RESECTION FOR STAGE I LUNG CANCER: BIGGER IS NOT BETTER

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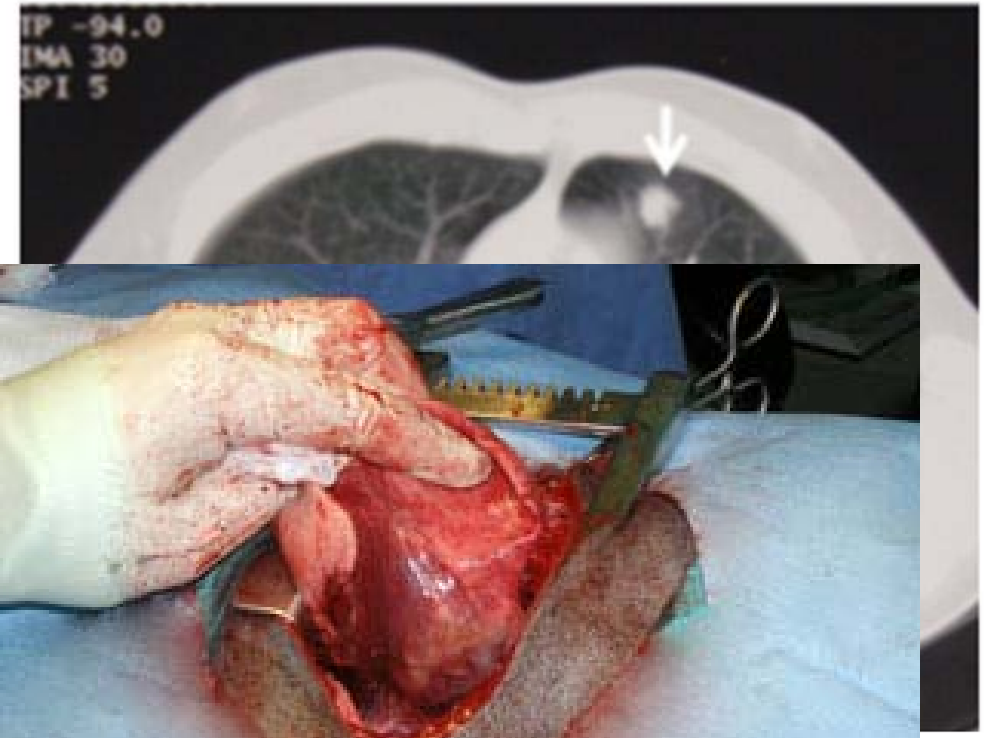
But first, a recap…

- We have debated many times. Here are the topics, and a recap of the last few…
- Pre-operative nutrition
  - Babu pro; Damle con
- Utility of ECMO
  - Babu pro; Damle con
- Transplant vs. LVAD
  - Babu Transplant; Damle VAD
- Thoracic Aneurysm: Open vs. Endovascular
  - Babu Open; Damle Endovascular
- And the winner was…

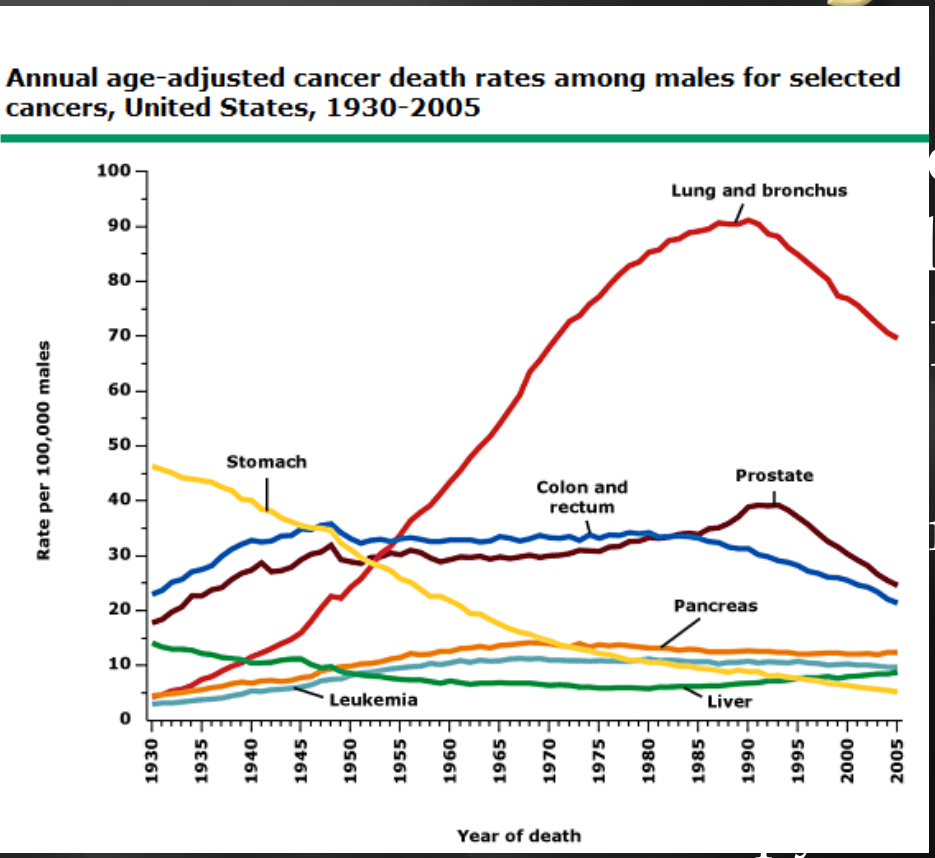
Dr. Babu will argue that…

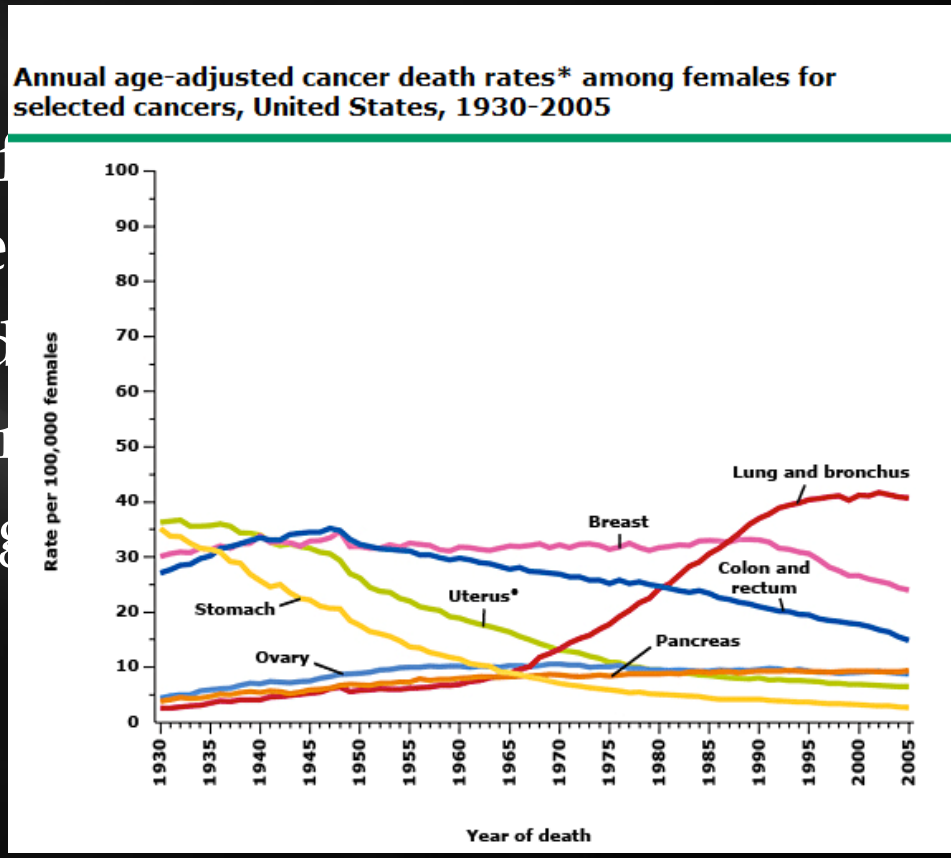


Lung Cancer

- Most common cause of cancer mortality…worldwide
  - 1.2 million deaths worldwide yearly
  - >220,000 deaths in US annually
  - Death in men decreasing, in women stable
- Risk factors
  - Smoking
  - Radiation Therapy

Lung Cancer


Annual age-adjusted cancer death rates among males for selected cancers, United States, 1930-2005
Rate per 100,000 males
Year of death
Lung and bronchus
Stomach
Colon and rectum
Prostate
Pancreas
Leukemia
Liver


Annual age-adjusted cancer death rates* among females for selected cancers, United States, 1930-2005
Rate per 100,000 females
Year of death
Lung and bronchus
Breast
Colon and rectum
Uterus*
Stomach
Pancreas
Ovary

Dx and Staging

- Typical workup: CT Chest, MRI Brain, PET scan
  - Mediastinal staging (PET, EBUS, Mediastinoscopy)

T Staging

	Diam	Scopy	Atelectasis	Invasion	Nodules
T1	T1a ≤ 2cm T1b >2-3cm	No invasion lobar bronchus			
T2	T2a: >3-5cm T2b: >5-7cm or	main bronchus > 2cm to carina	Atelectasis or obstructive pneumonia to hilus not entire lung	visceral pleura	
T3	> 7cm or	< 2cm to carina	Whole lung	Chest wall diafragm phrenic nerve mediast pleura parietal pericard	Nodules in same lobe
T4		Tumor in carina		Heart great vessels trachea esophagus spine	Nodules in other ipsilateral lobes

N Staging

Regional lymph nodes (N)	
N1	In ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes
N2	In ipsilateral mediastinal and/or subcarinal lymph nodes
N3	In contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes

Overall Stage

	T1a	T1b	T2a	T2b	T3	T4
N0	IA		IB	IIA	IIB	IIIA
N1	IIA		IIA	IIB	IIIA	IIIA
N2	IIIA		IIIA		IIIA	IIIB
N3	IIIB		IIIB		IIIB	IIIB

For this debate…

- We will focus on stage Ia tumors
- Which equals:
  - T1 (Tumors < 3 cm in size without involvement of pleura)
    - T1a: <2cm
    - T1b: 2-3cm
  - N0 (No positive nodes)
  - M0 (No distant mets)
- Why is this important?
  - Widespread use of CT
  - Implementation of screening programs.

Why *might* lobectomy be better?

- Wider resection margin
  - ? Improved clearance
  - ? Improved local recurrence
- More nodes sampled
  - ? Impact on survival
- Minimal added cost and hospital stay

Rationale for limited resection

- Patients with lung CA also typically have COPD/emphysema
  - Limited resection better for long-term pulm function
- Smaller operation with quicker recovery
- Most NSCLC are peripheral and amenable to limited resection

In the next slides, I will prove:

1) Short-term: Periop Issues favor Wedge/Limited Resection
    1) Cost and LOS
    2) Pulmonary function
    3) Perioperative morbidity & mortality

2) Long-term: Survival advantage for limited resection (and no significant difference in recurrence)
    1) All comers
    2) Segmentectomy vs lobectomy
    3) Specific histologies

Cost Analysis

Cost Analysis for Thoracoscopy: Thoracoscopic Wedge Resection and Lobectomy

Surg Today
Jpn J Surg (1998) 28:41–45

- Retrospective review 80 patients, early 90s
- Primary focus was VATS vs open
- Results:

	VATS Wedge (30)	VATS Lobe (10)
LOS	10 d	25 d
OR Time	1 h	5 h
Chest Tube Duration	2 d	7 d
Total Hospital Charges	$6,100	$18,000

Pulmonary Function

- LCSG (ATS 1995)

Test	Limited (Mean % Diff)	Lobe (Mean % Diff)	p Value
6 Month FEV1			
6 Month FVC			
12 Month FEV1			

Perioperative Morbidity and Mortality

WEDGE RESECTION VERSUS LOBECTOMY FOR STAGE I (T1 N0 M0) NON-SMALL-CELL LUNG CANCER *Landreneau et al.* (J Thorac Cardiovasc Surg 1997;113:691-700)

- Compared VATS Wedge vs open wedge vs open lobectomy

	Open WR	*VATS WR*	*vs*	*Lobectomy*	*p Value*
Age (yr)	68	71	vs	63	0.0002
COPD (%)	64	69	vs	14	0.001
FEV_1 (% predicted)	69	61	vs	88	0.0001
DLCO (% predicted)	73	51	vs	81	0.001

Sicker Patients

	Open WR	*VATS WR*	*vs*	*Lobectomy*	*p Value*
Operative mortality (%)	0	0	vs	3.3	0.20
Postop. stay (days)	7.7	6.3	vs	10.6	0.0002

Better Outcome

Perioperative Morbidity and Mortality

SUB-LOBAR LUNG RESECTION OF PERIPHERAL T1N0M0 NSCLC DOES NOT AFFECT LOCAL RECURRENCE RATE

Rome, Italy

Scandinavian Journal of Surgery 98: 225–228, 2009

Characteristics of patients of the two groups.

	Lobectomy 116 patients	Sub-lobar resection 36 patients	pValue
Male	99 (85%)	31 (86%)	0,57
Female	17 (15%)	5 (14%)	0,56
Age	64,8 ± 8,7	68,7±8,4	0,01
FEV1	84,9% ± 18,5	71% ± 25,6	0,01
Comorbidities	57 (49%)	26 (72%)	0,02
T1 NO M0	29 (25%)	22 (61%)	0,004
Adenocarcinom	50 (43,1%)	13 (36,1%)	0,58
Squamous cell	45 (38,8%)	10 (27,8%)	0,32
Bronchoalveola	10 (8,6%)	10 (27,8%)	0,007
Indifferentiated	11 (9,5%)	3 (8,3%)	0,9

Periop Summary

- This should come as no surprise. Lobe is a bigger operation that is more dangerous and most costly compared to a limited operation.

IS THERE A SURVIVAL ADVANTAGE?

LCSG: The Trial That Confused Us All

Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non–Small Cell Lung Cancer

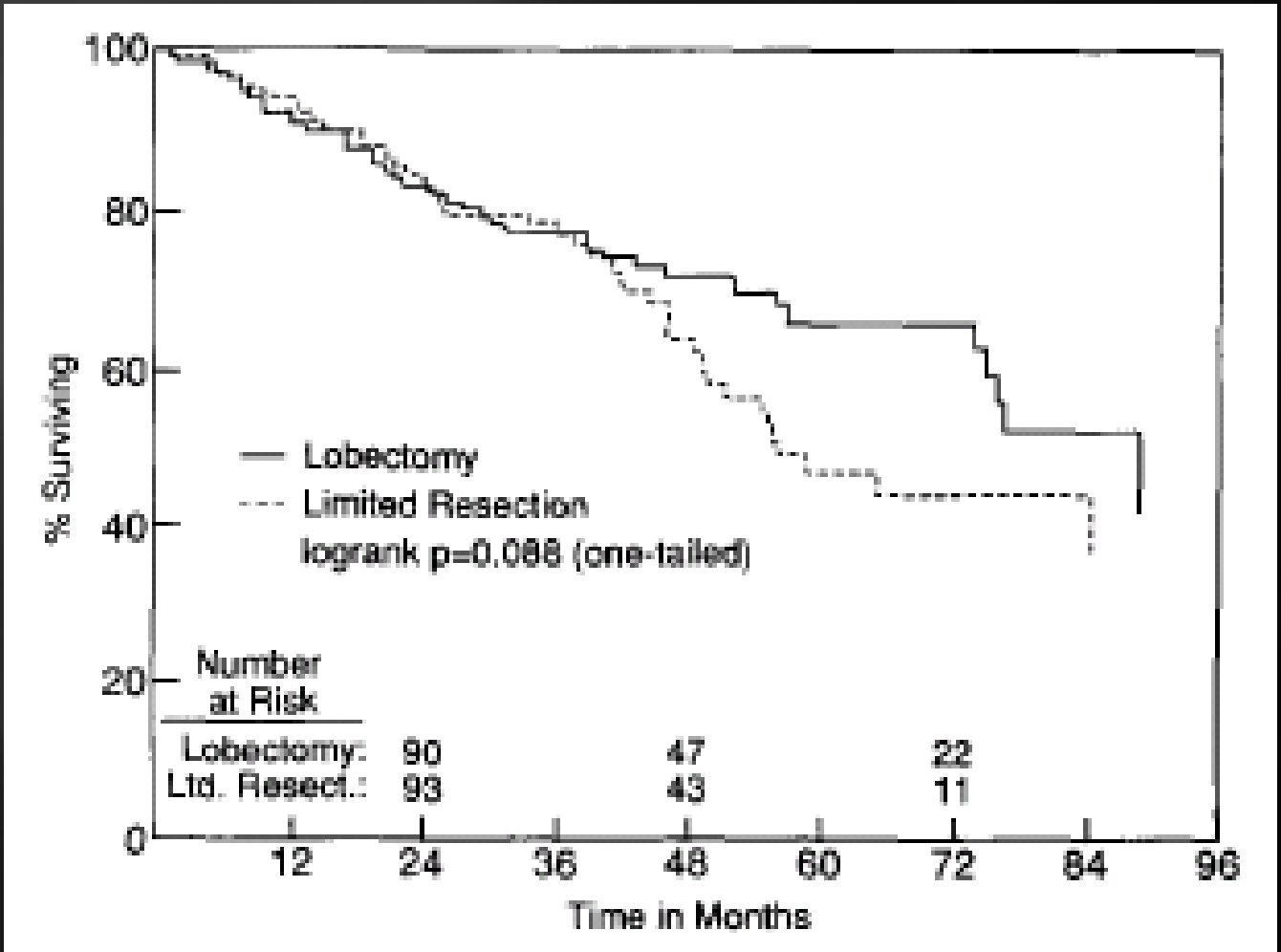
Lung Cancer Study Group (Prepared by Robert J. Ginsberg, MD, and Lawrence V. Rubinstein, PhD)

(Ann Thorac Surg 1995;60:615–23)

LCSG ATS 1995

- 1982-1988
- 247 patients with:
  - <3 cm tumor in all dimensions
  - No evidence of met dz (by labs)
  - Ability to undergo a lobectomy
- "Limited Resection" (122 pts)
  - Wedge with 2 cm margin
  - Segment with anatomical division of vessels and bronchus
  - All patient had lymph node sampling

LCSG ATS 1995

- Mortality Outcome
  - 

LCSG ATS 1995

- Mortality Outcome
  - No significant difference
- Local Recurrence
  - Higher in wedge resection…BUT
  - If you count secondary tumors…
    - Then, there is NO difference

Overall, we should conclude: NO difference

Problems with LCSG

- Few patients
  - 60+% of patient screened were excluded
- Dx by CXR!!!
- Lumped wedges and segmentectomies
- Tumor volume/size in each group not specified.

- Lets jump ahead almost 10 years…

Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

Nigata, Japan

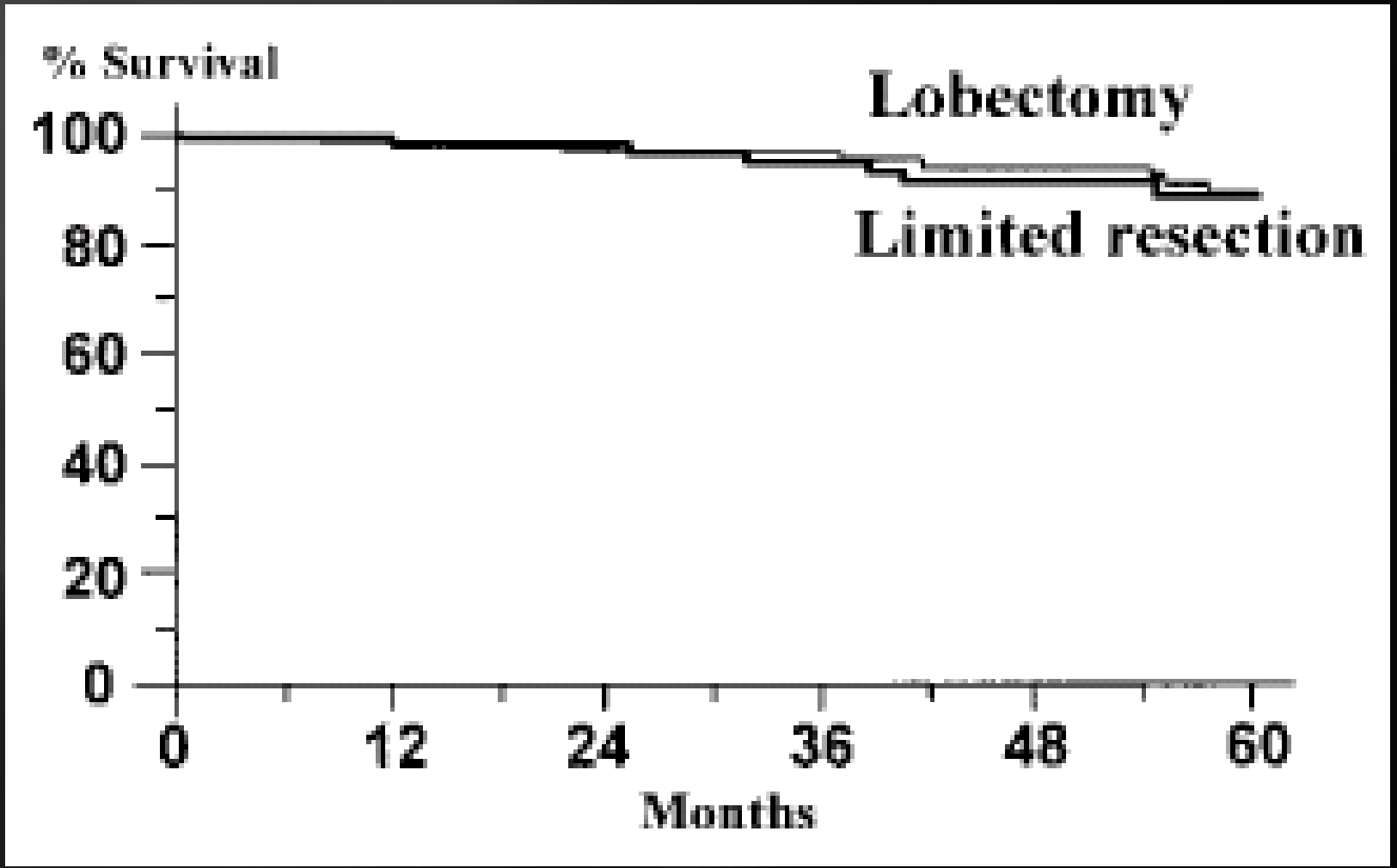
J Thorac Cardiovasc Surg 2003;125:924-928

- Prospective trial, 1992- 2000
  - Patient able to undergo lobectomy, asked to undergo wedge/segment instead
  - NSCLC < 2 cm in size
- Results
  - 74 limited resection (60 segment, 14 wedge), 159 lobes
  - Lymph node dissection variable
  - Primary outcomes: Survival and recurrence

Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

J Thorac Cardiovasc Surg 2003;125:924-928

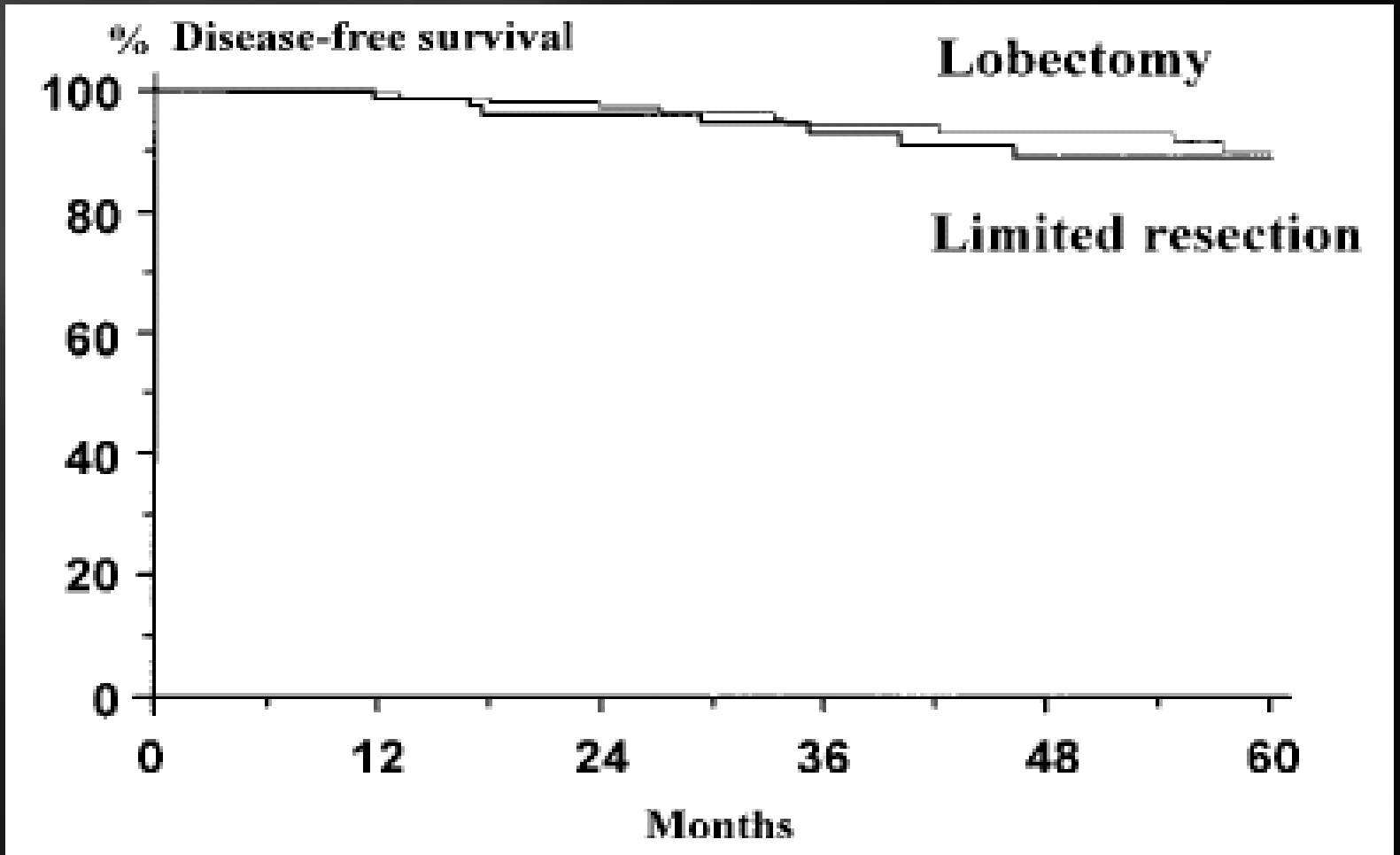
- Survival: IDENTICAL



Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

J Thorac Cardiovasc Surg 2003;125:924-928

- Recurrence: Same



Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

J Thorac Cardiovasc Surg 2003;125:924-928

- Conclusion:
  - Limited resection is an equivalent alternative in patients with T1 tumors < 2 cm in size.

SEER Database

- Run by NCI
- Geographic cancer registry of ~ 28% of population
- 2 papers based on this database
  - Wisnivesky JP et al. Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg 2010; 251:550-554
  - Kates M et al. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer $\leq$ 1 cm in size. Chest 2011; 139:491-496.

SEER Review

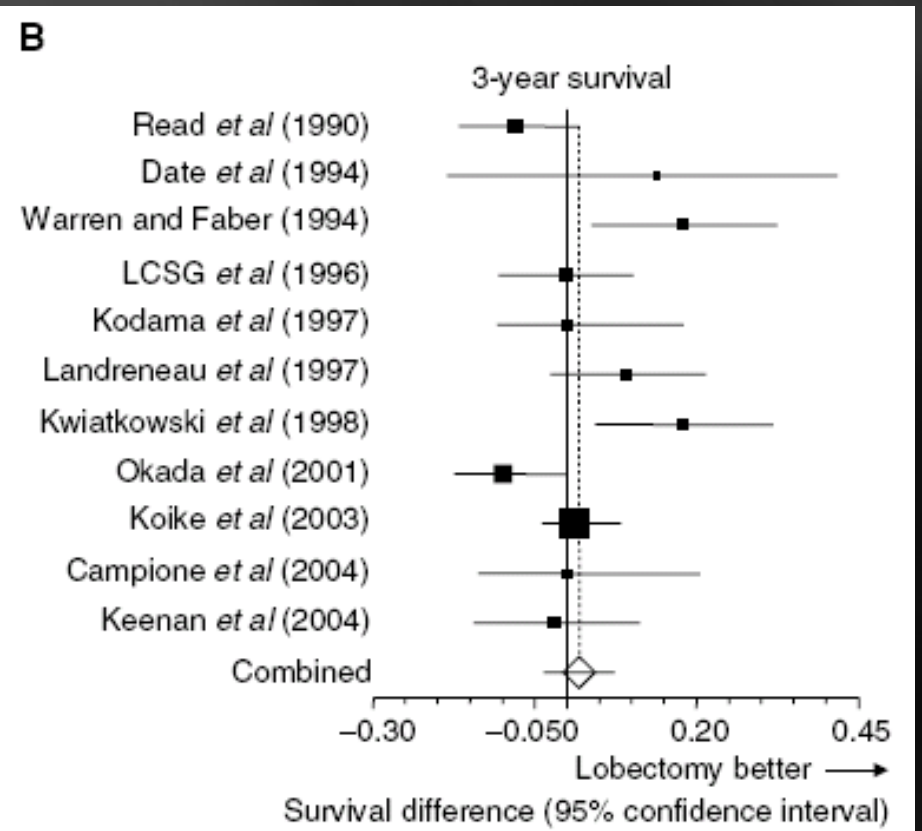
- Ann Surg 2010
  - 1165 patients (Older)
    - 17% limited resection
  - Outcome
    - Mortality the SAME for lesion ≤ 2 cm
- Chest 2011
  - ~2100 patients
    - 33% limited resection
  - Outcome
    - Mortality the SAME for lesion ≤ 1 cm

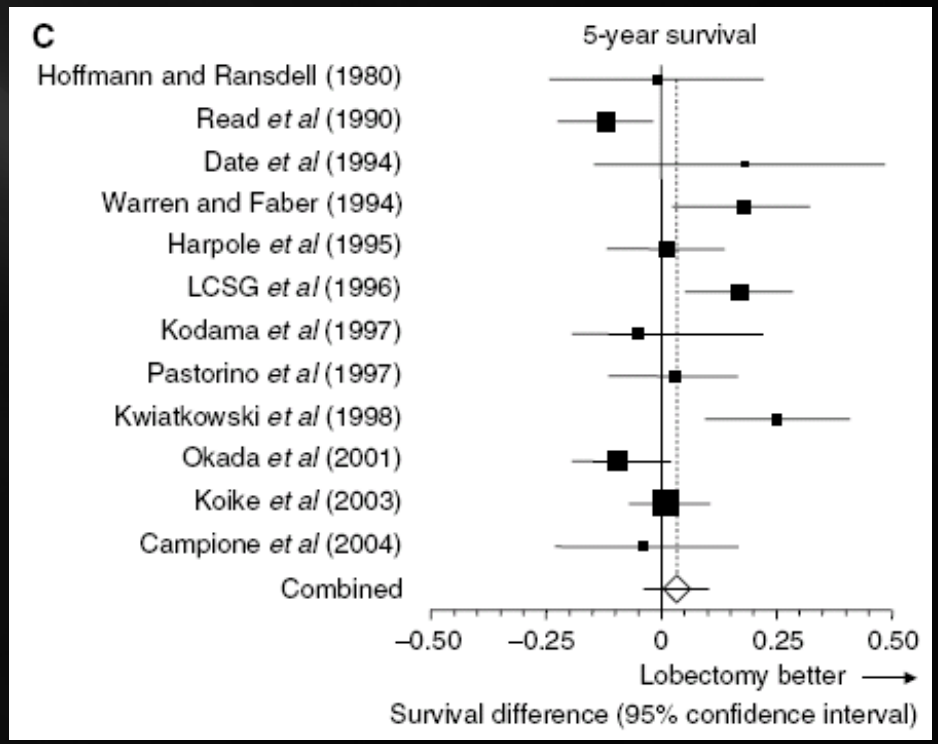
Meta-Analysis

Survival following lobectomy *vs* limited resection for stage I lung cancer: a meta-analysis

H Nakamura*,[1], N Kawasaki[1], M Taguchi[1] and K Kabasawa[2]

- Meta-analysis of 14 publications





British Journal of Cancer (2005) 92, 1033 – 1037

Anyone else?

	Mortality	Morbidity
Giacomo TD. Scand J of Surg 2009. Italy	Same	Same
Sugi K. EJCTS 2010. Japan.	Same	Same
Kraev K. Chest 2007. OR	Same (all comers)	

No mortality or significant recurrence benefit to lobectomy in all comers

- But, a criticism of many of these papers has been mixed bag of wedge and segmentectomy and a mixed bag of histologies.

- Is there any benefit to segmentectomy vs lobectomy?

Segment vs Lobe

- UK. EJCTS 2005
- Case-matched study for high-risk stage I
  - Se
  - 17
  - Av
  - Mean FEV1 = 45%
- Results

Postoperative results

	Lobectomy	Segmentectomy	*P*
Hospital mortality	1 (5.9%)	1 (5.9%)	NS
Complications	3 (18%)	3 (18%)	NS
Hospital stay	6 (3-30) days	8 (4-31) days	NS
Drainage time	4 (2-13) days	3 (1-30) days	NS

Expressed as median (range) or number (%).

Long-term results

	Lobectomy	Segmentectomy	*P*
Total recurrence	3 (18%)	3 (18%)	NS
Loco-regional recurrence	2 (12%)	0	NS
Actuarial 3-year survival	69%	94%	NS
Actuarial 5-year survival	64%	70%	NS

Flawed data…

- Role of adjuvant therapy
  - Some data to support wedge + XRT
- In most data, wedge resection patient lot sicker than lobectomy patients
  - Skews mortality results
- Outcome results are small so need large populations to show significant differences
- Not all NSCLCs are the same (BAC vs SCC)

In Summary…

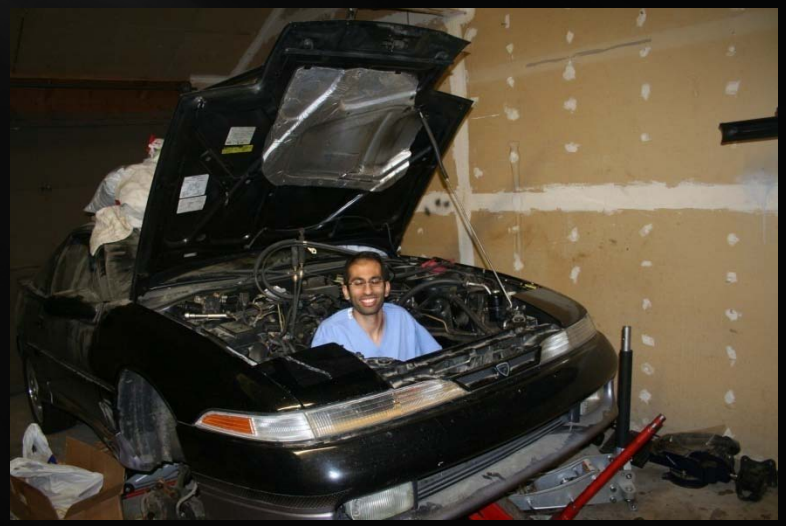
- Lobectomy is a risky operation for potential for disaster
  - Longer LOS, more pain, etc
- Lobectomy offers NO mortality advantage for these early stage tumors
- Recurrence rates are essentially the same
  - And, prior wedge offers ability for re-resection

Conclusion

- Lobectomy offers NO advantage over limited resection in the treatment of stage I lung cancer. Therefore, bigger is not always better.

Ashok the salesman…

- He will try to sell you this as a reliable old car that has proven data…
- But, if you look a little closer, you'll find there is nothing there to support it!



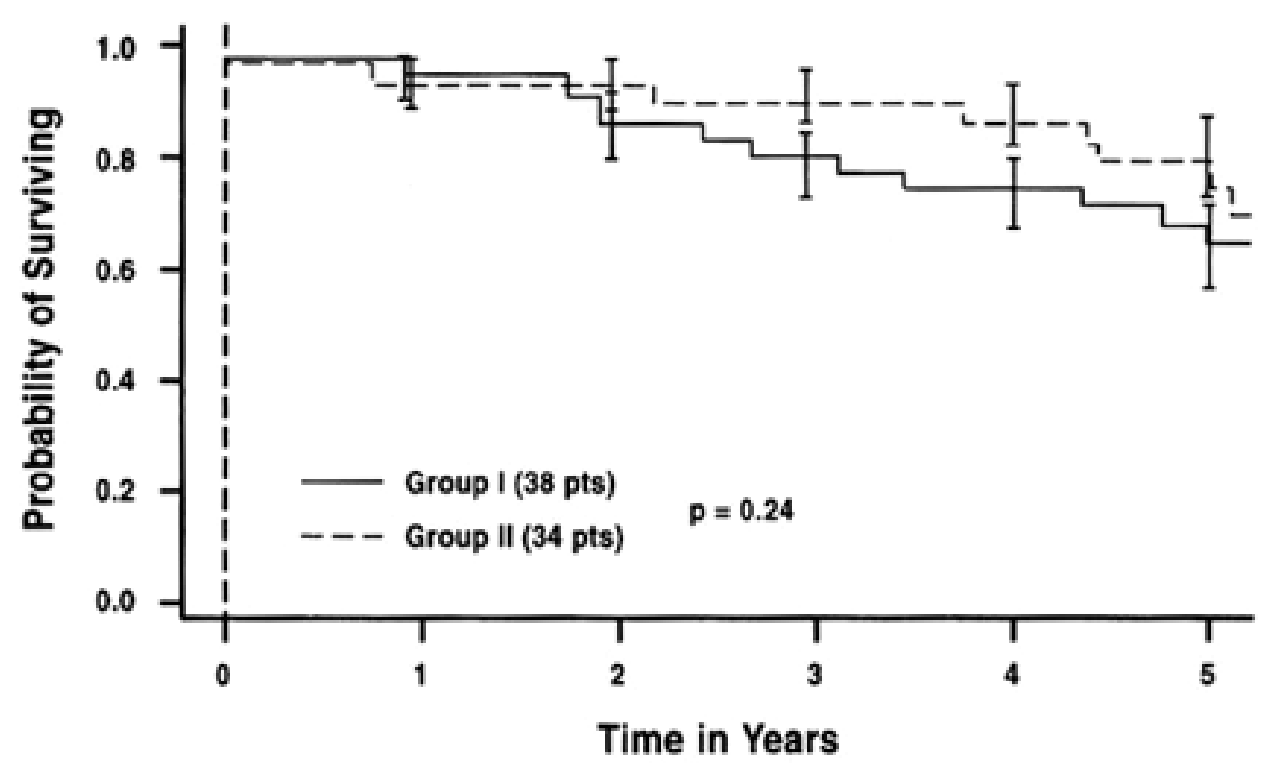
My opponent, the "classy" salesman.

- His arguments:
  - Only 1 "Great" RCT
    - Long time ago
    - No statistical mort difference
    - Can't effectively do new RCTs
  - Recurrence worse after limited resection
    - Modern studies show no difference
    - Some data suggests that recurrence s/p sublobar resection can be re-resected with good results.

Segmentectomy vs Lobectomy In Patients With Stage I Pulmonary Carcinoma

- Warren WH & Faber P. JTCVS 1994; 107:1087-94
- Retrospective review 1980-1988
- Segment vs lobe for T1N0 or T2No
- Excluded wedge resection
- No evaluation of pre-op variables.
- Results
  - 169 pts (66 segmentectomy, 103 lobectomies)

Tumors < 2 cm…



- No difference.
- But, recurrences were higher.

Outcome of Recurrence

- Segmental Resection with recurrence
  - 4 patients underwent further resection with 50% survival @ 5 yrs AFTER second resection
  - Remainder had adjuvant tx (not surgical candidates) with median survival 10 mo
- Lobectomy with recurrence
  - NONE could have further surgical therapy
  - Remainder had adjuvant tx with median survival 11 mo

Repeat Conclusion

- Lobectomy offers NO periop benefit.
- Lobectomy offers NO survival benefit.
- Limited resection is better tolerated and does not prevent further surgical therapy for recurrence.

- There should be a paradigm shift to treat small tumors with limited resection.

THANK YOU.

RESECTION FOR STAGE I LUNG CANCER: BIGGER IS NOT BETTER

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THANK YOU

Future Direction

- Wedge + adjuvant therapy
  - Radioactive seeds
  - XRT
  - Low-dose chemotherapy
- 2 large trials ongoing for segment vs lobe
  - US and Japan

Issue of recurrence

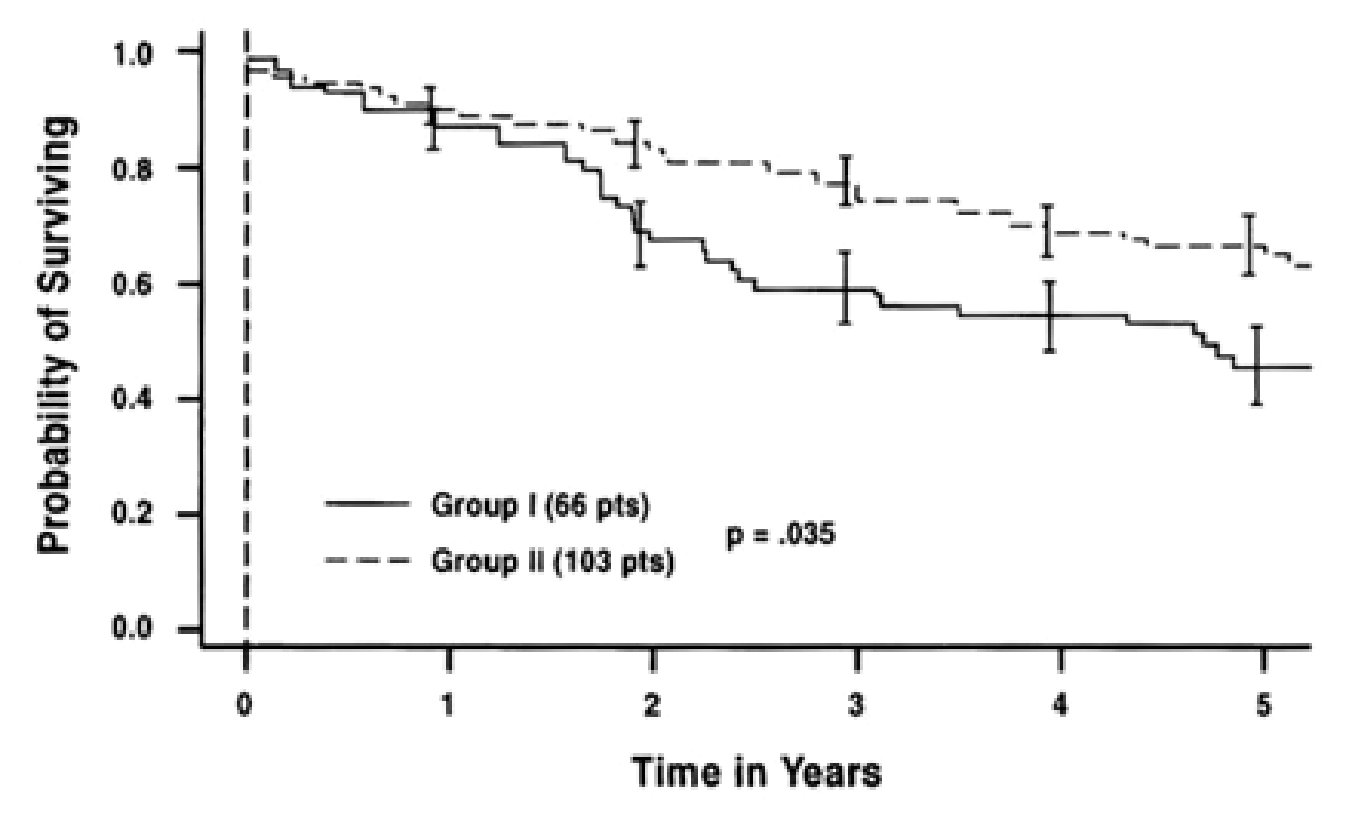
- Biggest criticism of limited resection = RECURRENCE
- But, if you look at the data, recurrences are either the same or only somewhat elevated in sublobar.
- What is the consequence of a recurrence?

Warren paper

Table II. Distribution of carcinomas according to diameter

Tumor size(cm)	*Group I(segmentectomy)* %	*Group II(lobectomy)* %	*Totals*
≤2.0	58	33	72
2.1-3.0	20	10	23
>3.0	23	57	74

But, survival better in lobectomy patients. Warren



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H Nakamura*[,1], N Kawasaki[1], M Taguchi[1] and K Kabasawa[2]

- Meta-analysis of 14 publications
  - 12 retrospective
  - 1 case-matched
  - 1 RCT (LCSG)
- Results
  - Survival differences @ 1,3 and 5 years:

NO STATISTICAL DIFFERENCE