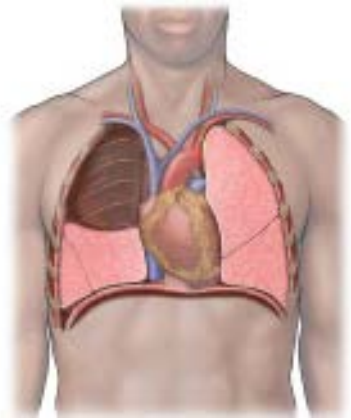
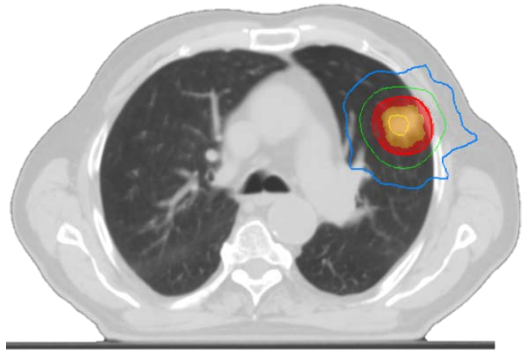
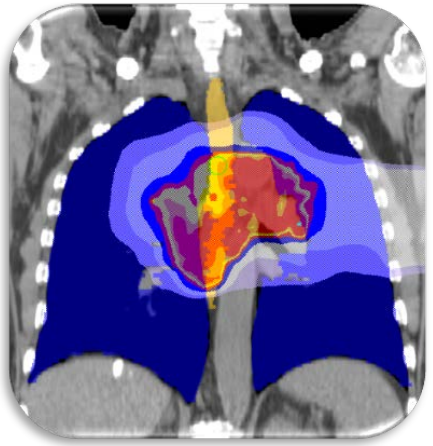
The Management of Lung Cancer







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Disclosures

Disclosures

for the following presenter

David Palma

Employment Relationship

- London Health Sciences Centre: Radiation Oncologist

Compensation, Remuneration, Funding

- Ontario Institute for Cancer Research: Research Grant

Ownership or Investment Interests

- Group patent on a computer analysis technique used to assess CT scans after patients have radiation treatment. No income made. Not licensed.

Leadership Positions

- None

Today's Roadmap

- **Part I: The Basics (15 min)**
  - Epidemiology, Screening, and Staging
- **Part II: Non-Small Cell Lung Cancer (40 min)**
  - Stage I
  - Stage II/III – Resectable and Unresectable
  - Stage IV
    - Oligometastases
    - Palliative Approaches (covered this afternoon)
- **Part III: Small Cell Lung Cancer (20 min)**

Links to Articles

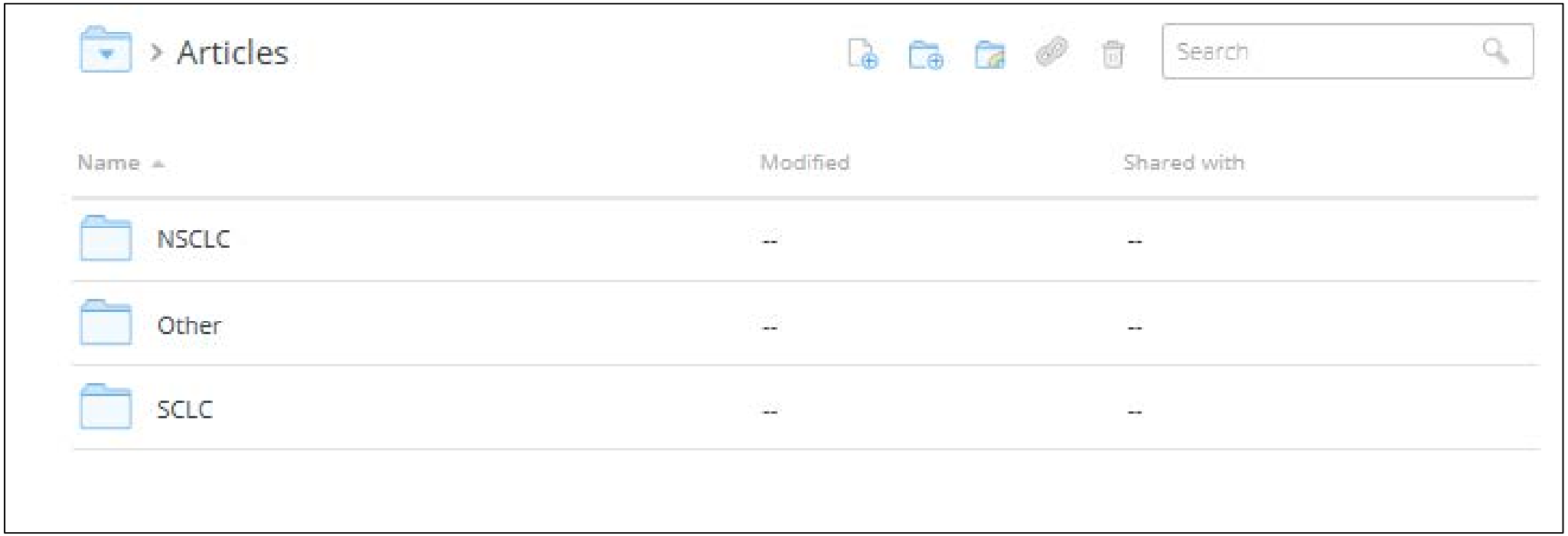
- Key Articles are identified with this icon: 

- All Key Articles available to you as PDFs via Dropbox
- Shortened URL – type this into your browser:

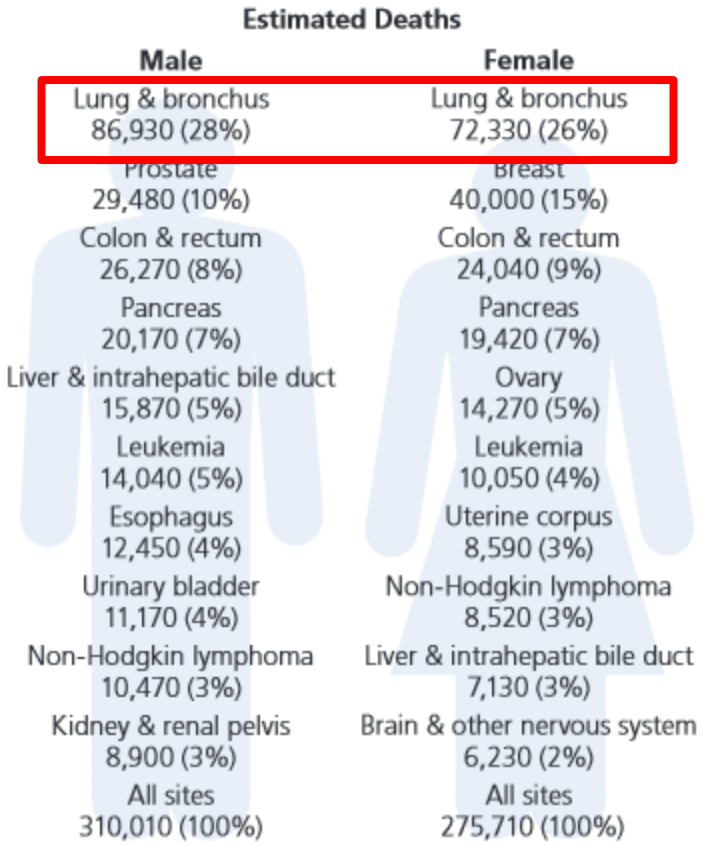
www.goo.gl/WmkgZ9

- Password is: refresher
- **Folder will be available to you for 24 hours**

Links to Articles



Lung Cancer: A Public Health Problem



Estimated Deaths	
Male	**Female**
Lung & bronchus 86,930 (28%)	Lung & bronchus 72,330 (26%)
Prostate 29,480 (10%)	Breast 40,000 (15%)
Colon & rectum 26,270 (8%)	Colon & rectum 24,040 (9%)
Pancreas 20,170 (7%)	Pancreas 19,420 (7%)
Liver & intrahepatic bile duct 15,870 (5%)	Ovary 14,270 (5%)
Leukemia 14,040 (5%)	Leukemia 10,050 (4%)
Esophagus 12,450 (4%)	Uterine corpus 8,590 (3%)
Urinary bladder 11,170 (4%)	Non-Hodgkin lymphoma 8,520 (3%)
Non-Hodgkin lymphoma 10,470 (3%)	Liver & intrahepatic bile duct 7,130 (3%)
Kidney & renal pelvis 8,900 (3%)	Brain & other nervous system 6,230 (2%)
All sites 310,010 (100%)	All sites 275,710 (100%)

Lung cancer is the leading cause of cancer death in the world.

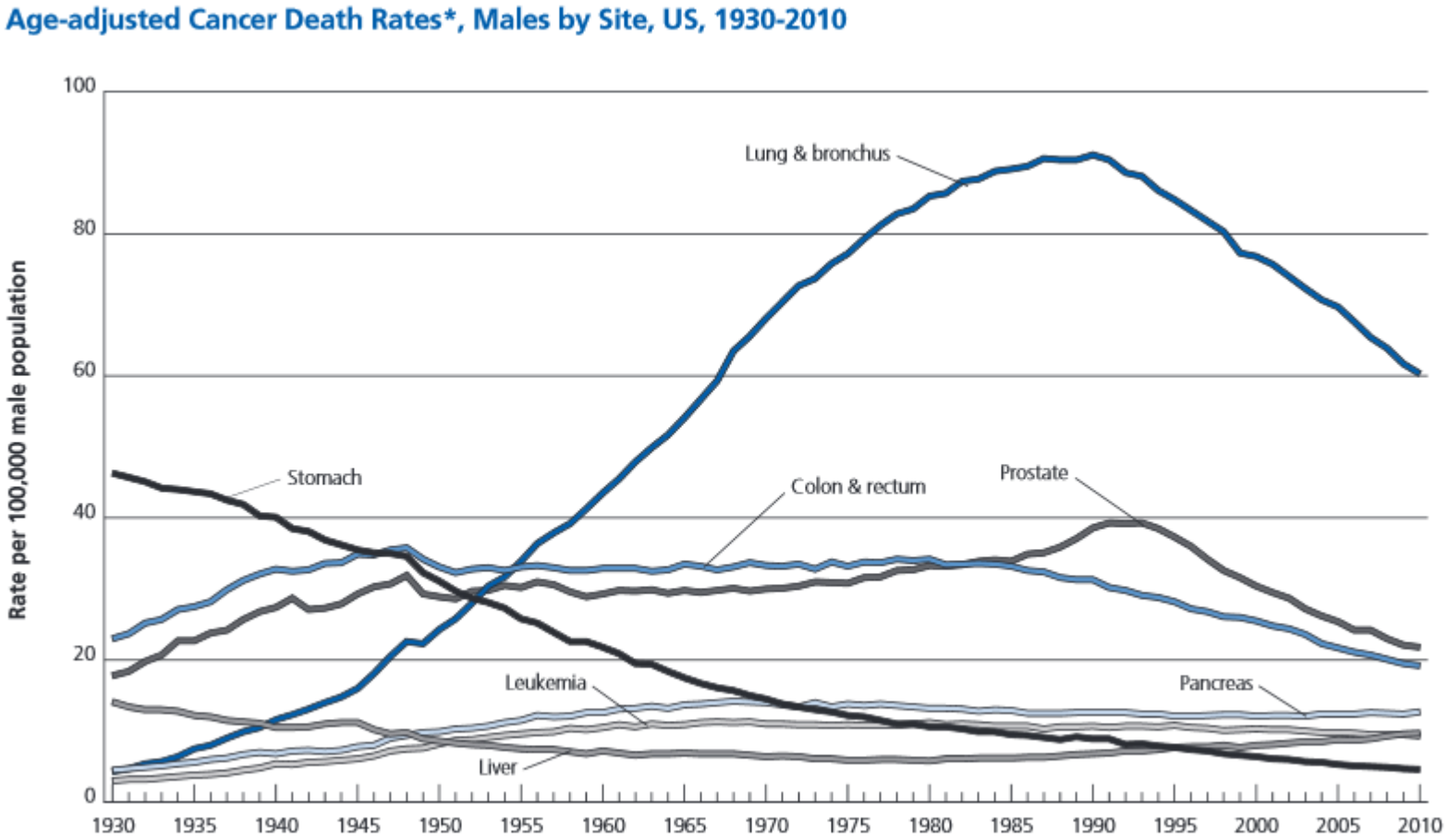
Alberg, CHEST 2013; 143(5)(Suppl):e1S–e29S

Western UNIVERSITY · CANADA

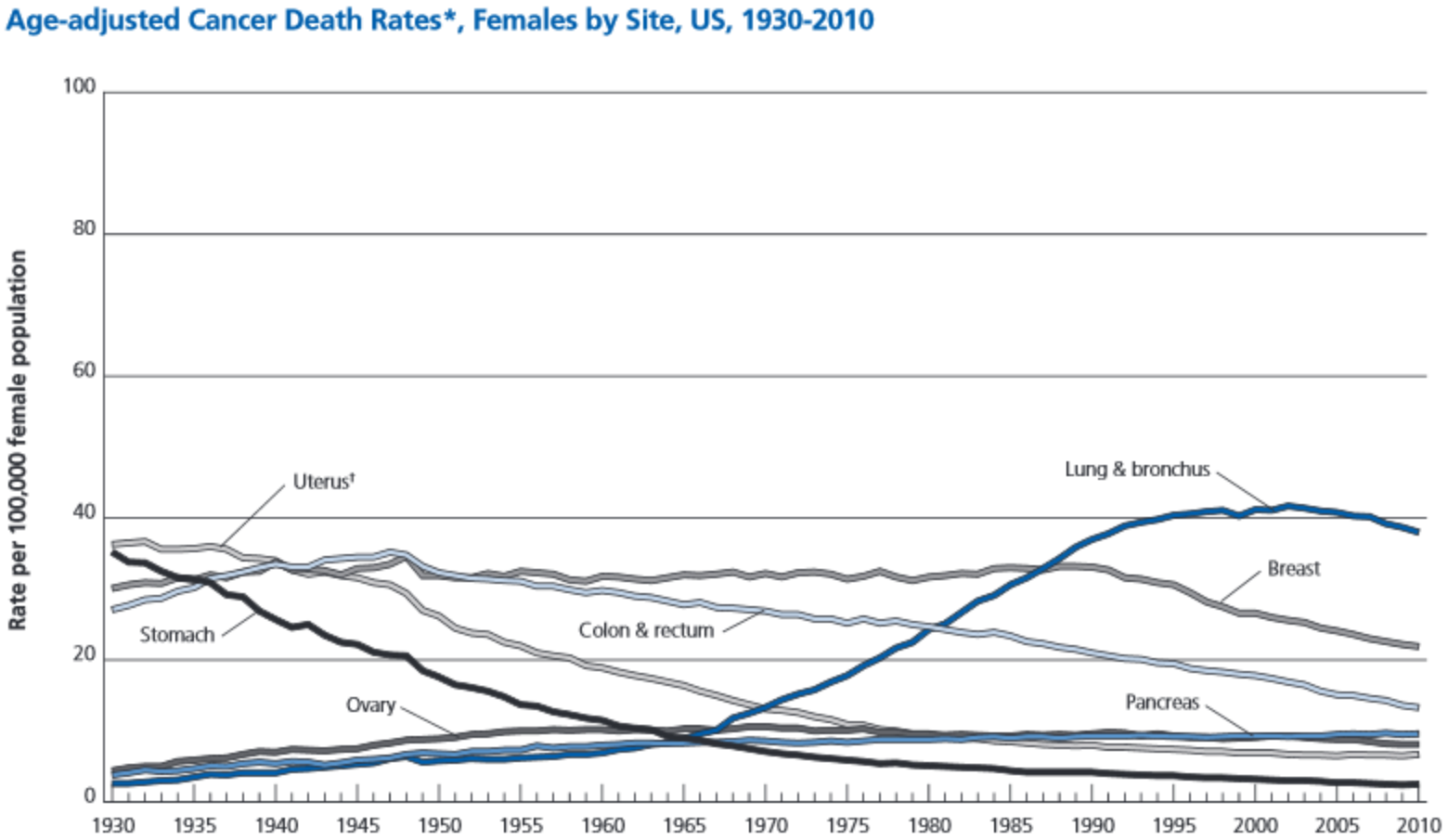
www.goo.gl/WmkgZ9

OICR Ontario Institute for Cancer Research

A Public Health Problem



A Public Health Problem



Risk Factors

- **Active Cigarette Smoking**
- **<u>Other causal agents</u>**: Secondhand smoke, ionizing radiation (including radon), occupational exposures (arsenic, chromium, nickel, asbestos), indoor and outdoor pollution
- **<u>Additional risk indicators</u>**: Age, male sex, family history, acquired lung disease (e.g. IPF)

Alberg, CHEST 2013; 143(5)(Suppl):e1S–e29S

Screening

- At least 6 large RCTs evaluated lung cancer screening with CXR, and none showed a mortality benefit to screening
- Refinements in low-dose CT technology led to the NLST
  - Average dose 2 mSv.
- Eligible patients:
  - 55-74 years
  - 30 pack years of smoking; if quit, then within 15 years
  - 53,454 randomized to 3 annual LDCTs vs. 3 annual CXRs

NEJM Aug 2011: 365(5)

Screening

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

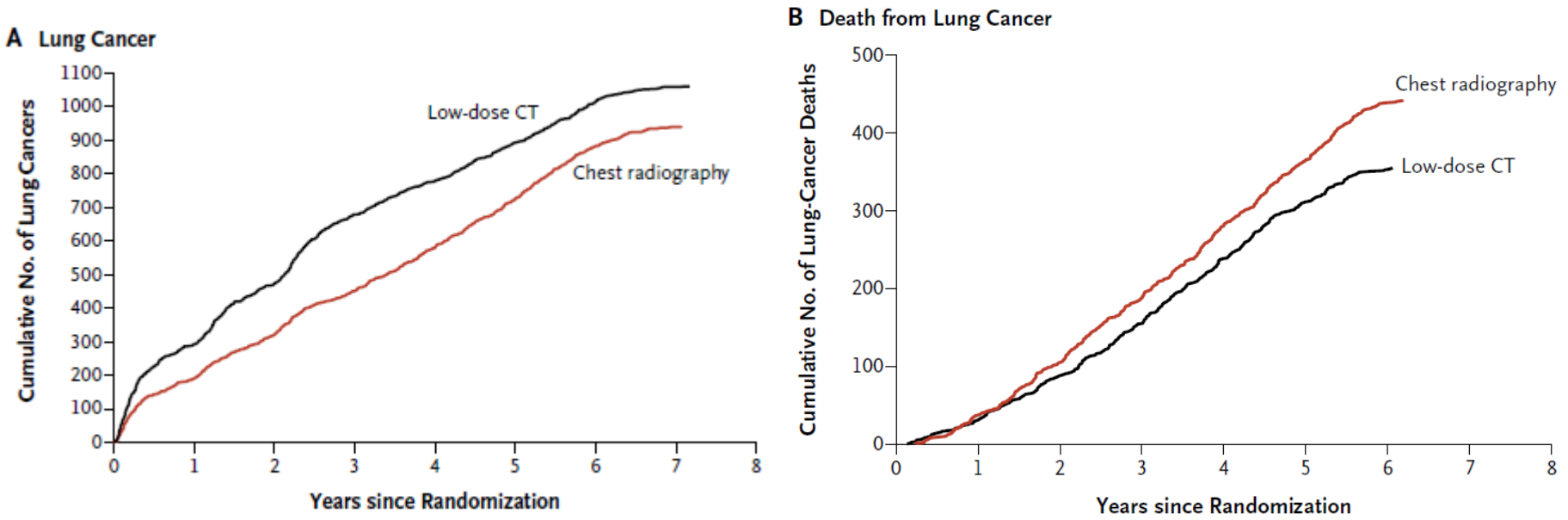
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

Variable	Low-Dose CT				Chest Radiography			
	T0	T1	T2	Total	T0	T1	T2	Total
	number (percent)							
Total positive tests	7191 (100.0)	6901 (100.0)	4054 (100.0)	18,146 (100.0)	2387 (100.0)	1482 (100.0)	1174 (100.0)	5043 (100.0)
Lung cancer confirmed	270 (3.8)	168 (2.4)	211 (5.2)	649 (3.6)	136 (5.7)	65 (4.4)	78 (6.6)	279 (5.5)
Lung cancer not confirmed†	6921 (96.2)	6733 (97.6)	3843 (94.8)	17,497 (96.4)	2251 (94.3)	1417 (95.6)	1096 (93.4)	4764 (94.5)

NEJM Aug 2011: 365(5)

Screening



- 20% relative reduction in lung cancer mortality
- 6.7% relative reduction in all-cause mortality
- Subsequent NEJM publication: ICER= $81,000 per QALY

NEJM Aug 2011: 365(5)

Staging Investigations

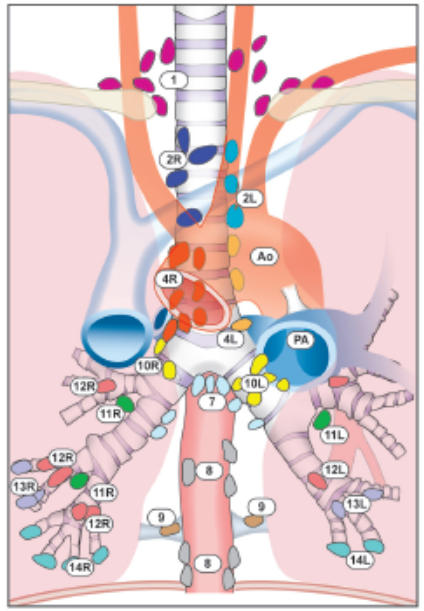
- History, Physical, Appropriate Labs
- CXR, CE-CT chest/upper abdomen
- Whole body PET/CT
  - 2 RCTS show that use of PET (or PET/CT) avoids unnecessary surgery in ~10-20%
  - MRI head for stage III/IV

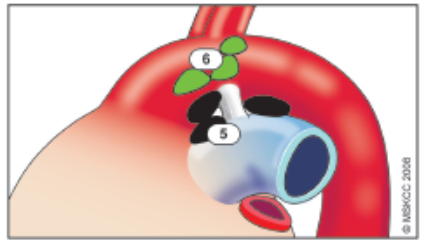
Getting Tissue from the Thorax

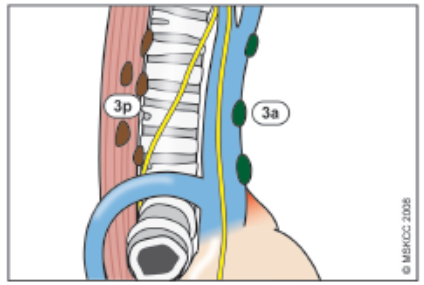
- Sputum cytology
- Bronchoscopy
- Endobronchial ultrasound
- Esophageal ultrasound
- Transthoracic biopsy
- Mediastinoscopy
- Electromagnetic navigation
- VATS

- Notes:
  - When nodes are positive on imaging, nodal biopsy is preferred first attempt at tissue as it provides diagnosis and stage
  - Histopathology preferred over cytology

Addressing the Mediastinum







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **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

N_1 Nodes

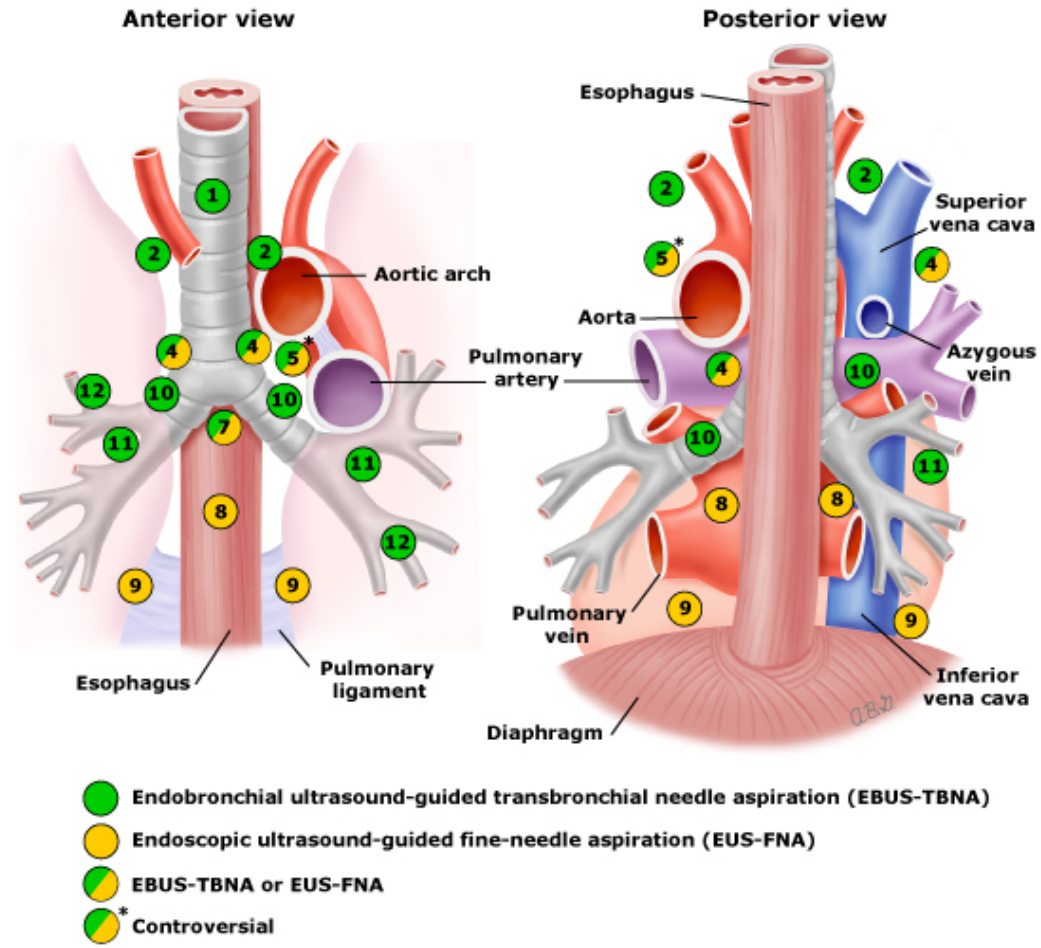
Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

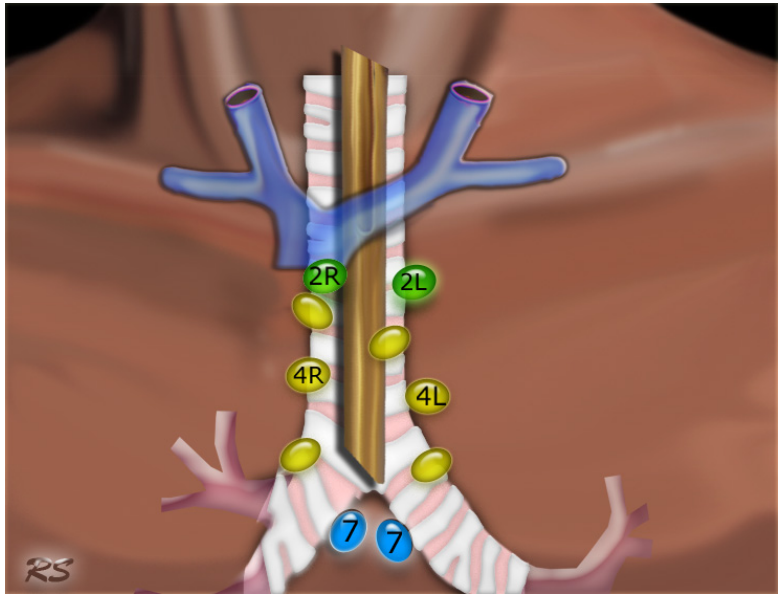
Needle or Surgical Approach?



Surgical Approaches

Cervical: 1, 2, 3, 4, 7, +/- 10

Anterior: predominantly 5, 6



Needle vs. Surgical

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

- 241 patients with resectable NSCLC in whom mediastinal staging was indicated
- Randomized to surgical staging vs. combined EUS-FNA and EBUS-TBNA followed by surgical staging if negative

Annema et al , JAMA 2010

Needle vs. Surgical

Table 2. Diagnostic Performance[a]

Nodal Invasion, N2/N3	No./Total No. (%) [95% Confidence Interval] Surgical Staging (n = 118)	Endosonography and Surgical Staging (n = 123)	*P* Value
Sensitivity	41/52 (79) [66-88]	62/66 (94) [85-98]	.02
Negative predictive value	66/77 (86) [76-92]	57/61 (93) [84-97]	.18

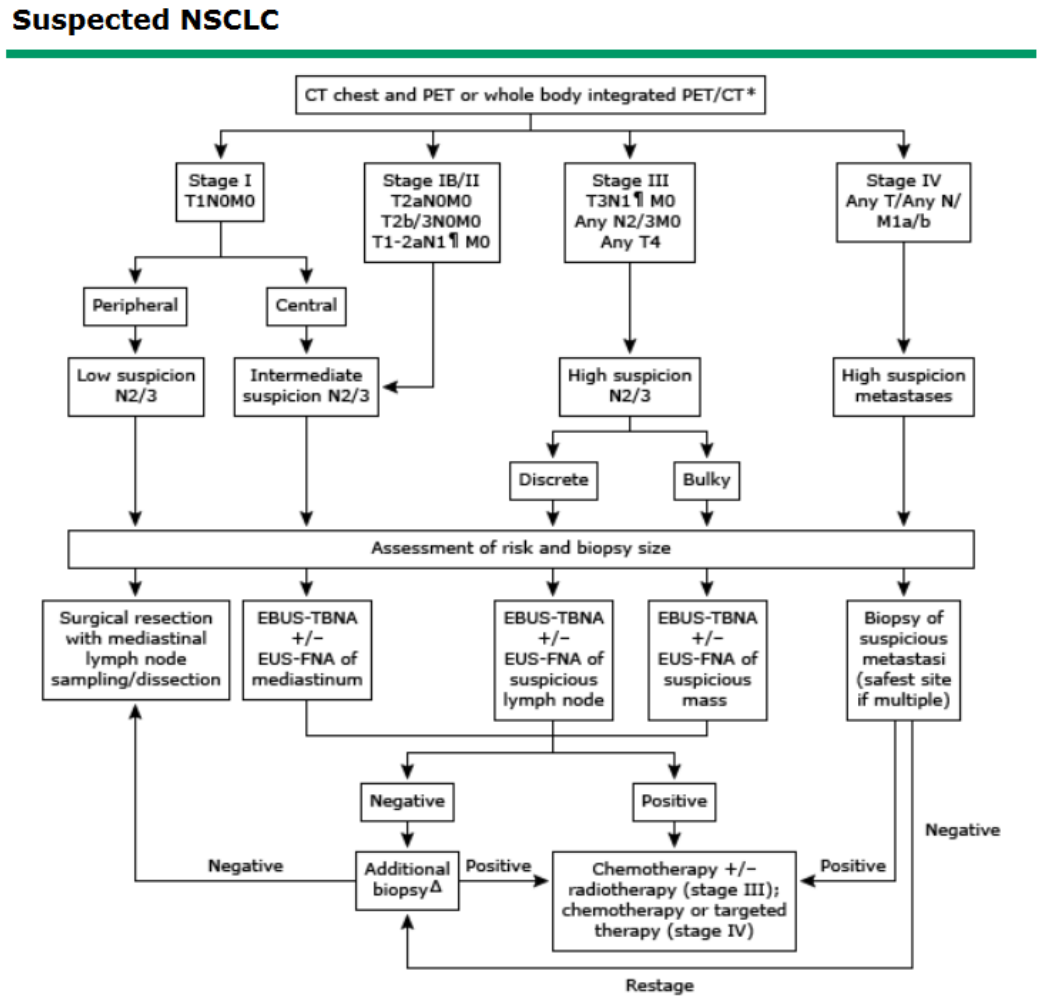
Table 3. Secondary Outcomes

	Surgical Staging, No. (n = 118)	Endosonography and Surgical Staging, No. (n = 123)	*P* Value
Unnecessary thoracotomies, all	21	9	
pN2	9	4	
Combination pN2/death	1	1	
Combination pN2/pT4	2	0	
Combination pN2/pM1	1	0	
pT4[a]	6	1	.02
pM1	0	2	
Small cell lung cancer	0	1	
Exploratory thoracotomy	2	0	
Benign lesion	2	0	
Death within 30 days	2	1	

- 47% in EUS/EBUS arm avoided surgical staging

Annema et al , JAMA 2010

Staging Pathway



"When EBUS-TBNA (+/- EUS-FNA) is negative or inconclusive, disease can be missed and staging is imprecise. Thus, in this setting further biopsy is indicated."

Utdol.com

Staging System

Primary tumor (T)	
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus*
T1a	Tumor ≤2 cm in diameter
T1b	Tumor >2 cm but ≤3 cm in diameter
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:
	Involves main bronchus, ≥2 cm distal to carina
	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or any of the following:
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
	Atelectasis or obstructive pneumonitis of the entire lung
	Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe

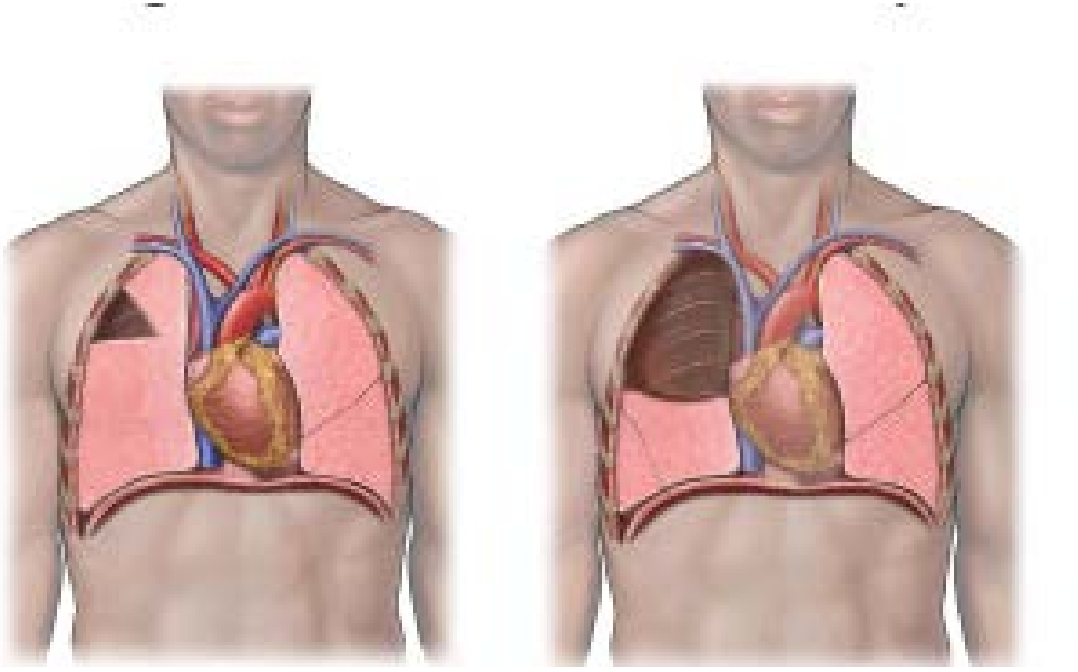
Regional lymph nodes (N)	
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis (in extrathoracic organs)

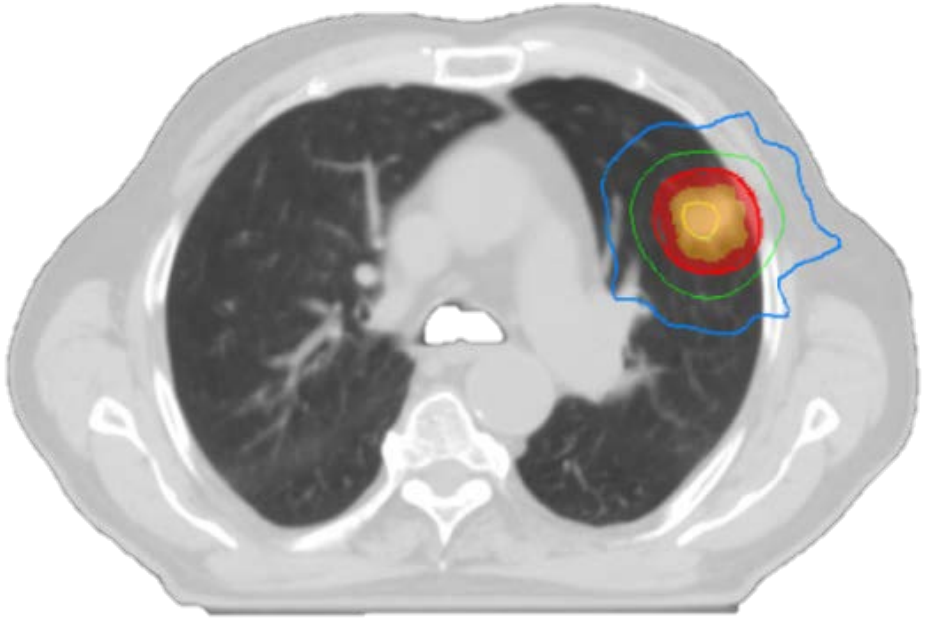
www.utdol.com

Staging System

T/M	Subgroups	N0	N1	N2	N3
T1	T1a	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	T2a	IB	IIA	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3 >7	IIB	IIIA	IIIA	IIIB
	T3 *Inv*	IIB	IIIA	IIIA	IIIB
	T3 *Satell*	IIB	IIIA	IIIA	IIIB
T4	T4 *Inv*	IIIA	IIIA	IIIB	IIIB
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIB
M1	M1a *Contr Nod*	IV	IV	IV	IV
	M1a *Pl Dissem*	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Detterbeck, Chest 2010





Management: Stage I NSCLC

Medically Inoperable Patients: Older XRT

The role of radiotherapy in treatment of stage I non-small cell lung cancer

Author	BED (acute)	Local failure alone (%)	Any local failure (%)
Krol et al. [15]	–	27.8	65.7
Hayakawa et al. [8]	68.1	11.1	19.4
Kaskowitz et al. [16]	65.1	41.5	43.4
Slotman et al. [9]	76.4	0	6.4
Jeremic et al. [4]	71	–	45
Sibley et al. [20]	–	16.3	19.1
Slotman et al. [17]	–	19.1	25.2
Sandler et al. [18]	62.8	42.8[a]	42.8[a]
Haffty et al. [19]	59	39	39
Noordijk et al. [13]	63.4	–	70
Morita et al. [14]	65.3	–	44.3
Gauden et al. [5]	62.5	–	–

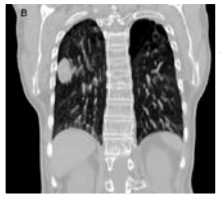
Qiao et al, Lung Cancer 2003

Stereotactic Radiation by Two Names

təˈmeɪtoʊ

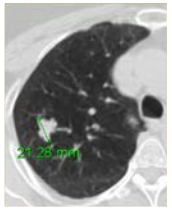
təˈmɑːtoʊ

Features of Lung SABR



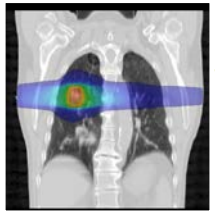
Accounting for Motion

- 4D Planning



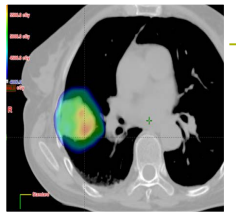
Small tumour volumes

- Small margins



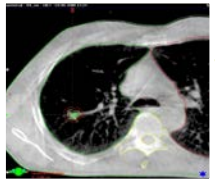
Many Beam Directions

- 7-11 Beams / Arc Therapy



Steep dose gradients

- Inhomogeneous target dose



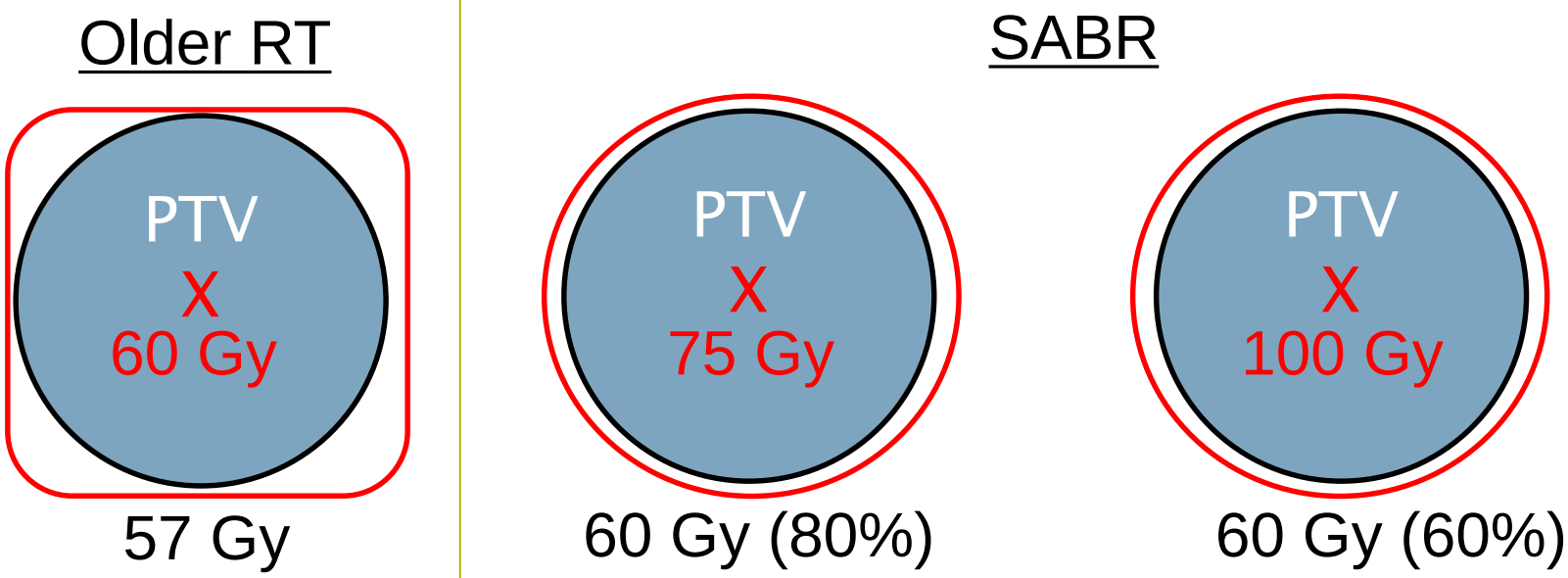
Accurate Targeting

- CBCT pre-RT

High dose per fraction

- Short total treatment duration

60 Gy in a Different Way



Senan, Palma, Lagerwaard, J Thorac Dis 2011

RTOG 0236

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

JAMA 2010

- Multicenter phase II trial
- Equivalent of 54 Gy in 3 fractions
- Primary tumor control 98%
- Lobar control 91%

Table 5. Protocol-Specified Adverse Events Related to Stereotactic Body Radiation Therapy[a]

	Patients by Tumor Grade					
	All (N = 55)			First Evaluable (n = 49)		
Adverse Event	3	4	5	3	4	5
FEV_1	2	0	0	2	0	0
Hypocalcemia	0	1	0	0	1	0
Hypoxia	2	0	0	2	0	0
Pneumonitis NOS	2	0	0	2	0	0
Pulmonary function test decreased NOS	3	1	0	3	1	0
Maximum for protocol, No. (%)	7 (13)	2 (4)	0	7 (14)	2 (4)	0

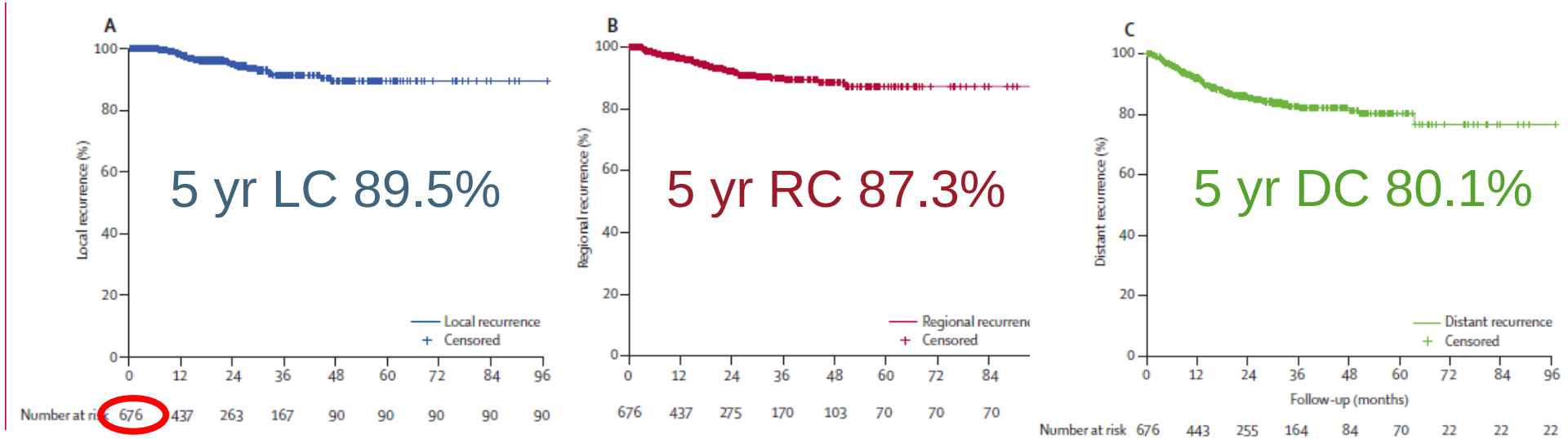
Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; NOS, not otherwise specified.
[a] Includes adverse events in which relationship to treatment was missing.

- 2014 ASTRO update -- 5-year outcomes: primary tumor recurrence 7%, involved lobar recurrence 20%, regional recurrence 38% and distant recurrence 31%.

SABR Outcomes: VUMC Amsterdam

Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthi, Frank J Lagerwaard, Cornelis J A Haasbeek, Ben J Slotman, Suresh Senan



Senthi et al Lancet Oncology 2012

VUmc: A Risk-Adapted Strategy

Tumor description	Dose	
	Older algorithms	AAA/RapidArc/Pinnacle
T1 tumor surrounded by lung tissue		
T2 tumor or broad contact with chest wall		
Central tumor or near brachial plexus		

Dose*: How much and where?

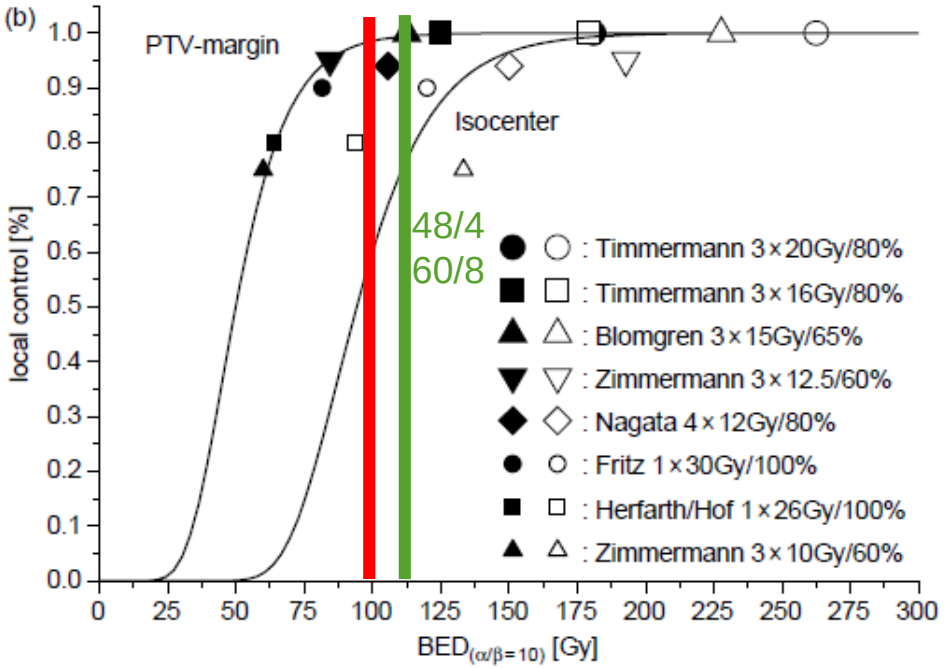
Radiotherapy and Oncology 77 (2005) 83–87
www.thegreenjournal.com

Extracranial stereotactic RT

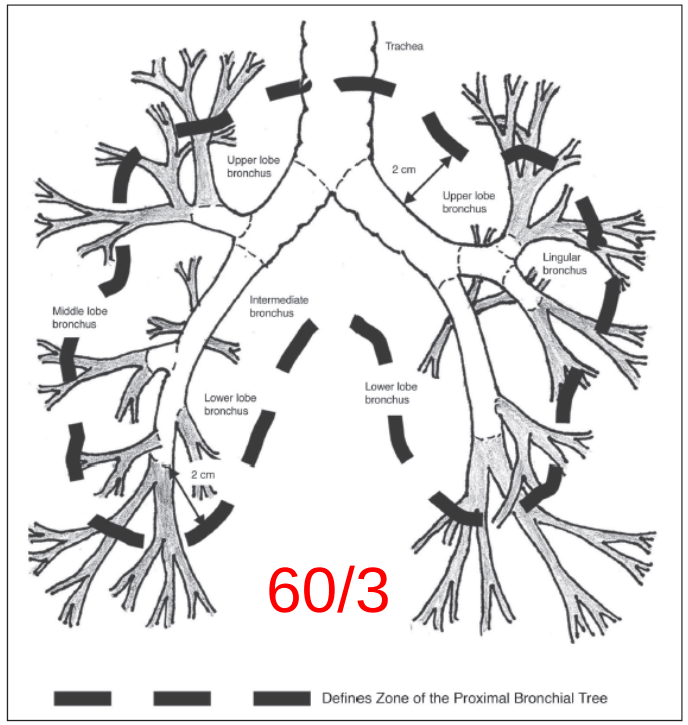
Dose-response in stereotactic irradiation of lung tumors

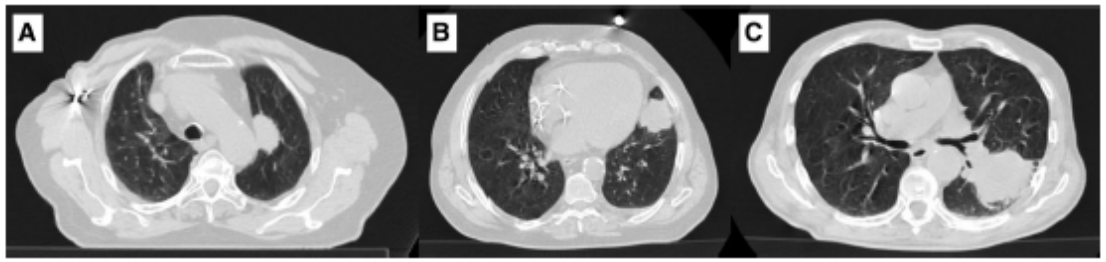
Joern Wulf[a,b], Kurt Baier[a], Gerd Mueller[a], Michael P. Flentje[a,*]

[a]*Department of Radiotherapy, University of Wuerzburg, Wuerzburg, Germany,*
[b]*Department of Radiotherapy, Lindenhofspital, Bern, Switzerland*



Central Tumors





60/8

TABLE 3. Early and Late Toxicity After SABR in 63 Patients with Central Stage Early-Stage NSCLC (Absolute Patient Numbers)

	Acute Toxicity			Late Toxicity (>3 mo)		
	I	II	III	I	II	III
Dyspnea	5	2	—	3	2	2
Chest wall pain	3	1	1	4	2	1
Fatigue	10	1	—	4	1	—
Coughing	5	—	—	—	—	—
Nausea	3	—	—	—	—	—
Radiation dermatitis	1	1	—	—	1	—
Hemoptysis	1	1	—	—	1	—
Esophagitis	1	—	—	—	—	—
Pleural effusion	—	—	—	—	1	—
Rib fracture	—	—	—	—	—	1
Bronchial stenosis	—	—	—	—	1	—
Total (% of patients)	29 (62)	6 (10)	1 (2)	11 (17)	9 (14)	4 (6)

SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer.

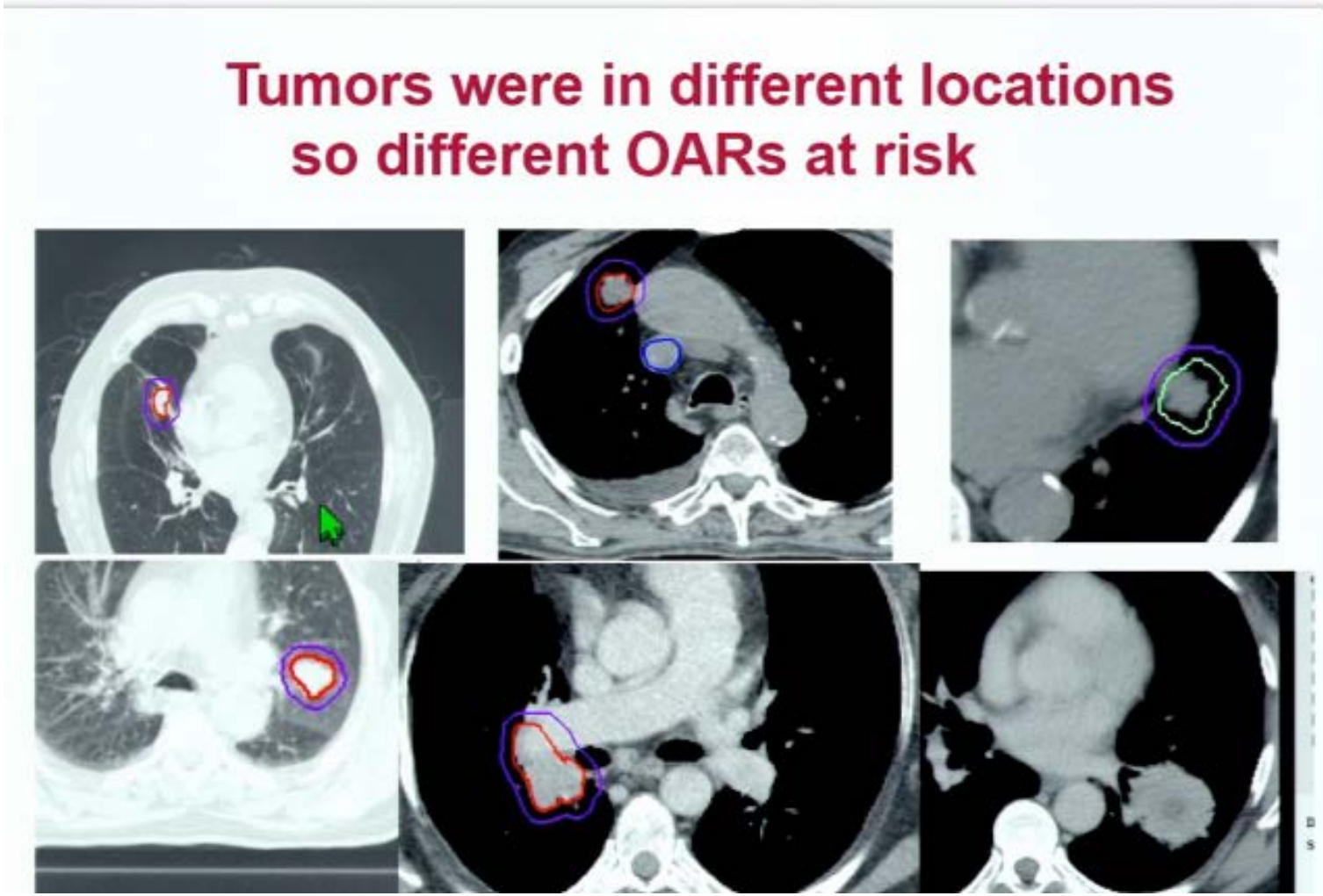
- Meta-analysis (Senthi 2012):
  - $BED_{10} \geq 100$ to maximize local control
  - $BED_3 \leq 240$ to keep risk of fatal toxicity to 1%.

Timmerman et al JCO 2006
Haasbeek et al JTO 2011

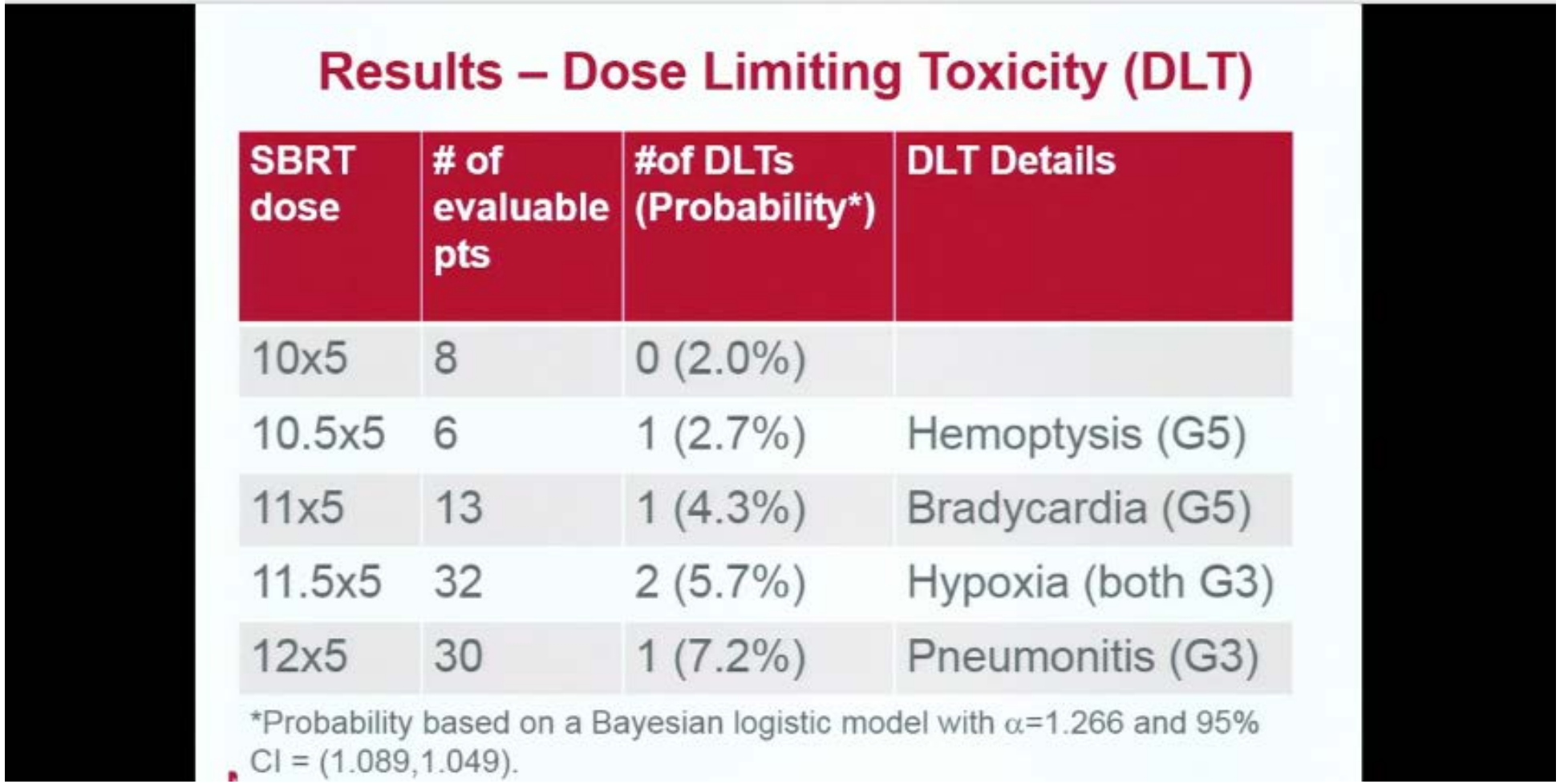
Central Tumors: RTOG 0813

Dose Level	Dose per Fraction	Total Dose
1	8 Gy	40 Gy
2	8.5 Gy	42.5 Gy
3	9 Gy	45 Gy
4	9.5 Gy	47.5 Gy
5	**10 Gy†**	**50 Gy**
6	10.5 Gy	52.5 Gy
7	11 Gy	55 Gy
8	11.5 Gy	57.5 Gy
9	12 Gy	60 Gy

RTOG 0813: ASTRO 2015

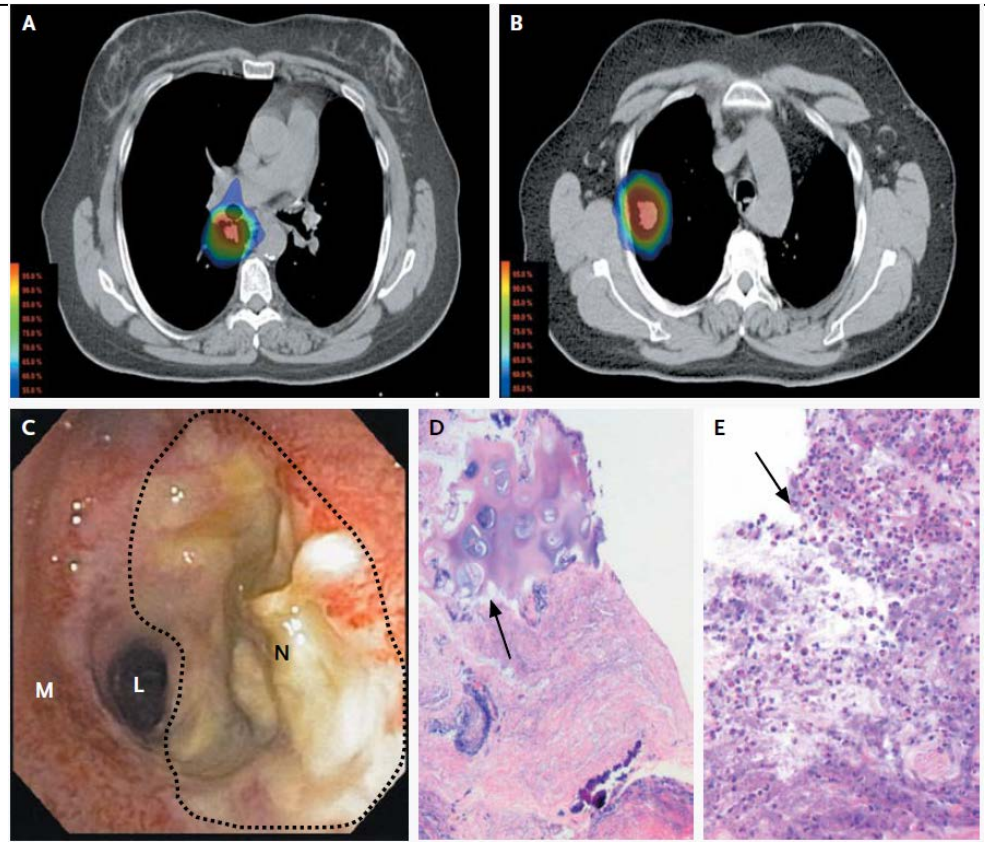


RTOG 0813: ASTRO 2015



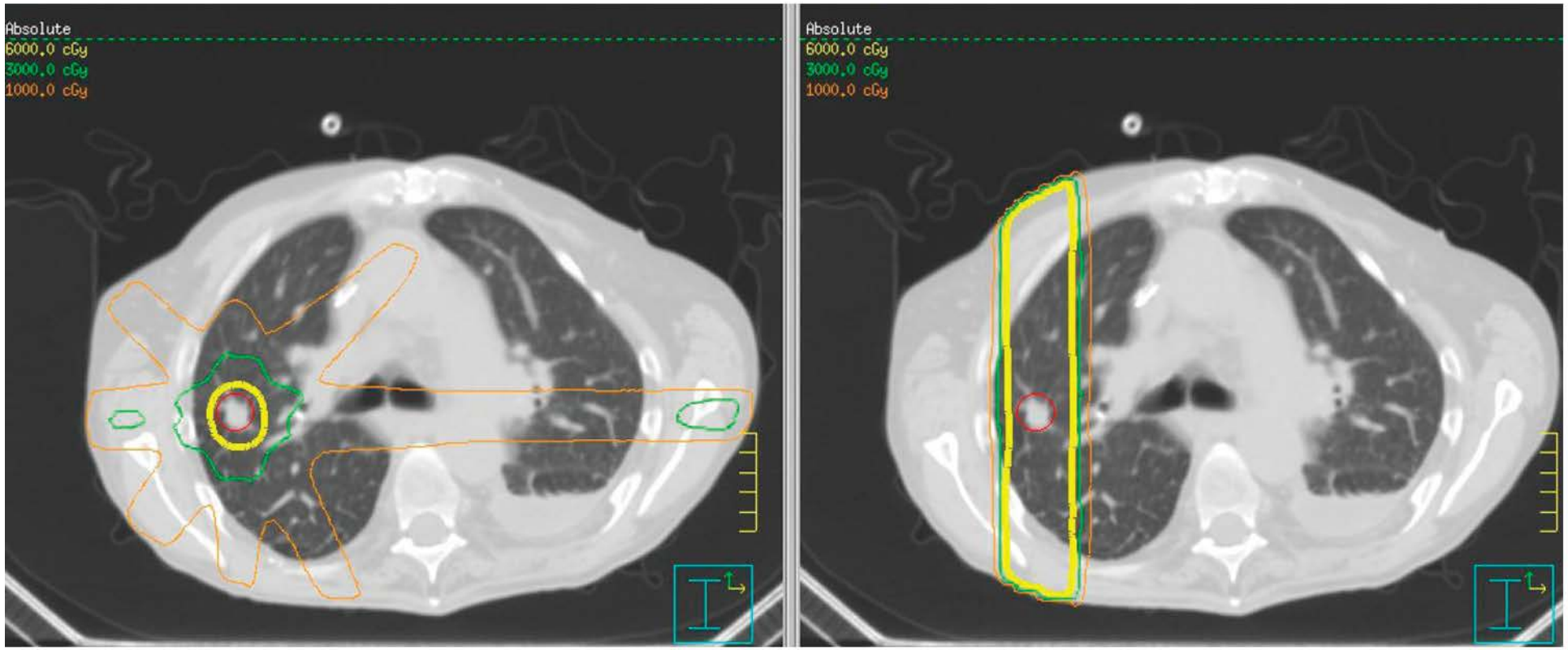
Still need to be cautious

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy



Corradeeti, Haas, Rengan NEJM 2012

Is SABR better than older techniques?



Timmerman J Clin Oncol 32:2847-2854

SABR vs. older techniques

- Several population-based studies suggest SABR better for OS:
  - Palma, Amsterdam Cancer Registry, JCO 2010
  - Haasbeek, Netherlands Cancer Registry, Annals of Oncology 2011
  - Shirvani, SEER-Medicare, IJROBP 2012

- At least 3 RCTs launched comparing SABR with standard or less-hypofractionated regimens
  - SPACE (Sweden) - completed
  - CHISEL (Australia)
  - LUSTRE (Canada)

RCT #1: SPACE

Stereotactic **P**recision **A**nd **C**onventional radiotherapy **E**valuation

Comparison

66 Gy in 3 fractions (0.5 – 1 cm margin)

vs. 70 Gy in 35 fractions (2 cm margin)

Major Inclusion Criteria

- T1-2 N0 M0
- Medically Inoperable or Refusing Surgery
- WHO 0-2
- Biopsy proven or growing on CT with positive PET

Nyman et al, ESTRO 2014, OC-0565

SPACE

Stereotactic Precision And Conventional radiotherapy Evaluation

Variable	SABR N=49	Conventional N=53
Median Age	72.7	75.3
Male	45%	36%
COPD	71%	64%
T2	47%	25%
SCC	18%	28%
Adenocarcinoma	45%	36%

Nyman et al, ESTRO 2014, OC-0565

SPACE

Stereotactic Precision And Conventional radiotherapy Evaluation

- No differences in local control or survival outcomes

Variable	SABR N=49	Conventional N=53
Pneumonitis (any)	16%	34%
Esophagitis (any)	9%	32%
Any toxicity G3-5	18%	16%

- SABR appears to improve the therapeutic ratio compared to older techniques

Nyman et al, ESTRO 2014, OC-0565

SABR without histology

When Is a Biopsy-Proven Diagnosis Necessary Before Stereotactic Ablative Radiotherapy for Lung Cancer?

A Decision Analysis

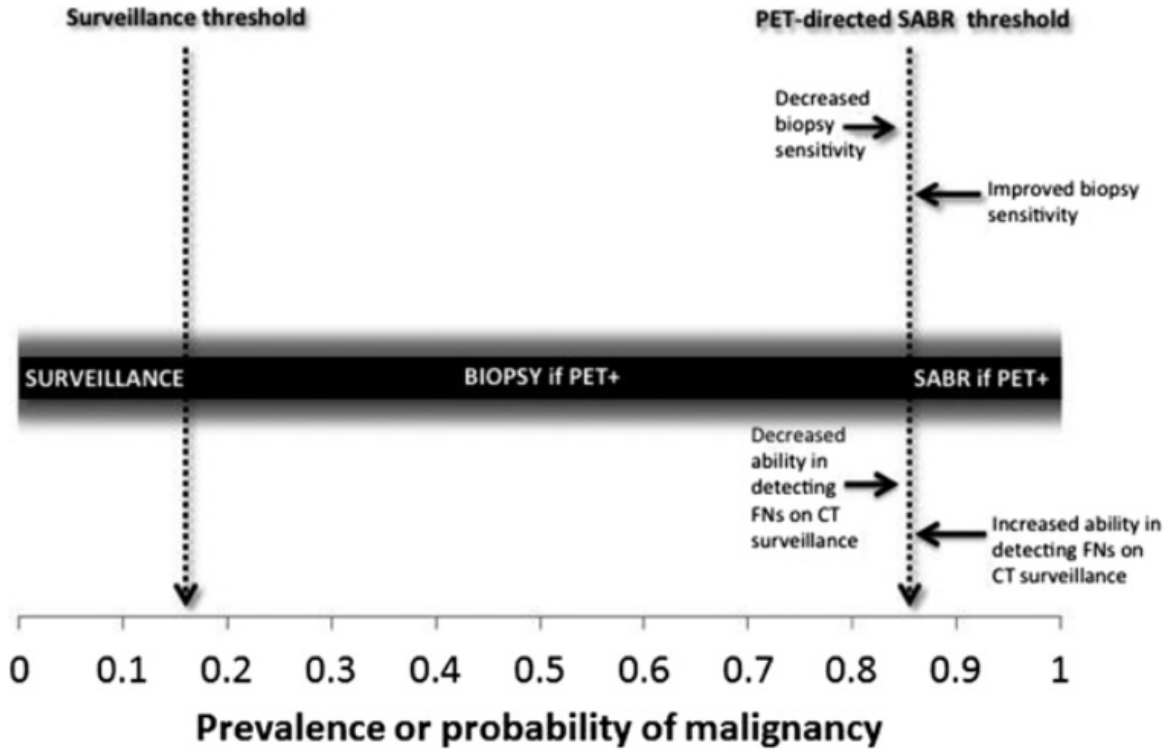
- Decision analysis and Markov model assessing QALYs achieved, comparing 3 approaches to a nodule ≥1 cm
  - Surveillance
  - PET then biopsy if PET+
  - PET, the treat if PET+
- Sensitivity analysis to determine factors influencing outcome

Louie et al Chest, 2014; 146(4):1021-1028

SABR without histology

When Is a Biopsy-Proven Diagnosis Necessary Before Stereotactic Ablative Radiotherapy for Lung Cancer?

A Decision Analysis



Louie et al Chest, 2014; 146(4):1021-1028

Stage I Inoperable: Summary

- SABR has been widely adopted as standard treatment for inoperable patients
- Non-randomized comparisons suggest better local control, better survival than with conventional treatments
- Convenience of SABR probably improves access to care
- Preliminary randomized data (SPACE) suggests that long-course treatments can also achieve good local control
- More randomized data is coming

Stage I Operable

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)

- 247 patients with T1N0 NSCLC analyzed

Table 3. Recurrence and Death Rates for the 247 Eligible Patients on LCSG 821[a]

Event	Limited Resection No. of Patients	Limited Resection Rate (per person/y)	Lobectomy No. of Patients	Lobectomy Rate (per person/y)	p Value
Recurrence (excluding second primary)	38	0.101	23	0.057	0.02[b]
Recurrence (including second primary)	42	0.112	32	0.079	0.079[b]
Locoregional recurrence[d]	21	0.060	8	0.020	0.008[c]

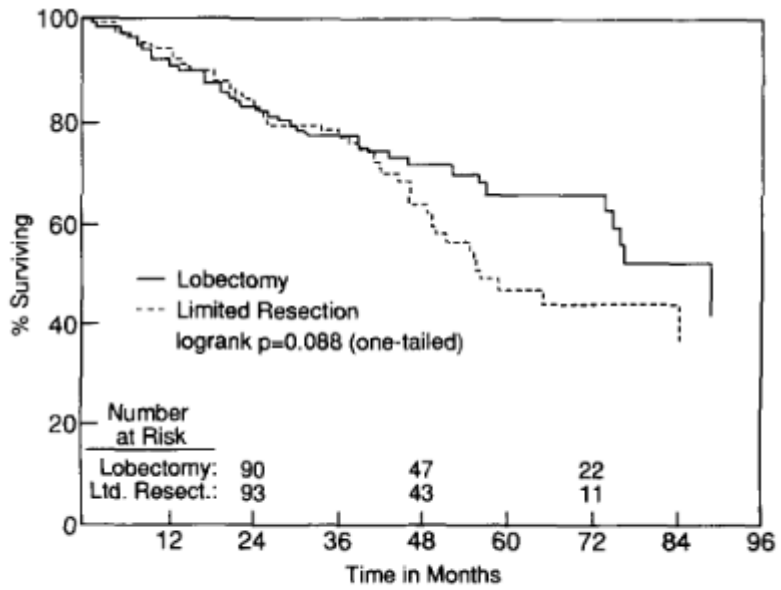


Fig 1. Time to death (from any cause) by treatment for 247 eligible patients.

Annals of Thoracic Surgery 1995

Western UNIVERSITY · CANADA

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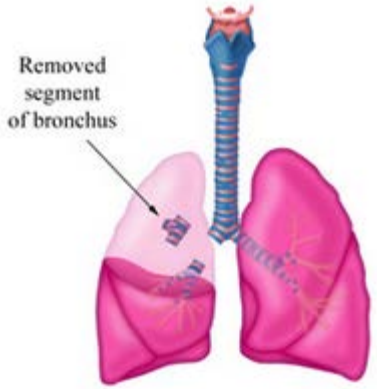
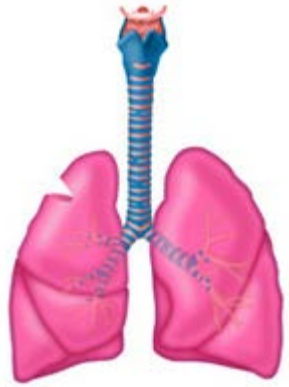
Operable Patients: Types of Surgical Resections

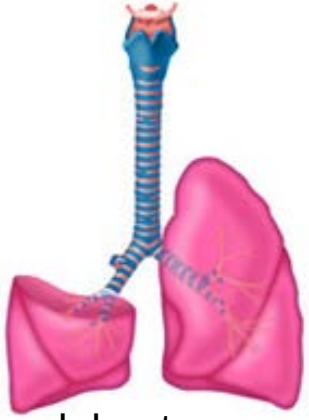
pneumonectomy



sleeve lobectomy



wedge resection



lobectomy

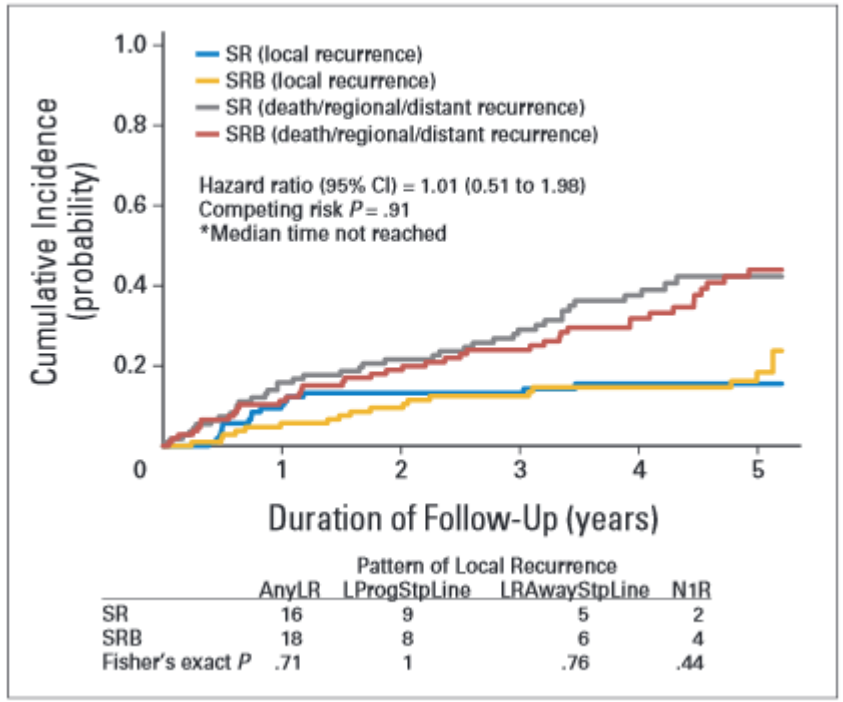
segmentectomy

www.cts.esc.edu

Modern Sublobar Resection Outcomes

Impact of Brachytherapy on Local Recurrence Rates After Sublobar Resection: Results From ACOSOG Z4032 (Alliance), a Phase III Randomized Trial for High-Risk Operable Non–Small-Cell Lung Cancer

Hiran C. Fernando, Rodney J. Landreneau, Sumithra J. Mandrekar, Francis C. Nichols, Shauna L. Hillman, Dwight E. Heron, Bryan F. Meyers, Thomas A. DiPetrillo, David R. Jones, Sandra L. Starnes, Angelina D. Tan, Benedict D.T. Daly, and Joe B. Putnam Jr



	Pattern of Local Recurrence			
	AnyLR	LProgStpLine	LRAwayStpLine	N1R
SR	16	9	5	2
SRB	18	8	6	4
Fisher's exact *P*	.71	1	.76	.44

LR was defined as recurrence within the primary tumor lobe at the staple line (local progression), recurrence within the primary tumor lobe away from the staple line (involved lobe failure), or recurrence within hilar lymph nodes.

JCO 2014

SABR in Operable Patients

CLINICAL INVESTIGATION **Lung**

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

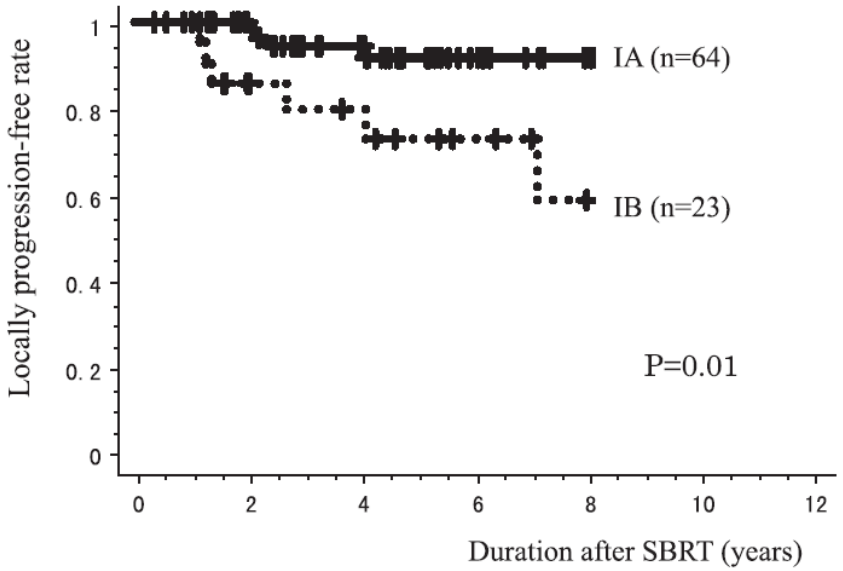


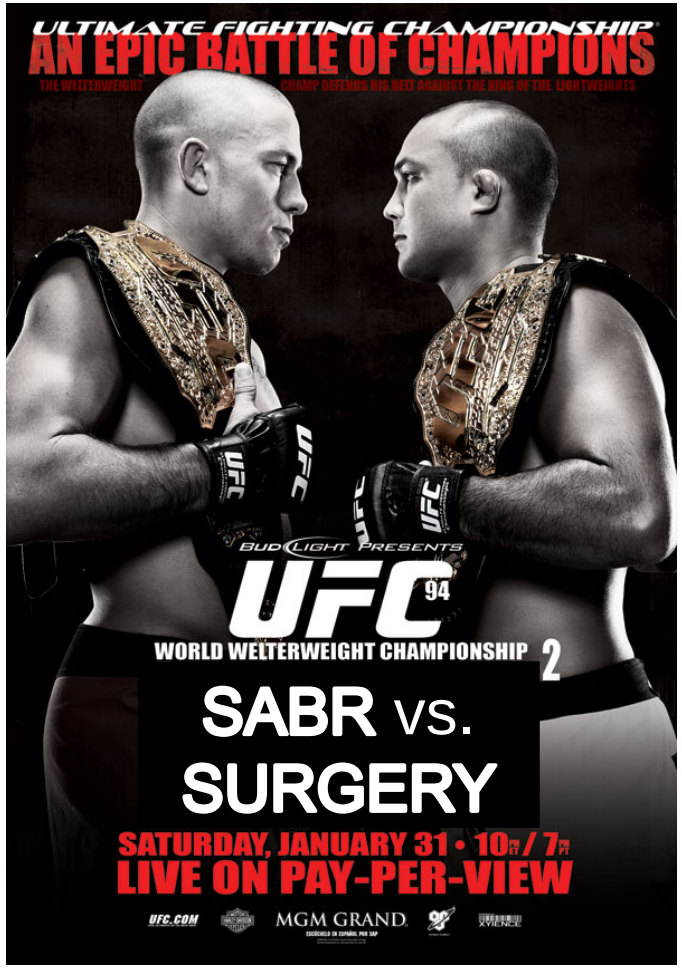
Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy.
Values are percentages.

Onishi et al IJROBP 2011

The Debate


ULTIMATE FIGHTING CHAMPIONSHIP
AN EPIC BATTLE OF CHAMPIONS
BUD LIGHT PRESENTS
UFC 94
WORLD WELTERWEIGHT CHAMPIONSHIP 2
SABR vs.
SURGERY
SATURDAY, JANUARY 31 • 10PM ET / 7PM PT
LIVE ON PAY-PER-VIEW
UFC.COM
MGM GRAND

SABR vs. Surgery: Systematic Review

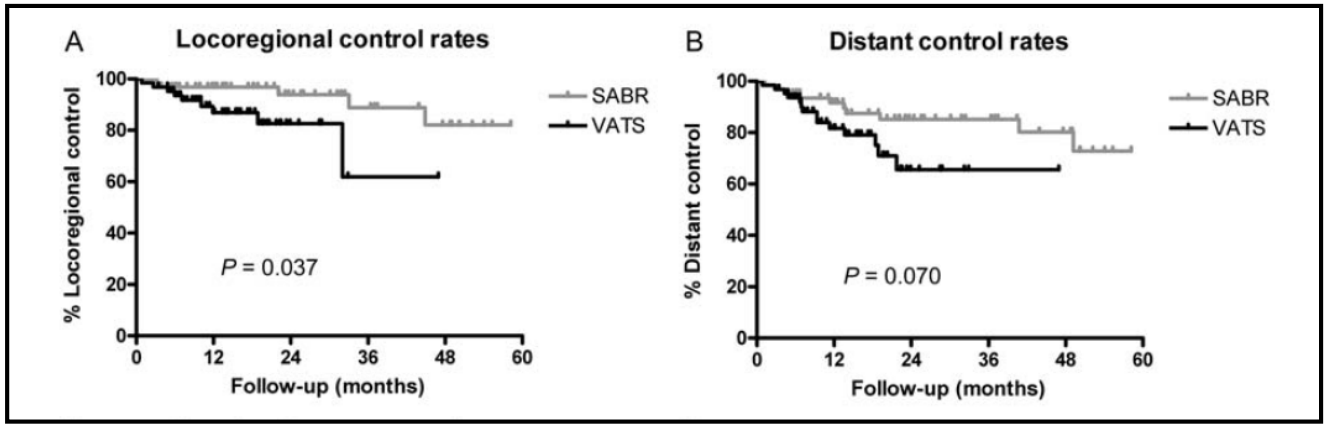
- 20 comparative effectiveness studies comparing survival after surgery vs. SABR
- 12 found no difference between SABR and surgery
- 8 found surgery superior to SABR
  - 4 of these had no statistical adjustment for baseline factors

WCLC abstract 18.08

SABR vs. VATS lobectomy

Stage I–II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis

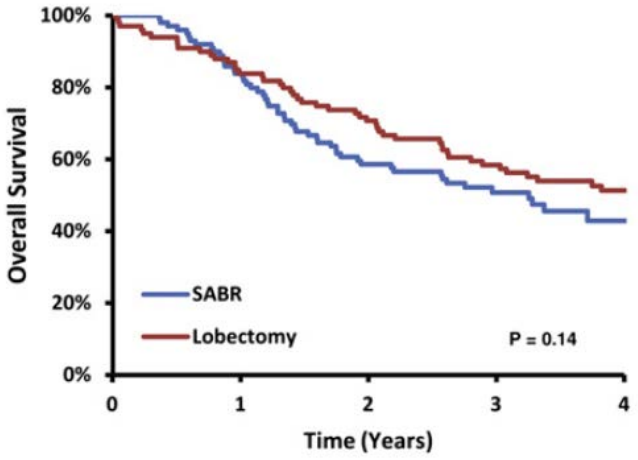
N. E. Verstegen[1*], J. W. A. Oosterhuis[2], D. A. Palma[3], G. Rodrigues[3], F. J. Lagerwaard[1], A. van der Elst[4], R. Mollema[5], W. F. van Tets[6], A. Warner[3], J. J. A. Joosten[7], M. I. Amir[8], C. J. A. Haasbeek[1], E. F. Smit[9], B. J. Slotman[1] & S. Senan[1]



Characteristic	SABR ($n = 64$)	VATS ($n = 64$)	P-value
Age[a], mean ± SD	70.53 ± 9.91	67.95 ± 8.84	0.123
Sex[a], *n* (%)			
Male	37 (57.8)	36 (56.3)	0.858
Female	27 (42.2)	28 (43.8)	
Inoperable			
Yes	29 (45.3)	–	–
No	35 (54.7)	–	
cTNM[a], *n* (%)			
T1	39 (60.9)	39 (60.9)	1.00
T2	25 (39.1)	24 (37.5)	
T3	–	1 (1.6)	
Tumor diameter[a] (mm), mean ± SD	28.83 ± 12.87	28.63 ± 12.41	0.928
Location[a], *n* (%)			
Right upper lobe	26 (40.6)	23 (35.9)	0.949
Left lower lobe	14 (21.9)	17 (26.6)	
Right lower lobe	11 (17.2)	12 (18.8)	
Left lower lobe	10 (15.6)	10 (15.6)	
Right middle lobe	3 (4.7)	2 (3.1)	
Pathology pretreatment[a], *n* (%)			
Yes	34 (53.1)	32 (50.0)	0.724
No	30 (46.9)	32 (50.0)	
Histology pretreatment[a], *n* (%)			
No	30 (46.9)	32 (50.0)	0.618
Adenocarcinoma	15 (23.4)	19 (29.7)	
NSCLC	10 (15.6)	6 (9.4)	
Squamous	9 (14.1)	7 (10.9)	
FEV1[a,b] (%), mean ± SD	92.66 ± 27.59	86.84 ± 18.52	0.165
FEV1 (l), mean ± SD	2.34 ± 0.85	2.32 ± 0.67	0.894
WHO performance score[a], *n* (%)			
0	12 (18.8)	14 (21.9)	0.912
1	51 (79.7)	49 (76.6)	
2	1 (1.6)	1 (1.6)	
Charlson comorbidity score[a], *n* (%)			
0	12 (18.8)	12 (18.8)	0.995
1	23 (35.9)	23 (35.9)	
2	12 (18.8)	10 (15.6)	
3	13 (20.3)	14 (21.9)	
4	3 (4.7)	4 (6.3)	
5	1 (1.6)	1 (1.6)	

Annals of Oncology Mar 2013

SEER–Medicare: SABR vs. other techniques



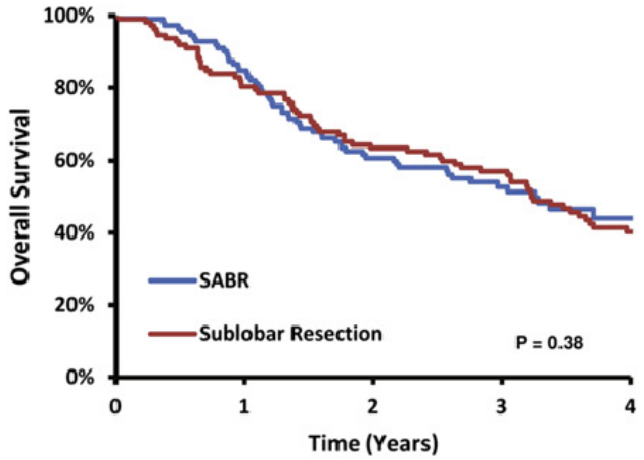


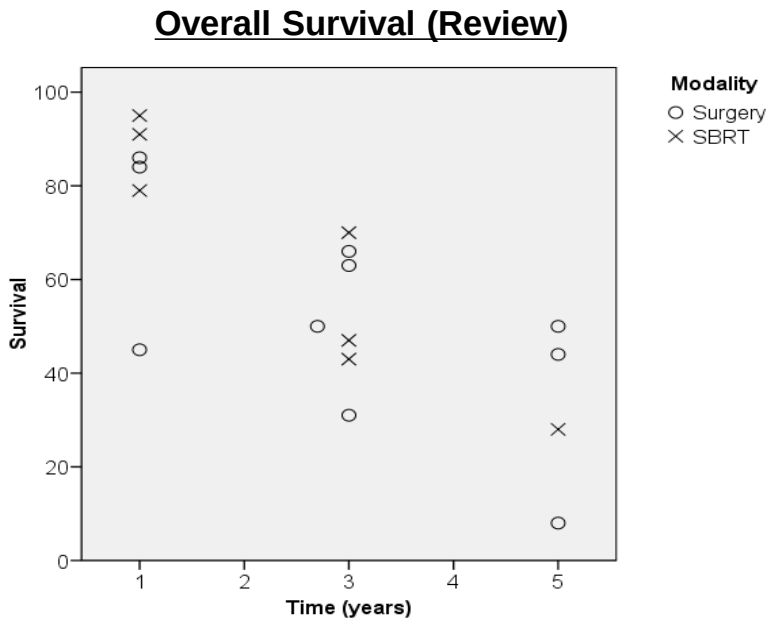
Table 4 Proportional hazards models for propensity-matched pairs of SABR cases and non-SABR controls

Comparison	Overall survival			Lung cancer-specific survival		
	HR	95% CI	$P > \chi^2$	HR	95% CI	$P > \chi^2$
Lobectomy vs SABR*	0.71	(0.45-1.12)	.14	1.00	(0.40-2.52)	>.99
Sublobar resection vs SABR	0.82	(0.53-1.27)	.38	2.14	(0.87-5.26)	.10
Conventional XRT vs SABR	1.97	(1.31-2.96)	.001	1.56	(0.67-3.59)	.30
Adj for age and grade	1.96	(1.28-3.00)	.002	1.59	(0.67-3.80)	.30
Observation vs SABR	2.10	(1.37-3.08)	<.001	3.88	(1.78-8.43)	<.001
Adj for tumor size	2.03	(1.34-3.07)	<.001	3.90	(1.76-8.61)	<.001

Abbreviations: adj = adjustment; CI = confidence interval; HR = hazard ratio; SABR = stereotactic ablative radiation; XRT = radiation therapy.
* SABR is the referent group for all comparisons.

High Risk Patients: Severe COPD

- Systematic Review of the Literature
  - Four papers reported patients with severe/very severe COPD or ppo-FEV1<40%
  - All reported local control of ≥89%
  - 30 day mortality: all SABR studies = 0%, surgical average = 10%



Palma et al IJROBP 2011

In Search of Level 1 Evidence…

Randomized Trials

ROSEL study

- Peripheral stage IA tumors
- **Primary**: 2- and 5-year local+ regional control, QoL and treatment costs.
- **Secondary**: Overall survival, quality adjusted life years (QALYs), pulmonary function, total costs (direct and indirect)

STARS study

- Stage IA tumors; T2 if ≤4cm
- **Primary**: 3-year overall survival.
- **Secondary**: DFS, PFS at 3 years; acute and chronic toxicities; predictive value of pre- and post-treatment PET scans

ACOSOG

American College Of Surgeons Oncology Group

Surgeons, Science, and Collaborations in Action

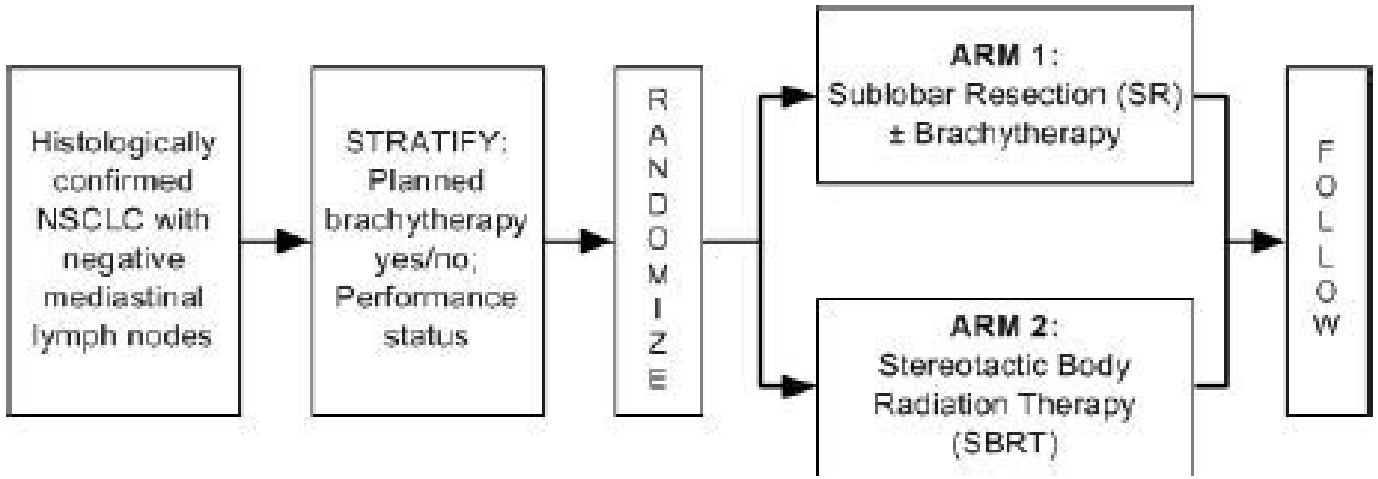
Thoracic Disease Site Committee

ACOSOG Study Chair: Hiran Fernando, MD
RTOG Study Chair: Robert Timmerman, MD
ACOSOG Committee Chair: Bryan Meyers, MD

PROTOCOL ACTIVATION: MAY 2, 2011

TITLE	**ACOSOG Z4099/RTOG 1021: A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)**

SCHEMA



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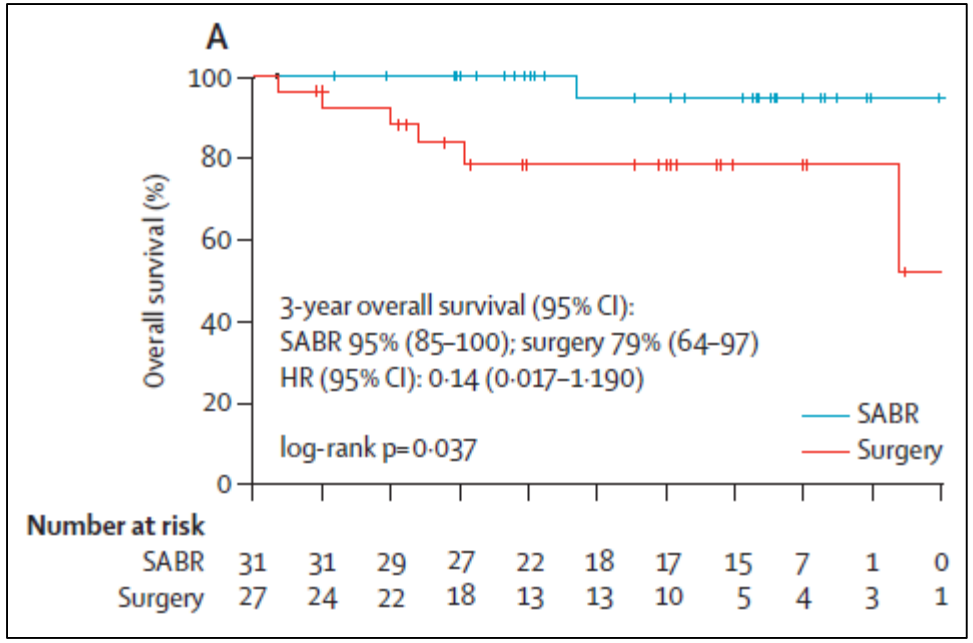
STARS–ROSEL Pooled analysis

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*



Lancet Oncology 2015

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STARS-ROSEL: Other Outcomes

Toxicity

- SABR:
  - 3 grade 3 events (10%)
- Surgery
  - 1 death (4%)
  - 1 grade 4 event (4%)
  - 11 grade 3 events (40%)

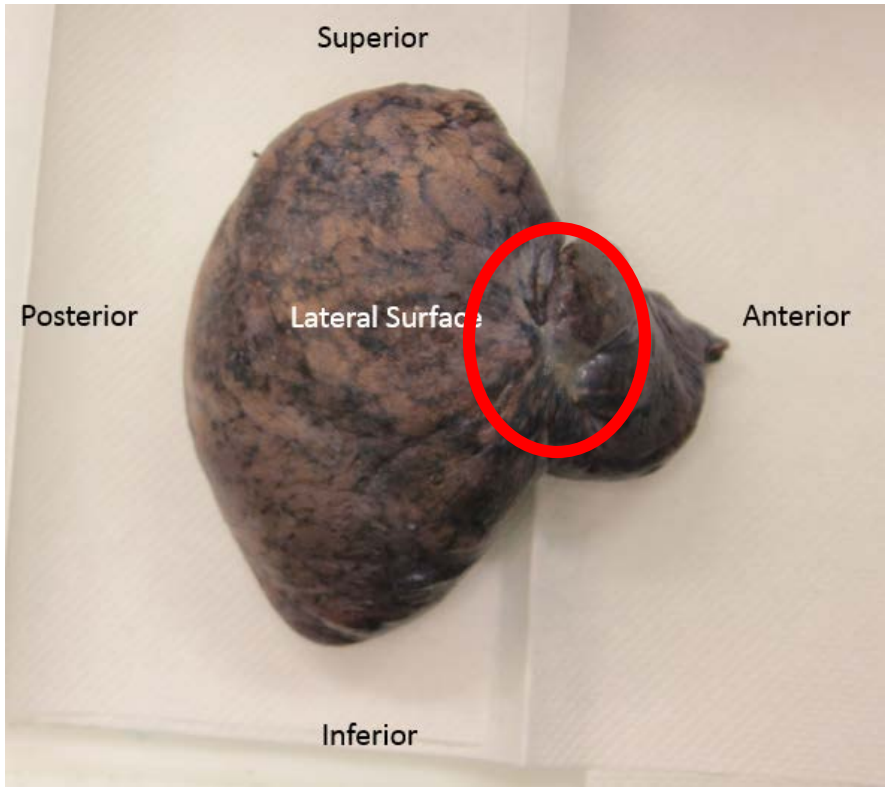
Locoregional Recurrence Events

- SABR:
  - 5 (1 local, 4 regional)
- Surgery
  - 1 (regional)

Lancet Oncology 2015

Local vs Lobar Recurrence

- 90% “local control” at 3 years is our standard quote
- Primary tumor control is different than lobar control



MISSILE Trial
NCT02136355
Slide: Sarah Mattonen

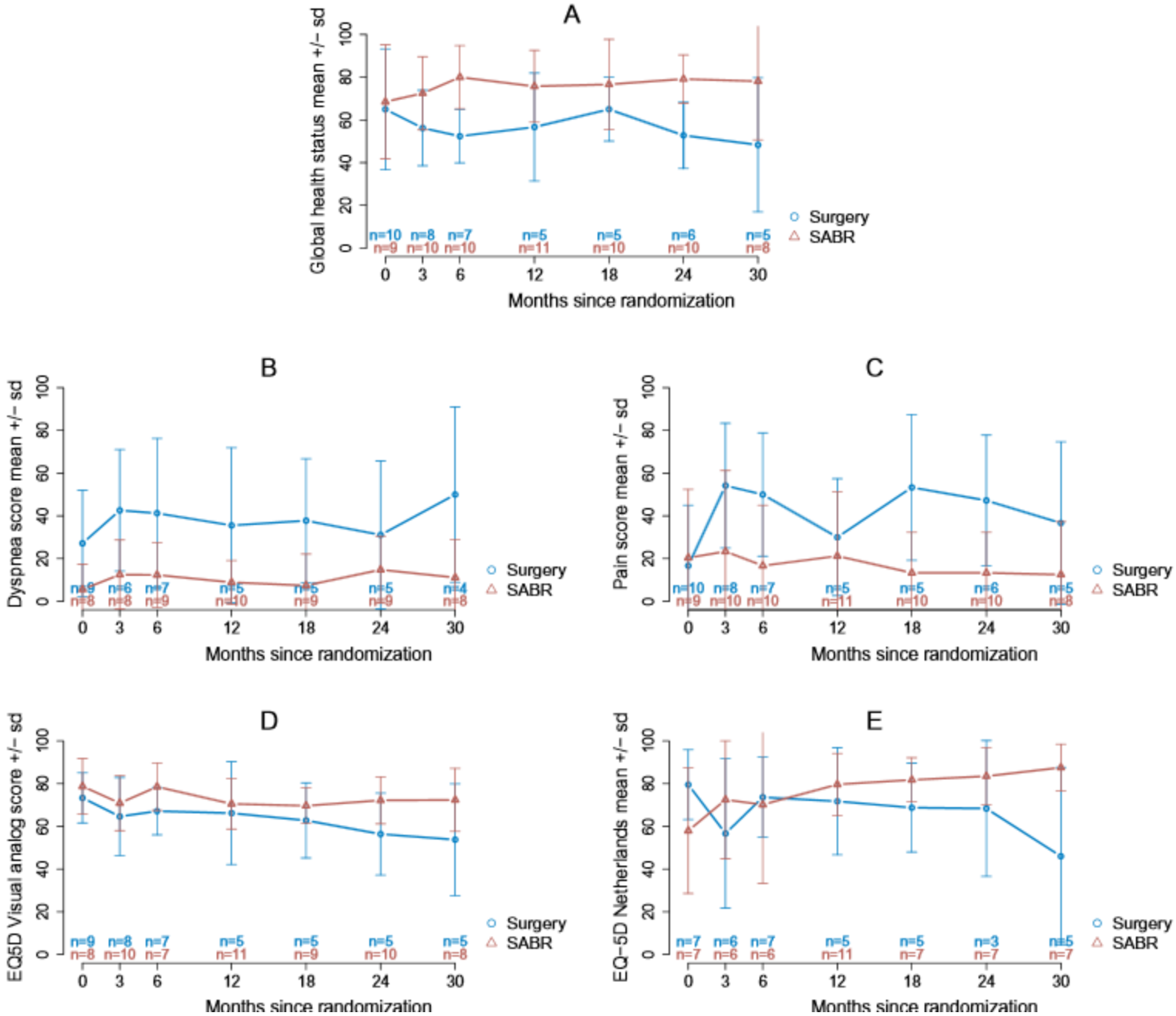
Patient Reported Outcomes from RCT

Patient reported outcomes in lung cancer

Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: Results from the ROSEL multicenter randomized trial

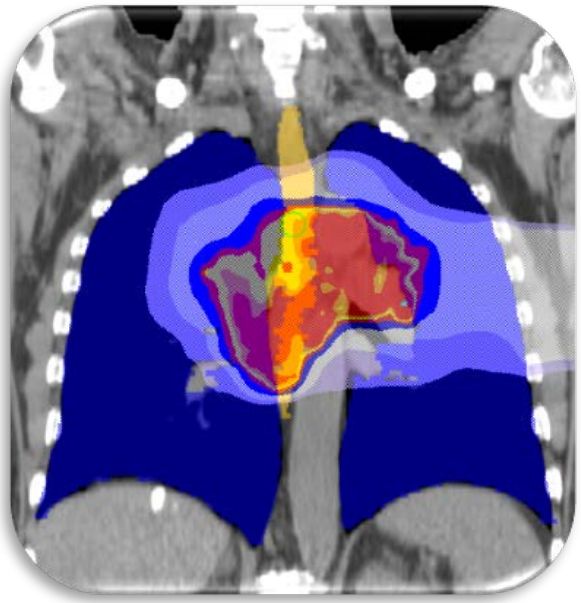
Alexander V. Louie [a,b,*], Erik van Werkhoven [c], Hanbo Chen [b], Egbert F. Smit [d], Marinus A. Paul [e], Joachim Widder [f], Harry J.M. Groen [g], Ben E.E.M. van den Borne [h], Katrien De Jaeger [i], Ben J. Slotman [a], Suresh Senan [a]

Radiotherapy and Oncology 2015


A
Global health status mean +/− sd
0
20
40
60
80
100
n=10 n=8 n=7 n=5 n=5 n=6 n=5
n=9 n=10 n=10 n=11 n=10 n=10 n=8
0 3 6 12 18 24 30
Months since randomization
Surgery
SABR
B
Dyspnea score mean +/− sd
n=9 n=6 n=7 n=5 n=5 n=5 n=4
n=8 n=8 n=9 n=10 n=9 n=9 n=8
Months since randomization
Surgery
SABR
C
Pain score mean +/− sd
n=10 n=8 n=7 n=5 n=5 n=6 n=5
n=9 n=10 n=10 n=11 n=10 n=10 n=8
Months since randomization
Surgery
SABR
D
EQ5D Visual analog score +/− sd
n=9 n=8 n=7 n=5 n=5 n=5 n=5
n=8 n=10 n=7 n=11 n=9 n=10 n=8
Months since randomization
Surgery
SABR
E
EQ−5D Netherlands mean +/− sd
n=7 n=6 n=7 n=5 n=5 n=3 n=5
n=7 n=6 n=6 n=11 n=7 n=7 n=7
Months since randomization
Surgery
SABR

Summary: Stage I Treatment

- Surgery remains standard of care, but non-randomized data suggests that SABR can achieve comparable outcomes
- New trials being launched: STABLEMATES, VALOR, and in China
- SABR beats 3D-CRT on convenience and toxicity, but early RCT data suggests that good local control can also be achieved with very prolonged fractionation schedules



Management of Stage III NSCLC

Unresectable: RT alone

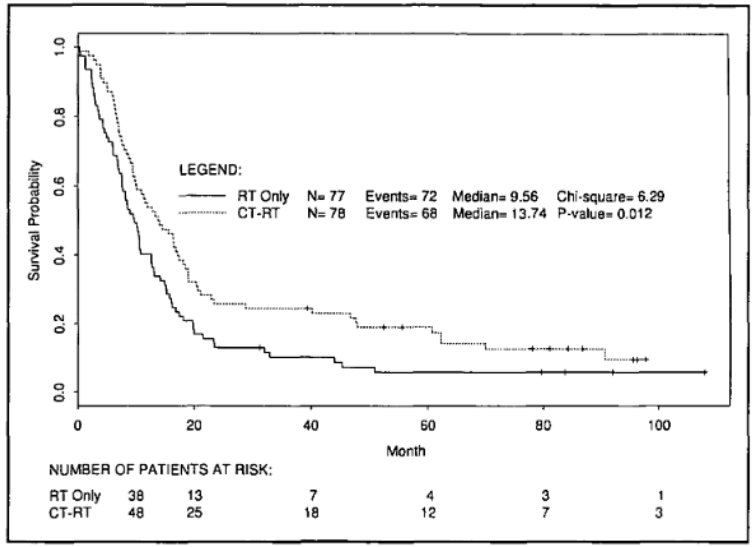
- Perez et al RTOG RCT (IJROBP 1986) established 60 Gy in 30 fractions based on highest rates of local control (no survival differences vs. 40 or 50 Gy).

- Altered fractionation provides a 2.5% benefit in 5-year survival (meta-analysis JCO 2012) at the expense of increased esophagitis

Chemo + RT vs. RT alone

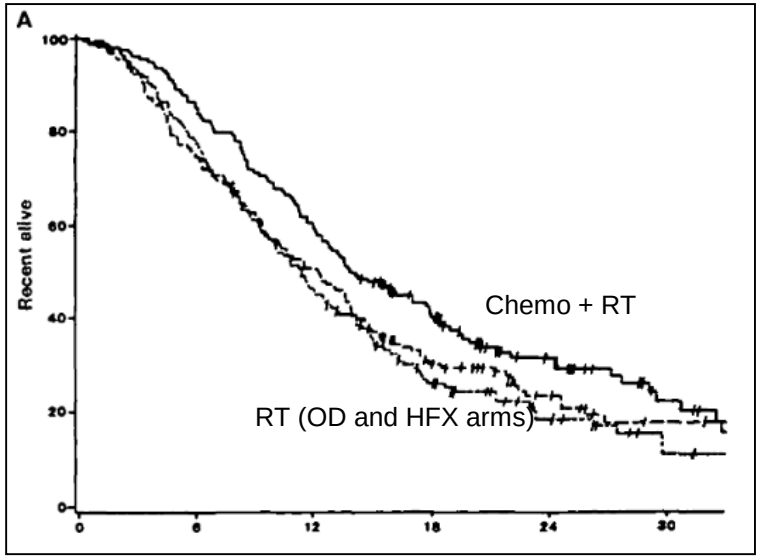
Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial

*Robert O. Dillman, James Herndon, Stephen L. Seagren, Walter L. Eaton, Jr., Mark R. Green**



Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary Results of a Phase III Trial in Regionally Advanced, Unresectable Non–Small-Cell Lung Cancer

*William T. Sause, Charles Scott, Samuel Taylor, David Johnson, Robert Livingston, Ritsuko Komaki, Bahman Emami, Walter J. Curran, Roger W. Byhardt, Andrew T. Turrisi, A. Rashid Dar, James D. Cox**

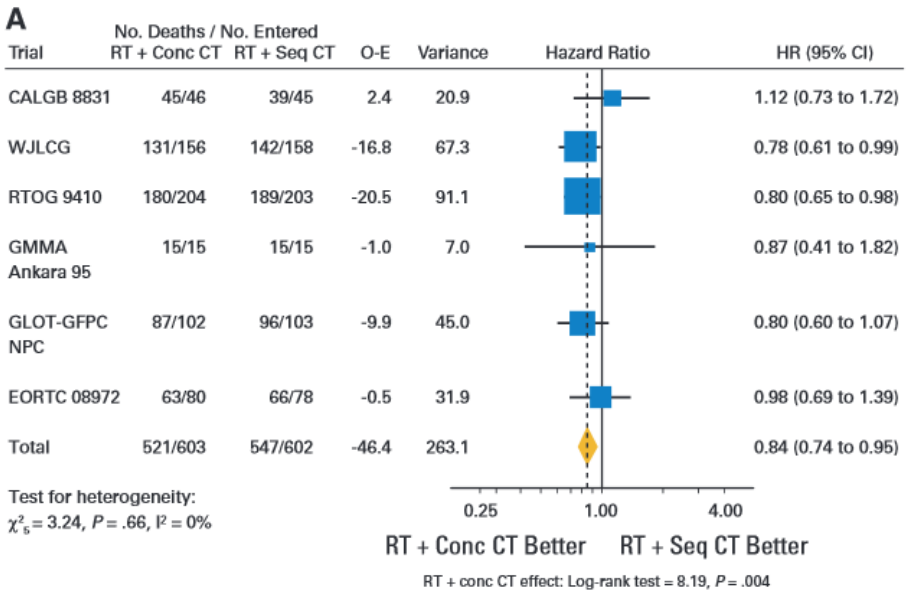


JNCI 1995 and 1996
Chest 2000

Chemo: Concurrent vs. Sequential

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon



Auperin, JCO 2012

Optimal Chemotherapy Unknown

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JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

Concurrent Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer: What Is the Best Regimen?

Wilfried Ernst Erich Eberhardt, *West German Cancer Centre; and University Hospital of University Duisburg-Essen, Essen, Germany*

- Most common options in U.S. are carboplatin/paclitaxel and cisplatin/etoposide
- No phase III data to compare these
  - Pneumonitis rates appear higher with carbo/paclitaxel
  - Phase II survival data favors cisplatin/etoposide
- Cis-Vinca alkaloid also reasonable

STRIPE Pneumonitis Meta-analysis

Clinical Investigation

Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-analysis

David A. Palma, MD, MSc, PhD,* Suresh Senan, MRCP, FRCR, PhD,† Kayoko Tsujino, MD,‡ Robert B. Barriger, MD,§ Ramesh Rengan, MD, PhD,|| Marta Moreno, MD,¶ Jeffrey D. Bradley, MD,** Tae Hyun Kim, MD,†† Sara Ramella, MD,‡‡ Lawrence B. Marks, MD,§§ Luigi De Petris, MD, PhD,|||| Larry Stitt, MSc,¶¶ and George Rodrigues, MD, MSc*,¶¶

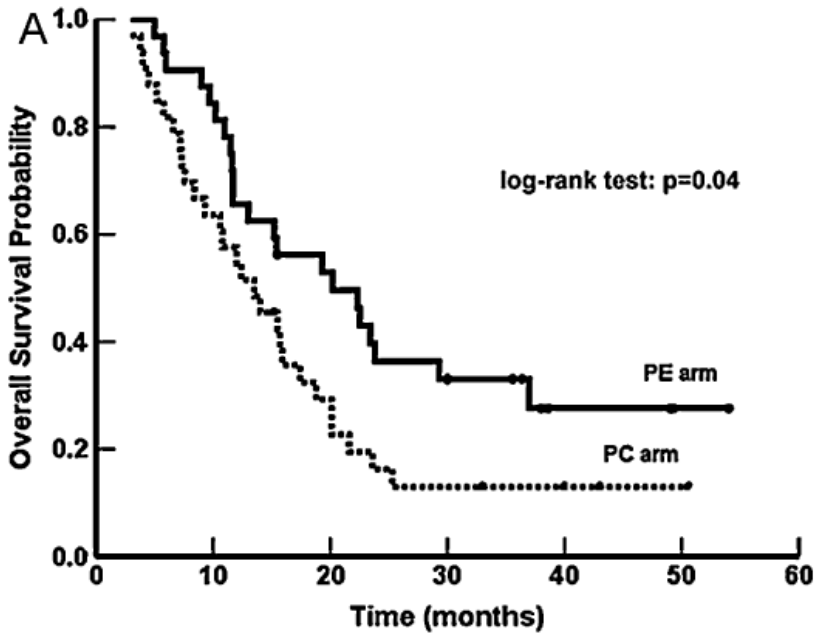
Factor	Multivariable analysis		
	OR	95% CI	*P* value
Age (per 10-y increase)	1.24	0.97-1.59	.090
Chemotherapy regimen			<.001
Cisplatin-etoposide	1	Reference	
Carboplatin-paclitaxel	3.33	1.89-5.87	
Other	1.38	0.78-2.41	
Volume of lung receiving ≥20 Gy (V_{20})	1.03	1.01-1.05	.008

IJROBP 2011

Cis/Etoposide or Carbo/Paclitaxel?

Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer☆

Luhua Wang[a,*], Shixiu Wu[b], Guangfei Ou[a], Nan Bi[a], Wenfeng Li[b], Hua Ren[a], Jianzhong Cao[a], Jun Liang[a], Junling Li[c], Zongmei Zhou[a], Jima Lv[a], Xiangru Zhang[c]



Cis/Etoposide or Carbo/Paclitaxel?

Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer☆

Luhua Wang[a,*], Shixiu Wu[b], Guangfei Ou[a], Nan Bi[a], Wenfeng Li[b], Hua Ren[a], Jianzhong Cao[a], Jun Liang[a], Junling Li[c], Zongmei Zhou[a], Jima Lv[a], Xiangru Zhang[c]

Table 2
Treatment-related toxicities.

	PE	PC	*P* value
Neutropenia			
Grade 1/2	7 (25%)	16 (48.5%)	
Grade 3/4	25 (78.1%)	17 (51.5%)	0.05
Hemoglobin			
Grade 1/2	28 (87.5%)	29 (87.9%)	
Grade 3/4	4 (12.5%)	4 (12.1%)	0.74
PLT			
Grade 1/2	27 (84.4%)	29 (87.9%)	
Grade 3/4	5 (15.6%)	4 (12.1%)	0.26
Esophagitis			
Grade 1	20 (62.5%)	20 (60.1%)	
Grade 2/3	12 (37.5%)	13 (39.9%)	0.94
Radiation pneumonitis			
Grade 1	24 (75%)	17 (51.5%)	
Grade ≥2	8 (25%)	16 (48.5%)	0.09

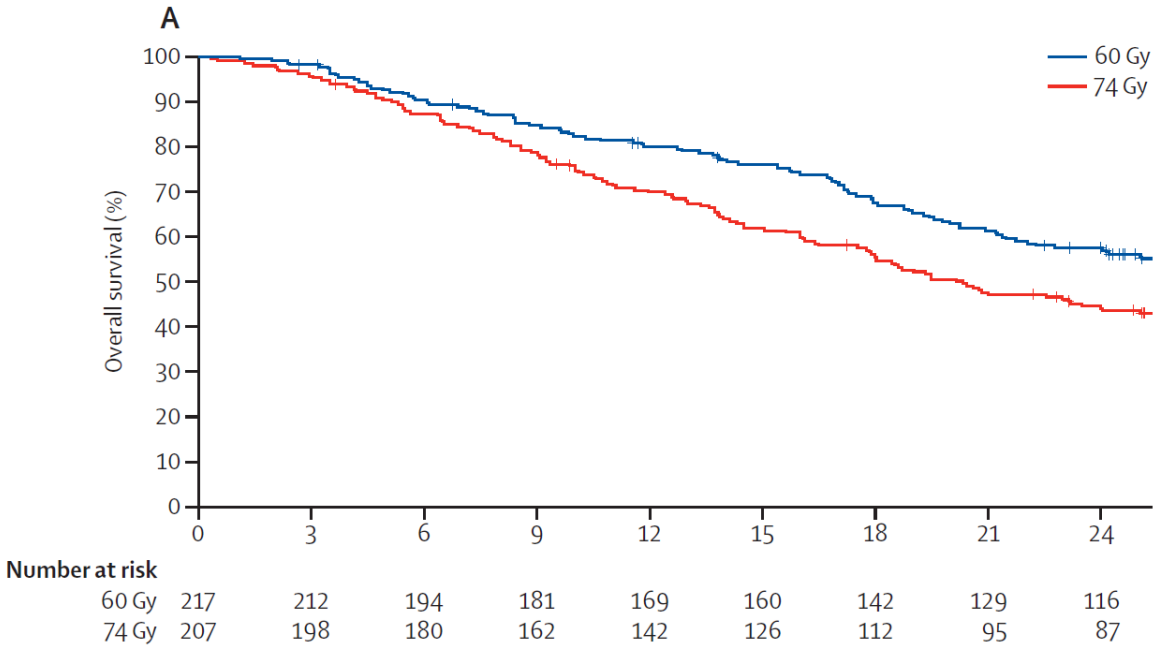
Optimal RT Dose – RTOG 0617

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory Masters, George Blumenschein, Steven Schild, Jeffrey Bogart, Chen Hu, Kenneth Forster, Anthony Magliocco, Vivek Kavadi, Yolanda I Garces, Samir Narayan, Puneeth Iyengar, Cliff Robinson, Raymond B Wynn, Christopher Koprowski, Joanne Meng, Jonathan Beitler, Rakesh Gaur, Walter Curran Jr, Hak Choy

	Concurrent Treatment	Consolidation Treatment
RANDOMIZE	**Arm A** Concurrent chemotherapy: → Carboplatin & Paclitaxel RT to 60 Gy, 5 x per week for 6 weeks	**Arm A** Consolidation chemotherapy: Carboplatin & Paclitaxel
	Arm B: Closed 6/17/11 Concurrent chemotherapy: → Carboplatin & Paclitaxel RT to 74 Gy, 5 x per week for 7.5 weeks	**Arm B: Closed 6/17/11** Consolidation chemotherapy: Carboplatin & Paclitaxel
	Arm C Cetuximab Loading Dose: → Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 60 Gy, 5 x per week for 6 weeks	**Arm C** Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel
	Arm D: Closed 6/17/11 Cetuximab Loading Dose: → Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 74 Gy, 5 x per week for 7.5 weeks	**Arm D: Closed 6/17/11** Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel

Optimal Dose – RTOG 0617



	60 Gy (n=217)*	74 Gy (n=207)
Overall survival		
Dead	127	140
1 year	80·0% (73·9–84·7)	69·8% (63·1–75·6)
2 year	57·6% (50·6–63·9)	44·6% (37·7–51·3)
Median (months)	28·7 (24·1–36·9)	20·3 (17·7–25·0)
HR	1·38 (1·09–1·76)	..
p value (log-rank, one-sided)	0·004	..
Progression-free survival		
Fail	164	164
1 year	49·2% (42·3–55·6)	41·2% (34·4–47·8)
2 year	29·1% (23·1–35·3)	21·4% (16·1–27·3)
Median (months)	11·8 (10·2–14·3)	9·8 (8·8–11·6)
HR	1·19 (0·95–1·47)	..
p value (log-rank, two-sided)	0·12	..
Local failure		
Fail	77	86
1 year	16·3% (11·4–21·3)	24·8% (18·9–30·7)
2 year	30·7% (24·5–36·9)	38·6% (31·9–45·3)
HR	1·26 (0·93–1·71)	..
p value (Gray, two-sided)	0·13	..

- **Factors predictive of OS**: Radiation dose (60 Gy), maximum esophagitis grade, PTV size, heart V5 and V30

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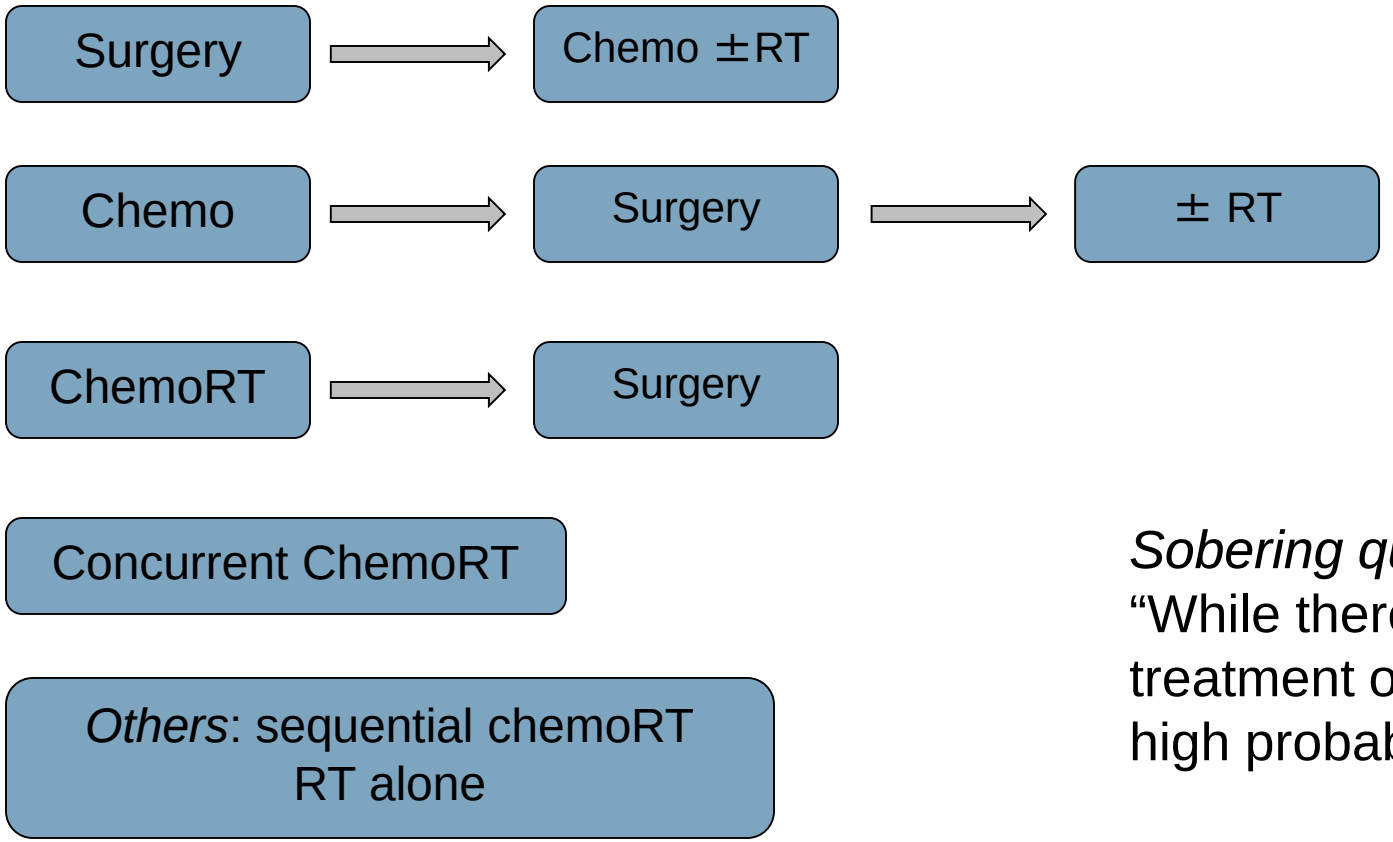
Unresectable Stage III – Summary

- Concurrent chemoradiotherapy is preferred
  - Optimal chemotherapy is an open question
- Randomized evidence best supports a total dose of 60 Gy in 2 Gy daily fractions with chemotherapy
- Sequential chemoradiation, and radiation alone are options in less-fit patients

Resectable Stage III NSCLC

- Options for curative-intent treatment:



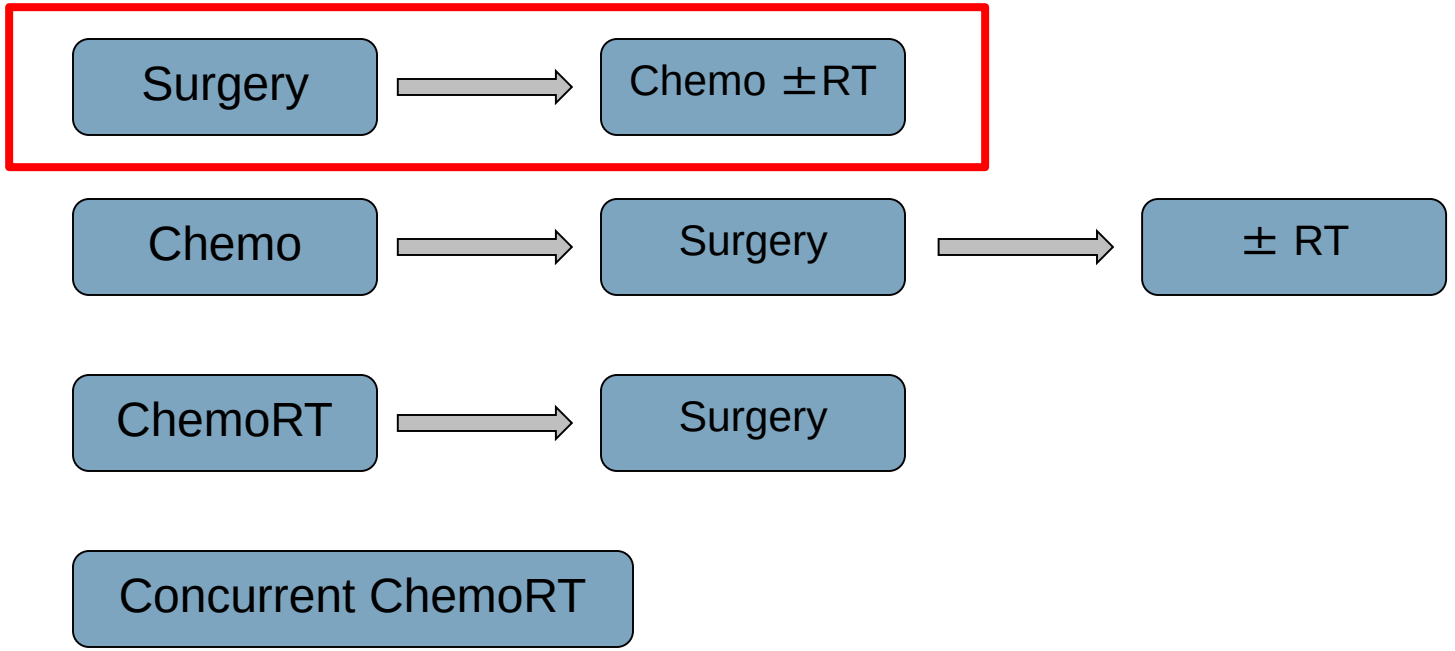
Sobering quote:
"While there are many potential treatment options, none yields a high probability of cure."

– Schild et al, utdol.com

- Insufficient randomized data to identify which option is best
- Some RCTs include non-standard arms – this makes conclusions difficult
- **Overarching Theme of This Section**:
  - Randomized trials have consistently failed to show that <u>two</u> local treatments are better than <u>one</u> local treatment.

Resectable Stage III NSCLC

- Options for curative-intent treatment:



Option 1: Surgery first

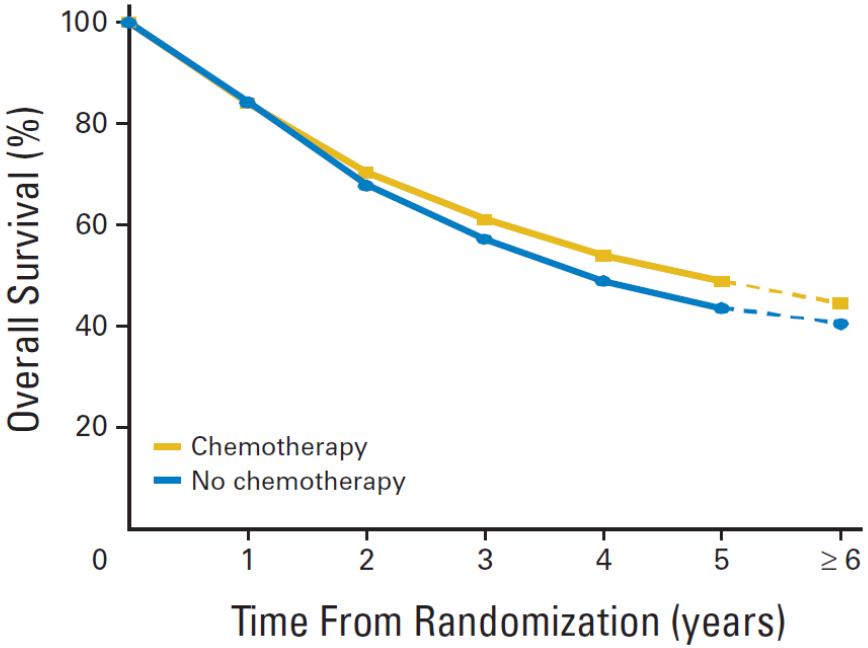
- In carefully selected patients with limited stage IIIA disease that can be completely resected, initial surgery is often the treatment of choice
  - Examples include T3N1 disease, or T4 disease due to multiple tumor nodules in one lung.

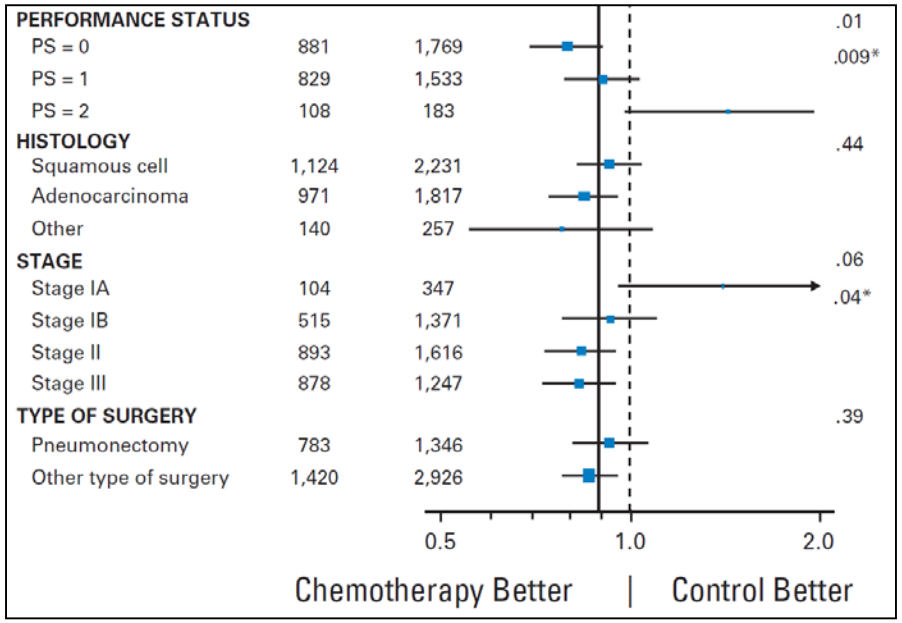
- Superior sulcus (Pancoast) tumors are a special case
  - SWOG 9416 evaluated neoadjuvant chemoRT for T3-T4 N0/1 superior sulcus tumors (45 Gy with concurrent cis/eto then resection)
  - 2-year survival 55%

Surgery first? Then what…?

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier





JCO 2008

Post-Operative Radiotherapy: PORT

- Why consider PORT?
  - R1 resection (positive margins)
  - R0 resection with positive nodes

Lancet 1998

PORT: Positive Margins

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non–Small-Cell Lung Cancer

Elyn H. Wang, Christopher D. Corso, Charles E. Rutter, Henry S. Park, Aileen B. Chen, Anthony W. Kim, Lynn D. Wilson, Roy H. Decker, and James Byunghoon Yu

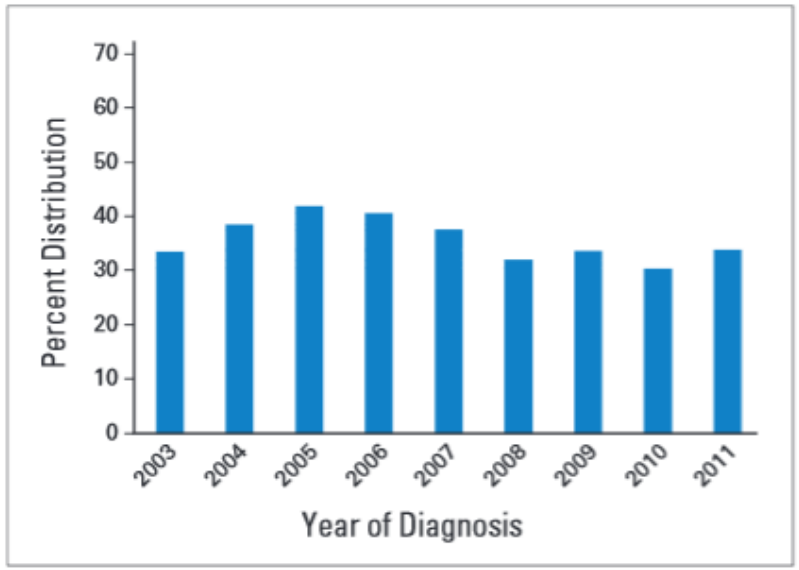
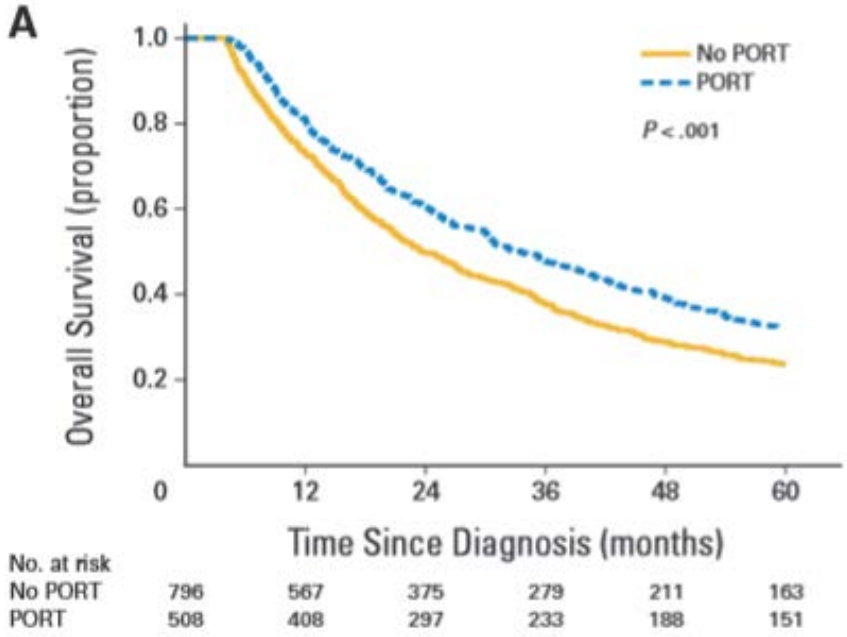


Fig 1. Percent distribution by year of diagnosis of patients receiving postoperative radiotherapy.



JCO 2015

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PORT Based on Nodal Status

PORT = Pretty Old Radiotherapy

Many centers used old techniques (Cobalt, APPA) and large doses per fraction

Articles

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

*PORT Meta-analysis Trialists Group**

Trial	Radiotherapy do				Prescription technique	Machine used	Average field size (cm)	Clinical target volume	Technique
	Total dose (Gy)			/day					
Belgium[10]	60					Co60	15x9	Bronchial stump, hilum, mediastinum	SCB,OF,LF
LCSG 773[11]	50					60 &	*	Bronchial stump, hilum, mediastinum	SCB,OF,LF
CAMS[12]	60							Hilum, mediastinum	SCB,OF,LF
Lille[13]	45–60							pper n	SCB,OF,LF
EORTC 08861	56	28						astinum	Composite plans
MRC LU11[14]	40	15	3					diastinum, icular fossae†	SCB,OF,LF
GETCB 04CB86	60	24–30	6	2·0–2·5	Isocent			l stump, mediastinum	SCB,OF,LF
Slovenia[15]	30	10–12	2	2·5–3·0	Central axis, at midplane			mediastinum	OF,LF
GETCB 05CB88	60	24–30	6	2·0–2·5	Isocentre	Co60 linac		hial stump, n, mediastinum	SCB,OF,LF

Lancet 1998

SCB = spinal cord blocks; OF = oblique fields; LF = lateral fields; linac=linear accelerator; Co60=cobalt-60.
Only one trial (EORTC 08861) used computed tomography for planning, and two trials (EORTC 08861 and Lille) used lung-factor corrections.
*Information not available; †For upper lobe tumours.

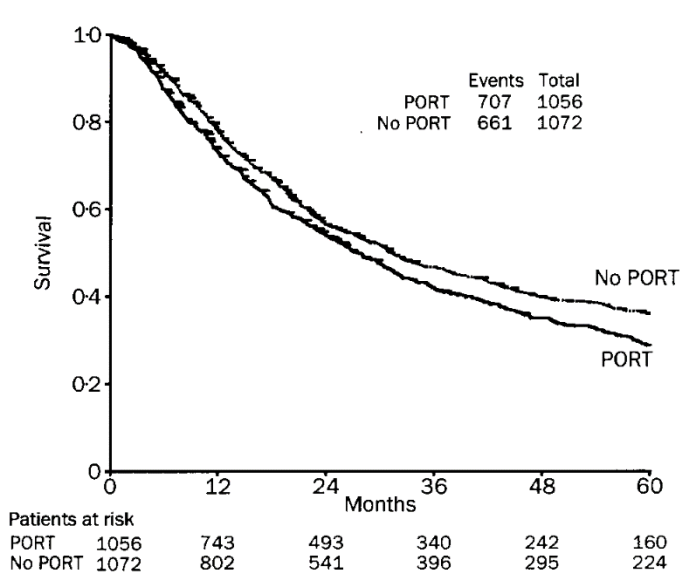
Table 3: **Details of radiotherapy**

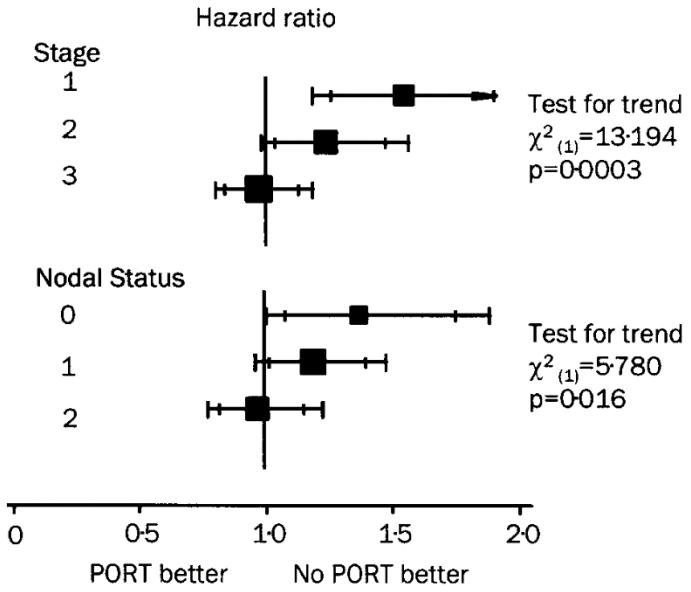
PORT Based on Nodal Status

Articles

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

*PORT Meta-analysis Trialists Group**





Lancet 1998

PORT Based on Nodal Status

- Several subsequent observational studies suggest some value for PORT
  - Data sources:
    - ANITA trial (post hoc analysis – IJROBP 2008)
    - SEER (JCO 2006)
    - National Cancer Database (JTO 2014)

- PORT in N2 disease is the current topic of the Phase III European LUNG-ART randomized trial (EORTC 22055) – dose is 54 Gy in 30 fractions

Lancet 1998

Where to treat? LUNG-ART guideline

VARIATIONS IN TARGET VOLUME DEFINITION FOR POSTOPERATIVE RADIOTHERAPY IN STAGE III NON–SMALL-CELL LUNG CANCER: ANALYSIS OF AN INTERNATIONAL CONTOURING STUDY

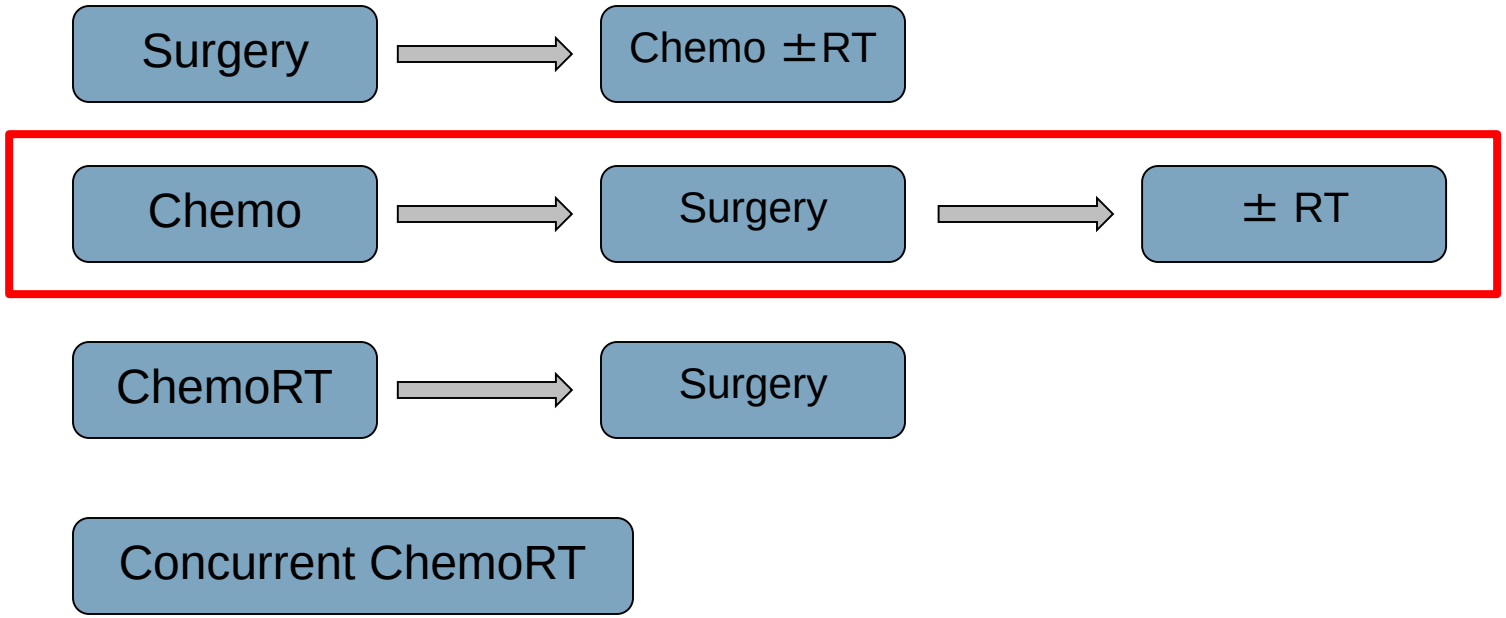
Surgically involved mediastinal nodes	LN stations to be included in the CTV
1–2R	1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
1–2L	1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
3 (Right -sided tumor)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
3 (Left-sided tumor)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
4R	2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
4L	2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
5	2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*
6	2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
7 (Right-sided tumor)	4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
7 (Left-sided tumor)	4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
8 (Right-sided tumor)	4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction
8 (Left-sided tumor)	4L, 5, 6, 7 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction

Abbreviations: LN = lymph node; CTV = clinical target volume.
* Unless other nodes are involved.

Spoelstra, IJROBP

Resectable Stage III NSCLC

- Options for curative-intent treatment:



Option 2: Chemo before surgery

- Pre-operative chemotherapy improves survival compared to surgery alone (Meta-analysis, Lancet 2014).
- But, compared to post-operative chemotherapy, outcomes are similar (NATCH RCT).
- Induction chemotherapy may be considered in patients planned for surgery who have low volume/microscopic mediastinal disease

JNCI 2007

Option 2: Chemo before surgery

- **If choosing induction chemotherapy** before surgery, should you deliver induction chemoradiation instead?

JNCI 2007

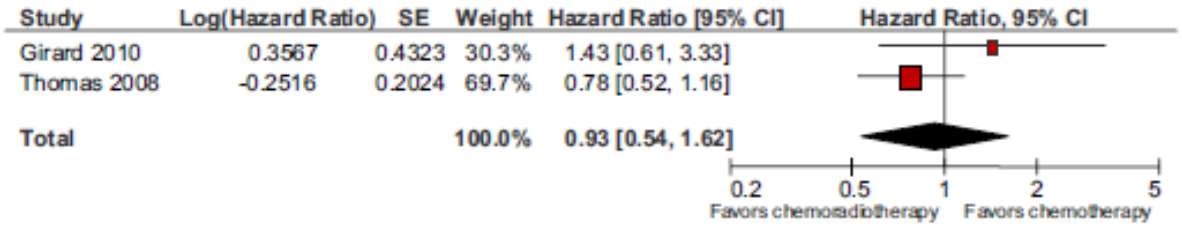
Option 2: Chemo before surgery: SAKK 16/00

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

232 patients randomized to cis-doc vs. cis-doc-RT (44Gy) before surgery

2 older RCTs showed similar results (Shah, ATS 2012)



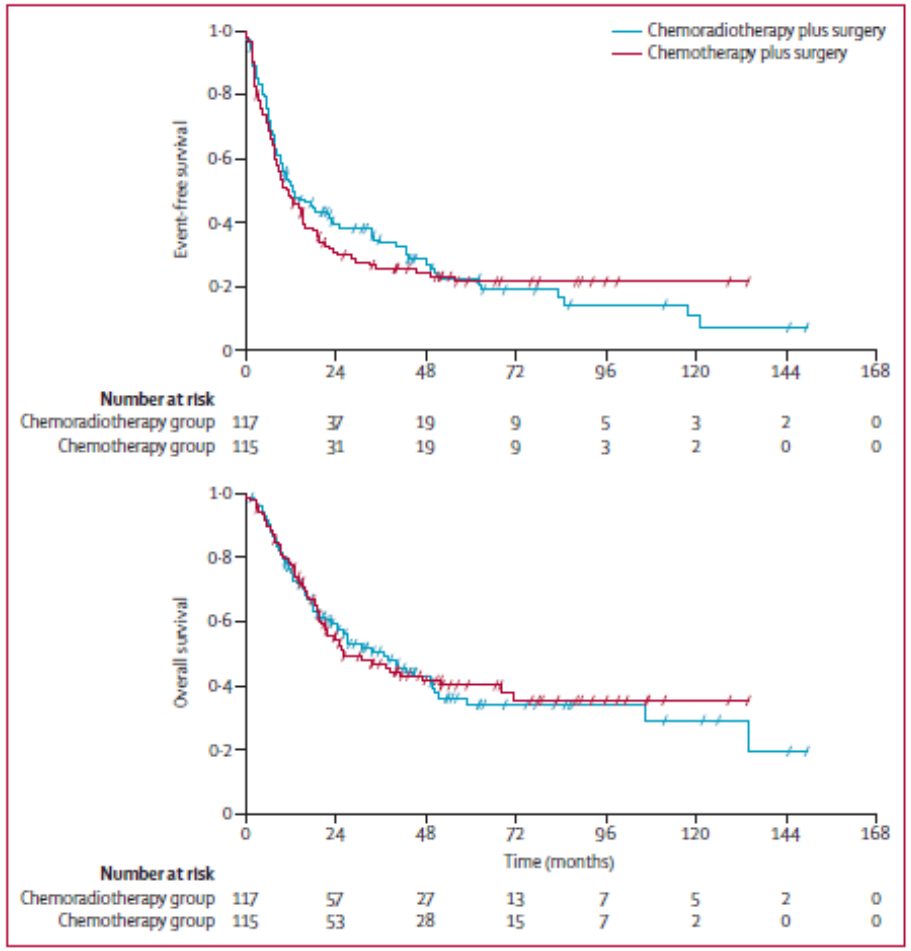
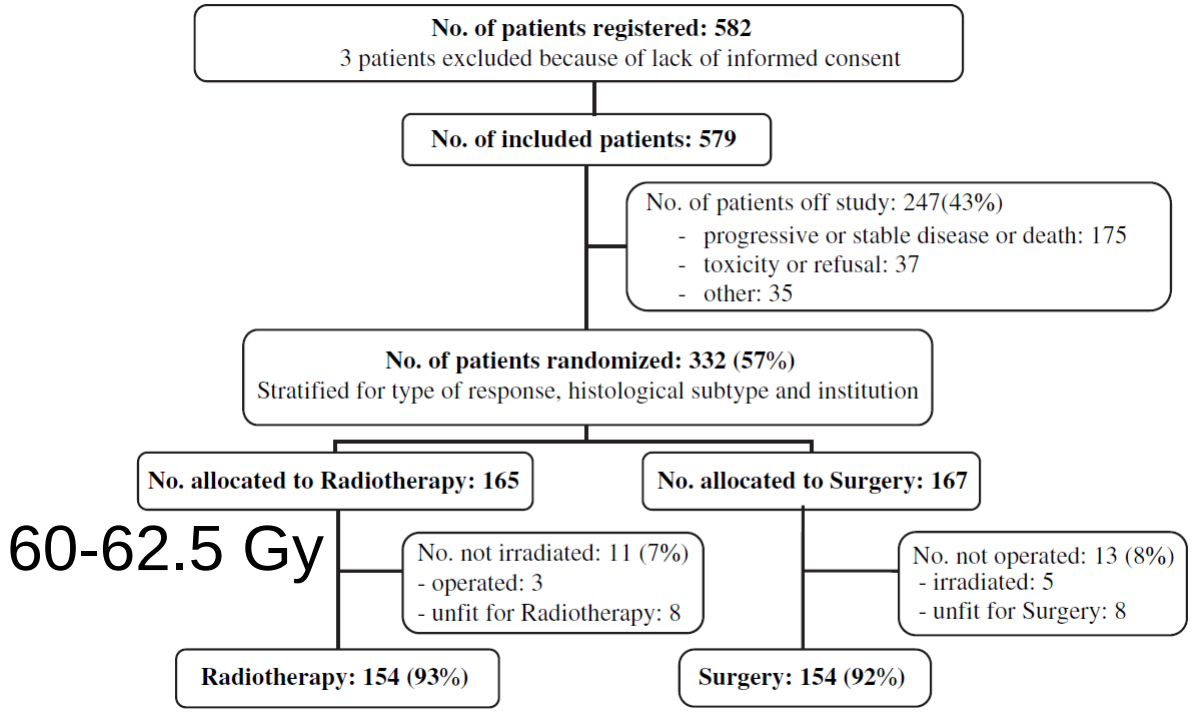


Figure 2: **Event-free and overall survival**
Analysis was done by intention to treat.

Option 2: Chemo before surgery or RT?

Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

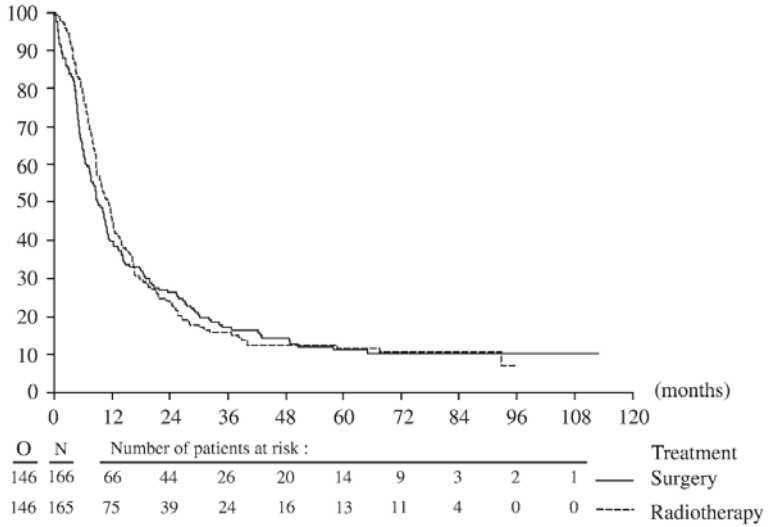
Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone



JNCI 2007

Option 2: Chemo before surgery or RT

PFS



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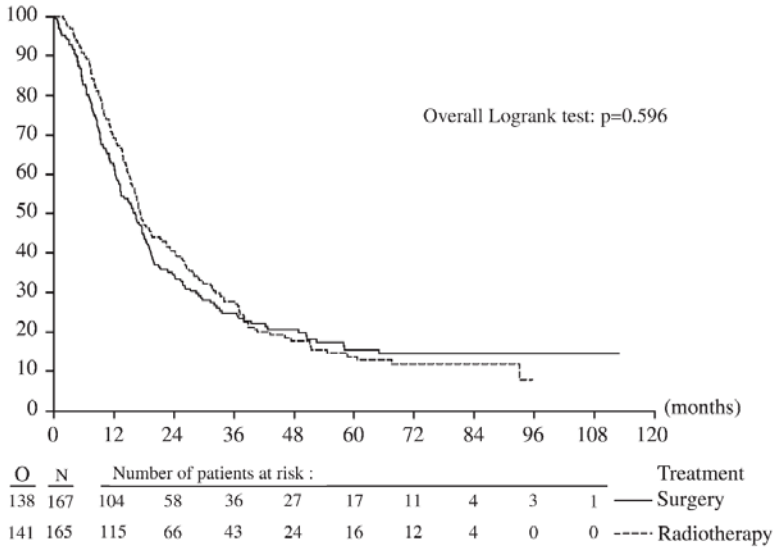
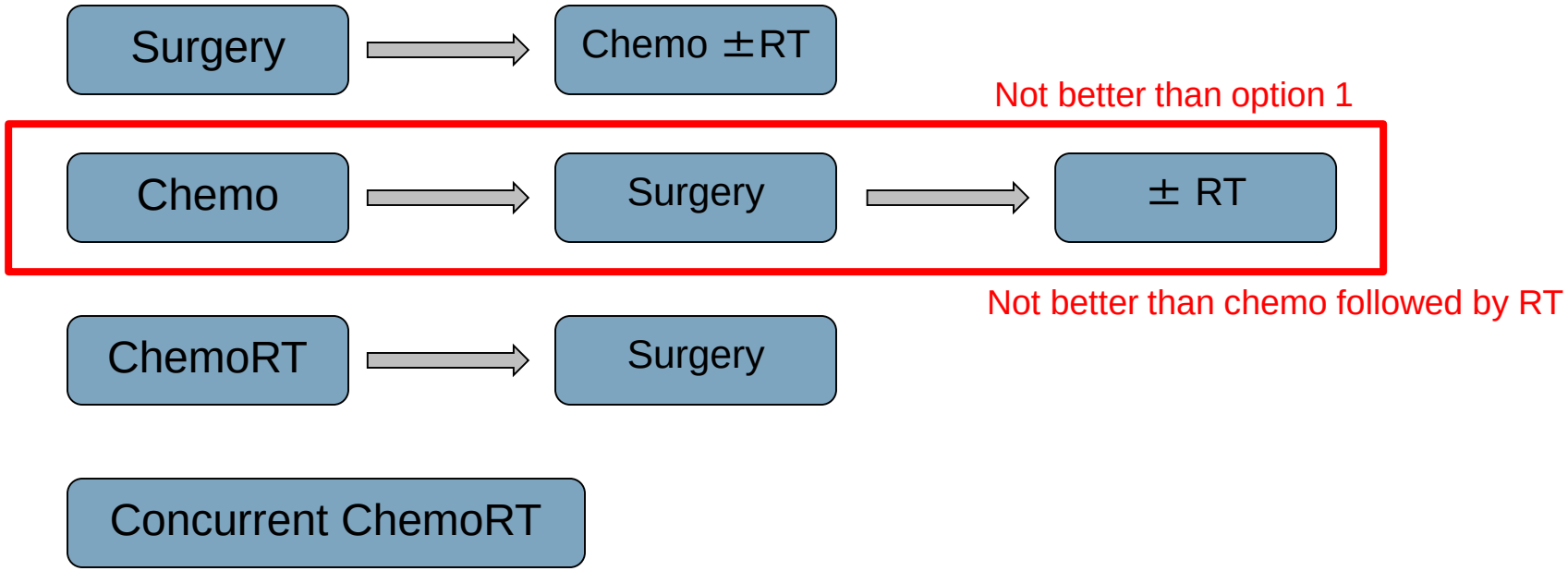


"In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment."

JNCI 2007

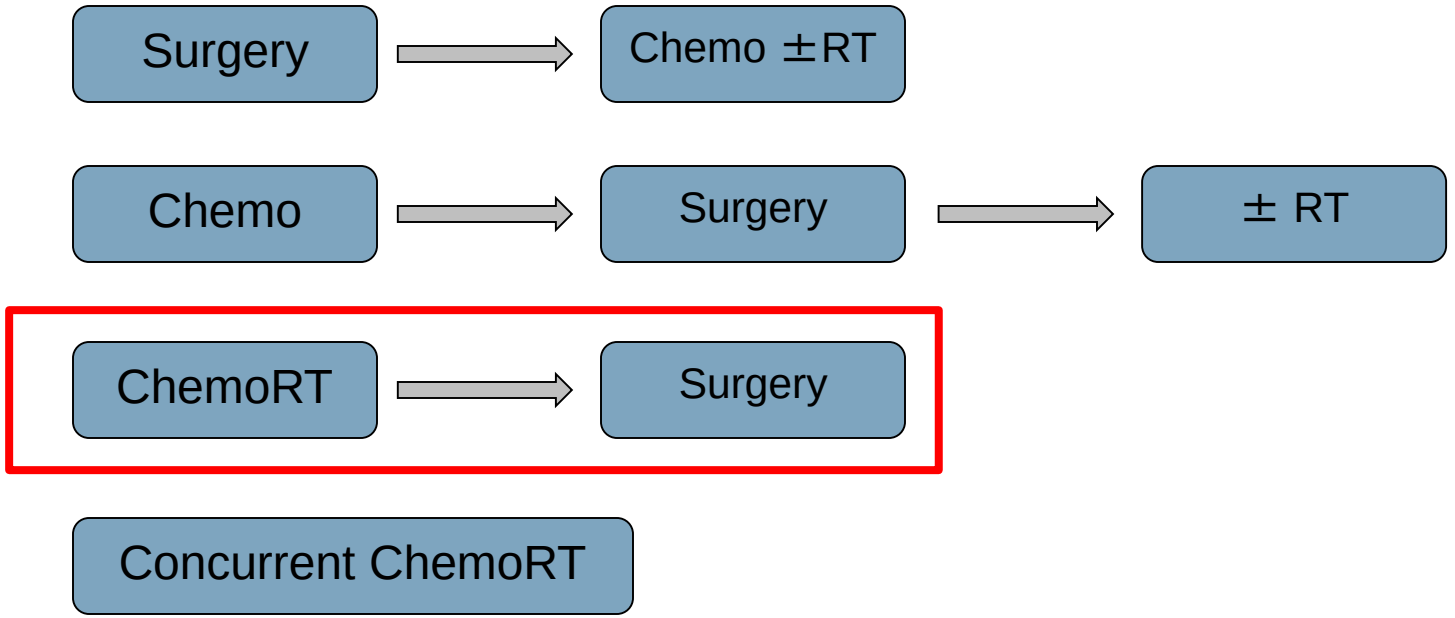
Resectable Stage III NSCLC

- Options for curative-intent treatment:



Resectable Stage III NSCLC

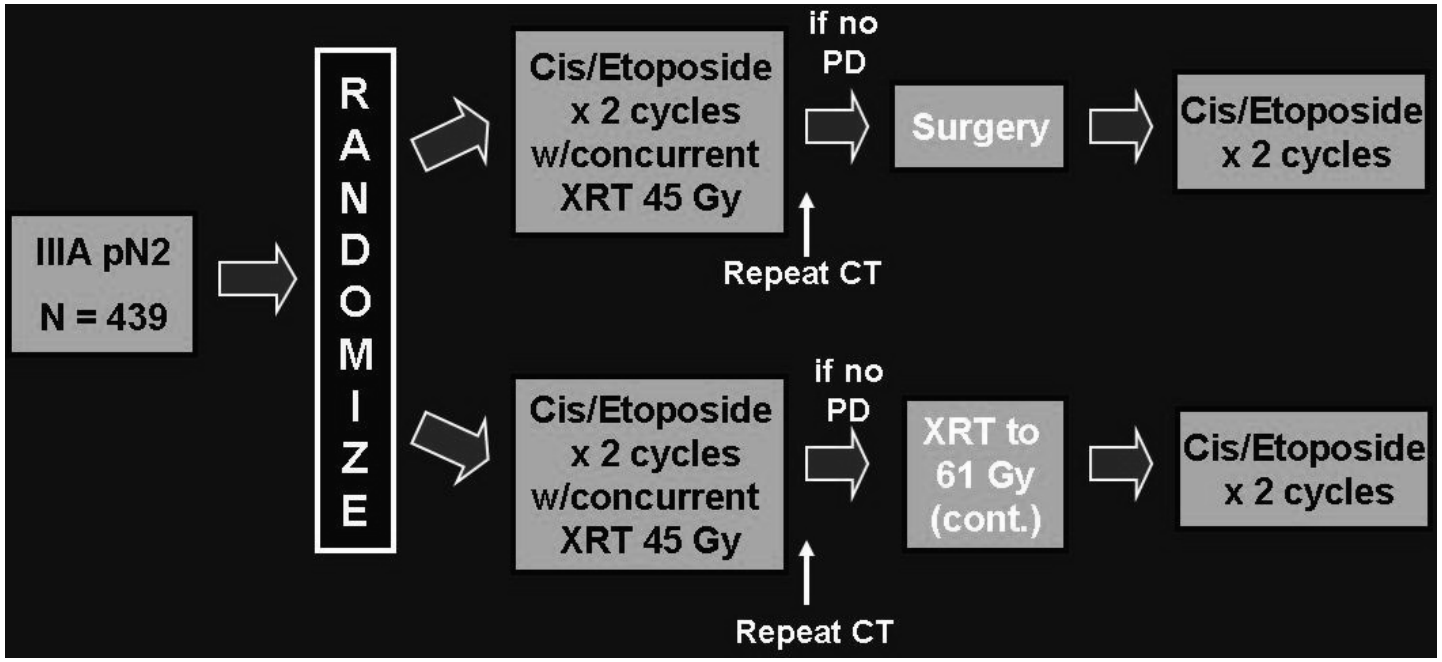
- Options for curative-intent treatment:



Option 3: ChemoRT first – or alone

Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

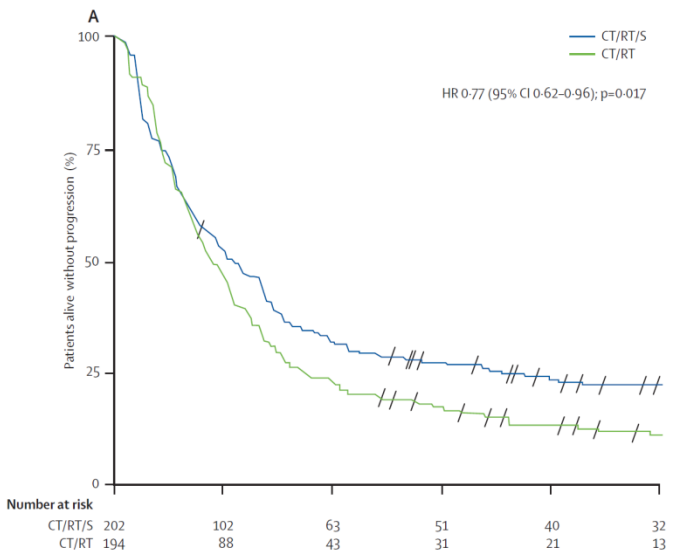
Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, Willliam T Sause, James D Cox



Lancet 2009

Albain Trial

PFS



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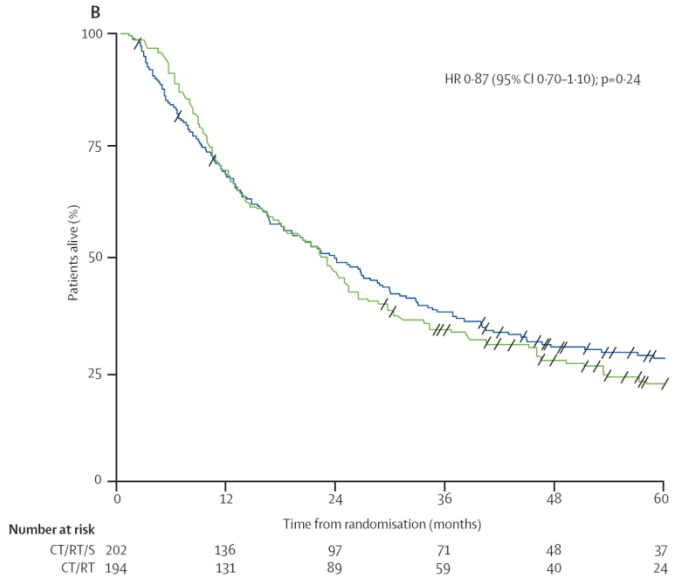
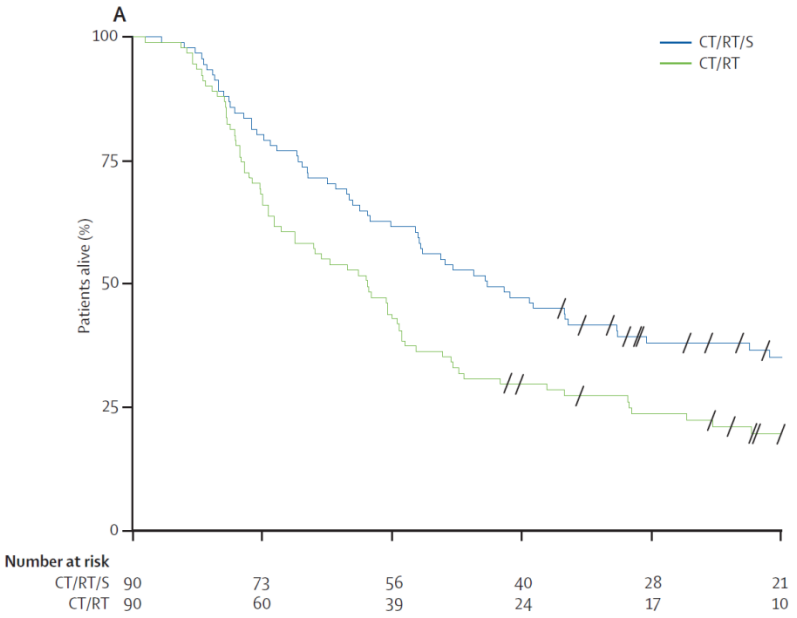


- Pneumonectomy operative mortality rate: 26% (15/54)

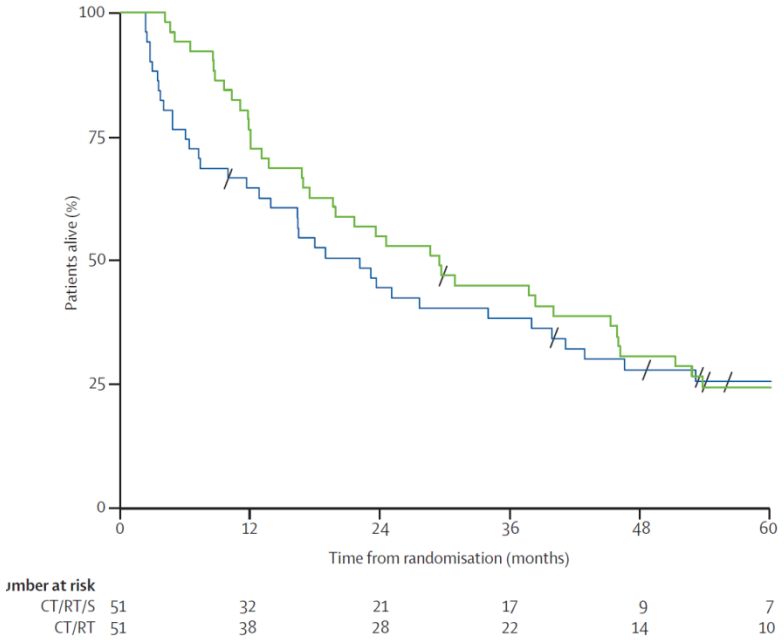
Lancet 2009

Albain Trial – Exploratory Analysis

Lobectomy vs. Matches



Pneumonectomy vs. Matches



Lancet 2009

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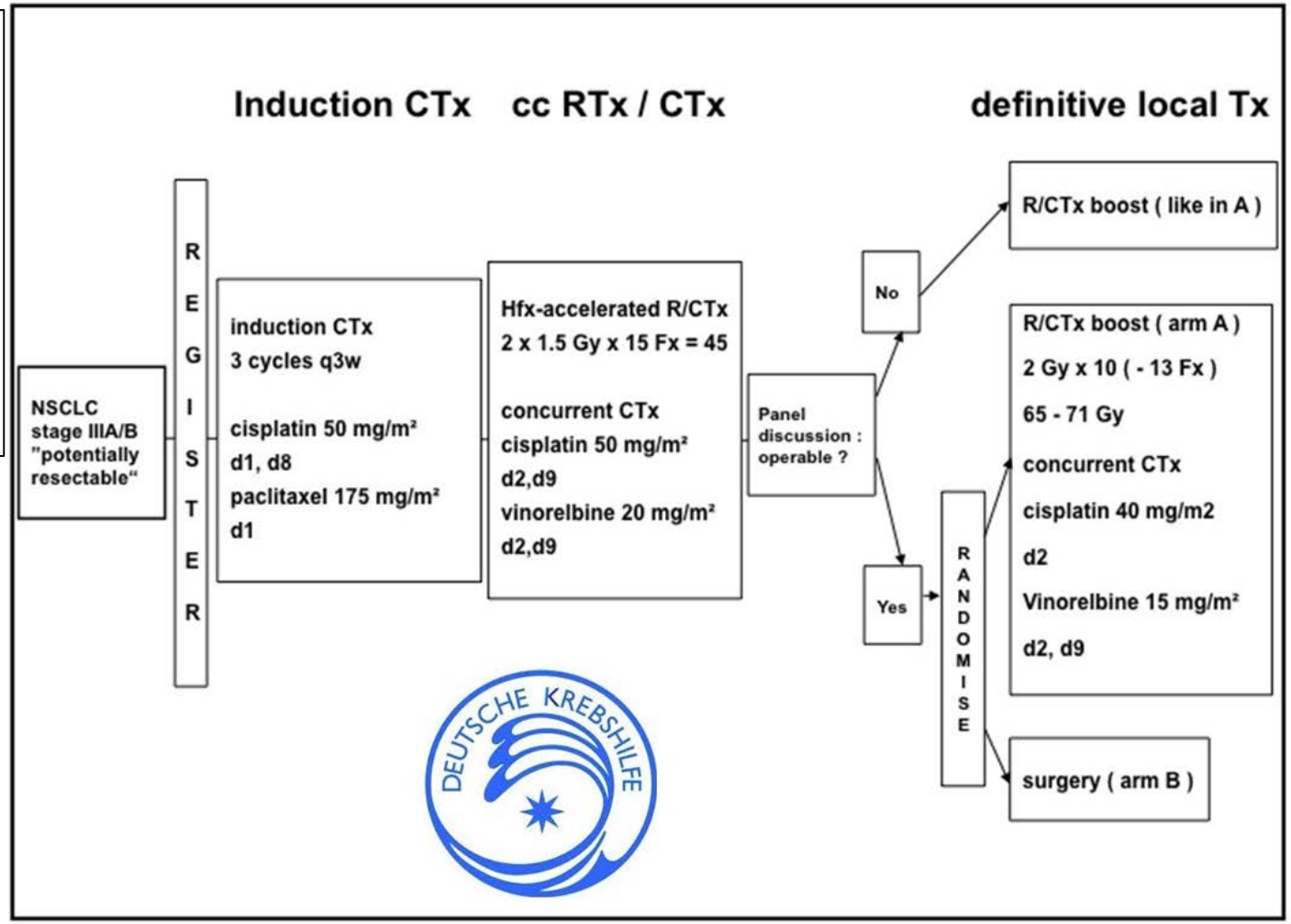
ESPATUE Trial

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

Wilfried Ernst Erich Eberhardt, Christoph Pöttgen, Thomas Christoph Gauler, Godehard Friedel, Stefanie Veit, Vanessa Heinrich, Stefan Welter, Wilfried Budach, Werner Spengler, Martin Kimmich, Berthold Fischer, Heinz Schmidberger, Dirk De Ruysscher, Claus Belka, Sebastian Cordes, Rodrigo Hepp, Diana Lütke-Brintrup, Nils Lehmann, Martin Schuler, Karl-Heinz Jöckel, Georgios Stamatis, and Martin Stuschke



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ESPATUE Trial

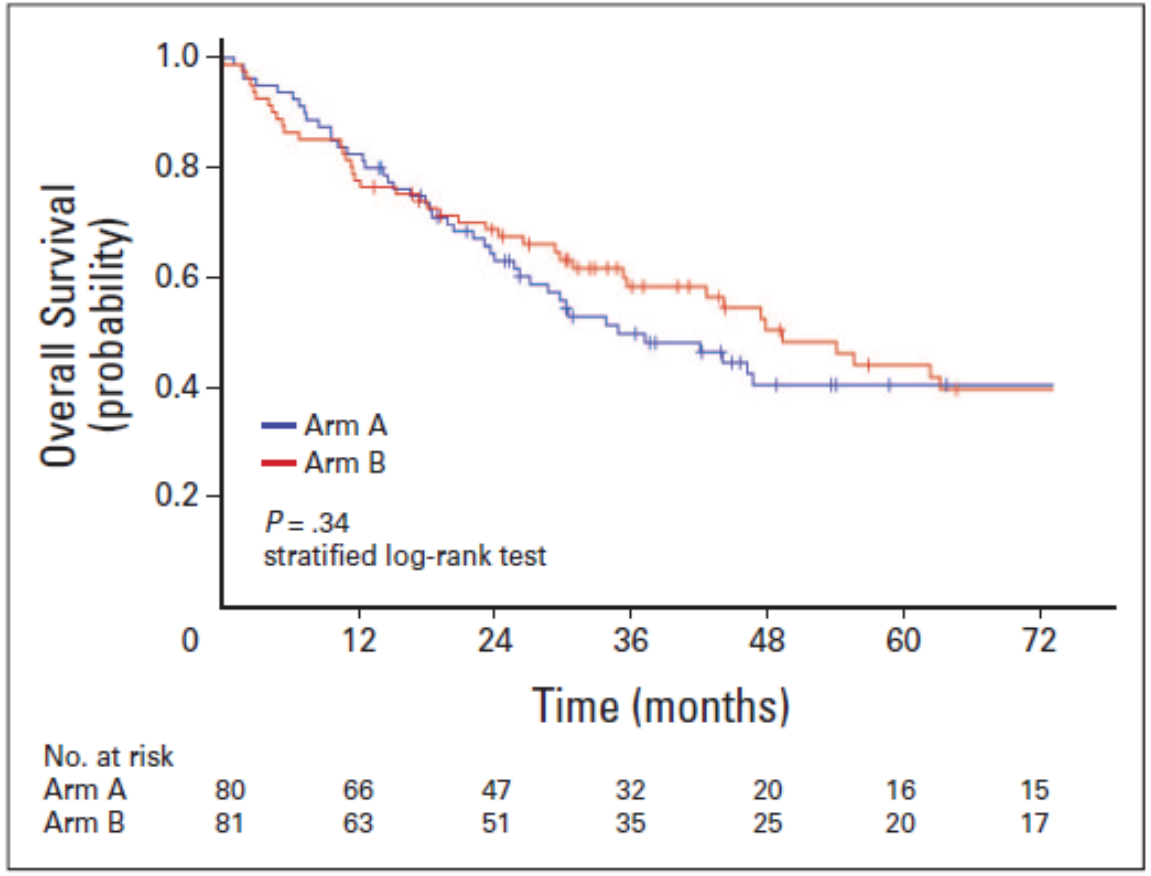


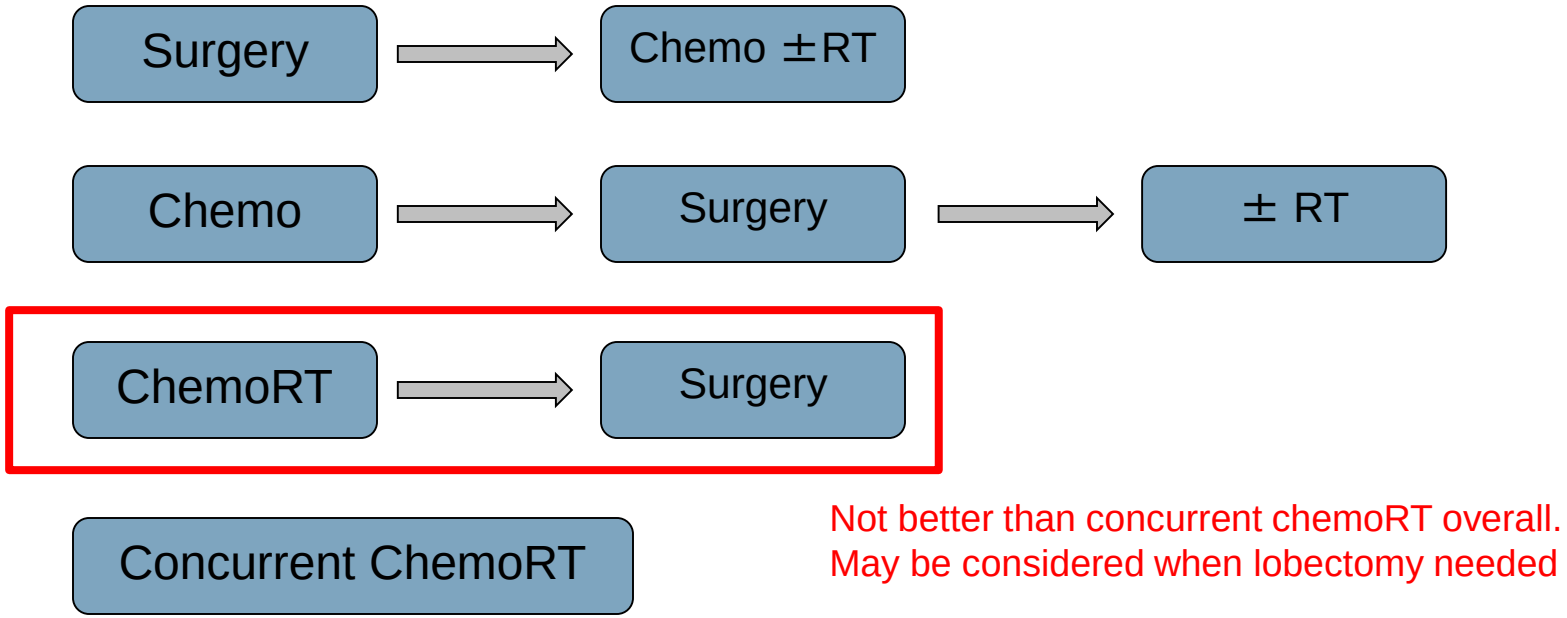
Fig 2. Overall survival of randomly assigned arms.

Table 3. Surgical Procedures and Maximum Postoperative Toxicity Observed in Arm B

Toxicity by Procedure	No. of Toxicities by Grade in Arm B (surgery; n = 70)		
	Grade 3	Grade 4	Grade 5
Lobectomy (n = 39)			
Anemia	2	0	0
Pulmonary	3	0	4
Other GI or renal	1	0	0
Cardiac	3	0	0
Miscellaneous infection	2	0	0
Pain	6	0	0
Pneumonectomy (n = 23)			
Anemia	3	0	0
Cardiac	1	0	0
Miscellaneous infection	1	0	0
Pain	5	0	0
Bilobectomy (n = 7)			
Anemia	1	0	0
Pulmonary	0	0	1
Segmentectomy (n = 1)			
Other GI or renal	1	0	0

Resectable Stage III NSCLC

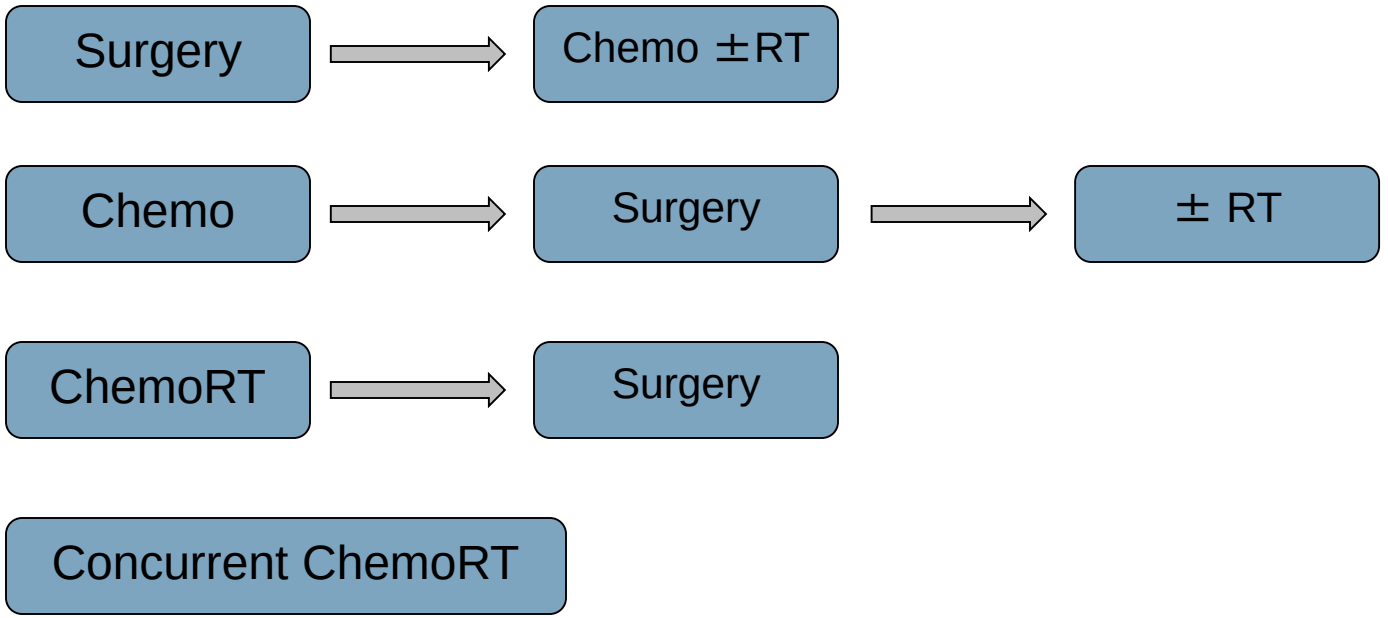
- Options for curative-intent treatment:



Not better than concurrent chemoRT overall.
May be considered when lobectomy needed

Resectable Stage III NSCLC

- Options for curative-intent treatment:



  - No strong evidence as to which approach is best.
  - The “Two Local Modality” approach has failed in several RCTs
  - Treatment decisions must be individualized

Resectable Stage III – Summary

- Based on randomized data, outcomes appear to be similar whether the definitive local treatment is surgical or radiotherapy based

- Primary surgical patients: adjuvant chemotherapy is standard, PORT is indicated if margin positive and debatable for N2.
  - The benefit of neoadjuvant treatment in resectable cases is unclear (compared to just post-operative chemotherapy)

- Primary chemoradiotherapy: benefit of adding surgery afterward, or instead of RT, is unclear

Resources: Treatment Guidelines

Practical Radiation Oncology (2015) 5, 149-155

www.practicalradonc.org

Special Article

Adjuvant radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline

George Rodrigues MD PhD [a,*], Hak Choy MD [b], Jeffrey Bradley MD [c], Kenneth E. Rosenzweig MD [d], Jeffrey Bogart MD [e], Walter J. Curran Jr. MD [f], Elizabeth Gore MD [g], Corey Langer MD [h], Alexander V. Louie MD, MSc [a], Stephen Lutz MD [i], Mitchell Machtay MD [j], Varun Puri MD, MSCI [k], Maria Werner-Wasik MD [l], Gregory M.M. Videtic MD, CM [m]

Practical Radiation Oncology (2015) 5, 141-148

www.practicalradonc.org

Special Article

Definitive radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline

George Rodrigues MD, PhD [a,*], Hak Choy MD [b], Jeffrey Bradley MD [c], Kenneth E. Rosenzweig MD [d], Jeffrey Bogart MD [e], Walter J. Curran Jr. MD [f], Elizabeth Gore MD [g], Corey Langer MD [h], Alexander V. Louie MD, MSc [a], Stephen Lutz MD [i], Mitchell Machtay MD [j], Varun Puri MD, MSCI [k], Maria Werner-Wasik MD [l], Gregory M.M. Videtic MD, CM [m]

Resources: Planning

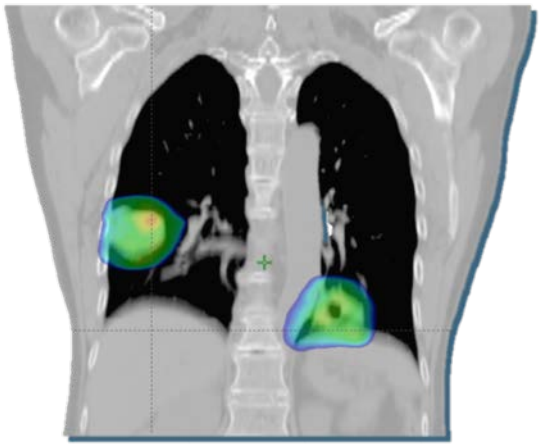
JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

European Organization for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Dirk De Ruysscher, Corinne Faivre-Finn, Ursula Nestle, Coen W. Hurkmans, Cécile Le Péchoux, Allan Price, and Suresh Senan

JCO 2010



Oligometastatic NSCLC

Oligomets: A Hot Topic

CNN politics 2016 Washington Nation World Our Team Search CNN

Jimmy Carter announces he is cancer-free

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NSCLC Phase II Data

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

Long-Term Results of a Prospective Phase II Trial (Nct01282450)

Dirk De Ruysscher, MD, PhD,# Rinus Wanders, MD,* Angela van Baardwijk, MD, PhD,* Anne-Marie C. Dingemans, MD, PhD,† Bart Reymen, MD,* Ruud Houben, MSc,* Gerben Bootsma, MD, PhD,‡ Cordula Pitz, MD, PhD,§ Linda van Eijsden, MD,¶ Wiel Geraedts, MD,|| Brigitta G. Baumert, MD, PhD,* and Philippe Lambin, MD, PhD**

Localization metastasis	
Adrenal gland	4 (10.3%)
Bone	7 (17.9%)
Brain	17 (43.9%)
Gastro-hepatic ligament	1 (2.6%)
Liver	1 (2.6%)
Lung	1 (2.6%)
Lymph node	2 (5.1%)
Muscle	2 (5.1%)
Ovary	1 (2.6%)
Pleura	3 (7.7%)
Number metastases	
1	34 (87.2%)
2	4 (10.3%)
3	1 (2.6%)

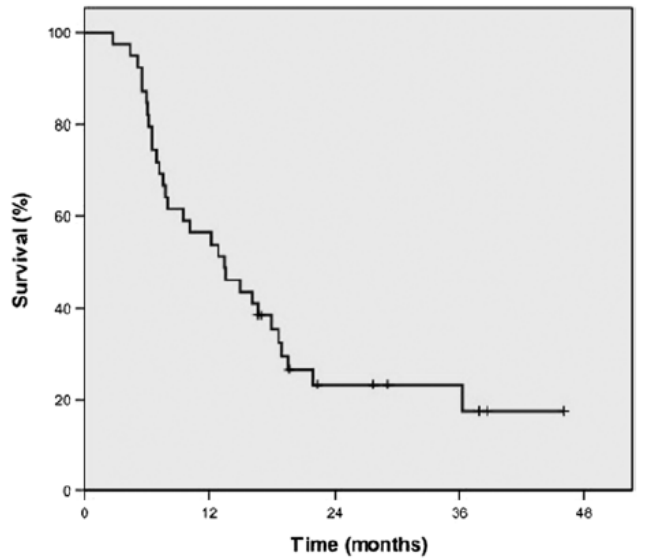

FIGURE 1. Overall survival (n = 39).

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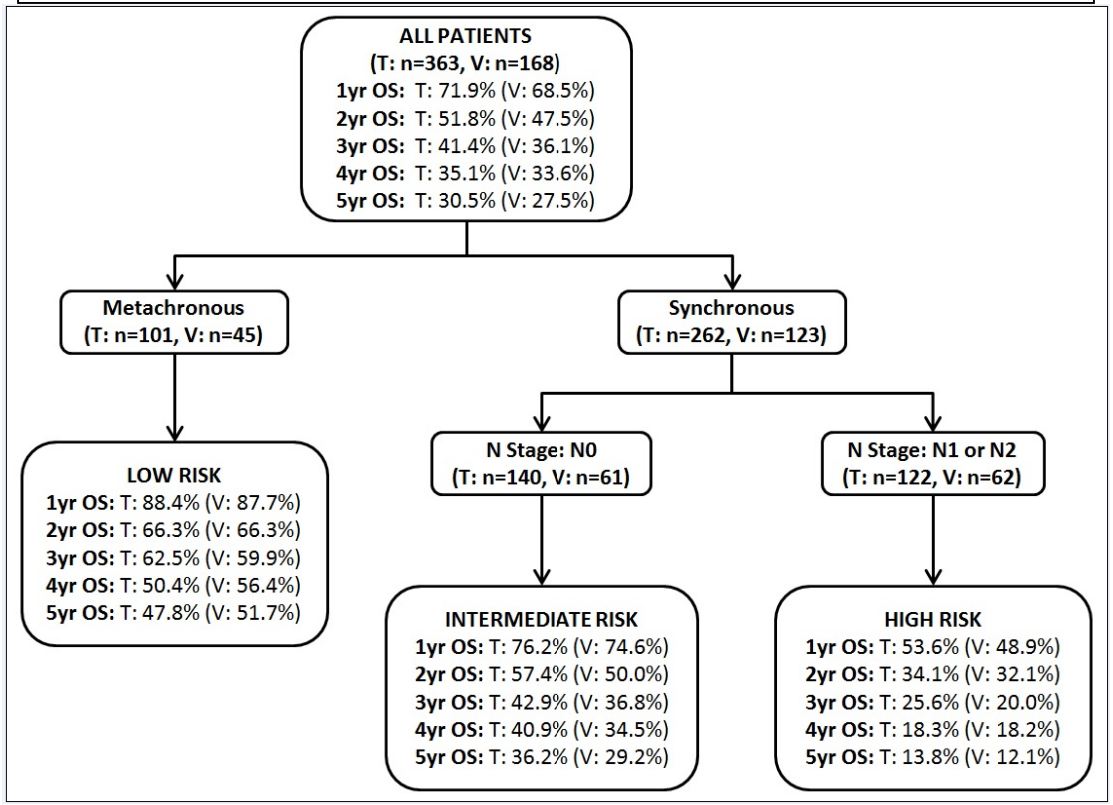
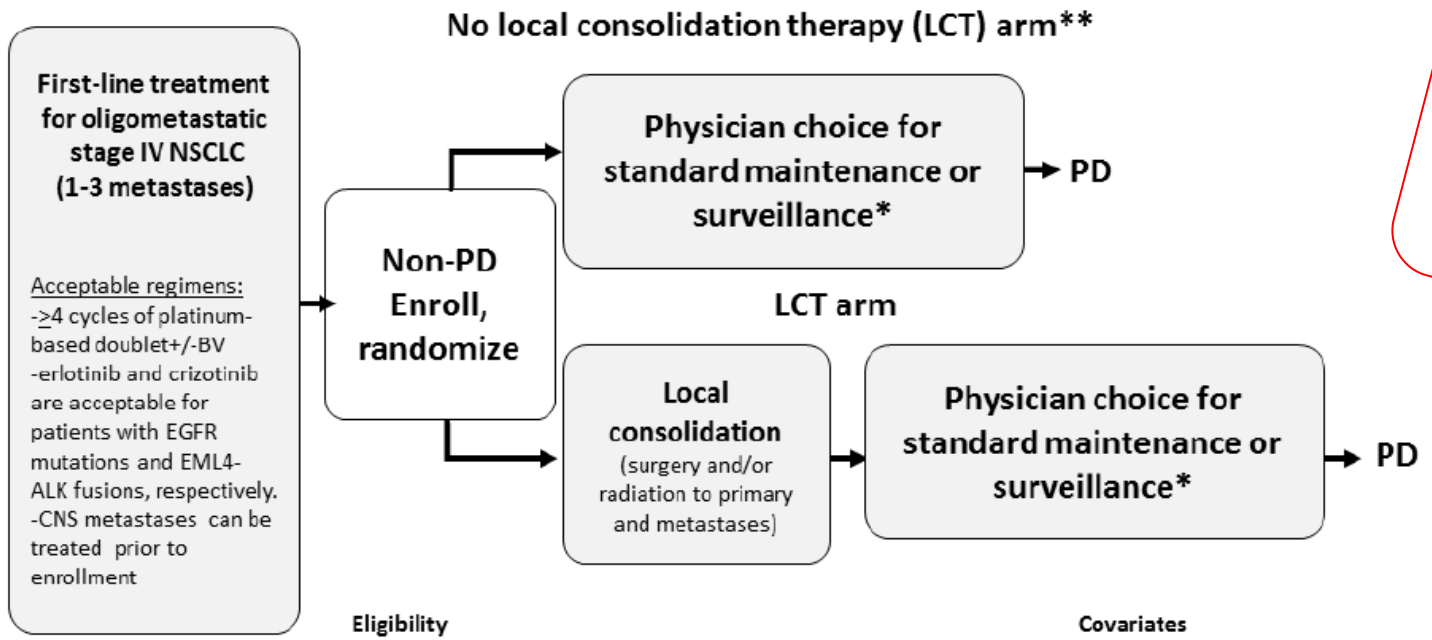
Prognosis: Oligometastatic NSCLC

An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer



Ashworth, Clin Lung Ca 2014

MDACC/Colorado Trial



Results submitted to ASCO 2016

Eligibility
- 1-3 mets after completion of first-line treatment
- Non-PD
- PS 0-2
- Candidate for local therapy

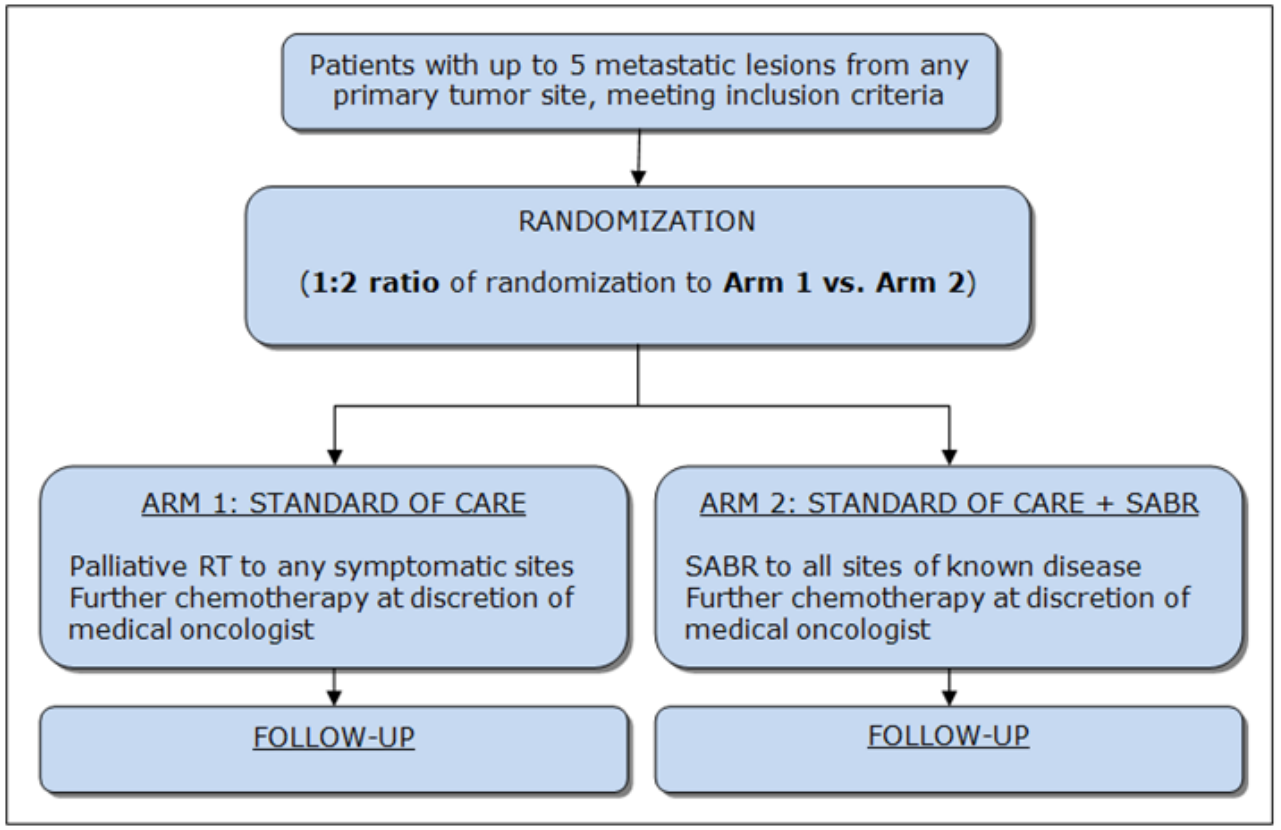
Covariates
- Number of mets (1 vs. 2-3)
- Response to first-line chemo (SD vs. PR/CR)
- N0/N1 vs. N2/N3
- CNS Mets (yes/no)
- EGFR/EML4ALK status

**Recommended systemic therapy options include bevacizumab, pemetrexed, and erlotinib

Slide courtesy Dr. D Gomez MDACC

The COMET Trial

STEREOTACTIC ABLATIVE RADIOTHERAPY FOR COMPREHENSIVE TREATMENT OF OLIGOMETASTATIC TUMORS (SABR-COMET): A RANDOMIZED PHASE II TRIAL



http://clinicaltrials.gov/ct2/show/NCT01446744

Principal Investigators
D. Palma, S. Senan

Target Sample Size
99

Open Sites
London, ON
Amsterdam, NL
BCCA
Surrey, BC
Sudbury, ON
Hamilton, ON

Opening Soon:
Beatson, Scotland
McGill
Royal Alfred, Australia

Palma et al, *BMC Cancer* 2012, **12**:305

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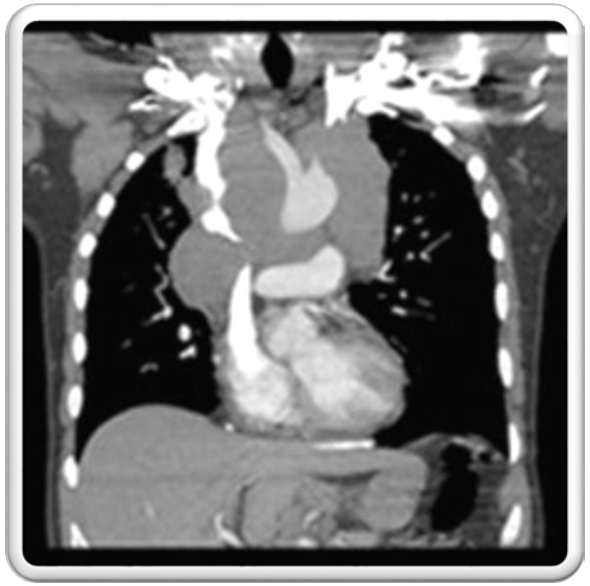


Small Cell Lung Cancer

Epidemiology

- Approximately 15% of lung cancers – small decrease over past 30 years, higher proportion of women

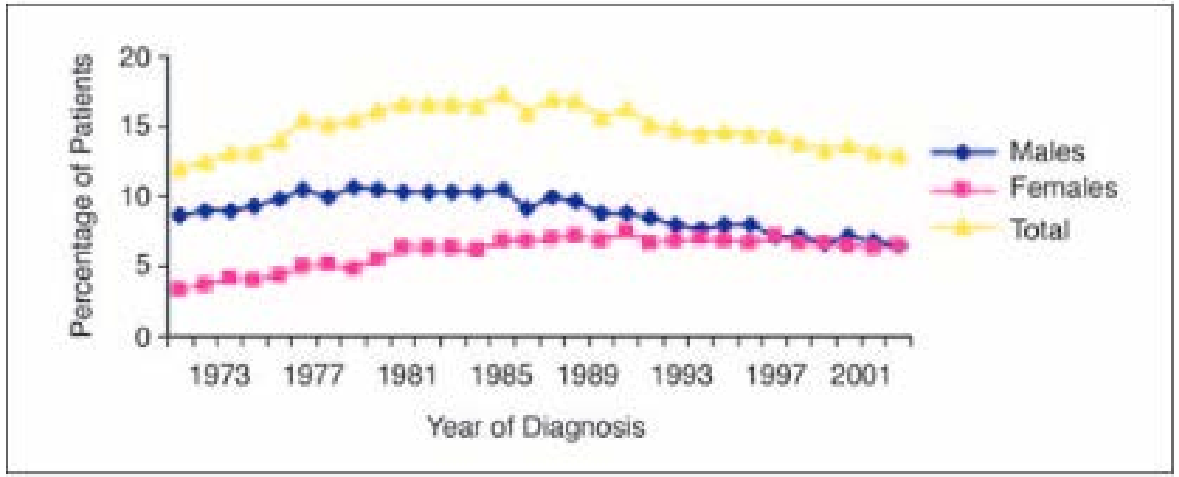
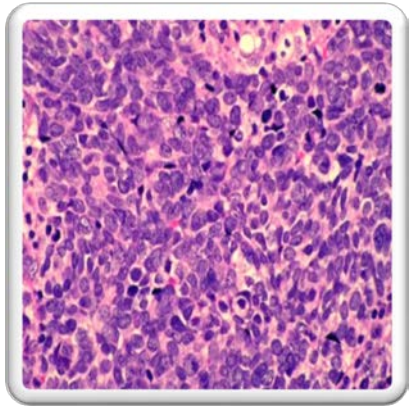


Fig 1. The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

Govindan, JCO 2006

Pathology

- Small round blue cell tumor
- Virtually all are reactive for keratin and epithelial membrane antigen
- 75% have one more neuroendocrine markers
  - Chromogranin, synaptophysin, NSE, etc.



Staging – officially AJCC but…

NCCN Definitions

Limited Stage

- AJCC (7th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

Extensive Stage

- AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

Stage Distribution and Survival

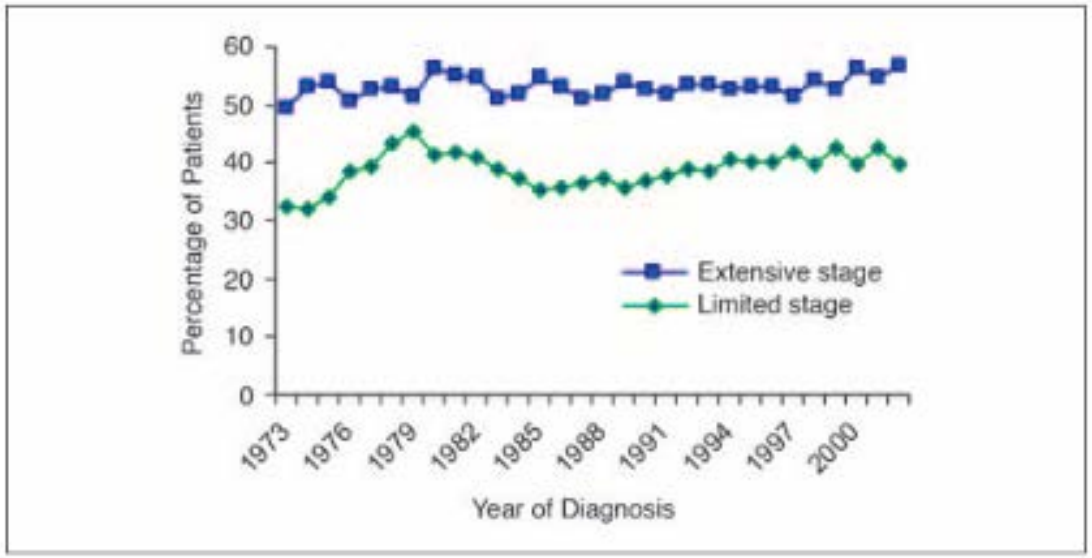


Fig 5. The diagnosis of small-cell lung cancer by stage.

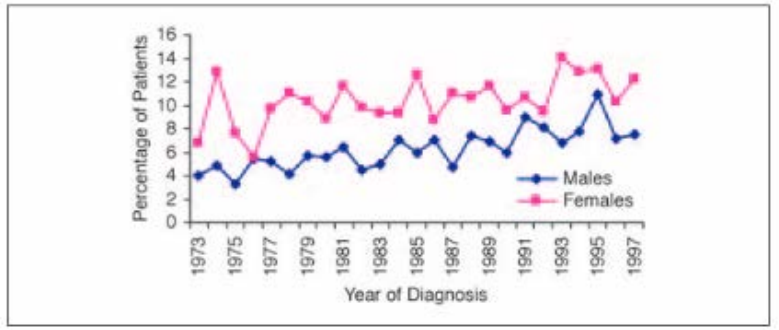


Fig 10. The all-cause survival trends in limited-stage small-cell lung cancer.

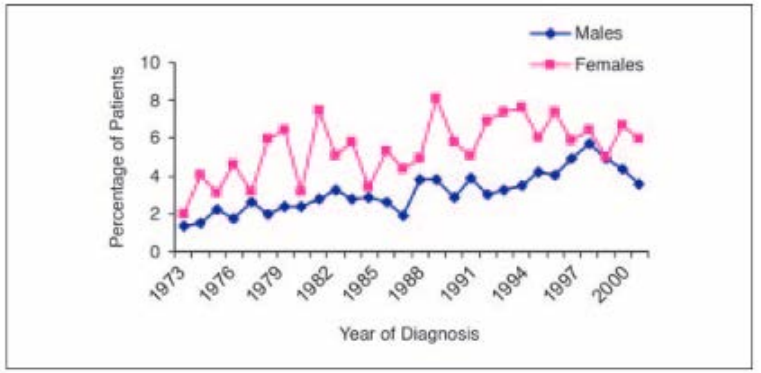
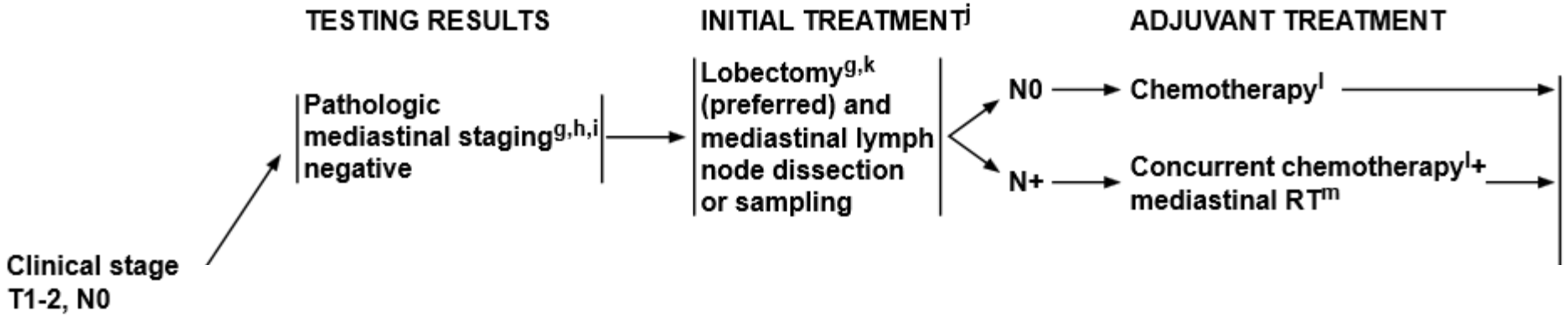


Fig 7. The all-cause survival trends in extensive-stage small-cell lung cancer.

Govindan JCO 2006

Unique Scenario: T1–T2N0 lesions



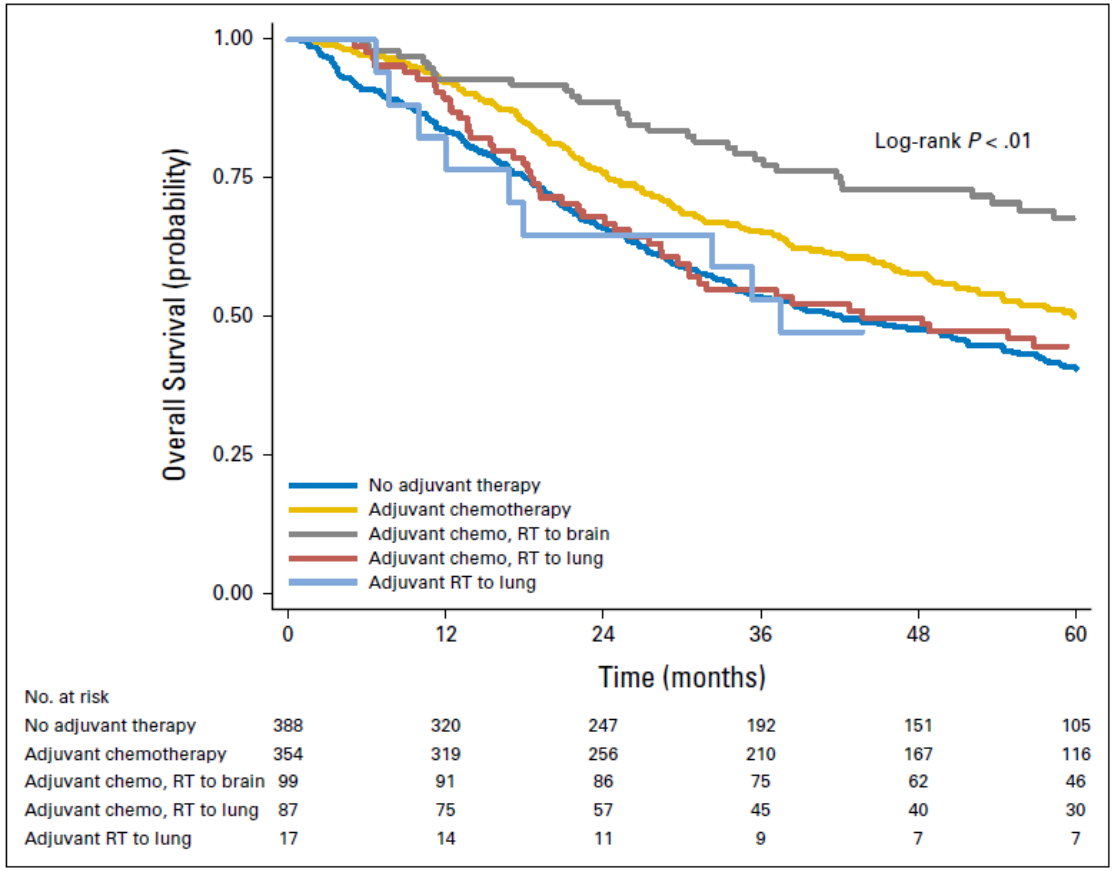
- Surgery alone provides poor outcomes, but in combination with chemotherapy, outcomes are reasonable
- IASLC data: 439 patients with resected SCLC. In patients with stage I disease, 5-yr OS = 48%

Resected T1T2N0 SCLC – What Next?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer

Chi-Fu Jeffrey Yang, Derek Y. Chan, Paul J. Speicher, Brian C. Gulack, Xiaofei Wang, Matthew G. Hartwig, Mark W. Onaitis, Betty C. Tong, Thomas A. D'Amico, Mark F. Berry, and David H. Harpole



No. at risk						
No adjuvant therapy	388	320	247	192	151	105
Adjuvant chemotherapy	354	319	256	210	167	116
Adjuvant chemo, RT to brain	99	91	86	75	62	46
Adjuvant chemo, RT to lung	87	75	57	45	40	30
Adjuvant RT to lung	17	14	11	9	7	7

The Role of Radiotherapy

- Similar data from two meta-analysis from 1992:

Pignon, NEJM: 13 trials: 5.4% OS benefit at 3-years

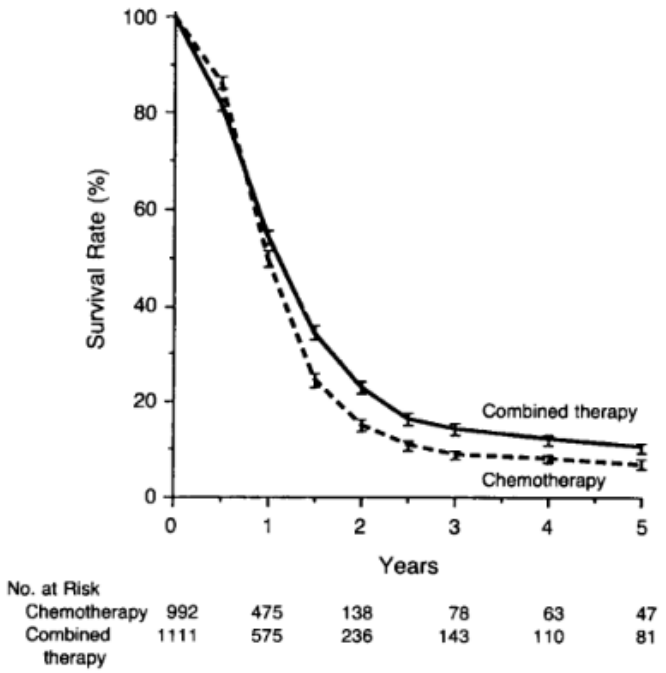
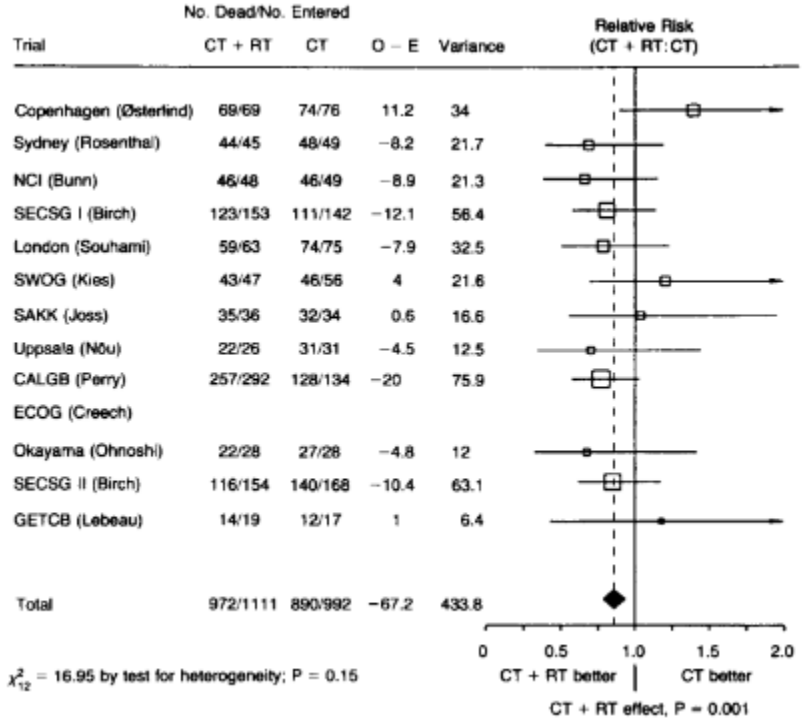


Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.



What About the Elderly?

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer

Christopher D. Corso, Charles E. Rutter, Henry S. Park, Nataniel H. Lester-Coll, Anthony W. Kim, Lynn D. Wilson, Zain A. Husain, Rogerio C. Lilenbaum, James B. Yu, and Roy H. Decker

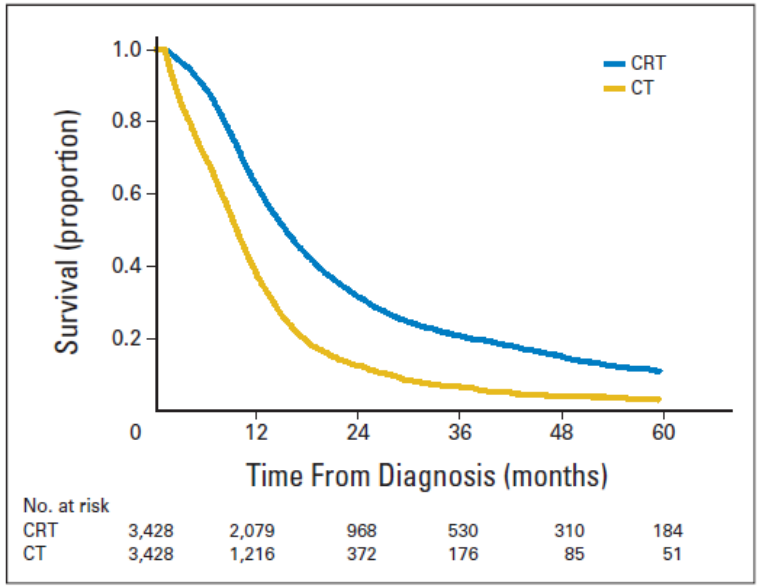


Fig 3. Kaplan-Meier overall survival stratified by treatment regimen for propensity score–matched cohort. CRT, chemoradiotherapy; CT, chemotherapy.

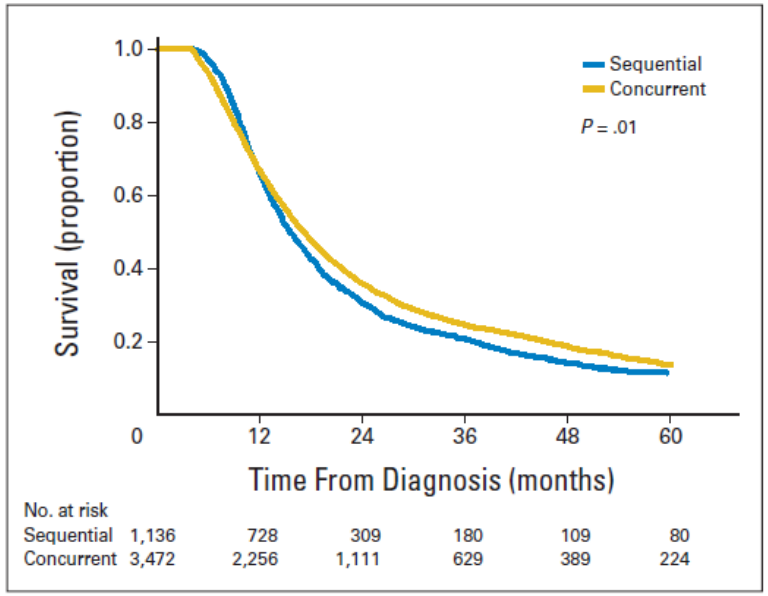


Fig 4. Kaplan-Meier overall survival analysis stratified by sequential or concurrent chemoradiotherapy.

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Which Fractionation?

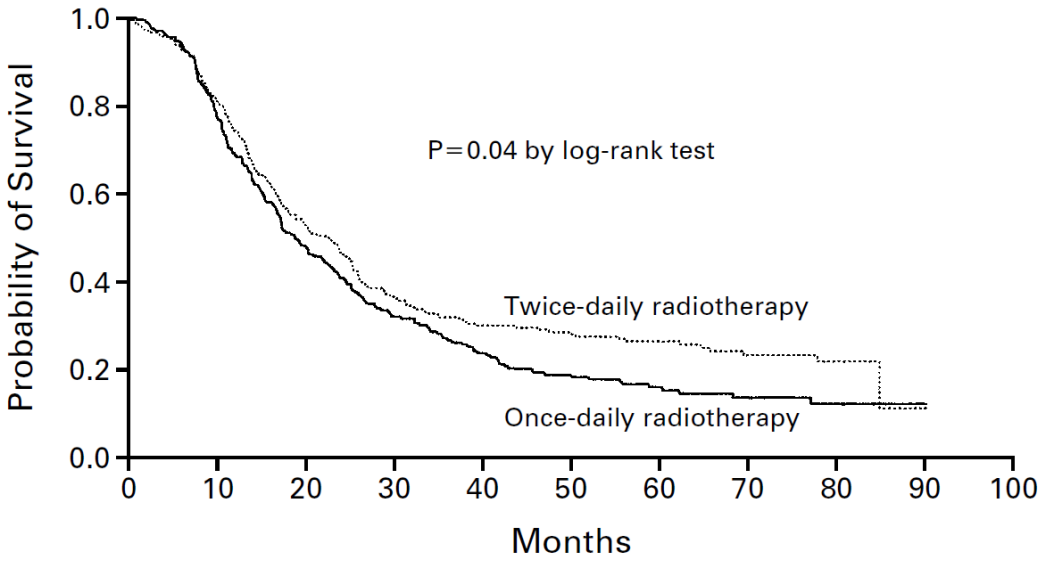
TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III, M.D., KYUNGMANN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

- 419 patients enrolled, all patients received 45 Gy starting with cycle 1 of EP: 45/30 BID vs. 45/25 OD
- Patients with CR offered PCI

NEJM 1999

Which Fractionation?



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

- OS benefit at a cost of increased esophagitis
- Control arm (45/25) may be a low bar to clear

NEJM 1999

Which Fractionation?

70 GY THORACIC RADIOTHERAPY IS FEASIBLE CONCURRENT WITH CHEMOTHERAPY FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: ANALYSIS OF CANCER AND LEUKEMIA GROUP B STUDY 39808

JEFFREY A. BOGART, M.D.,* JAMES E. HERNDON II, PH.D.,† ALAN P. LYSS, M.D.,‡ DOROTHY WATSON,† ANTONIUS A. MILLER,§ MICHAEL E. LEE,¶ ANDREW T. TURRISI, M.D.,‖ AND MARK R. GREEN, M.D.‖

- 2 cycles of paclitaxel + topotecan
- 70 Gy in 35 fractions with EP
- Phase II design, 63 patients

Table 5. Comparison of INT-0096 and CALGB 39808

Trial	INT-0096	CALGB 39808
Thoracic radiotherapy regimen	45 Gy twice daily	70 Gy every day
Patient and tumor characteristics		
Male	58%	54%
Weight loss > 5%	18%	31%
Age, years (median)	61	60
Supraclavicular adenopathy	4%	0
Toxicity profile		
Hematologic toxicity	87%	83%
Esophagitis	32%	21%
Outcome		
Median overall survival	20.3 months	22.4 months
2-year overall survival	44%	48%
2-year DFS	29%	31%

IJROBP 2004

Ongoing Trials

- Two ongoing trials:
  - CALGB 30610: 70 Gy/35 OD vs. 45 Gy/30 BID
  - CONVERT: 66 Gy/33 OD vs. 45 Gy/30 BID

- Reasonable doses include:
  - 60-70 Gy in 1.8 – 2 Gy per fraction
  - 45 Gy in 30 fractions BID (or similar short-course regimens)

When to Deliver RT?

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

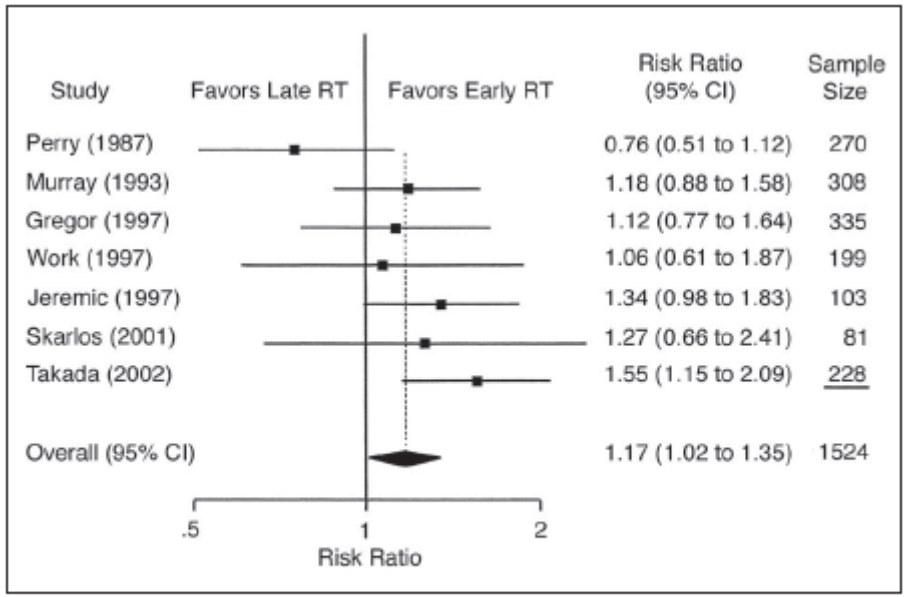


Fig 1. Two-year overall survival risk ratio forest plot for early *v* late thoracic radiation therapy (RT).

JCO 2007

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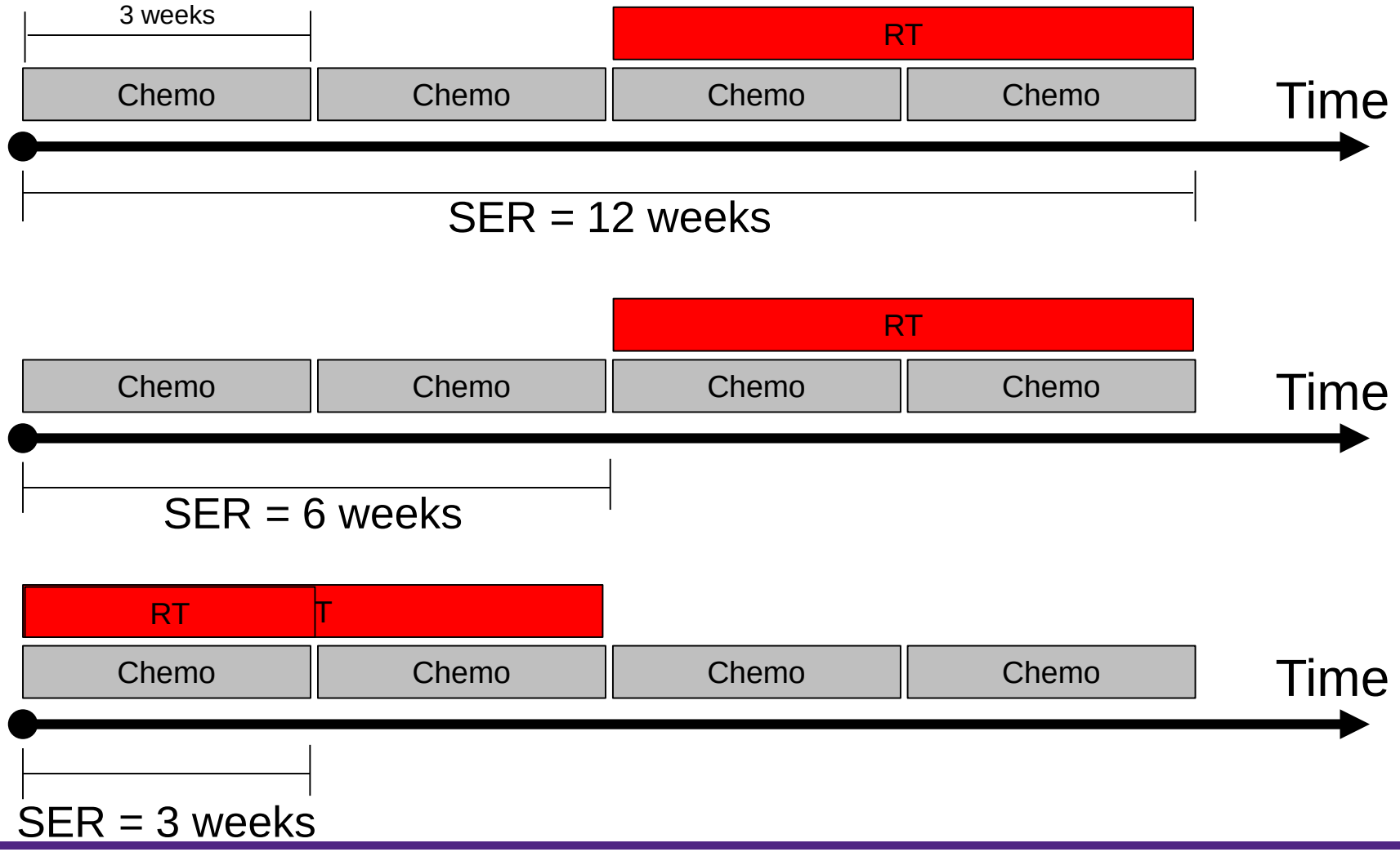
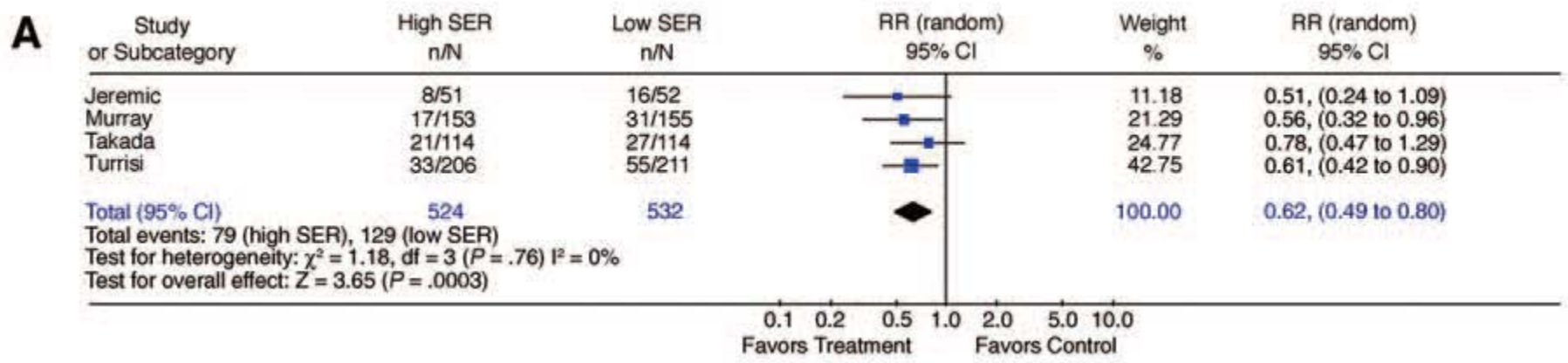
The SER: Start date to End of RT



The SER: Start date to End of RT

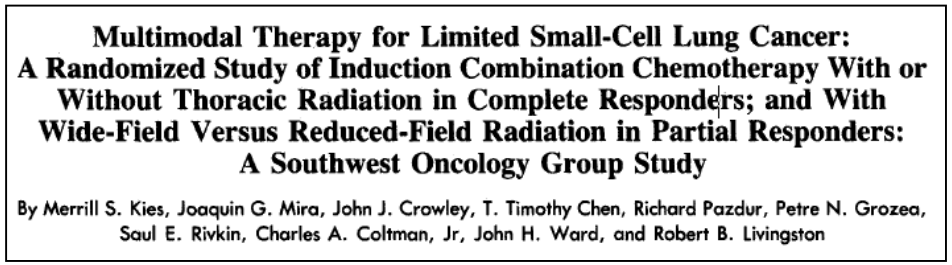
Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

Dirk De Ruysscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minken, Rinus Wanders, Ludy Lutgens, Monique Hochstenbag, Liesbeth Boersma, Bradly Wouters, Guido Lammering, Johan Vansteenkiste, and Philippe Lambin



- Survival decrease of 1.86% per 1 week prolongation of SER
- Increased esophagitis with low SER

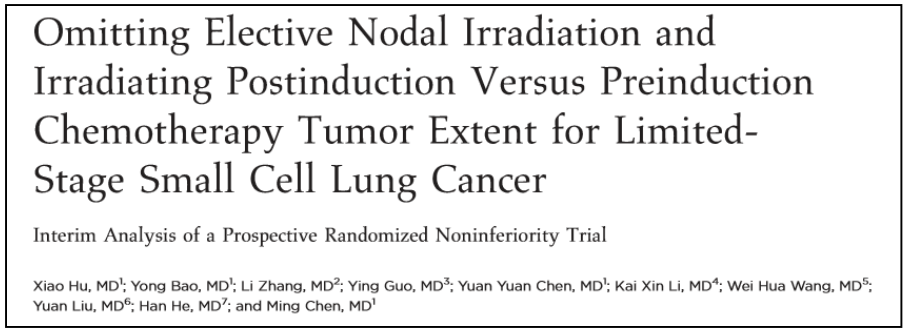
Treatment Volumes?



Multimodal Therapy for Limited Small-Cell Lung Cancer: A Randomized Study of Induction Combination Chemotherapy With or Without Thoracic Radiation in Complete Responders; and With Wide-Field Versus Reduced-Field Radiation in Partial Responders: A Southwest Oncology Group Study

By Merrill S. Kies, Joaquin G. Mira, John J. Crowley, T. Timothy Chen, Richard Pazdur, Petre N. Grozea, Saul E. Rivkin, Charles A. Coltman, Jr, John H. Ward, and Robert B. Livingston

JCO 1987



Omitting Elective Nodal Irradiation and Irradiating Postinduction Versus Preinduction Chemotherapy Tumor Extent for Limited-Stage Small Cell Lung Cancer

Interim Analysis of a Prospective Randomized Noninferiority Trial

Xiao Hu, MD[1]; Yong Bao, MD[1]; Li Zhang, MD[2]; Ying Guo, MD[3]; Yuan Yuan Chen, MD[1]; Kai Xin Li, MD[4]; Wei Hua Wang, MD[5]; Yuan Liu, MD[6]; Han He, MD[7]; and Ming Chen, MD[1]

Cancer 2011

- Two RCTs have compared Pre-chemotherapy vs. Post-chemotherapy volumes
- SWOG study (started in 1979) used wide-field vs. limited-field 2-D planning
- Chinese study used 3D planning
- No differences in relapse rates or toxicity

- Dutch phase II data suggests that ENI is not required if a PET/CT is done for staging, but in the absence of PET/CT, isolated nodal relapse may be >10%.

Prophylactic Cranial Irradiation

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

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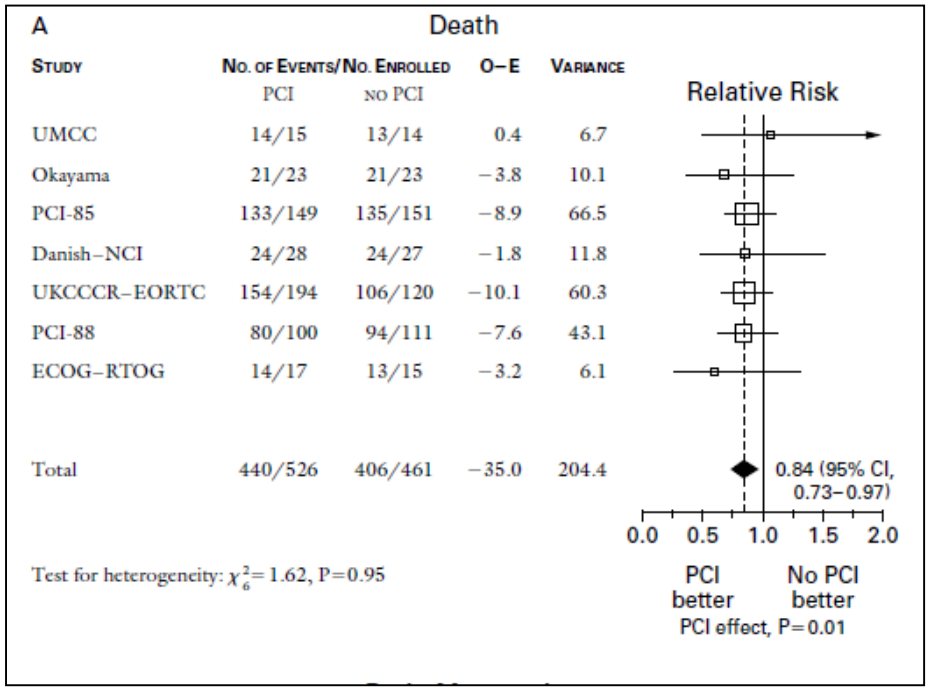


Caveats:

- In some trials, CR was defined by CXR
- A subsequent RCT showed no benefit to doses >25 Gy in 10 fractions

NEJM 1999

Extensive Stage SCLC

- Majority of SCLC patients have extensive stage disease
- Disease is highly responsive to chemotherapy, but median survival is 8-13 months
- Multiple RCTs have evaluated chemotherapy combinations and timing. Two-drug regimens are better than single-drug regimens, but >2 is not very beneficial but more toxicity
- Platinum + Etoposide (4-6 cycles) remains standard first-line in most centers
- Can radiation help improve survival?

PCI in ES-SCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

- 286 patients with ES-SCLC randomized after any response to chemotherapy: PCI vs no PCI
- Several fractionations allowed: 20 Gy/5 and 30 Gy/10 most common
- Brain imaging was not part of standard staging and follow-up procedures, unless symptoms present

Slotman 2007

PCI in ES-SCLC

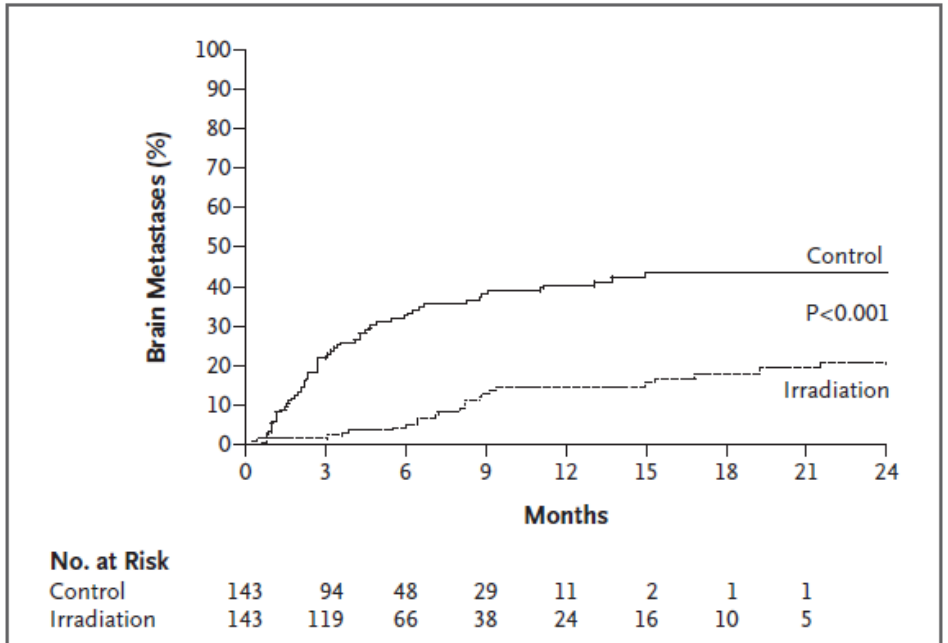


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

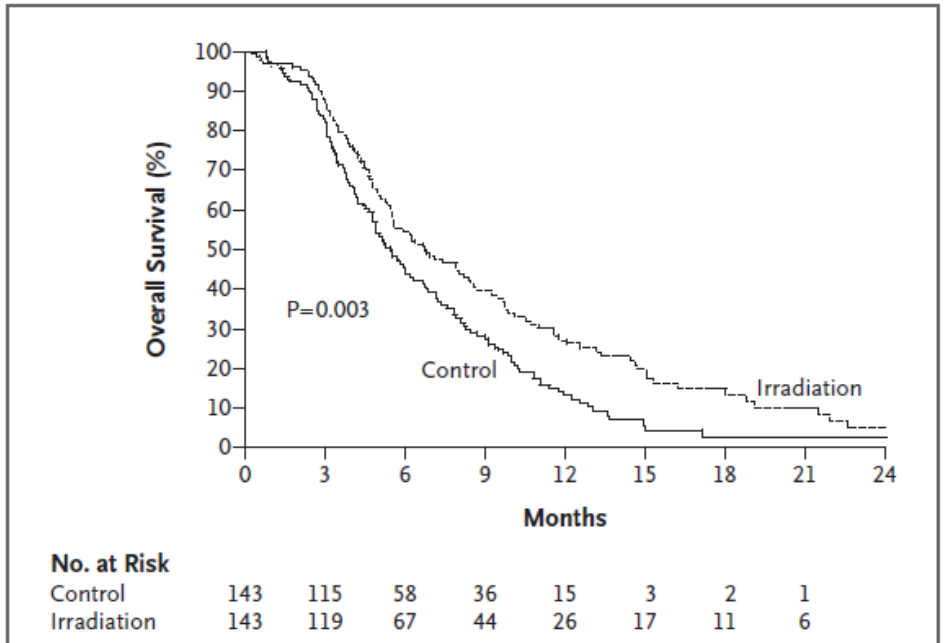


Figure 3. Overall Survival.

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman 2007

Thoracic Radiotherapy

Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Branislav Jeremic, Yuta Shibamoto, Nebojsa Nikolic, Biljana Milicic, Slobodan Milisavljevic, Aleksandar Dagovic, Jasna Aleksandrovic, and Gordana Radosavljevic-Asic

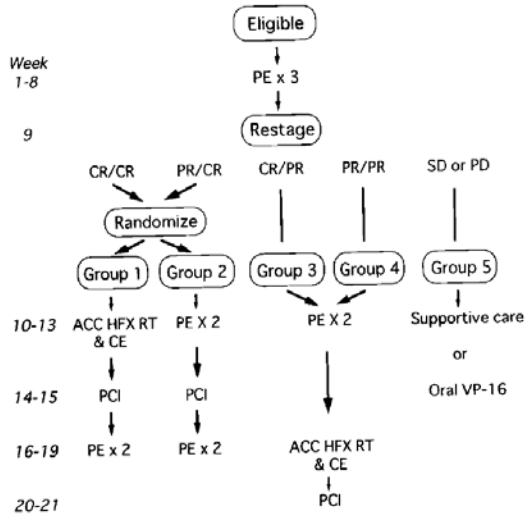
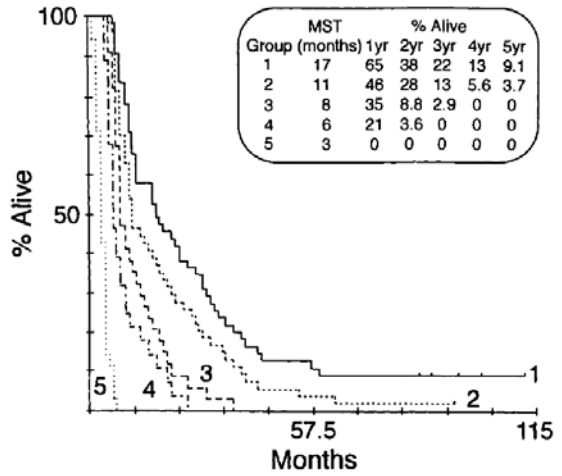


Fig 1. Treatment schema. VP-16, etoposide.



Group	MST (months)	% Alive 1yr	2yr	3yr	4yr	5yr
1	17	65	38	22	13	9.1
2	11	46	28	13	5.6	3.7
3	8	35	8.8	2.9	0	0
4	6	21	3.6	0	0	0
5	3	0	0	0	0	0

Fig 2. Overall survival in group 1 (——), group 2 (- - - -), group 3 (– – – –), group 4 (- · - · - ·), and group 5 (· · · · ·).

JCO 1999

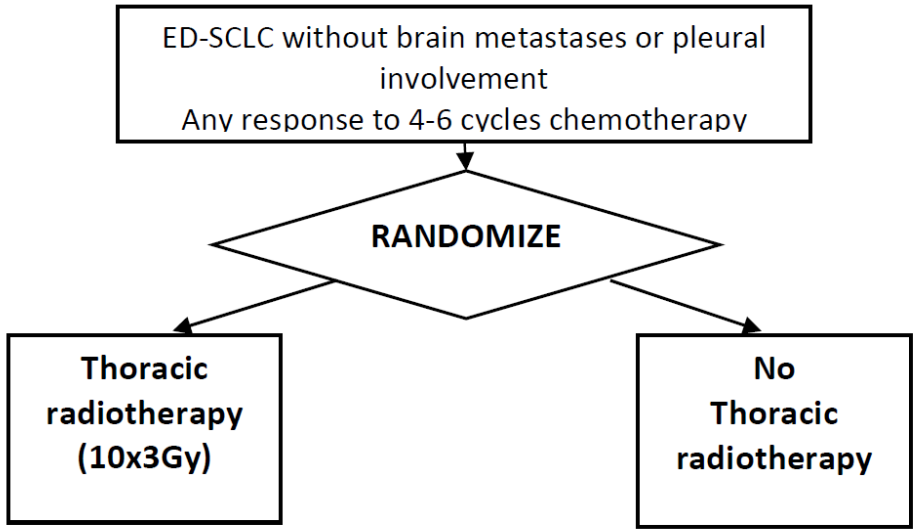
Western UNIVERSITY · CANADA

OICR Ontario Institute for Cancer Research

Thoracic Radiotherapy

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn*, Suresh Senan*



All patients will receive PCI

Lancet 2014

Thoracic Radiotherapy

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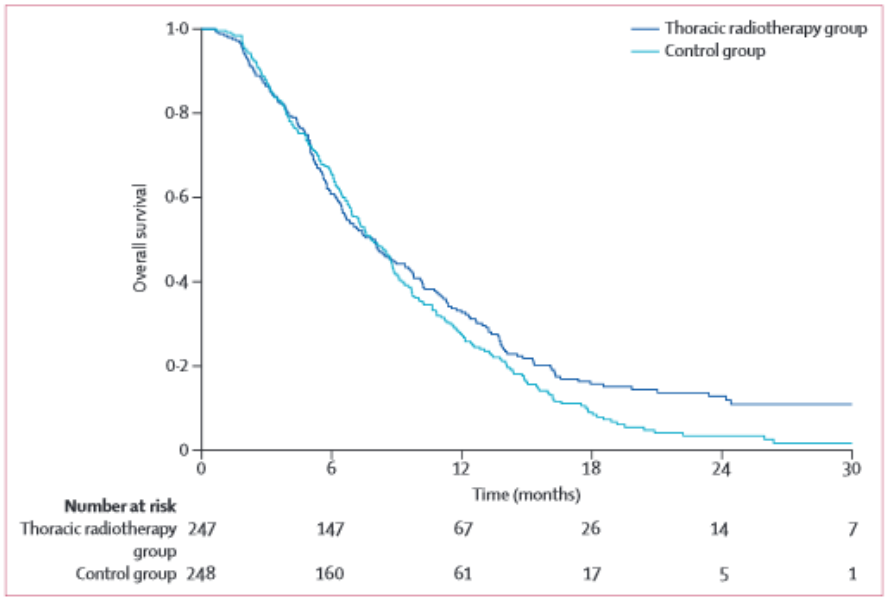

Figure 2: Kaplan-Meier curves for overall survival

1^0 Endpoint: 1-yr OS:

33% (TRT) vs. 28% (no TRT)

HR 0.84, p=0.066

2^0 Endpoint: 2-yr OS:

13% (TRT) vs. 3% (no TRT)

p=0.004

Lancet 2014

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	Thoracic radiotherapy group (n=247)	Control group (n=248)
Cough (grade 3)	0 (0·0%)	1 (0·4%)
Dysphagia (grade 3)	1 (0·4%)	0 (0·0%)
Dyspnoea (grade 3)	3 (1·2%)	4 (1·6%)
Oesophagitis (grade 3)	4 (1·6%)	0 (0·0%)
Fatigue (grade 3)	11 (4·5%)	8 (3·2%)
Fatigue (grade 4)	0 (0·0%)	1 (0·4%)
Insomnia (grade 3)	3 (1·2%)	2 (0·8%)
Nausea or vomiting (grade 3)	1 (0·4%)	0 (0·0%)
Headache (grade 3)	3 (1·2%)	2 (0·8%)

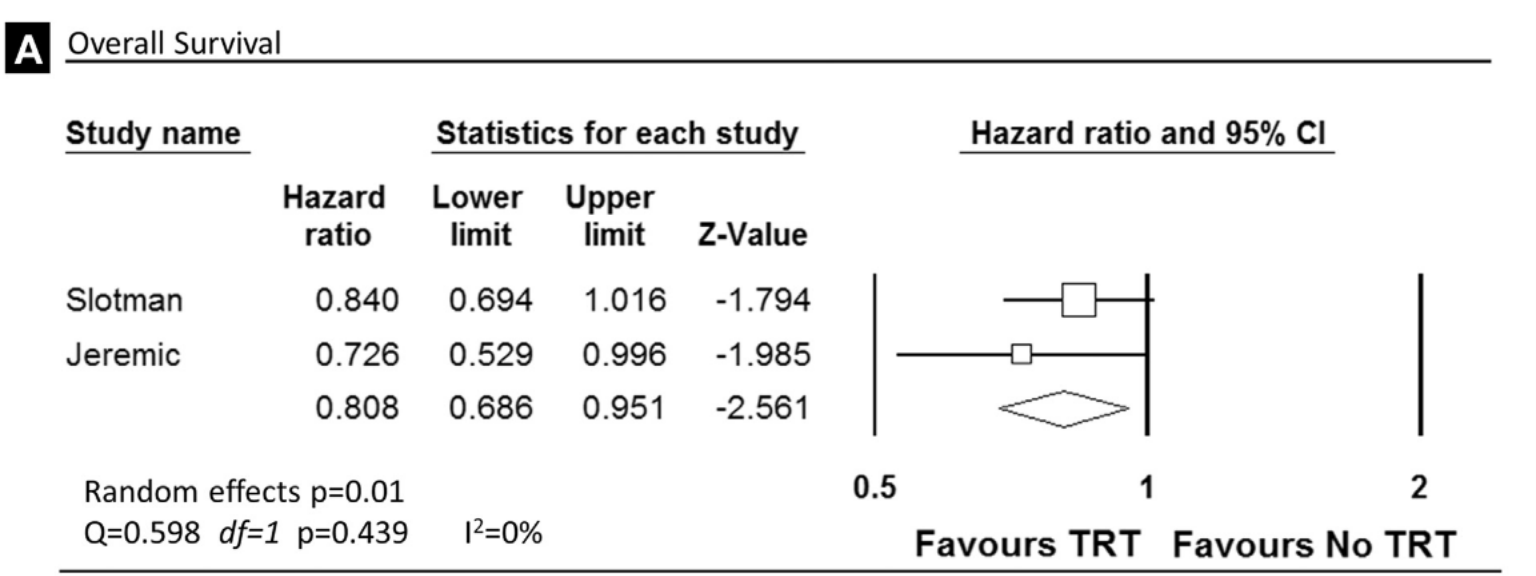
Table 2: Grade 3 and higher toxic effects

Slotman et al Lancet 2014

Thoracic Radiotherapy

Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis

David A. Palma,[1] Andrew Warner,[1] Alexander V. Louie,[1] Suresh Senan,[2] Ben Slotman,[2] George B. Rodrigues[1]



Clinical Lung Cancer 2015

Oligometastatic SCLC: RTOG 0937

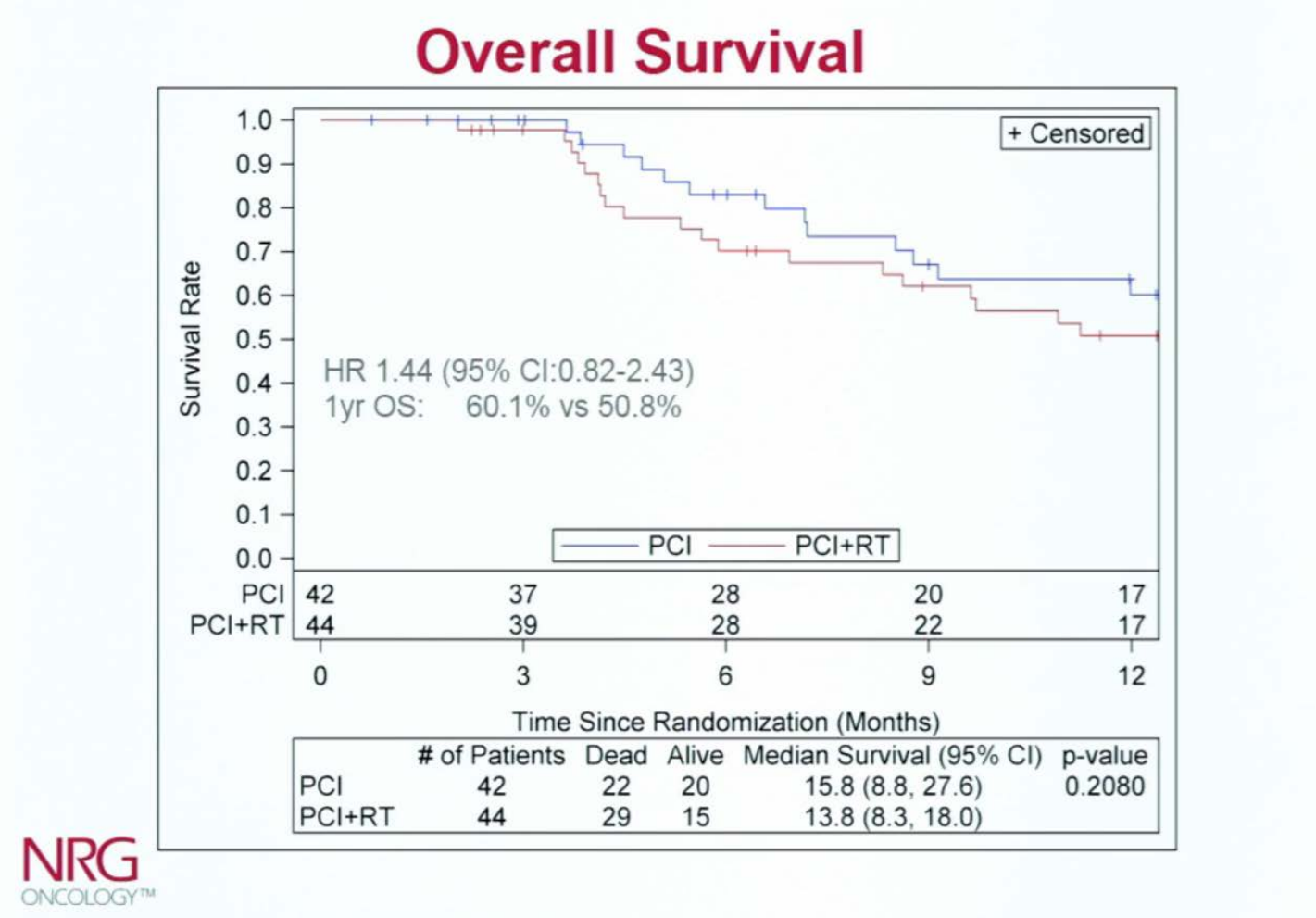
S	**Response to Treatment**	**R**	**Arm 1: Prophylactic Cranial Irradiation**
T	1. Complete Response (CR)	**A**	2.5 Gy per fraction for a total of 25 Gy
R	2. Partial Response (PR)	**N**	
A		**D**	**ylactic Cranial Irradiation**
T			per fraction for a total of 25 Gy
I	**Number of Metastat**		and
F	1. 1		**Consolidative Radiation to**
Y	2. 2-4	**Z**	**Locoregional and Residual Metastatic Disease**
	Age	**E**	45 Gy at 3 Gy per fraction*
	1. <65		
	2. ≥65		*Acceptable alternative regimens: 30-40 Gy in 10 fractions

CLOSED

Also noted is a disproportionate distribution of grade 4 and 5 toxicities.
PCI only arm (n=40): 16 deaths, no grade 4 or 5 toxicities.
PCI + consolidative RT (n=39): 23 deaths, 7 patients with grade 4 or 5 toxicities.

Patients still on the investigational arm (Arm 2) should discontinue and convert to appropriate standard of care

Oligometastatic SCLC: RTOG 0937



SCLC: Take Home Messages

- Limited Stage
  - Chemoradiotherapy (with early RT)
  - Several reasonable radiation fractionations
    - 45/30 BID, 70/35 (CALGB), 60/30, 40/15 (NCIC BR-6)
  - PCI in responders

- Extensive Stage
  - Doublet platinum-based chemotherapy
  - In patient with a response, consider thoracic radiotherapy and PCI

SCLC Resource

CRITICAL REVIEW

RADIOTHERAPY IN SMALL-CELL LUNG CANCER: LESSONS LEARNED AND FUTURE DIRECTIONS

BEN J. SLOTMAN, M.D., PH.D., AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

Although chemotherapy is an essential component in the treatment of small-cell lung cancer, improvements in survival in the past two decades have been mainly achieved by the appropriate application of radiotherapy. The aim of the present study was to review the key developments in thoracic radiotherapy and prophylactic cranial radiotherapy and to discuss the rationale behind key ongoing studies in small-cell lung cancer.

Articles: www.goo.gl/WmkgZ9

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