UCLA Health

Radiation Oncology

David Geffen School of Medicine

HEALING MANKIND ONE PATIENT AT A TIME

PREDICTING TUMOR CONTROL FROM LUNG SBRT/SABR: A CLINICIAN'S PERSPECTIVE

JULY 22, 2014

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DISCLOSURES

- None

OBJECTIVES

- Understand the increasing role for lung SBRT/SABR
- Understand the need to balance tumor control and toxicity in choosing dose
- Understand difficulties and controversies in comparing dose amongst regimen (3DCRT to SBRT/SABR)
- Understand goals of SBRT Thoracic TCP Working Group – Preliminary Findings

SCOPE OF THE PROBLEM

LUNG CANCER

Estimated New Cases*

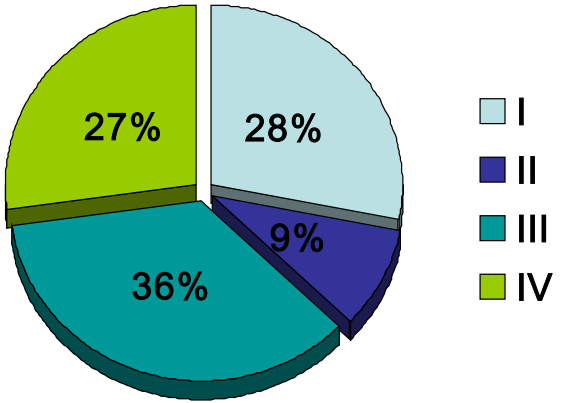
	Males			Females	
Prostate	217,730	28%		Breast	207,090	28%
Lung & bronchus	116,750	15%		Lung & bronchus	105,770	14%
Colon & rectum	72,090	9%		Colon & rectum	70,480	10%
Urinary bladder	52,760	7%		Uterine corpus	43,470	6%
Melanoma of the skin	38,870	5%		Thyroid	33,930	5%
Non-Hodgkin lymphoma	35,380	4%		Non-Hodgkin lymphoma	30,160	4%
Kidney & renal pelvis	35,370	4%		Melanoma of the skin	29,260	4%
Oral cavity & pharynx	25,420	3%		Kidney & renal pelvis	22,870	3%
Leukemia	24,690	3%		Ovary	21,880	3%
Pancreas	21,370	3%		Pancreas	21,770	3%
All Sites	**789,620**	**100%**		**All Sites**	**739,940**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	86,220	29%		Lung & bronchus	71,080	26%
Prostate	32,050	11%		Breast	39,840	15%
Colon & rectum	26,580	9%		Colon & rectum	24,790	9%
Pancreas	18,770	6%		Pancreas	18,030	7%
Liver & intrahepatic bile duct	12,720	4%		Ovary	13,850	5%
Leukemia	12,660	4%		Non-Hodgkin lymphoma	9,500	4%
Esophagus	11,650	4%		Leukemia	9,180	3%
Non-Hodgkin lymphoma	10,710	4%		Uterine Corpus	7,950	3%
Urinary bladder	10,410	3%		Liver & intrahepatic bile duct	6,190	2%
Kidney & renal pelvis	8,210	3%		Brain & other nervous system	5,720	2%
All Sites	**299,200**	**100%**		**All Sites**	**270,290**	**100%**

Stage Distribution: IASLC Lung Cancer Data Base

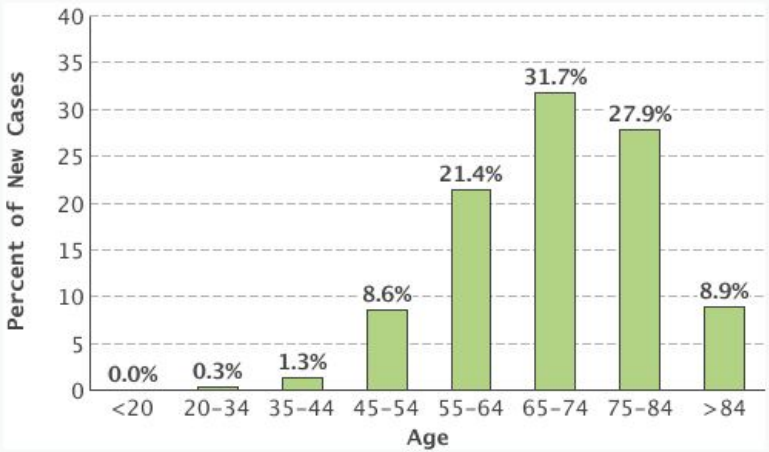
Clinically Staged Cases, N = 53,646



Jemal *et al*, CA Cancer J Clin 2010

LUNG CANCER BY AGE

Percent of New Cases by Age Group: Lung and Bronchus Cancer



Lung and bronchus cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

70

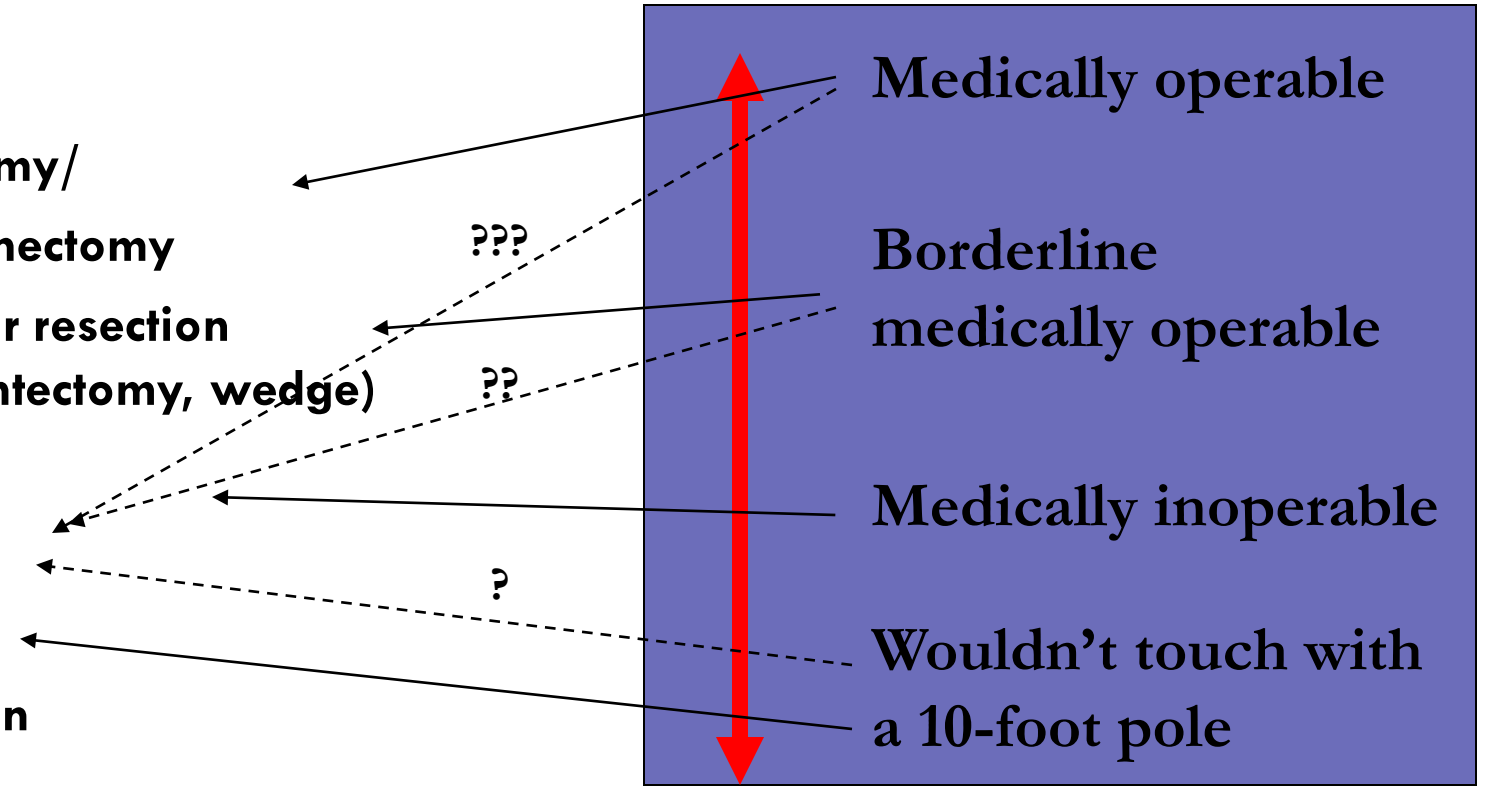
SEER 18 2007-2011, All Races, Both Sexes

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Lung and Bronchus Cancer

SEER, 2007-2011

EARLY STAGE NSCLC TREATMENT OPTIONS

- **Surgery**
  - **Lobectomy/ pneumonectomy**
  - **Sublobar resection (segmentectomy, wedge)**
- **Radiation**
  - **SBRT**
  - **EBRT**
- **Observation**



Courtesy of J. Bradley

Percy Lee, M.D.

COULD LUNG SBRT PLAY A BIGGER ROLE IN THE TREATMENT OF EARLY STAGE NSCLC IN THE NEAR FUTURE?

Percy Lee, M.D.

UCLA Jonsson Comprehensive Cancer Center

David Geffen School of Medicine

LUNG CANCER SCREENING: NLST

- Purpose: Could yearly CT screening reduce lung cancer mortality compared to CXR screening?

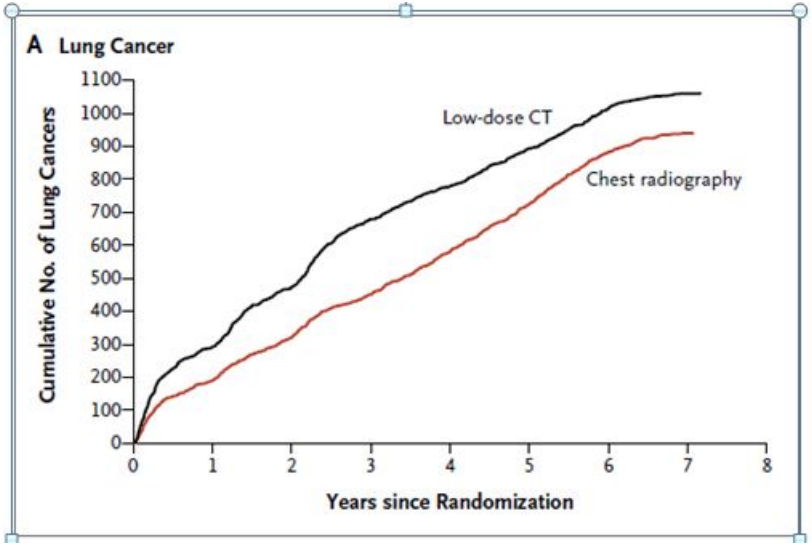
Aberle D, et al., NEJM 2011

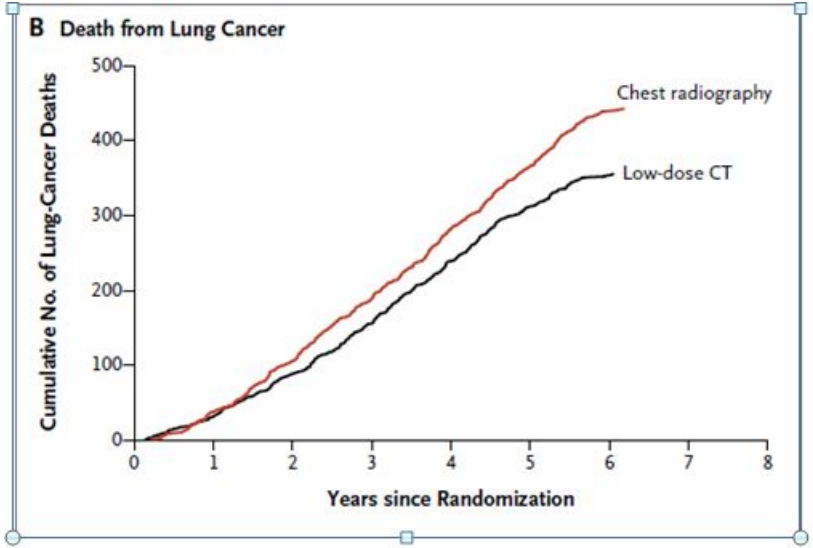
NLST

- Results:
  - 53,454 patients
  - High risk: 55-74 years old, 30 pk-year, if former smoker, quit within previous 15 years
  - Rates of positive screen: 24% vs. 7% (CT vs. CXR)
  - 247 vs. 309 deaths from lung cancer per 100,000 person-year from CT vs. CXR
  - 20% relative reduction in lung cancer mortality from low-dose CT screening (6.7% absolute reduction) compared to CXR screening

Aberle D, et al., NEJM 2011

NLST FINDINGS



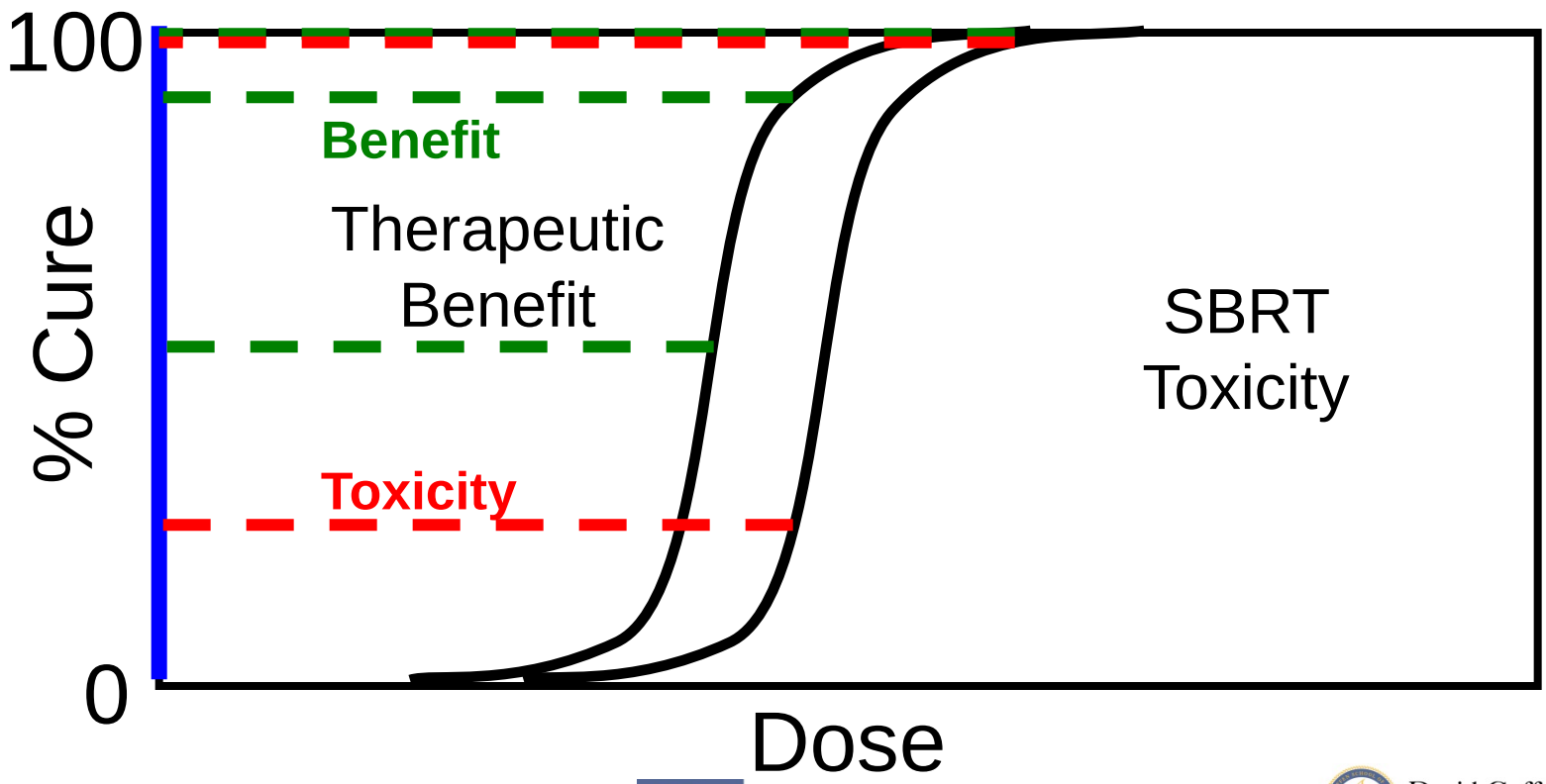


NLST CONCLUSIONS

- Yearly low-dose CT screening in high-risk population reduce lung cancer mortality compared to CXR screening
- Potentially, many of these patients are too frail for surgery: SBRT
- Possibly, more cancers are detected at earlier stage, obviating the need for surgery: SBRT

SBRT/SABR

THERAPEUTIC RATIO



RTOG 0236 – Peripheral Tumor SBRT Dose

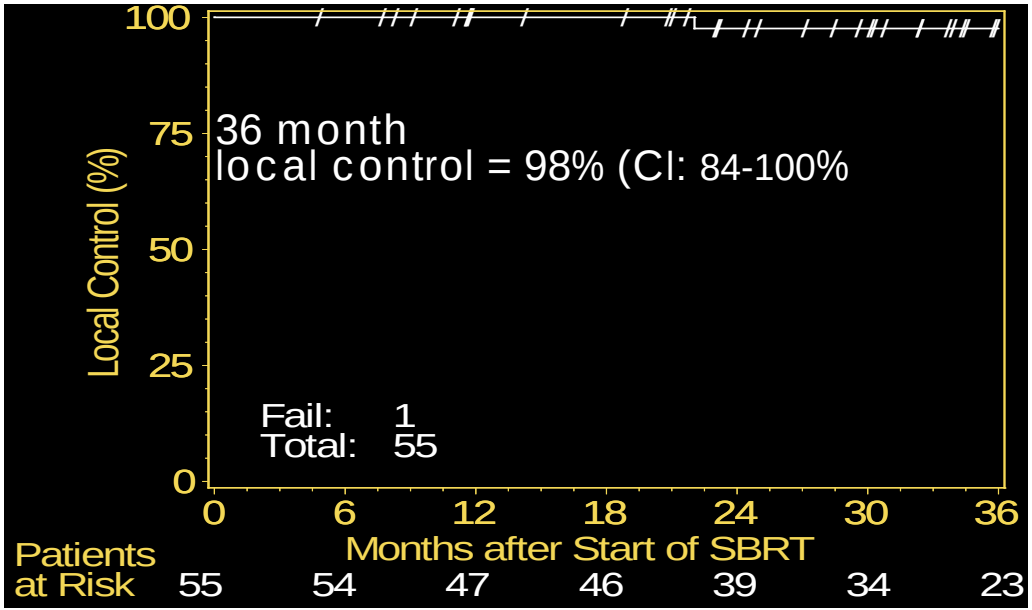
JAMA®

Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer

Robert Timmerman; Rebecca Paulus; James Galvin; et al.

RTOG 0236:

- **First North American cooperative group trial of SBRT**
- **Phase II: 55 pts (44 Stage IA, 11 Stage IB), medically inoperable, peripheral tumors**
- **54 Gy in 3 treatments**
- **Tumor control: 98%, Survival 72% at 3 years, median OS 48 months**



Central Tumor Toxicity with SBRT

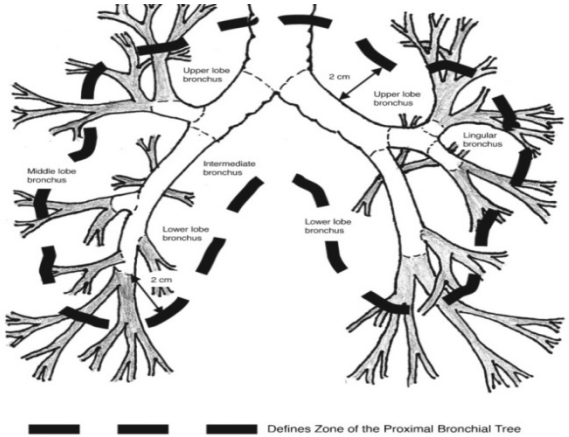
VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher



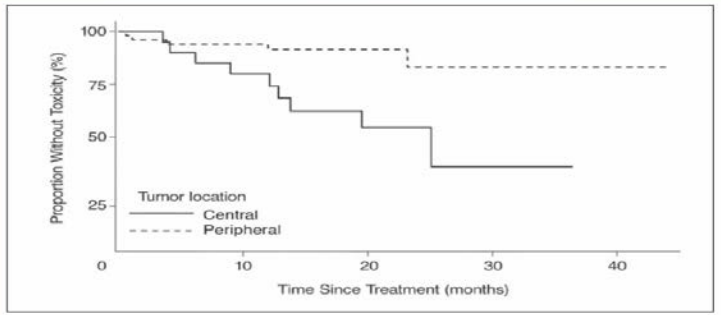


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

TUMOR CONTROL RATE BY BED_{10}

Control Rates by BED_{10} For All Patients

TABLE 2. Recurrence Rate According to the BED and Stage

	Total cases	BED <100 Gy	BED ≥100 Gy	*p*	Stage IA	Stage IB	*p*
Local tumor	36/257 (14.0%)	18/42 (42.9%)	18/215 (8.4%)	<0.01	20/164 (12.2%)	16/93 (17.2%)	0.21
Regional nodal metastasis	29/257 (11.3%)	9/42 (21.4%)	20/215 (9.3%)	<0.05	17/164 (10.4%)	12/93 (12.9%)	0.54
Distant metastasis	51/257 (19.8%)	11/42 (26.2%)	40/215 (18.6%)	0.3	32/164 (19.5%)	19/93 (20.4%)	0.87

BED, biological effective dose.

5y overall survival	**19.7%**	**53.9%**	**sig**

Onishi, H, JTO, 2007

OPTIMAL DOSE FOR PERIPHERAL TUMORS?

5 yr. OS by BED_{10} in Medically *Operable Patients*

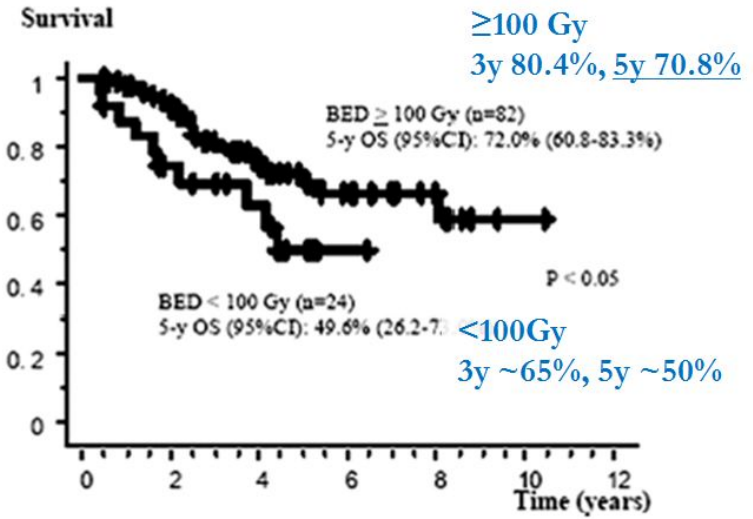


FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

$$BED = nd(1+d/\alpha/\beta)$$

Schemes > 100 Gy:

16 Gy x 3 = 48 Gy

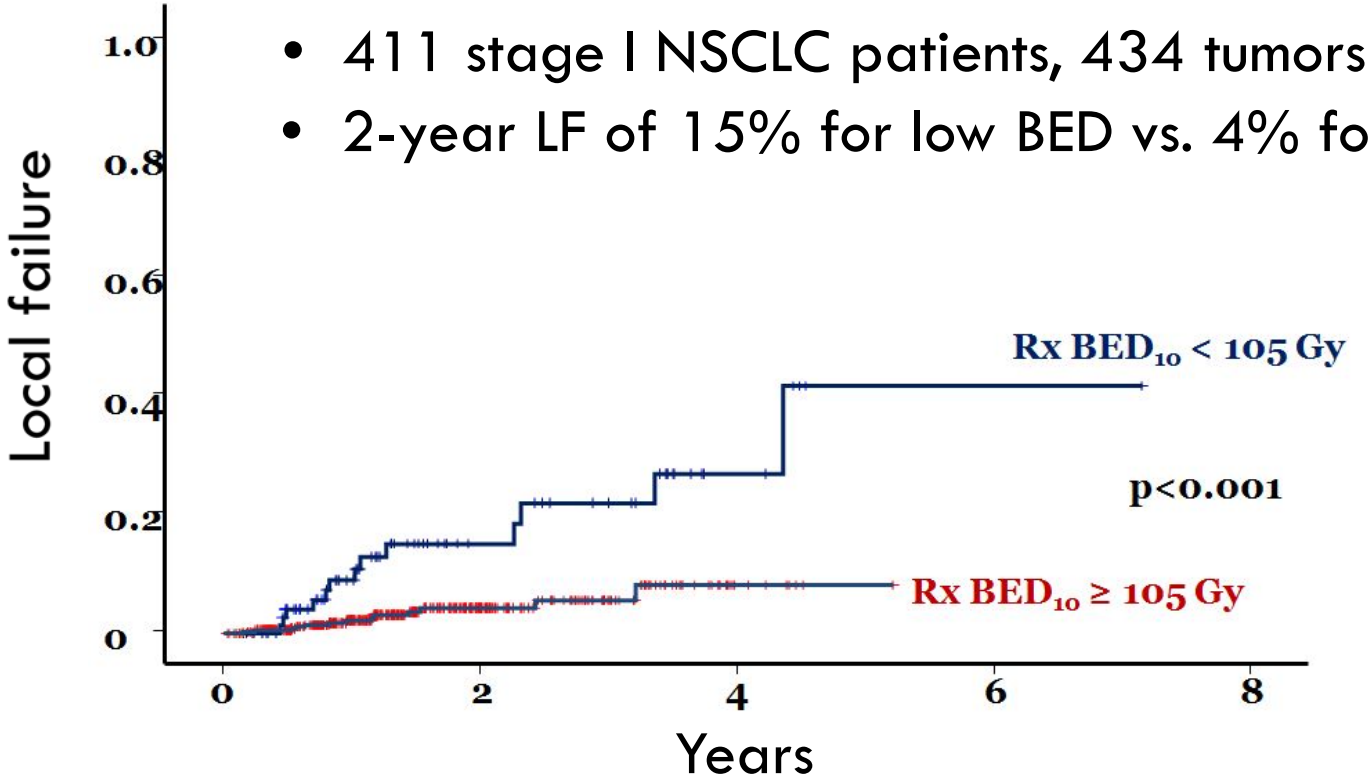
12 Gy x 4 = 48 Gy

10 Gy x 5 = 50 Gy

Onishi, H, JTO, 2007

ELEKTA CONSORTIUM: LOCAL FAILURE BY DOSE

- 411 stage I NSCLC patients, 434 tumors
- 2-year LF of 15% for low BED vs. 4% for high BED



Grills, I et al., JTO, 2012

practical radiation oncology
pro
www.practicalradonc.org

Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control

Niraj Mehta MD, Christopher R. King MD, PhD, Nzhde Agazaryan PhD, Michael Steinberg MD, Amanda Hua BA, Percy Lee MD*

Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

DOSE RESPONSE LUNG SBRT

- PURPOSE:
  - Is there a relationship between tumor control probability (TCP) and the Biological Effective Dose (BED) in Stage I NSCLC?
  - Is there evidence for further dose escalation?
  - Are we really doing better than before (SBRT vs. 3DCRT)?

N. Mehta and P. Lee et al., PRO, 2012

METHODS

- 42 PUBLISHED STUDIES (48 DATA POINTS) – Heterogeneous!
- July 1988-March 2010
- Crude Local Control (TC) ≥ 2 years as a function of BED
- Scatter plot TC vs. BED
- TCP = $\exp([\text{d-TCD}_{50}]/k) / [1+\exp([\text{d-TCD}_{50}]/k)]$
- Daily fraction size ≥ 6 Gy considered SBRT- Assumptions!

N. Mehta and P. Lee et al., PRO, 2012

RESULTS

- 2696 patients (SBRT: 1640; 3D-CRT: 1050
- 704 adenoCA, 847 SCC, 1145 NOS
- Daily fx size 1.2 – 4 Gy (total dose: 48-103) for 3D-CRT
- Daily fx size 6-26 Gy (total dose 20-66) for SBRT
- Median aBED 105.6 Gy (59.6 – 286.6)

N. Mehta and P. Lee et al., PRO, 2012

RESULTS

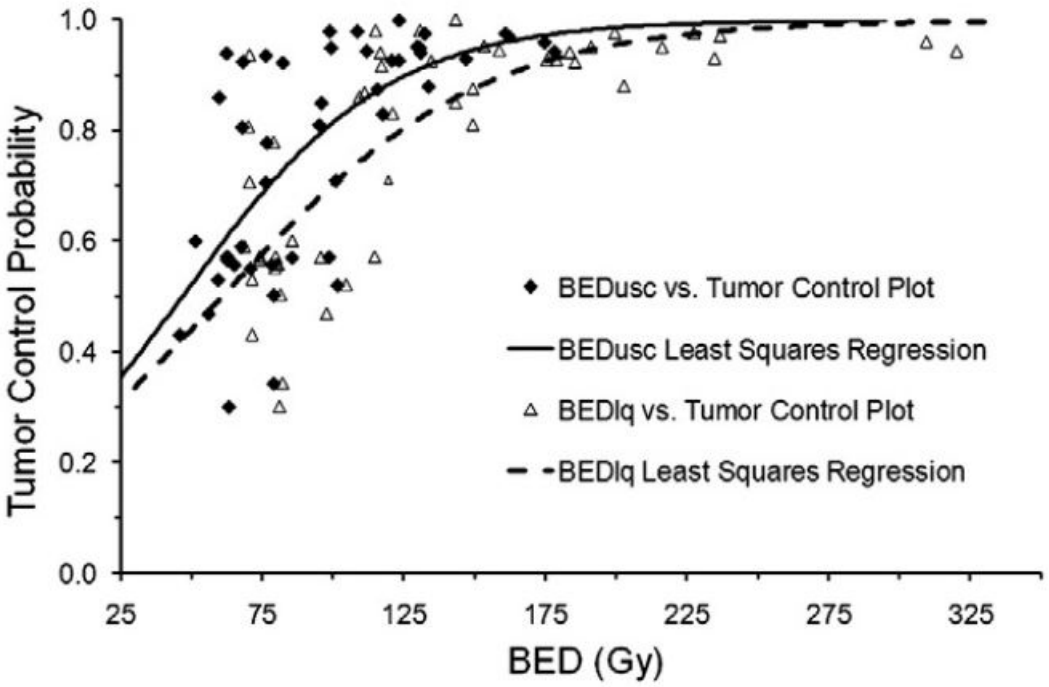


Table 3 Demographics, radiation therapy details, and tumor control

No. of patients	2696
Age, y	73 (22-95)
Histology	
Adenocarcinoma	704 (26%)
Squamous cell carcinoma	847 (31%)
NOS	1145 (42%)
T stage	
T1	1585 (56%)
T2	1128 (40%)
NOS	96 (3%)
Operable	
Yes	421 (14%)
No	2531 (86%)
RT technique	
3D-CRT	1046 (39%)
SBRT	1640 (61%)
Absolute dose range, Gy	
3D-CRT	48-102.9 (1.2-4 Gy/fx)
SBRT	20-66 (4.4-26 Gy/fx)
No. of fractions, range	
3D-CRT	12-49
SBRT	1-10
Median aBED, Gy	105.6
aBED range, Gy	59.6-286.6

3D-CRT, 3-dimensional conformal radiation therapy; aBED, average biological effective dose; NOS, not otherwise specified; RT, radiation therapy; SBRT, stereotactic body radiation therapy.

CONCLUSIONS

- Largest meta-analysis to model TCP as a function of BED for curative radiotherapy for stage I NSCLC
- Near plateau, TCP is ≥ 90% with BED ≥ 124 Gy (USC)
- Corresponds to 53 Gy in 3 fractions at isocenter (48 Gy in 3 fractions at periphery)

N. Mehta and P. Lee et al., PRO, 2012

CONTROVERSY

Dose escalation, not "new biology", can account for the efficacy of SBRT with NSCLC

J. Martin Brown, PhD[1], **David J. Brenner, PhD**[2], and **David J. Carlson, PhD**[3]

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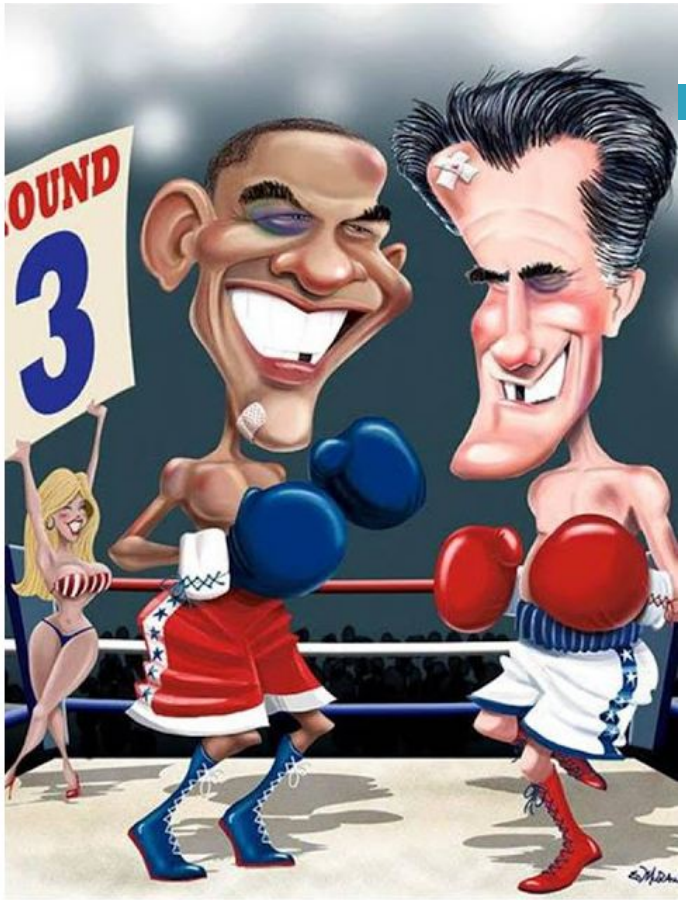
NEW BIOLOGY



OLD BIOLOGY

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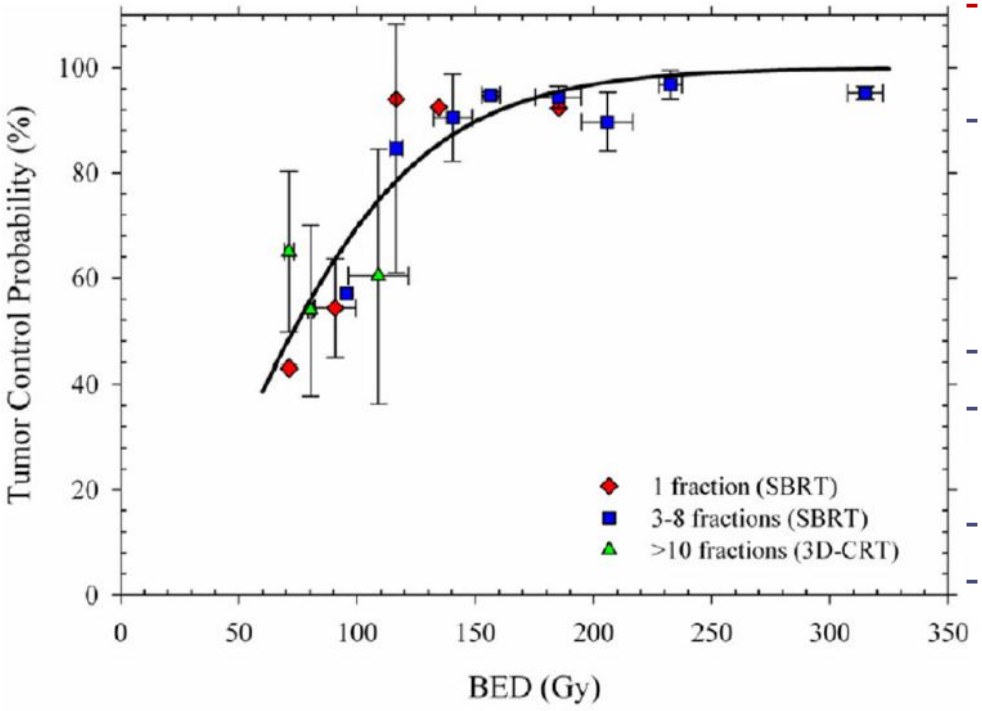
OLD BIOLOGY VS. NEW BIOLOGY



- Brown et al. argues for a monotonic relationship between TCP and BED
- We avoided Old vs. New Biology
  - Equation is poor man way to normalize the dose
  - Unknown (model ≠ mechanism)
- As dose increase, TC asymptote to 100%
- BED is derived from LQ/USC models, flawed; Circular argument
- Abscopal and vascular effects of SBRT?
- Timing of normal tissue effects: e.g.. pneumonitis
  - different between 3DCRT and SBRT

ARGUMENTS THAT IF IT AIN'T BROKE WHY FIX IT

Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

HYPOXIA?

J. Martin Brown, PhD,* David J. Carlson, PhD,† and David J. Brenner, PhD‡

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Counter Arguments

COMMENTS

Dose Escalation, Not "New Biology," Can Account for the Efficacy of Stereotactic Body Radiation Therapy With Non-Small Cell Lung Cancer

In Regard to Brown et al

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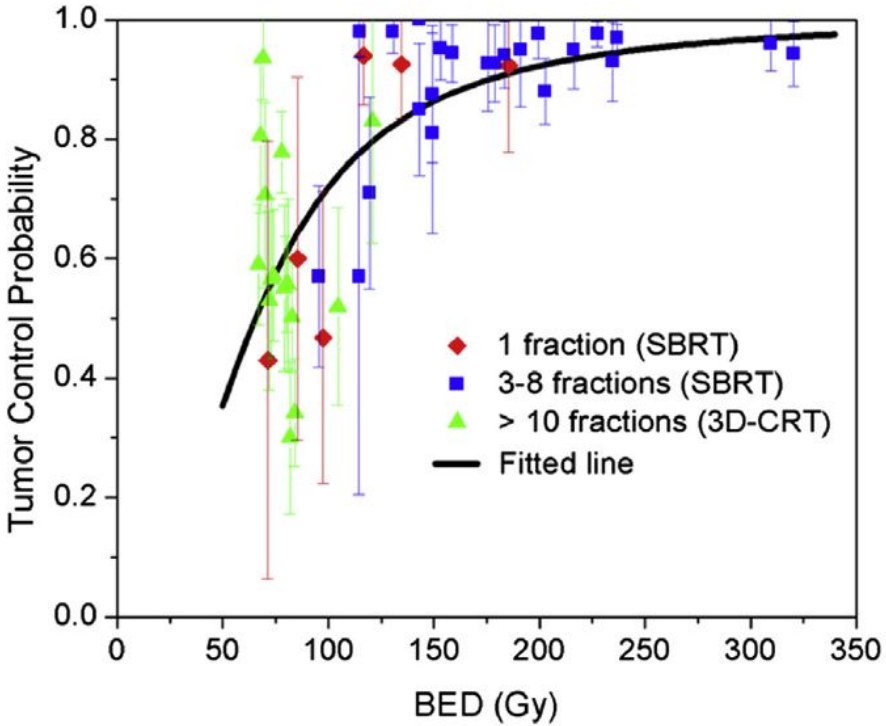

OTHER FACTORS THAT MIGHT INFLUENCE TUMOR CONTROL

Patient Factors:

- Age, histology (in situ vs. invasive), tumor size/volume, tumor location, tumor doubling time, lung function?

Treatment Factors:

- Total dose, dose per fraction, number of fractions?
- Length of treatment? Time effects (BED 100 can be achieved with 3DCRT but takes many weeks). Tumor cell repopulation?
- Treatment techniques, margins, image-guidance, etc.?
- Prescription standards? Normalized to isocenter as best as possible

Working Group on Biological Effects of Hypofractionated Radiotherapy/SBRT (WGSBRT)

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UCLA Jonsson Comprehensive Cancer Center

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WGSBRT Organization

- Five top-level groups:
- Tumor Control Probability (TCP)
- Normal Tissue Complication Probability (NTCP)
- Radiobiology
- Rationale for Prescription Schemes
- Reporting Standards

WBSBRT Subgroups

- The TCP and NTCP groups have divided into six anatomical subgroup
  - Cranial
  - Head & Neck
  - Thoracic
  - Abdominal
  - Pelvic
  - Spine

WGSBRT – Thoracic TCP

- **Methodology:**
  - 118 clinical studies reviewed on SBRT for lung cancer
  - Reviews by 12 members of the Thoracic TCP Working Group – primary data
  - Selected re-review by group co-chairs for consistency
  - Data modeling by Allen Li and his group (KM/actuarial figure digitized).
- **Objectives:**
  - Better model than LQ, USC for thoracic SBRT TCP?
  - More accurate predictions for tumor control by biological and physical dose
  - Discern intrinsic radio sensitivity of lung tumors to SBRT (α/β)

Sample Data Review Sheet for Consistent Data Collection

AAPM Working Group on Biological Effects of SBRT
TCP Lung Version 01.05

Study	N Pts	N Tumors	Rx Dose (Gy)	nfx	Local Control (LC) Rate 1yr	Rate 2yr	Rate 3yr	Rate 5yr	Rate 10yr	Median LC (yrs)	Study Type	Median Followup (yrs)	Overall Survival (OS) Rate 1yr	Rate 2yr	Rate 3yr	Rate 5yr	Rate 10yr	Median OS (yrs)	Cause-Specific or Cancer-Specific Survival 1yr	2yr	3yr	5yr	10yr	Median CSS (yrs)	Regional or Involved Lobe Control 1yr	2yr	3yr	5yr	10yr	Median Control (yrs)
Fakiris2009 T1	34		60	3								4.18						3.23			83.4%									
Fakiris2009 T2	36		66	3								4.18						2.04			67.0%									
Salazar2008 OS vs time for different stages	102		40	4			82.0%					3.17																		
Salazar2008 Stage I	60		40	4			98.3%					3.17		73.0%	62.0%	47.0%				87.0%	82.0%	70.0%								
Salazar2008 Stage III	30		40	4			60.0%					3.17			22.0%			1.25			30.0%									
Uematsu 2001	50	50	50-60 Gy for no prior RT; 30-45 Gy for prior RT cases	5 to 10 fx						Note: At end of study, 30/50 pts alive with no recurren		1.67	~88%	77.0%	66% (All pts) 86% in operable pts				~95%	91.0%	88.0%									

Updated/Clean Version

Data for early stages (T1 and T2) used to fit models

0: means no data

unspecified = -1
all stage1 = 0

Study	N Pts	N Tumors	unspecified -1 assigned T1portion	patient population weighted dose (Gy)	patient population fractions n/fx	KM=1 Acturial=2 Crude=3 Analysis type	unkown = 0.4 ass Dose to PTV Rx (%)	unkown = 0.4 assi se to isocer Rx (%)	Patient Stage	GTV diameter (cm)	Tx time per fx (min)	Elapsed Days	Local Control (LC) Rate 1yr	Rate 2yr	Rate 3yr	Rate 5yr	Overall Survival (OS) Rate 1yr	Rate 2yr	Rate 3yr	Rate 5yr
Salazar2008 Stage I	60	T1=45, T2=15,	0.75	40	4	0	1	0.754717	0	0.00	0	21	0	0	0.98333	0	0	0.73	0.62	0.47
Salazar2008 Stage IA	45	T1=45	1	40	4	1	1	0.754717	1	0.00	0	21	0	0	1	0	0	0.81	0.72	0.47
Salazar2008 Stage IB	15	T2=15	0	40	4	1	1	0.754717	2	0.00	0	21	0	0	0.93	0	0	0.55	0.42	0.42
Nagata2005	45	T1=32, T2=13	0.711111111	48	4	1	0.4	1	0	0.00	0	12	1	1	0.96444	0.96444	0	0	0	0
Nagata2005 Stage IA	32	T1=32	1	48	4	1	0.4	1	1	0.00	0	12	1	1	0.95	0.95	0.93	0.93	0.83	0.83
Nagata2005 Stage IB	13	T2=13	0	48	4	1	0.4	1	2	0.00	0	12	1	1	1	1	0.82	0.72	0.72	0.72
Hof 2003	10	10 (T1=2, T2=8)	0.2	24.3	1	2	0.8	1	0	2.84	0	1	0.889	0.711	0	0	0.8	0.64	0	0
Bauman 2009	57	57 (T1=40, T2=17)	0.701754386	45	3	1	0.67	0.67	0	3.13	0	5	0	0	0.92	0	0.86	0.65	0.6	0
Timmerman 2010	55	53 (T1=44, T2=11)	0.8	54	3	1	0.99	0.99	0	0.00	0	12	0	0	0.976	0	0	0.73	0.558	0
Dunlap 2010	27	40 (T1=27, T2=13)	1	60	4	1	0.95	0.95	1	2.30	22	0.4	0.9	0.9	0	0	0.85	0.45	0.00	0.00
Dunlap 2010	13	40	0	55	4	1	0.95	0.95	2	2.30	22	0.4	0.7	0.7	0	0	0.85	0.45	0.00	0.00
Ricardi 2010	62	62 (T1=43, T2=19)	0.693548387	45	3	1	0.8	0.8	1	0.00	45	7	0.983	0.927	0.878	0	0.86	0.65	0.6	0
Bradley 2010	91	91 (T1=58, T2=22, T3=2, M1=6)	0.637362637	54	3	2	0.95	0.95	0	0.00	0	7	0.94	0.86	0.86	0	0.84	0.7	0.6	0
Videtic 2010	26	28 (T1=22, T2=6)	0.785714286	50	5	2	0.95	0.95	0	2.25	0	5	1	0.944	0.944	0	0.88	0.65	0.52	0
Xia 2006	25	I=25, II=18 (I used only)	-1	50	10	2	0.95	0.5	0	0.00	0	14	0.96	0.96	0.96	0	0.91	0.91	0.91	0
Fritz2006NSCLC	33		-1	30	1	2	0.8	1	0	0.00	0	0	1	1	0.83	0	0.83	0.63	0.53	0.4
Bral 2011 peripheral	40	T1=26, T2=14	0.65	60	3	2	0.9	0.9	0	0.00	0	10	0.97	0.84	0	0	0	0.52	0	0
Voort van Zyp 2009(periphe	59	T1=39, T2=31	0.557142857	60	3	1	0.8	0.8	0	2.82	100	0.4	0.96	0.96	0	0	0.83	0.62	0	0
	11		0.557142857	45	3	1	0.8	0.8	0	2.82	100	0.4	1	0.78	0	0	0	0	0	0
	35		1	60	3	1	0.8	0.8	1	2.82	100	0.4	1	1	0	0	0	0	0	0
	24		0	60	3	1	0.8	0.8	2	2.82	100	0.4	0.89	0.89	0	0	0	0	0	0
Mohammad2011	36	39 (T1=26, T2=10, M=3)	0.666666667	52	4.3	1	0.8	0.8	0	0.00	0	11	0.91	0	0	0	0	0	0	0
Nath2011	46	T1=31, T2=19	0.62	48	4	2	0.4	0.4	0	2.20	0	0.4	0	0.95	0	0	0	0.54	0	0
Matsuo2011	101	T1=73, T2=28	0.722772277	48	4	1	0.4	1	0	0.00	0	10	0.98	0.9	0.868	0.868	0.95	0.78	0.586	0.467
Matsuo2011 <20mm	33	T1	1	48	4	1	0.4	1	1	0.00	0	10	0	0	0.964	0	0	0	0.691	0
Matsuo2011 20-30mm	40	T1	0	48	4	1	0.4	1	1	0.00	0	10	0	0	0.845	0	0	0	0.572	0
Matsuo2011 30-50mm	28	T2	0	48	4	1	0.4	1	2	0.00	0	10	0	0	0.781	0	0	0	0.483	0
Koto 2007 T1	19		1	45	3	1	0.95	1	1	0.00	0	7	0.93824	0.779411765	0.779	0.779	0	0	0.717	0
Koto 2007 T2	12		0	60	8	1	0.95	1	2	0.00	0	14	0.90882	0.6	0.4	0.4	0	0	0.635	0
Wulf 2004 NSCLC	20	T1=2, T2=10, T3=8	0.1	34	3	2	1	0.666667	0	0.00	0	10	0.92	0.92	0.92	0.92	0	0.32	0.32	0.18
Wulf 2005 12Gy*3fx	31	31 (T1-3)	-1	37	3	2	0.65	0.65	0	0.00	0	8	0	0.92	0	0	0	0	0	0
Wulf 2005 26Gy*1fx	31	31 (T1-3)	-1	26	1	2	0.8	0.8	0	0.00	0	1	0	1	0	0	0	0	0	0
Beitler2006	75	83 (unspecified stages)	-1	40	5	1	0.4	0.4	0	3.71	0	27	0	0	0	0	0.63	0.45	0	0.17
Hara2006	47	59 (unspecified)	-1	30.16949153	1	1	1	0.4	0	2.12	0	1	0.93	0.78	0	0	0.765	0.41	0	0
McCammon 2009	105		-1	58.28571429	3	2	0.4	0.4	0	0.00	0	5	1	0.893	0.893	0	0	0	0	0
	59		-1	45	3	2	0.4	0.4	0	0.00	0	5	0.89	0.89	0.595	0	0.8	0.75	0	0
	82		-1	28	3	2	0.4	0.4	0	0.00	0	5	0.405	0.135	0.081	0	0	0	0	0
Onimaru 2003	13	18 peripheral and < 3 cm (T1)	1	60	8	2	0.8	1	1	0.00	0	14	1	1	1	0	0	0	0	0
	32	39 central or > 3 cm (T2)	0	48	8	2	0.8	1	2	0.00	0	14	0.86	0.77	0.696	0	0	0	0	0
Olsen 2011	111	111 (peripheral) (T1=100, T2=30)	0.769230769	54	3	2	0.95	0.95	0	2.48	0	8	0.99	0.91	0	0	0.8	0.6	0	0
	11	11 (T1=6, T2=5)	0.545454545	50	5	2	0.95	0.95	0	3.25	0	14	1	1	0	0	0.9	0.9	0	0
	8	8 (T1=3, T2=5)	0.375	45	5	2	0.95	0.95	0	3.72	0	16.5	0.75	0.5	0	0	0.6	0.5	0	0
Inoue 2013	109	T1=79, T2=30	0.724770642	42.20183486	4	2	0.95	1	0	2.20	0	6	0.95	0.88	0.81	0.78	0.9	0.8	0.68	0.64
Timmerman 2006	70	70 (T1=35, T2=35)	0.5	63	3	1	0.8	0.8	0	3.17	0	10	0.99	0.95	0.768	0	0	0.547	0	0
Baumann2006	138	T1=56, T2=85	0.391763121	40.17021277	3	2	0.65	0.65	0	4.21	0	10	0.975	0.933	0.858	0.8	0.85383	0.650385	0.564489	0
	56		1	40.17021277	3	2	0.65	0.65	1	0.00	0	10	1	1	1	0.885	0	0	0	0
	85		0	40.17021277	3	2	0.65	0.65	2	0.00	0	10	0.967	0.885	0.737	0.737	0	0	0	0
Zhang 2012 TK 4cm	68	68 (stages unspecified)	-1	50	4	2	0.8	0.8	1	2.73	0	4	1	0.985	0.985	0	0	0	0	0
Shioyama 2013	8	8 (T1=4, T2=4)	0.5	48	4	2	0.4	1	0	2.9	0	4	1	1	1	0	0	0.72	0	
Westover 2012	15	20 (T1=18, T2=2)	0.9	45	3	2	0.4	0.95	0	1.50	22.5	4	1	1	0	0	0.64	0	0	
Rowe 2012	47	(40 lesions central by RTOG definition (T1=24, T2=	0.470588235	50	4	2	0.95	0.9	0	2.90	0	0.4	1	0.94	0	0	0	0	0	
Grills 2012	505	505 (pooled study of 5 institutions) (T1=63%, T2=33	0.63	54	3	1	0.4	0.4	0	0.00	0	0.4	0	0.94	0.91	0	0	0.6	0.48	0
Bibault 2012	51	51 (single insitution) (T1=31, T2=20)	0.607843137	60	3	2	0.83	0.83	0	2.76	0	0.4	0.92	0.86	0	0	0.855	0.794	0	0
Clarke 2012	82	82 (single institution) (T1=58, T2=24)	0.707317073	53.30487805	3	1	0.4	0.4	0	0.00	0	0.4	0	0.9	0	0	0	0.67	0	0
Duncker-Rohr NSCLC	26		-1	35.57777778	4.244444444	1	0.6	0.6	0	2.71	0	0.4	0.95	0.95	0.95	0	0	0	0	0
Robinson 2013	78	(T1=56, T2=22)	0.717948718	54	3	1	0.84	0.84	1	2.00	0	0.4	1	0.952	0.952	0.952	0	0	0	0
Kopek2009	88	88 (T1=51, T2=36, T3=1)	0.579545455	51.64772727	3	1	0.67	1	0	3	0	0.4	0.965	0.89	0.89	0	0	0	0	0
Guckenberger2009 NSCLC	40	41 (NSCLC, T1=13, T2=19, T3=9)	0.317073171	34.51623268	3.146341463	1	0.675714286	0.675714	0	3.81	0	0.4	0	0	0.84	0	0	0	0.37	0
Takeda2009 T1	38	38	1	50	5	1	1	0.8	1	0.00	0	0.4	0.93	0.93	0.93	0	0	0.9	0	0

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