.91 [0.64, 1.29]**	

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 19.37$, df = 11 (P=0.05); $I^2 = 43\%$

Test for overall effect: Z=0.52 (P=0.61)



Overall Survival – HR 0.91 (0.64-1.29)

Cao. Ann CT Surg 2014;3:134

Types of Non-Randomized Comparisons

Subtype	Key Feature
Probably not confounded comparison	Cohorts well matched or multivariate model accounts for *all* known relevant factors
Possibly only mildly confounded comparison	Cohorts well matched or multivariate model accounts for most relevant factors
Probably confounded comparison	Inability to assess potential differences between cohorts Unclear impact of demonstrated differences
Clearly confounded comparison	Differences in cohorts being compared Known or presumed confounder is inseparable from the intervention

NCDB Outcomes – cT1a N0 M0 NSCLC

National Cancer Database Outcomes study, 2003 to 2011
clinical T1A N0 NSCLC, 13,606 patients
Short-term and long-term outcomes
(30-day mortatity, overall survival)
Detailed analysis - included most major prognostic factors

Propensity matched by all available prognostic factors

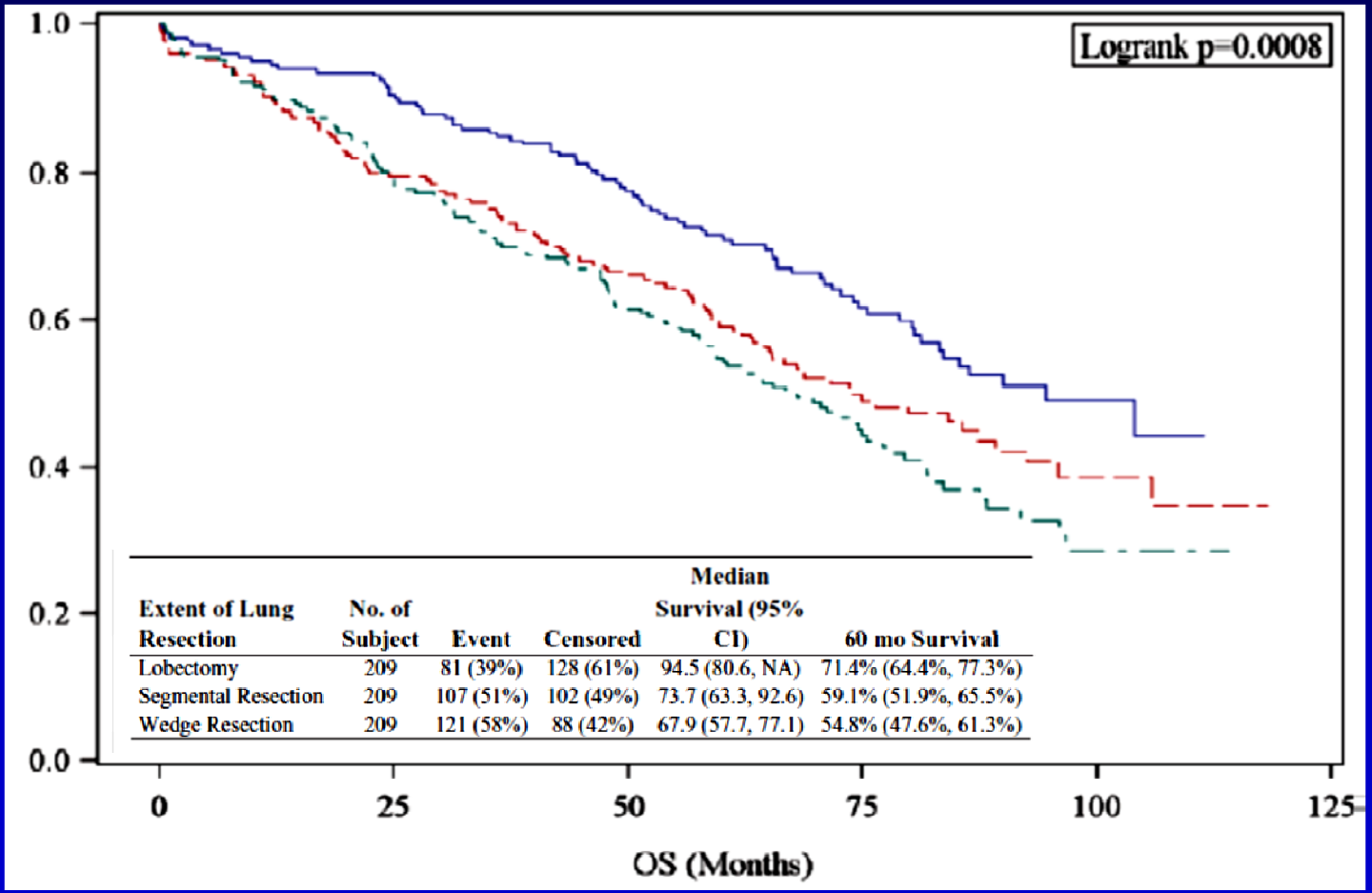
Categorized as a possibly only mildly confounded non-randomized comparison

Ref: Khullar J Thor Onc 2015;10:1625-33

NCDB Outcomes – cT1a N0 M0 NSCLC

Propensity –matched cohorts (n = 209 each)

(age, sex, race, comorbidity; size, histology, grade;
year, hosp type, insurance, income, education, urban/rural)



Extent of Lung Resection	No. of Subject	Event	Censored	Median Survival (95% CI)	60 mo Survival
Lobectomy	209	81 (39%)	128 (61%)	94.5 (80.6, NA)	71.4% (64.4%, 77.3%)
Segmental Resection	209	107 (51%)	102 (49%)	73.7 (63.3, 92.6)	59.1% (51.9%, 65.5%)
Wedge Resection	209	121 (58%)	88 (42%)	67.9 (57.7, 77.1)	54.8% (47.6%, 61.3%)

Lobectomy
Segment
Wedge

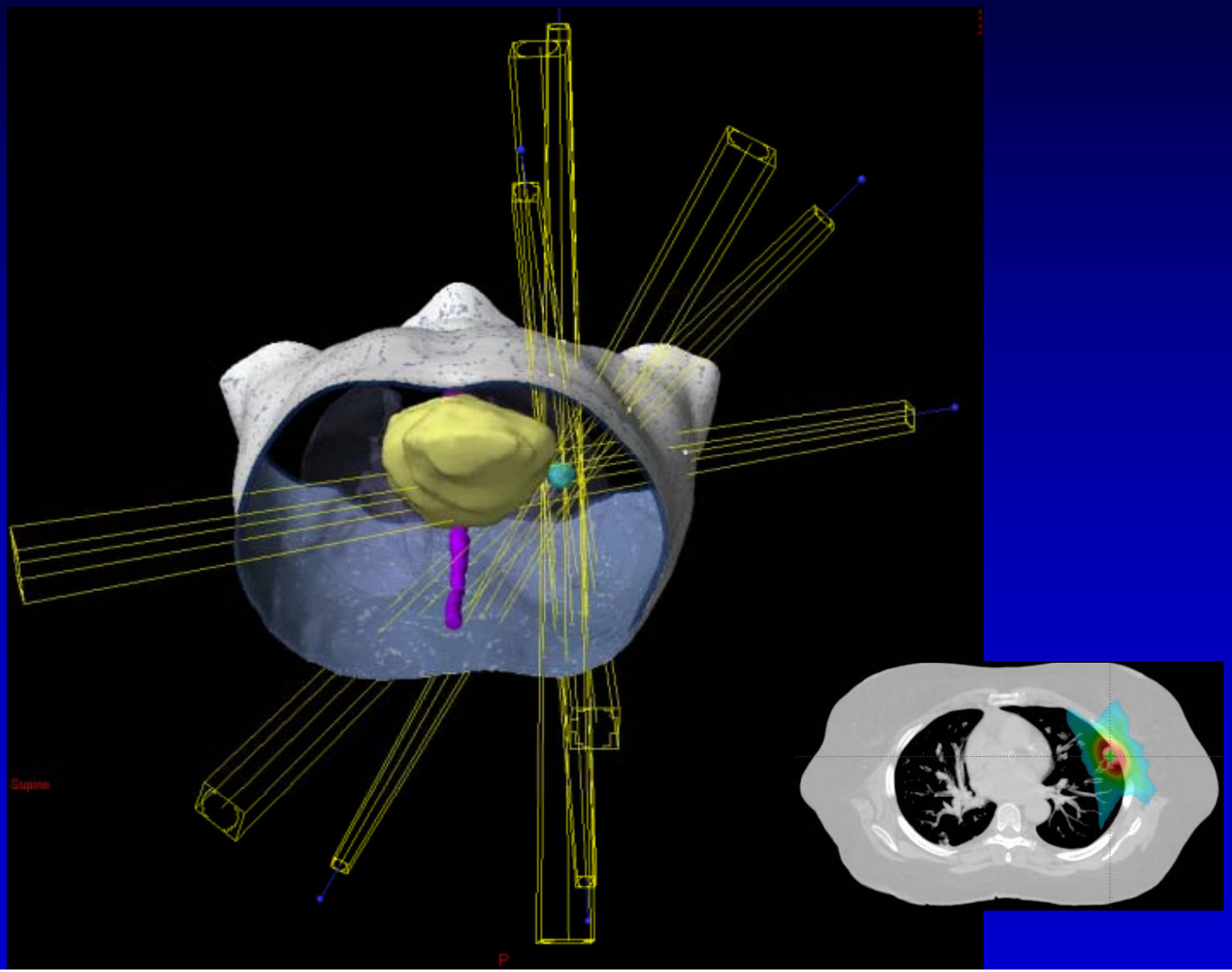
Ref: Khullar J Thor Onc 2015;10:1625-33

Prospective Studies

- CALGB 140503: RCT of lobe vs sublobar
  for T1aN0M0 solid NSCLC
  target accrual ~800
- WJOG 4607I: RCT of lobe vs Segment
  for T1aN0 Adeno semisolid GGO
  target 1100
- JCOG 0804/WJOG 1507I: phase II, wedge or Segment
  for pure GGO ± minimal solid component
  target accrual 330

SBRT – a Valuable Addition

Stereotactic Body Radiation Therapy



Selected SBRT Prospective Reports

Trial	n	Dose	Local Control %	Overall Surv %
Kyoto	45	12 Gy x 4	**94**	83/72 (3-yr)
Scandinavian	57	15 Gy x 3	**92**	60 (3-yr)
Indiana	70	20 -22 x 3	**88**	43 (3-yr)
RTOG 0236	55	20 Gy x 3	**90-97**	56 (3-yr)
Heidelberg	42	19 -30 x 1	**68**	37 (3-yr)
Torino	62	15 Gy x 3	**88**	57 (3-yr)
Tohoku	31	15 x 3, 7.5 x 8	**78/40**	71 (3-yr)
JCOG 0403	100	12 Gy x4		60 (3-yr)
VU Univ	676	Risk - adapted	**90**	64 (2-yr)

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non–Small-Cell Lung Cancer

Inga S. Grills, Victor S. Mangona, Robert Welsh, Gary Chmielewski, Erika McInerney, Shannon Martin, Jennifer Wloch, Hong Ye, and Larry L. Kestin

Retrospective comparison: Stage I NSCLC deemed ineligible for lobectomy

→ no significant differences in:

Local recurrence

4% SBRT v 20% wedge (p=0.07)

Regional recurrence

4% SBRT v 18% wedge

Distant Metastases

19% SBRT v 21% wedge

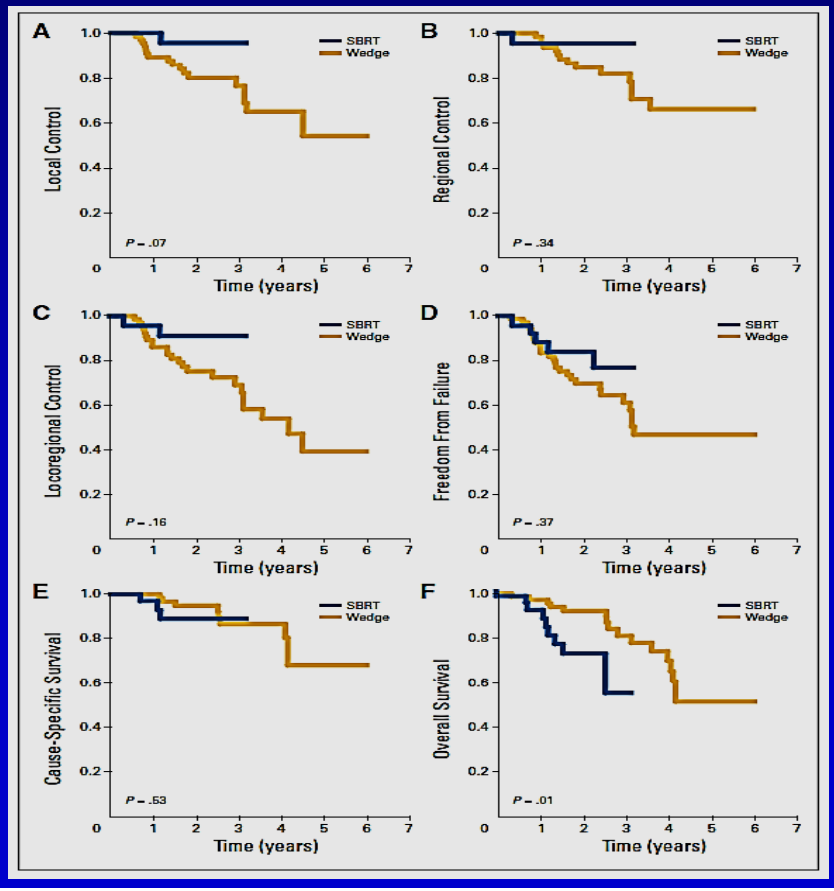
Cause-specific survival

93% SBRT v 94% wedge

Overall survival

72% SBRT v 87% wedge (p=0.01)

Clearly confounded non-randomized comparison

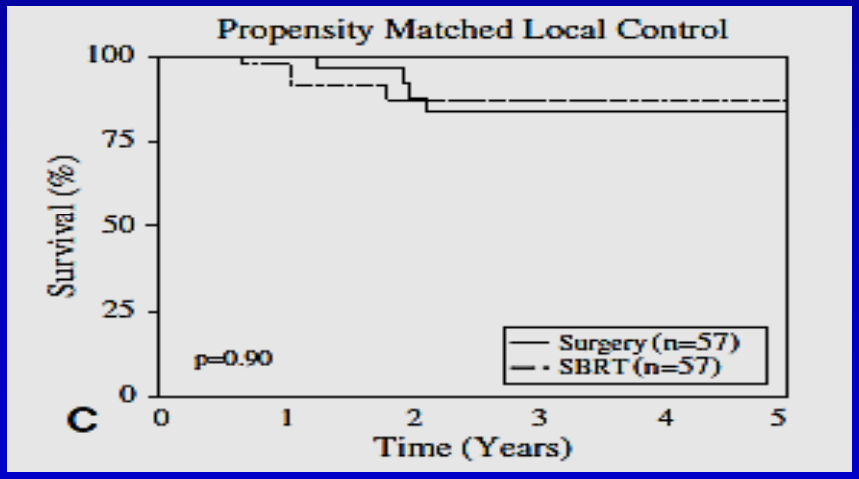


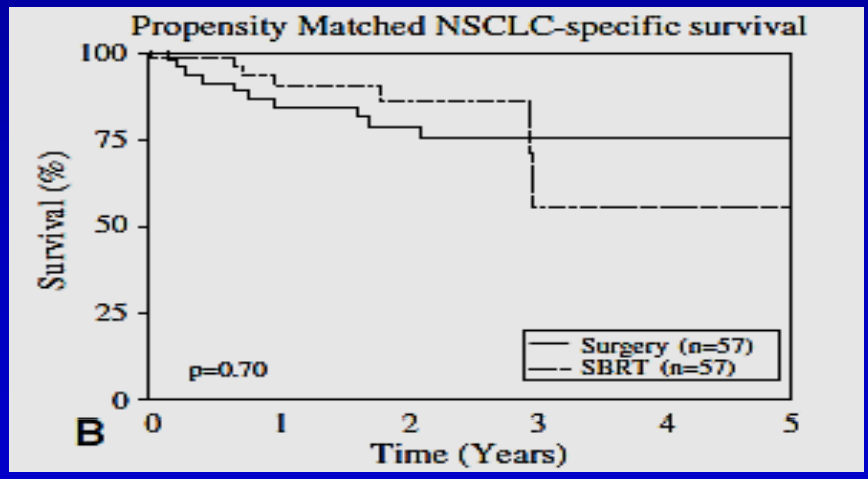
Stereotactic body radiation therapy versus surgical resection for stage I non–small cell lung cancer

Traves D. Crabtree, MD,[a] Chadrick E. Denlinger, MD,[a] Bryan F. Meyers, MD,[a] Issam El Naqa, PhD,[b] Jennifer Zoole, BSN,[a] A. Sasha Krupnick, MD,[a] Daniel Kreisel, MD,[a] G. Alexander Patterson, MD,[a] and Jeffrey D. Bradley, MD[b]

Propensity-matched retrospective review

- stage I NSCLC, included sub-lobe up to neumonectomy
- No difference in 4-year local control (90%)
- No difference in 4-year regional control (80%)
- No difference in NSCLC-specific survival





Probably confounded non-randomized comparison

SBRT for Operable Patients
Prospective Randomized Trials

Randomized

ROSEL Closed due to poor accrual
lobectomy versus SBRT

STARS Closed due to poor accrual
lobectomy versus SBRT (cyberknife)

ACOSOG Z4099/RTOG 1021 Closed due to poor accrual
sub-lobar resection versus SBRT

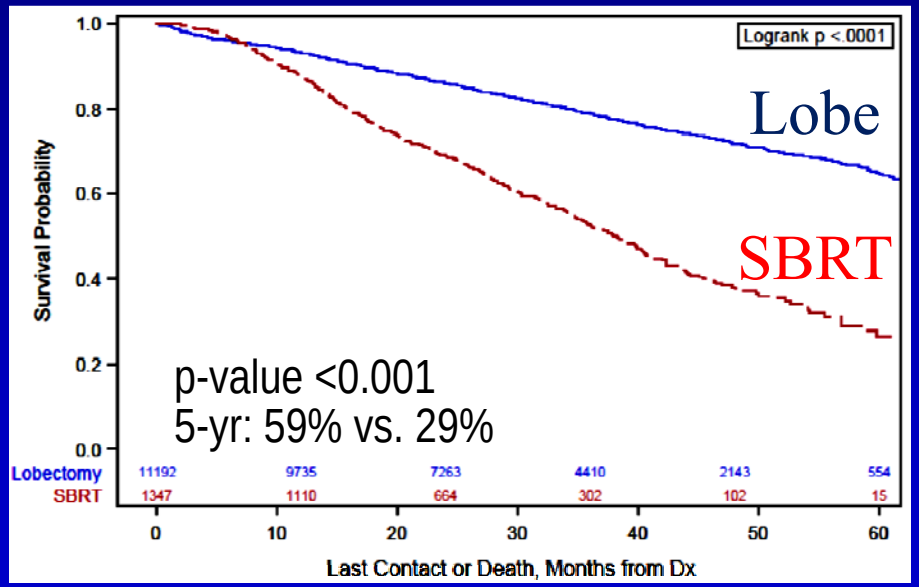
SABR-Tooth –ongoing, but

STABLEMATES-ongoing, but

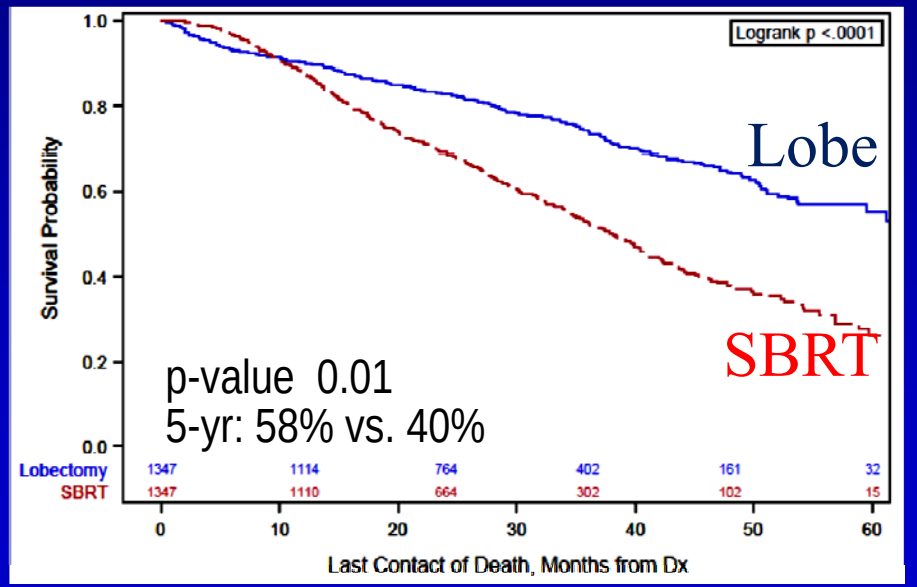
VALOR - ongoing, but…

NCDB - Healthy cI NSCLC (no comorbidities)

- NCDB 2008-12 healthy cI pts: 13,562 Lobectomy, 1781 SBRT (BED 100-200)
- Propensity matched (1,781 pairs; matched for age, sex, race, T size, T site, cT stage, histotype, grade, insurance, income, education, rural/urban, facility type, location)
- Subset recommended for lobe, but refused (256 matched pairs)



Propensity Matched Pairs



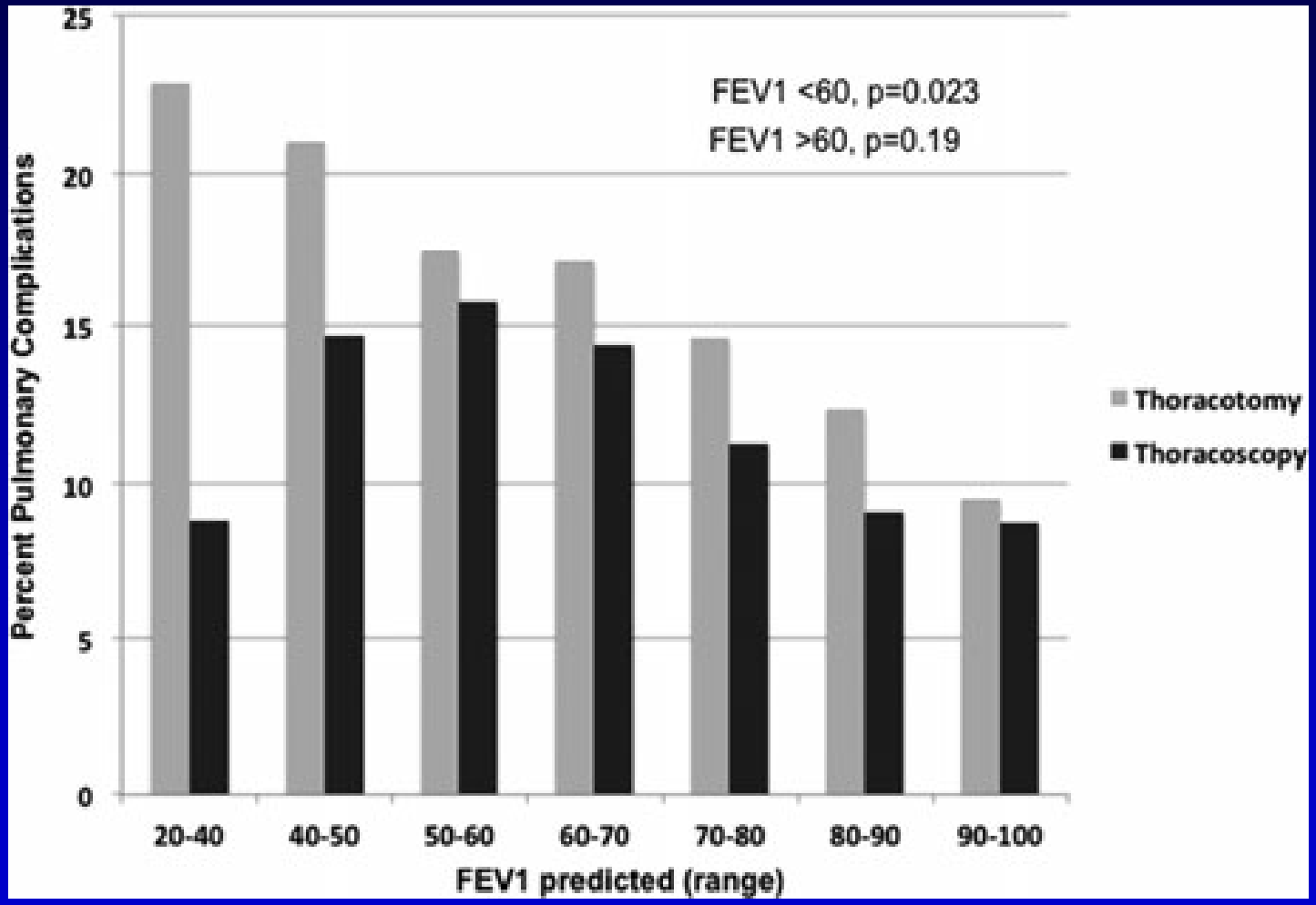
Lobe recommended, P-matched

Possibly only mildly confounded non-randomized comparison

Approach to the Compromised Patient

Outcomes in Compromised Pts

STS DB 2000-10, 12,970 lobectomies for Lung Cancer



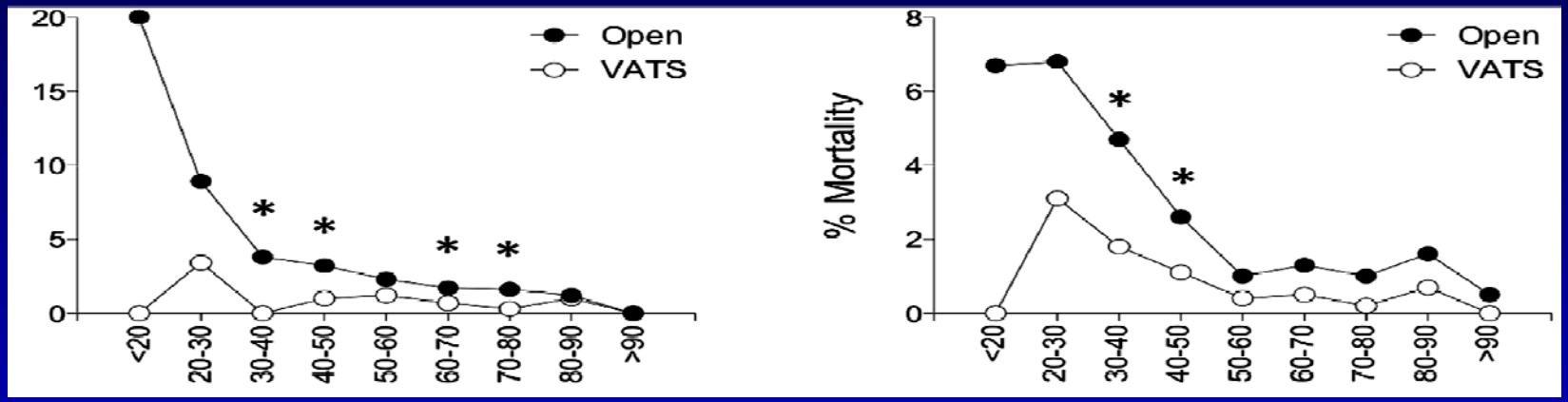
Ref: Ceppa Ann Surg 2012;256:487-93

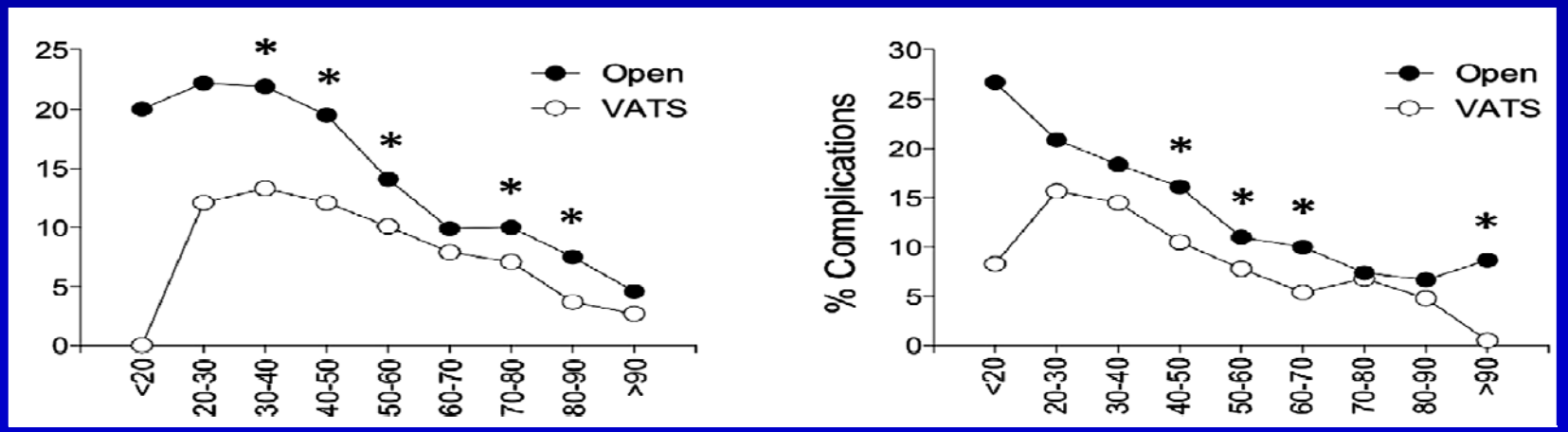
Outcomes in Compromised Patients

STS DB Lobectomies 2009-11 (n = 13,376)

ppoFEV1 %

ppoDLCO %





Ref: Burt JTCVS 2014;148:19-29

Outcomes in Compromised Patients

	1st Author, year	n	Source	Criteria	% Op Mort	% Complicatn	
						all	pulm
VATS	Sandri 15	141	Leeds	>75 yr, CAD, FEV1/DLCO <50	1.5		21[CP]
	Berry 10	47	Duke	ppoFEV1 ≤45%	-	-	13
	Berry 10	28	Duke	ppoDLCO ≤45%	-	-	14
	Burt 14	210	STS	ppoFEV1 30-40%	0		13[CP]
	Burt 14	127	STS	ppoDLCO 30-40%	1.7		14[CP]
	Zhang 15	350	Sys Rev	ppoFEV1/DLCO ≤40%[b]	2.5	39	26
	Ceppa[c] 12	-	STS	ppoFEV1 ≤40%	-	-	18
	Burt 14	58	STS	ppoFEV1 20-30%	3		12[CP]
	Burt 14	24	STS	ppoDLCO 20-30%	2.9		16[CP]
Open	Berry 10	40	Duke	ppoFEV1 ≤45%			45
	Berry 10	27	Duke	ppoDLCO ≤45%	-	-	37
	Burt 14	260	STS	ppoFEV1 30-40%	3.5		22[CP]
	Burt 14	148	STS	ppoDLCO 30-40%	4.4		18[CP]
	Zhang 15	257	Sys Rev	ppoFEV1/DLCO ≤40%[b]	7.8	58	46
	Ceppa[c] 12	-	STS	ppoFEV1 ≤40%	-	-	23
	Burt 14	45	STS	ppoFEV1 20-30%	7.5		22[CP]
	Burt 14	30	STS	ppoDLCO 20-30%	5.5		21[CP]

Outcomes in Older Patients

Author	Population	N		Morbidity %		Mortality %		5-year survival	
		lobe	SL	lobe	SL	lobe	SL	lobe	SL
Kilic	Stage I, age >75	106	78	25	11.5	4.7	1.3	47	46
Okami	Stage IA, age ≥75	79	54	24	24	-	-	74	68
Dell'Amore	Stage I-IIA age ≥75	218[a]	71	-	-	5.5[a]	2.8	40	38
Shirvani	Stage I SEER-MC	7215	1496	-	-	4	3.7	(75)[b]	(65)[b]
Liu	Stage I, age >70	122	45	-	-	0	0	61	63

[a] includes lobectomy and bilobectomy; [b] 3 year

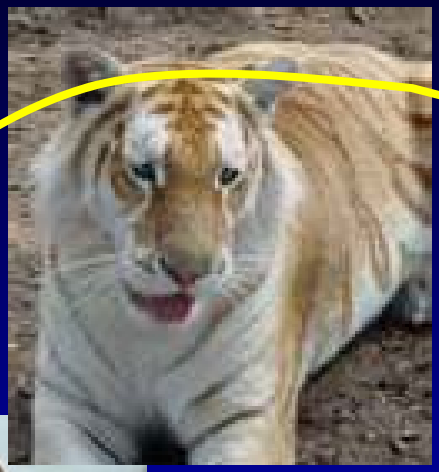
Limited Lung Resection: Outcomes

	Low-Risk Pts	
Surgical Technique	% Op. Mort	% 5yr Surv
Open Lobe	1-4	75
VATS Lobe	1	75
Open Segment	0-1	65
Open wedge	0-1	55

* Source: SWAG

Conclusions

All Beasts come in many Varieties





Tailored Approach: Summary

Binary treat/not treat thinking is inadequate

We know how to identify less aggressive lung cancers

Lung cancer may be a family of different cancers

We should weigh the behavior of (indolent) lung cancer vs co-morbidities

Observation allows you to assess behavior, weigh factors

Waiting for solid component >2mm (on mediastinal windows) is safe, may be best approach

Collect enough data points to be confident, given the variability in assessing small differences, different scans

Advances in Stage I NSCLC

- Consider changes in overall outcomes, understanding of the nature of the cancer in question
  - Focus on solid/invasive component
  - Don't overtreat inconsequential or well-behaved cancers
  - Multifocal GG/L adeno is an easily identified entity – treat each lesion separately as indicated
- Surgical advances: VATS, possibly segmentectomy (but be careful about margins!)
- SBRT: clearly less morbidity, a good alternative in patients in whom surgical risk deemed to be high
- Be critical of confounding factors when assing evidence