Radiation therapy: Challenging clinical scenarios and related management issues

Roy Decker, MD, PhD
Associate Professor of Therapeutic Radiology
Yale School of Medicine

Yale CANCER CENTER

Disclosure

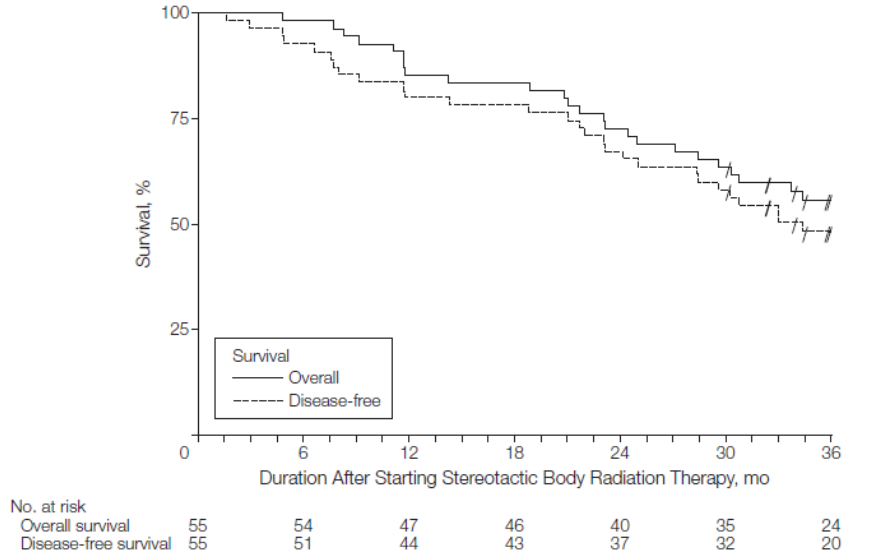
Contracted Research	Merck

- 60-year-old female has a chest x-ray prior to a procedure, and has an incidental LUL lung nodule measuring 1.2 cm. There is no prior imaging
- PET/CT shows this to be avid, with an SUV of 3.5. There is no distant disease
- CT-guided biopsy positive for adenocarcinoma, EGFRwt, and ALK-neg
- The patient is a long-term smoker (30+ pack/years) with long-standing COPD (FEV1 65% predicted, and DLCO 41% predicted)
- Multidisciplinary consultation
- Found to be “inoperable”

SBRT is preferred treatment for **inoperable** T1, T2 N0 NSCLC

RTOG 0236 — T1 and T2 peripheral lung tumors

Figure. Patient Course After Initiation of Stereotactic Body Radiation Therapy



The vertical bars indicate censored observations. The failure rate was 47% for overall survival and 54% for disease-free survival.

- 1 local (in-field) failure
  - 97.6% 3-year local control
- 3 failures in same lobe
  - 90.6% 3-year lobar control
- 2 regional failures
- 11 distant metastatic failures
- Grade 3 toxicity 12.7%
- Grade 4 toxicity 3.6%

3-year OS 55.8%

10 patients died of lung cancer

16 died of other causes

-Timmerman et al, JAMA 2010

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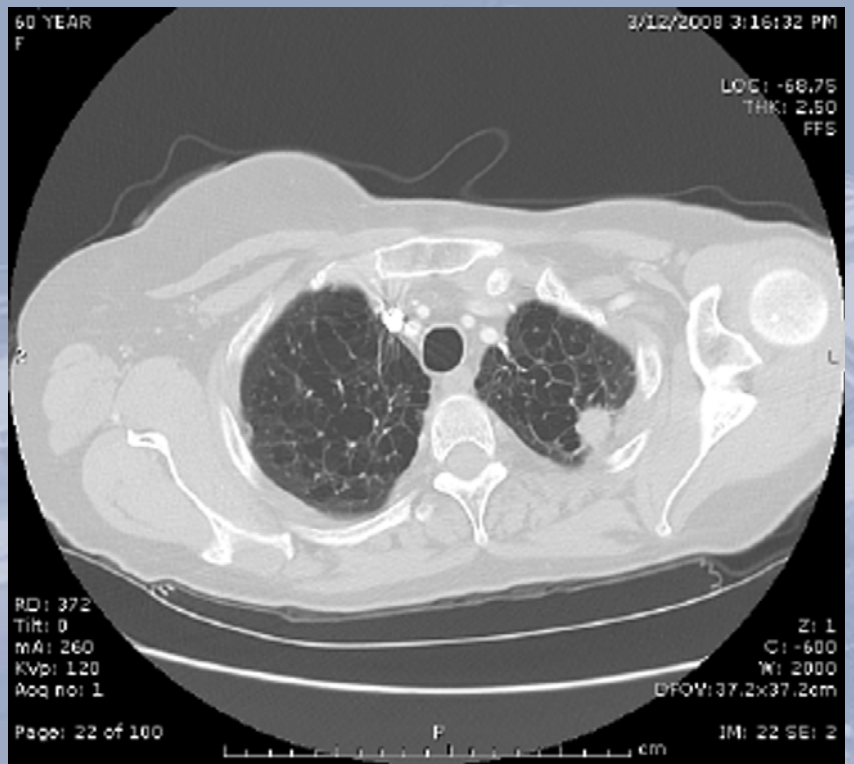
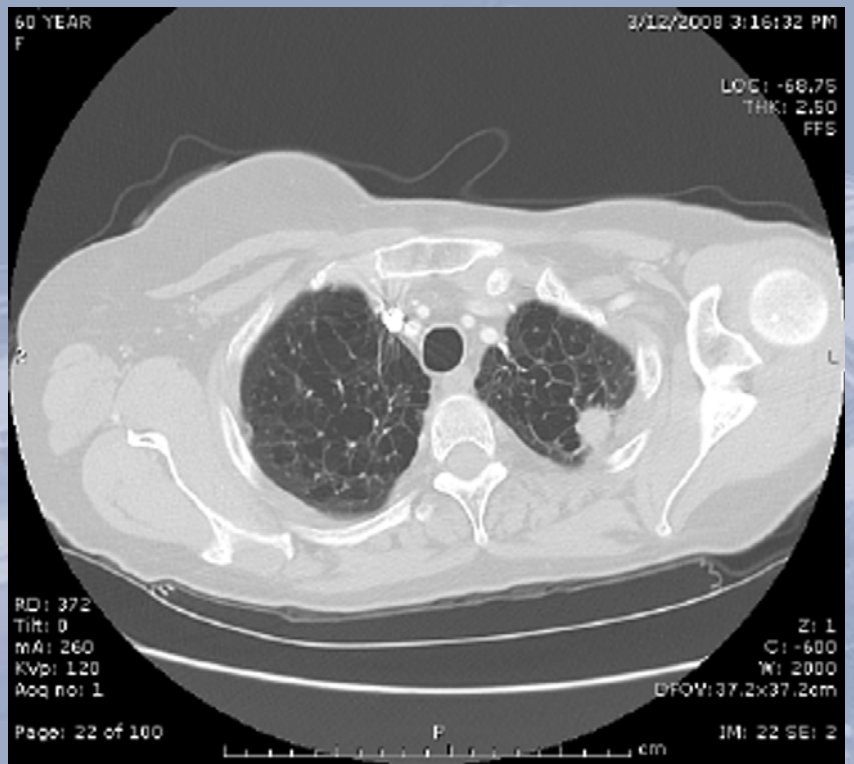


- 60-year-old female has a chest x-ray prior to a procedure, and has an incidental **LUL lung nodule measuring 1.2 cm**. There is no prior imaging
- PET/CT shows this to be avid, with an SUV of 3.5. There is no distant disease
- CT-guided biopsy positive for adenocarcinoma, EGFRwt, and ALK-neg
- The patient is a long-term smoker (30+ pack/years) with long-standing COPD **(FEV1 75% predicted, and DLCO 51% predicted)**
- Multidisciplinary consultation
- Found to be **“operable”**

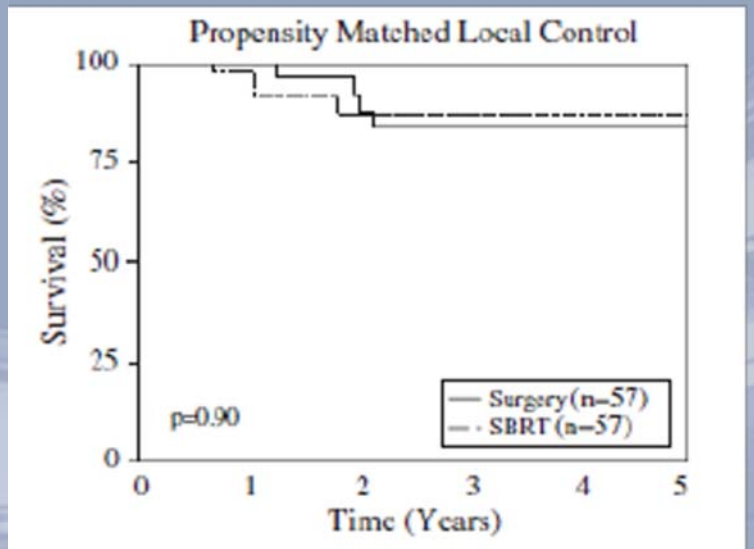


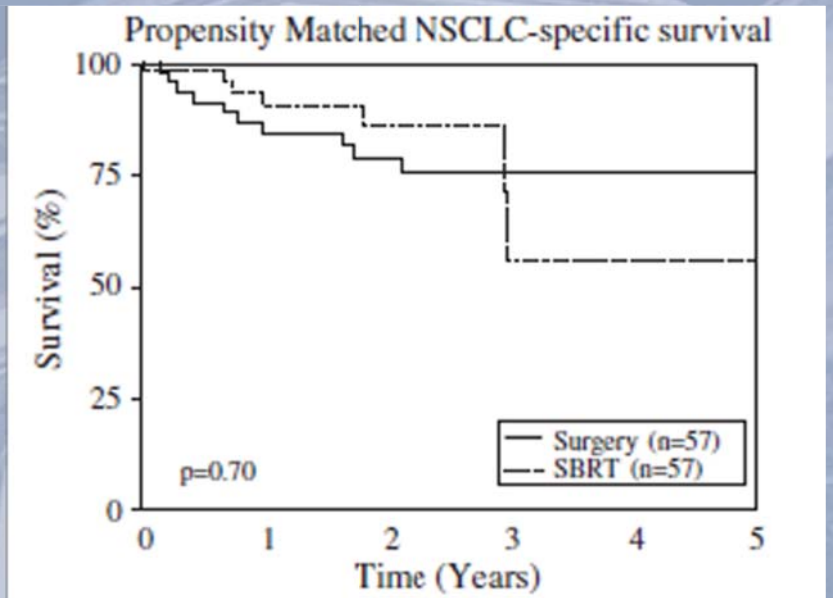
SBRT is an option for **operable** T1, T2 N0 NSCLC

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

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

- Propensity-matched retrospective review of patients with stage I NSCLC
- Included patients treated with sub-lobar, lobar, bilobar resections, pneumonectomy
- No difference in 4-year local control (90%)
- No difference in 4-year regional control (80%)
- No difference in NSCLC-specific survival





SBRT is an option for operable T1, T2 N0 NSCLC

CLINICAL INVESTIGATION

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

Hiroshi Onishi, MD, Hiroki Shirato, MD, Yasushi Nagata, MD, Masahiro Hiraoka, MD, Masaharu Fujino, MD, Kotaro Gomi, MD, Katsuyuki Karasawa, MD, Kazushige Hayakawa, MD, Yuzuru Nibe, MD, Yoshihiro Takai, MD, Tomoki Kimura, MD, Atsura Takeda, MD, Atsushi Ouchi, MD, Masato Hareyama, MD, Masaki Kokubo, MD, Takuyo Kozuka, MD, Takuro Arimoto, MD, Ryusuke Hara, MD, Jun Itami, MD, and Tsutomu Araki, MD

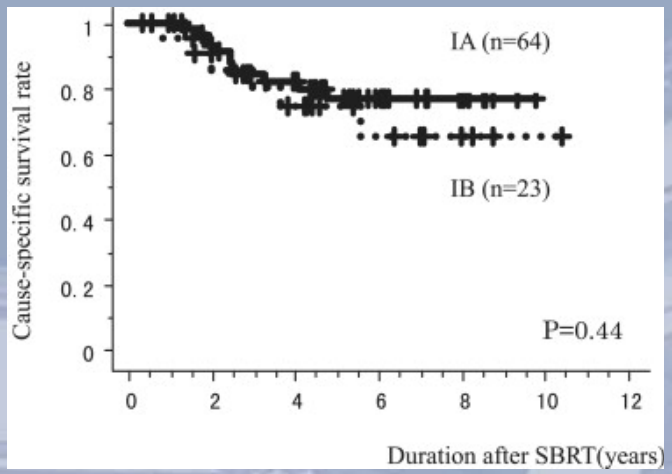
Retrospective review of 87 patients treated with SBRT who were medically eligible for surgical resection

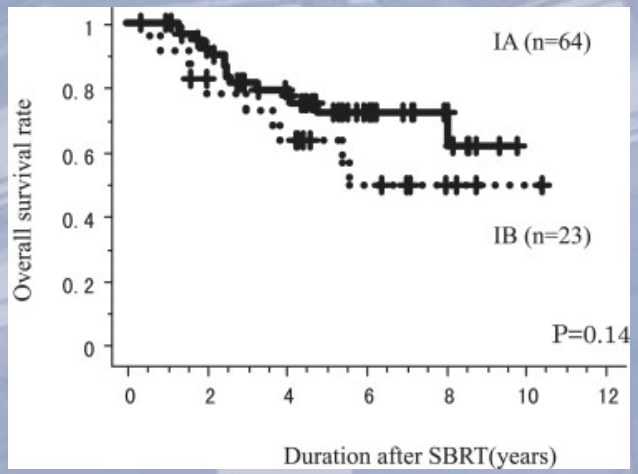
65 T1, 22 T2

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 2010

SBRT is an option for operable T1, T2 N0 NSCLC

Prospective Trials

Single-Arm

- RTOG 0618 — pilot study in operable patients, reported ASCO 2013
  - 26 patients with T1 (23) and T2 (3) biopsy-proven NSCLC
  - 2-year local and lobar failure 19%
  - 1 patient successfully underwent salvage lobectomy

- JCOG 0403, single arm, reported ASTRO 2010
  - 3-year local control 86%, overall survival 76%

Randomized

- ROSEL Closed due to poor accrual
  lobectomy versus SBRT
- STARS Closed due to poor accrual
  lobectomy versus SBRT (CyberKnife)
- ACOSOG Z4099/RTOG 1021 Closed due to poor accrual
  sub-lobar resection versus SBRT
- VALOR trial — open

SBRT is an option for operable T1, T2 N0 NSCLC

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

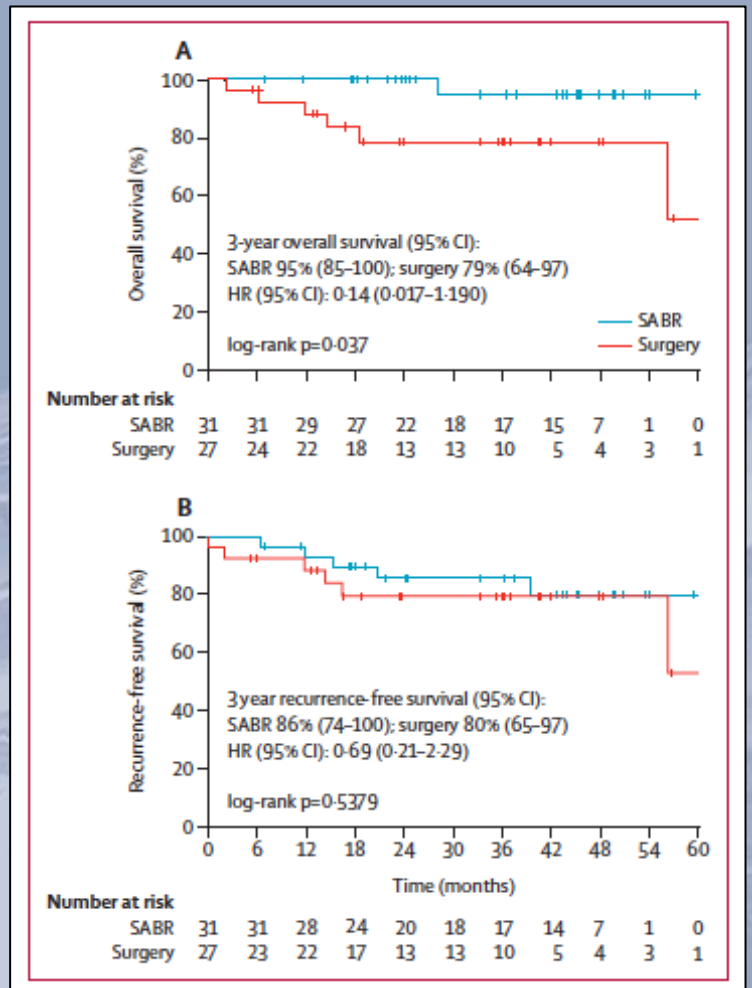
Joe Y Chang, Suresh Senan, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis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

Combined analysis of 2 trials and 58 pts

- 3-year OS 95% v 79% (p=0.037)
- 3-year RFS 86% v 80% (p=0.54)
- Both favoring SBRT

"…the results suggest that SABR is not inferior to surgery, with a hint that it might be better in terms of clinical effectiveness. The findings cast doubt over the superiority of lobectomy, sufficient to suggest group equipoise…"

-Treasure et al, Lancet Oncology

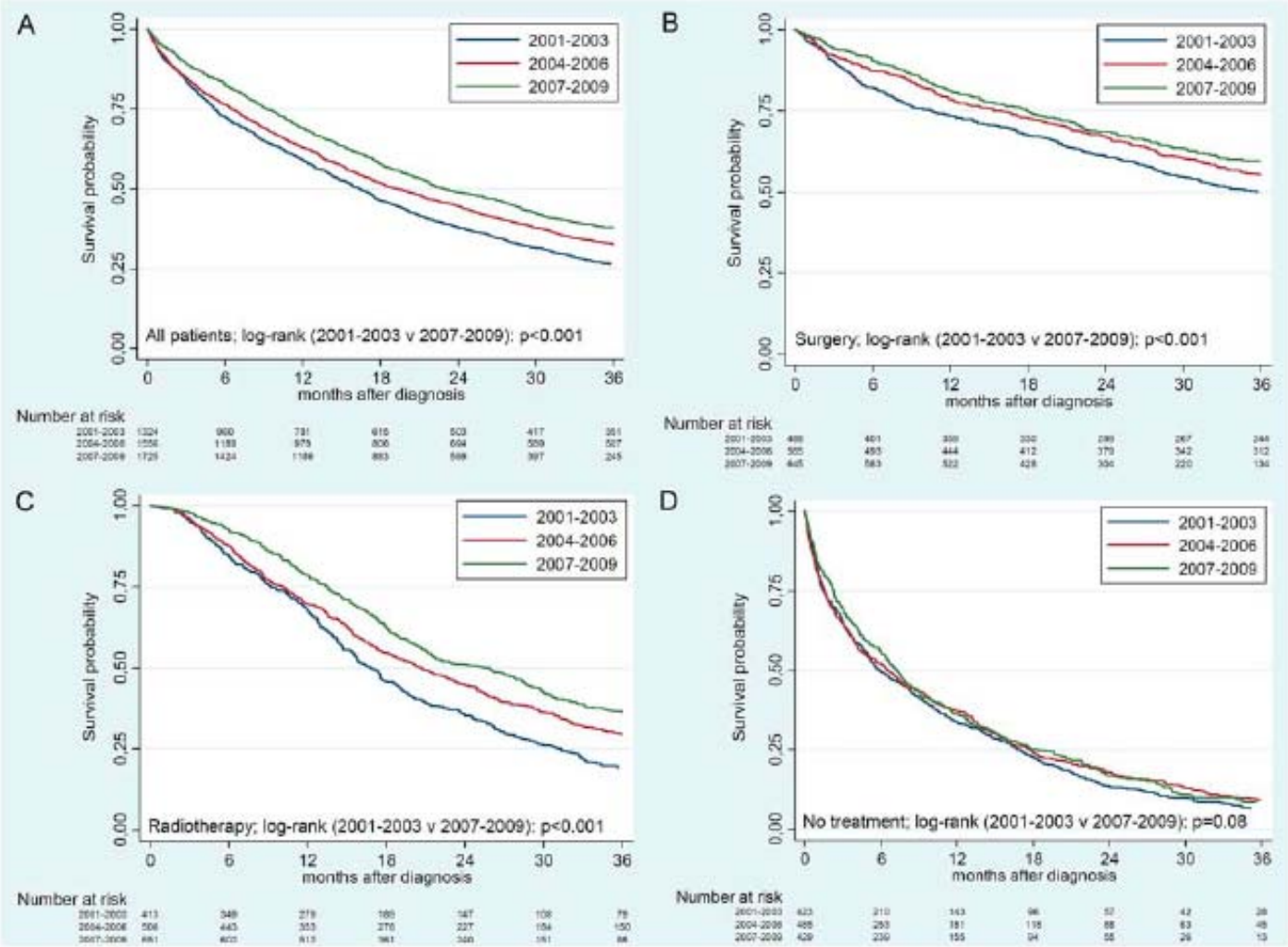


Early-stage lung cancer in elderly patients: A population-based study of changes in treatment patterns and survival in the Netherlands

C. J. A. Haasbeek[1], D. Palma[1,2], O. Visser[3], F. J. Lagerwaard[1], B. Slotman[1] & S. Senan[1]

[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Radiation Oncology, London Regional Cancer Program, London, Canada; [3]Comprehensive Cancer Center The Netherlands, Amsterdam, The Netherlands

-Ann Oncol 2013



Is the patient high risk for SBRT ?

After SBRT, patients retain excellent pulmonary function

No Clinically Significant Changes in Pulmonary Function Following Stereotactic Body Radiation Therapy for Early-Stage Peripheral Non-Small Cell Lung Cancer: An Analysis of RTOG 0236

Sinisa Stanic, MD, Rebecca Paulus, BS, Robert D. Timmerman, MD, Jeff M. Michalski, MD, Robert B. Barriger, MD, Andrea Bezjak, MD, Gregory M.M. Videtic, MD, and Jeffrey Bradley, MD

-IJROBP 2014

Table 2 Pulmonary function test distributions

Pulmonary function test	Baseline (n=55) n	Raw	Week 6 post-SBRT (n=41) n	Raw	n†	Change since baseline*	Month 3 post-SBRT (n=27) n	Raw	n†	Change since baseline*	2-y post-SBRT (n=24) n	Raw	n†	Change since baseline*
FVC (liters)	51	2.3 ± 0.7	40	2.4 ± 0.8	37	0.0 ± 0.5	26	2.3 ± 1.0	23	−0.02 ± 0.4	23	2.5 ± 0.9	20	0.0 ± 0.5
FVC (% predicted)	51	80.0 ± 23.0	40	81.4 ± 26.0	37	−0.32 ± 18.6	26	78.7 ± 29.8	23	0.8 ± 10.5	23	81.4 ± 26.6	20	0.9 ± 16.6
FEV1 (liters)	51	1.3 ± 0.6	40	1.2 ± 0.6	37	−0.08 ± 0.3	26	1.1 ± 0.7	23	−0.13 ± 0.3	23	1.1 ± 0.6	20	−0.12 ± 0.3
FEV1 (% predicted)	51	60.8 ± 33.2	40	57.1 ± 27.0	37	−6.09 ± 25.2	26	53.3 ± 29.6	23	−4.8 ± 11.0	23	51.0 ± 25.3	20	−5.79 ± 13.5
FEV1/FVC	51	0.5 ± 0.2	40	0.5 ± 0.2	37	−0.02 ± 0.1	26	0.5 ± 0.2	23	−0.05 ± 0.1	23	0.5 ± 0.1	20	−0.05 ± 0.1
FEV1/FVC (% predicted)	51	70.0 ± 30.0	40	70.0 ± 20.0	37	−5.0 ± 20.0	26	70.0 ± 20.0	23	−7.0 ± 20.0	23	60 ± 20.0	20	−7.0 ± 10.0
RV (liters)	39	3.2 ± 1.0	34	3.3 ± 1.4	25	0.1 ± 1.2	18	3.1 ± 0.8	12	−0.31 ± 0.4	12	3.5 ± 1.3	8	−0.34 ± 1.1
RV (% predicted)	39	154.6 ± 56.9	34	157.2 ± 59.4	25	5.0 ± 50.7	18	154.1 ± 45.7	12	−17.8 ± 20.8	12	148.1 ± 49.8	8	−20.8 ± 46.6
TLC (liters)	39	5.7 ± 1.4	34	5.9 ± 1.6	25	0.2 ± 0.8	18	5.7 ± 0.9	12	−0.23 ± 0.4	12	6.5 ± 1.6	8	−0.38 ± 0.8
TLC (% predicted)	39	113.1 ± 19.4	34	112.7 ± 20.8	25	2.6 ± 13.0	18	115.4 ± 16.7	12	−1.24 ± 22.7	12	113.2 ± 18.5	8	−9.17 ± 18.6
DLCO (mL/min/mm Hg)	42	10.6 ± 3.6	38	9.5 ± 4.0	29	−0.23 ± 1.7	25	9.5 ± 4.8	17	−0.46 ± 2.3	17	10.7 ± 4.8	13	−0.74 ± 2.4
DLCO (% predicted)	42	60.7 ± 30.4	38	48.3 ± 23.0	29	−3.4 ± 6.7	25	44.6 ± 18.1	17	−5.39 ± 7.6	17	46.6 ± 18.1	13	−6.29 ± 10.1
$PaCO_2$ (mm Hg)	37	40.5 ± 6.4	33	39.2 ± 7.4	25	0.0 ± 3.1	15	41.9 ± 10.8	14	0.3 ± 4.6	9	38.0 ± 5.5	7	−0.9 ± 6.4
PaO_2 (mm Hg)	37	72.6 ± 13.9	33	72.0 ± 14.1	25	1.2 ± 15.2	15	68.4 ± 12.4	14	−1.3 ± 16.0	9	74.0 ± 16.8	7	1.7 ± 5.4
SaO_2 (%)	33	93.3 ± 4.4	31	93.2 ± 4.0	24	0.9 ± 4.7	15	92.5 ± 4.0	14	−0.1 ± 4.9	10	94.0 ± 2.8	8	0.4 ± 3.9

Abbreviations: DLCO = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; PaCO2 = partial pressure of arterial carbon dioxide; PaO2 = partial pressure of arterial oxygen; RV = residual volume; SaO2 = oxygen saturation; SBRT = stereotactic body radiation therapy.

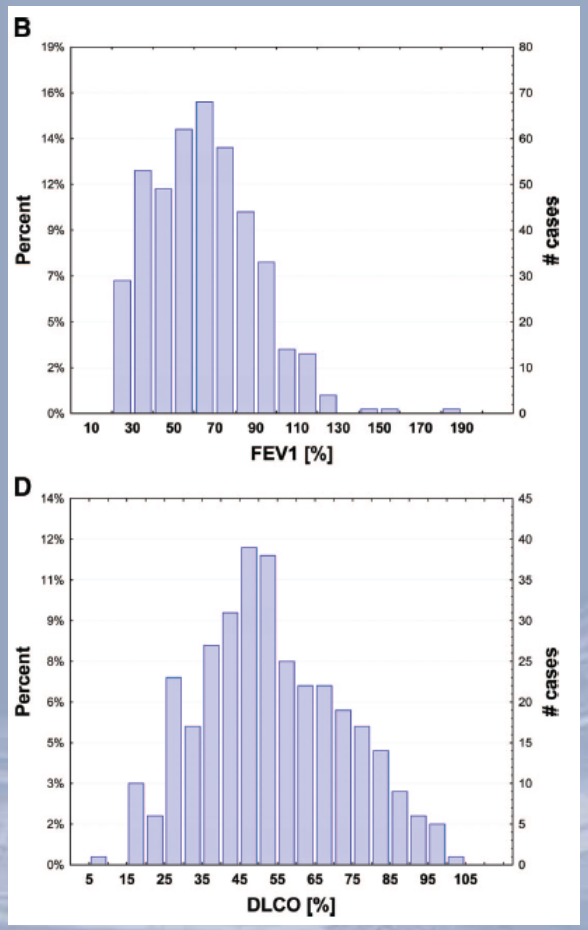
* Values are means ± SD. Actual raw changes were calculated by subtracting the baseline value from the follow-up value.

† Has both baseline and follow-up pulmonary function test (PFT) results. With the exception of DLCO (% predicted), all PFT result changes were not statistically significant ($P>.05$). The change in DLCO (% predicted) was significant at 6 weeks ($P=.008$) and at 3 months ($P=.007$).

Is There a Lower Limit of Pretreatment Pulmonary Function for Safe and Effective Stereotactic Body Radiotherapy for Early-Stage Non-small Cell Lung Cancer?

Matthias Guckenberger, MD, Larry L. Kestin, MD, Andrew J. Hope, MD, Jose Belderbos, MD, Maria Werner-Wasik, MD, Di Yan, DSc, Jan-Jakob Sonke, PhD, Jean Pierre Bissonnette, PhD, Juergen Wilbert, PhD, Ying Xiao, PhD, and Inga S. Grills, MD

-JTO 2012

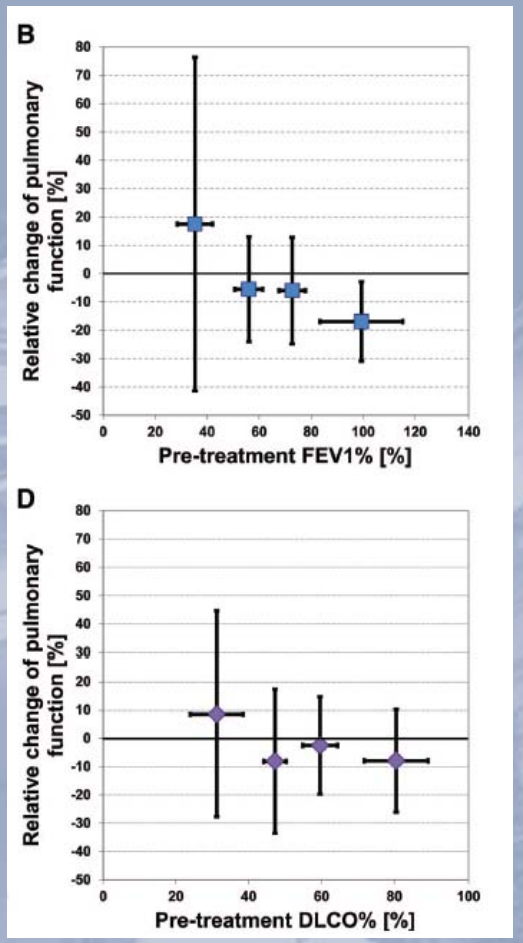


423 patients treated with SBRT
Stratified by pre-treatment pulmonary function (PF)

PF declined by 3.6% at 6 months
by 6.8% at 24 months

PF **improved** for patients with worst baseline PF

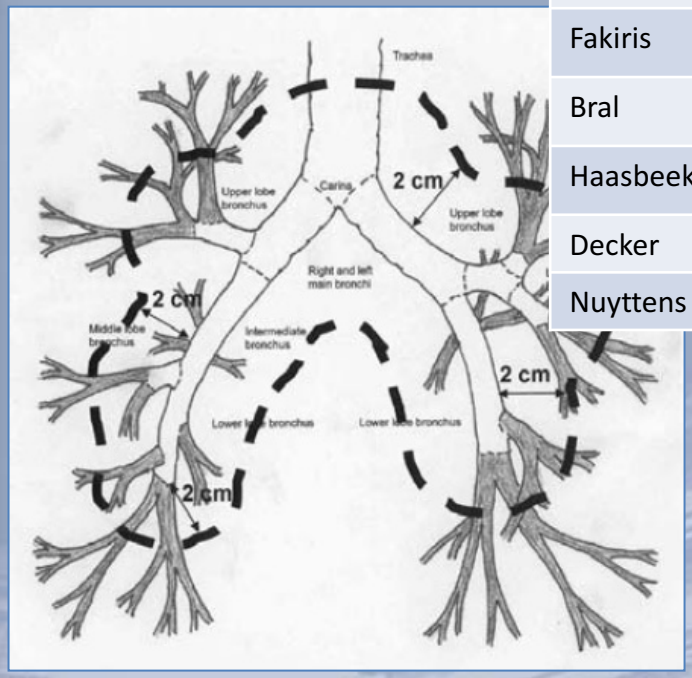
Largest PF decline seen in patients with best baseline PF



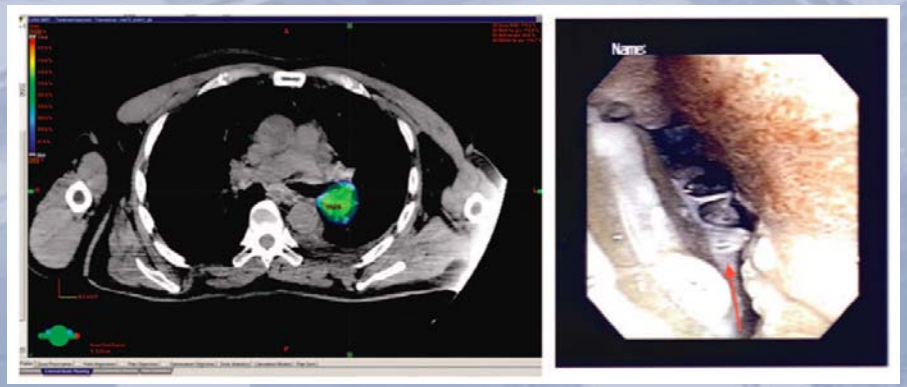
- 73-year-old male has a chest x-ray prior to a procedure, and has an incidental **RLL lung nodule measuring 1.2 cm**. There is no prior imaging
- PET/CT shows this to be avid, with an SUV of 3.5. There is no distant disease
- CT-guided biopsy positive for adenocarcinoma, EGFRwt, and ALK-neg
- The patient is a long-term smoker (30+ pack/years) with long-standing COPD **(FEV1 65% predicted, and DLCO 41% predicted)**
- Multidisciplinary consultation
- Found to be **“inoperable”**

SBRT is safe and effective in central T1, T2 N0 NSCLC using a modified dose and schedule

		Ref	#	Dose / # fx	BED-LQ	Severe toxicity
Onimaru	Hokkaido	IJROBP 2003	9	48 / 8	77	1 (1 G5)
Xia	AFGH	IJROBP 2006	9	50 / 10	75	0
Joyner	UT SA	Acta Oncol 2006	9	36 / 3	79	1
Chang	MDACC	IJROBP 2008	27	40-50 / 4	80-112	0
Song	U Ulsan	Lung Cancer 2009	9	40-60 / 4	80-150	3
Milano	Rochester	Rad Oncol 2009	63	40 / 10	56	1
Fakiris	Indiana	IJROBP 2009	22	60-66 / 3	180-211	11 (5 G5)
Bral	UZ Brussel	IJROBP 2010	17	60 / 4	150	0
Haasbeek	VU UMC	JTO 2011	63	60 / 8	105	4
Decker	Yale	JTO 2012	51	50 / 4-5	100-112	5 (1 G5)
Nuyttens	Rotterdam	Rad Oncol 2012	58	45-60 / 5	85-132	0



-Rowe et al, JTO 2012



SBRT is safe and effective in central T1, T2 N0 NSCLC

Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

RTOG 0813

SCHEMA

Escalating dose levels; at all levels, patients will receive q 2 day fractionation X 5 fractions over 1.5-2 weeks									
Dose Level	Level 1	Level 2	Level 3	Level 4	**†Level 5**	Level 6	Level 7	Level 8	Level 9
Dose per Fraction	8 Gy	8.5 Gy	9 Gy	9.5 Gy	**10 Gy**	10.5 Gy	11 Gy	11.5 Gy	12 Gy
Total Dose	40 Gy	42.5 Gy	45 Gy	47.5 Gy	**50 Gy**	52.5 Gy	55 Gy	57.5 Gy	60 Gy

†Protocol treatment begins at Level 5. Levels 1-4 will be employed if dose-limiting toxicity is seen with the Level 5 (10 Gy) starting dose.

Late Breaking Abstract #10

Dose level	Pts accrued (n)	Pts eligible (n)	Pts evaluable for DLT (n)	Number and type of DLT	Worst treatment-related AE at any time		
					Grade 3 (n)	Grade 4 (n)	Grade 5 (n)
10 Gy/fr	8	8	8	0	0	0	0
10.5 Gy/fr	8	7	6	1 (death)	0	0	1
11.0 Gy/fr	18	14	13	1 (bradycardia)	1	0	0
11.5 Gy/fr	43	38	32	2 (hypoxia)	4	0	2
12.0 Gy/fr	43	33	30	1 (pneumonitis)	5	1	1

-Proc ASTRO 2016

How can we apply precision radiation to more advanced tumors, or ultracentral tumors?

Prospective trials of hypofractionation in early NSCLC (conceived before SBRT)

	Inclusion	Dose	BED	Outcome	
CALGB 39904	T1 or T2	Escalated 4.1 Gy x 17	98 Gy		Bogart et al, JCO 2010
NCIC	T1, T2, or T3	4 Gy x 15	84 Gy	31% G3 2y LC 88%	Cheung et al, JCNI 2014

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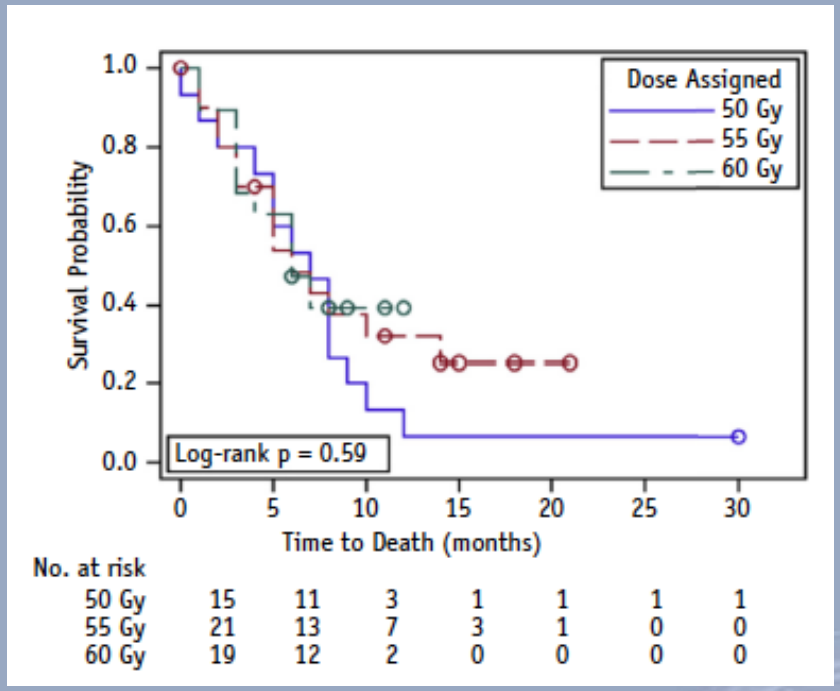
Retrospective reports of hypofractionation applied to ultracentral tumors

	Defn of Ultracentral	Dose	BED	Outcome	
MDACC	clinically challenging	7 Gy x 10	119 Gy	3.6% G3 toxicity	Li et al, Radiother & Oncol 2014
VU	PTV overlapping tracheobronchial tree	5 Gy x 12	90 Gy	38% G3+ 15% fatal pulmonary hemorrhage 100% LC	Tekatli et al, JTO 2016
Chinese Acad MS	?	6 Gy x 12	115 Gy	17% G2+ no G4/G5 3 y LC 91%	Jiang et al, Thorac Cancer 2016
Stanford	large or too central	4 Gy x 15	84 Gy	1 G3 1y LC 84%	Pollum et al, Clin Lung Canc 2016

Precision Hypofractionated Radiation Therapy in Poor Performing Patients With Non-Small Cell Lung Cancer: Phase 1 Dose Escalation Trial



atient, disease and treatment characteristics by dose level

Characteristic	50 Gy (n=15)	55 Gy (n=21)	60 Gy (n=19)
Patients			
Average age (y)	64.9 ± 2.8	70.4 ± 2.6	71.6 ± 2.7
Sex			
Female	3 (20)	6 (29)	9 (47)
Male	12 (80)	15 (71)	10 (53)
Smoking history			
<30 Pack-years	6 (40)	3 (14)	7 (37)
≥30 Pack-years	9 (60)	16 (76)	12 (63)
Average FEV (% of predicted)	55 ± 5	59 ± 4	70 ± 6
Average DLCO (% of predicted)	58 ± 7	59 ± 4	65 ± 5
CCI score	1.93 ± 0.37	2.90 ± 0.55	2.53 ± 0.71
Baseline performance status score			
0, 1	12 (80)	12 (57)	7 (37)
2, 3	3 (20)	9 (43)	11 (58)
Tumor			
Stage			
I-II	1 (7)	1 (5)	4 (21)
III	11 (73)	14 (67)	7 (37)
IV	3 (20)	6 (29)	6 (32)
pT			
T1, T2	2 (13)	5 (24)	8 (42)
T3	4 (27)	11 (52)	3 (16)
T4	5 (33)	1 (5)	4 (21)
Histology			
Adenocarcinoma	6 (40)	9 (43)	9 (47)
Squamous cell carcinoma	8 (53)	9 (43)	5 (26)
Other	1 (7)	3 (14)	5 (26)
Location: right/left			
Central	1 (7)	4 (19)	6 (32)
Right	8 (53)	10 (48)	11 (58)
Left	6 (40)	7 (33)	2 (11)
Location: upper/lower			
Central	1 (7)	4 (19)	6 (32)
Upper	11 (73)	13 (62)	10 (53)
Lower	3 (20)	4 (19)	3 (16)
Treatment			
Average PTV (cc)	673 ± 75	646 ± 96	454 ± 68
No. of days of treatment			
≤20	10 (67)	13 (62)	16 (84)
>20	5 (33)	8 (38)	3 (16)

Abbreviations: CCI = Charlson comorbidity index; DLCO = Diffusing capacity of the lungs for carbon monoxide; FEV = Forced expiratory volume in 1 second; PTV = planning target volume.

Table 3 Association between adverse events >G2 and treatment arm

Dose level (Gy)	>G2 dyspnea (n=13)	≤G2 dyspnea (n=42)	OR (95% CI)	*P* value
50	5 (38)	10 (24)	1.0 (reference)	.58
55	4 (31)	17 (40)	0.47 (0.10-2.17)	
60	4 (31)	15 (36)	0.53 (0.11-2.49)	
	>G2 esophagitis (n=2)	≤G2 esophagitis (n=53)		
50	0 (0)	15 (28)		
55	1 (50)	20 (38)	1.0 (reference)	.94
60	1 (50)	18 (34)	1.11 (0.06-19.09)	

-Westover et al, IJROBP 2015

Radiation therapy: Challenging clinical scenarios and related management issues

- SBRT is the preferred option for medically inoperable patients with early (T1, T2 N0) NSCLC
- SBRT is a reasonable alternative to surgery in selected operable patients with early NSCLC
- SBRT has a small impact on pulmonary function
- SBRT is safe and effective for centrally located tumors
  - The optimal dose and schedule is evolving (but generally lower dose)
  - Higher risk and severity of pulmonary side effects
- For tumors too large or too central for SBRT, hypofractionated radiation schedules may deliver equivalent control with lower risk