SBRT for High Risk Lung Tumors (Central ,Ultra central Tumors, ILD,Re-Irradiation,Multiple tumors)

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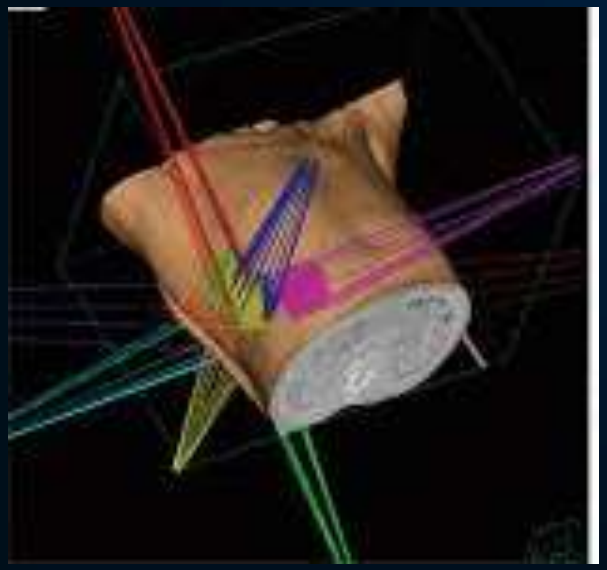
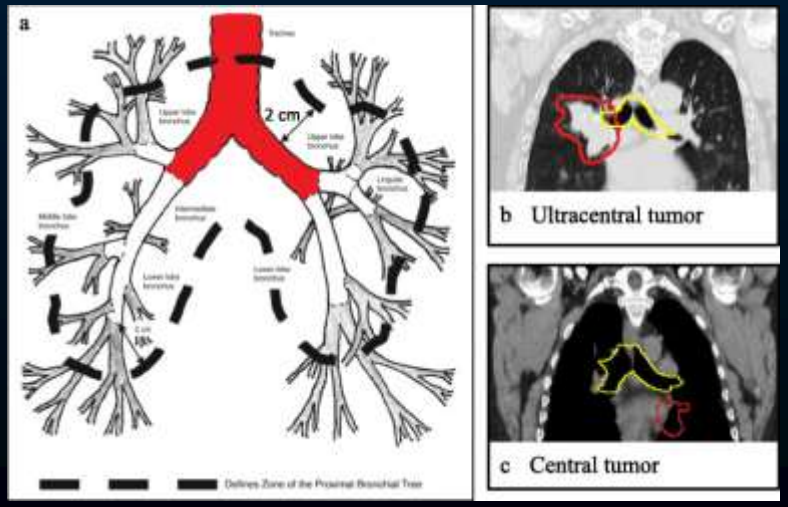
SABR in Central and Ultra central Tumors





No Fly Zone or Restricted Fly Zone

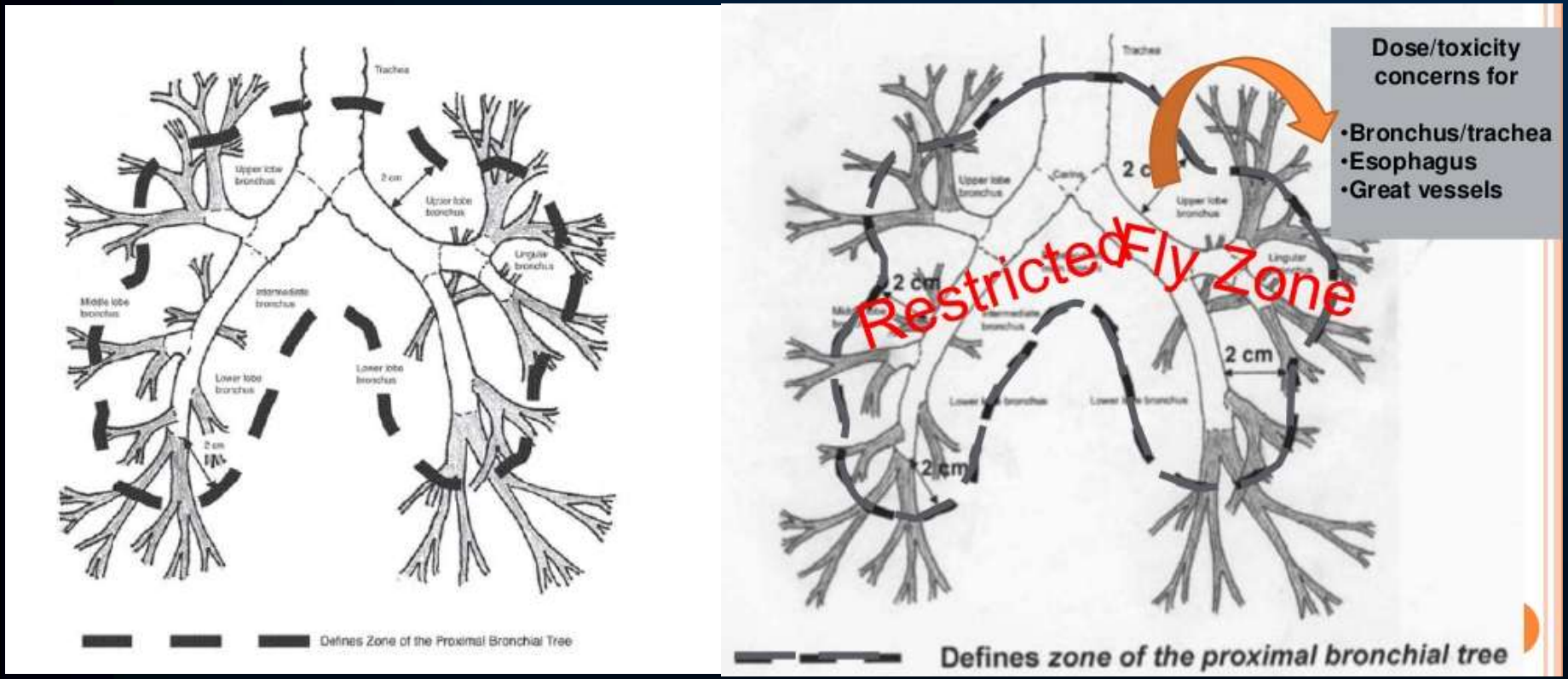


Figure 8.1: Timmerman 'central' zone definition: Any GTV within the 2 cm zone surrounding the proximal bronchial tree (PBT) [6].

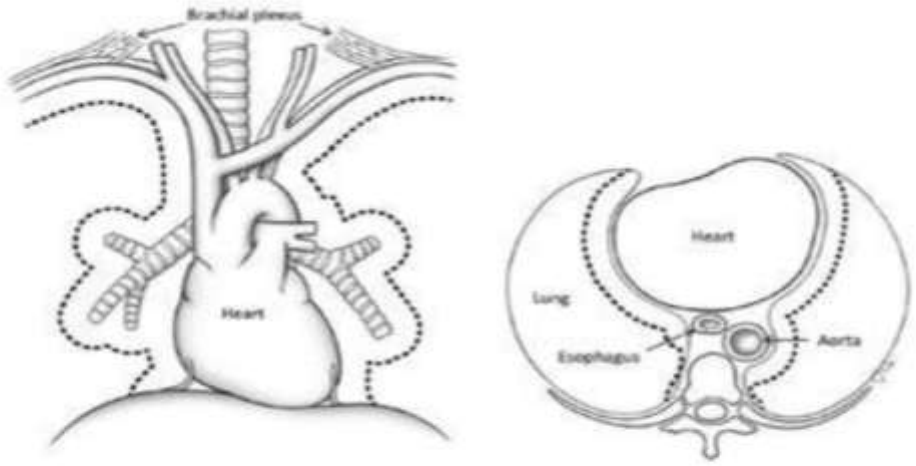


Figure 8.2: IASLC 'central' zone definition: Any GTV within the 2 cm zone around bronchial tree, major vessels, heart, oesophagus, spinal cord, phrenic & recurrent laryngeal nerve, brachial plexus [10].

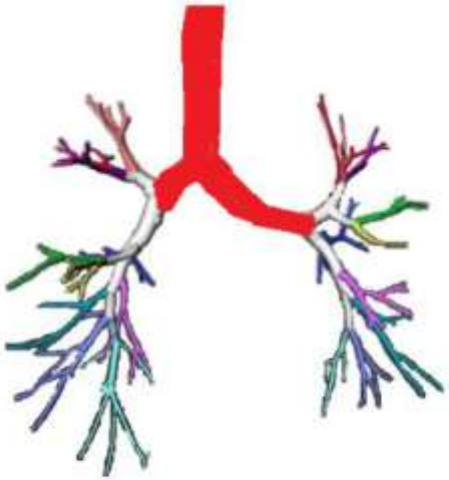
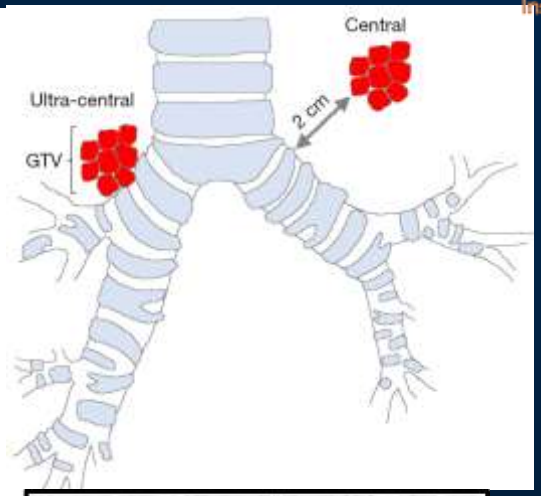
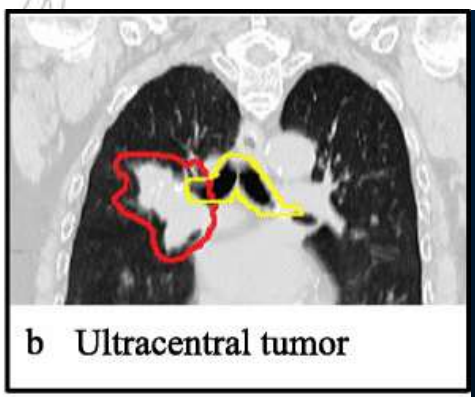
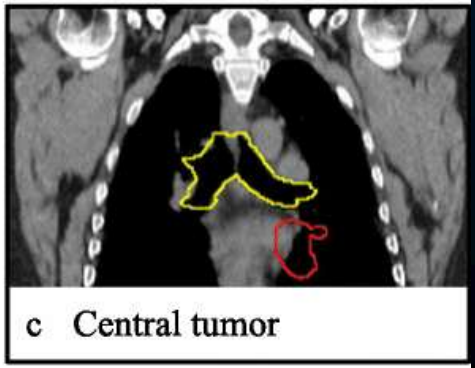


Figure 8.3: Nordic HILUS trial 'ultra-central' zone definition: Any GTV ≤1 cm from the proximal bronchial tree overlapping the trachea or main bronchi [16].





b Ultracentral tumor



c Central tumor

SABR for Central Primary Lung Tumours: Prospective data

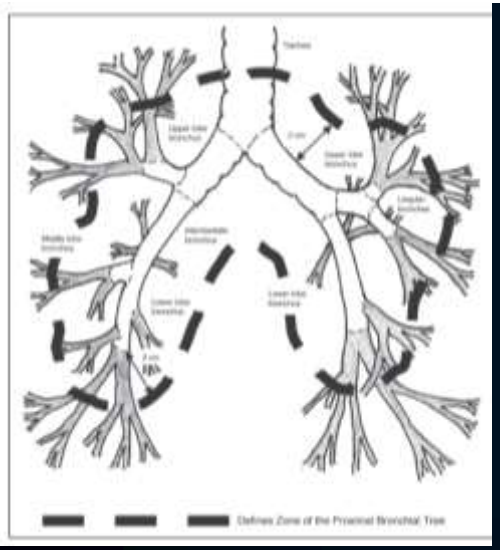
VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

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



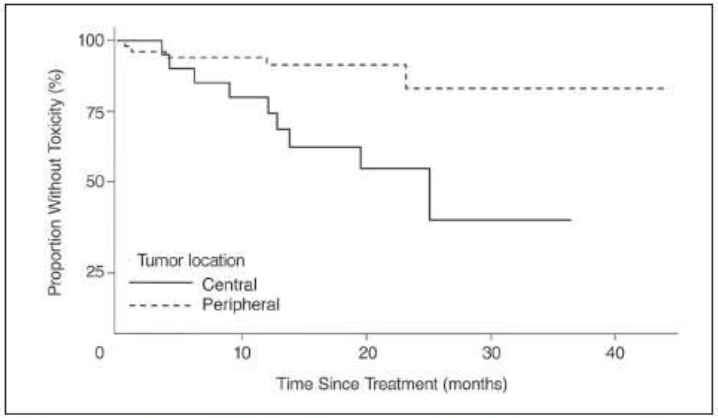


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

Patients with peripheral tumor locations had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with perihilar/central tumors. Patients with **perihilar/central tumors have an 11-fold increased risk of experiencing severe toxicity compared with more peripheral locations.** In addition, four of the six deaths as a result of toxicity observed in the study were in patients with perihilar/ central tumors.

Although these data are promising, **they reflect an initial report that was written mainly to warn clinicians of the excessive toxicities seen in patients with central lesion locations**

Table 2 - High grade clinical pulmonary and radiographic bronchial toxicity

	Description	Number of patients (%)	Time post-treatment (months)	Additional Remarks
High grade (grade ≥3) clinical toxicity (n = 193)				
Grade 3		12 (6%)	0.2-14.1	
	Radiation pneumonitis	10 (5%)	2.0-14.1	
	Atelectasis due to main stem bronchus occlusion	1 (1%)	13.7	
	Hemoptysis	1 (1%)	0.2	
Grade 4	Hemoptysis	1 (1%)	20.1	
Grade 5		15 (8%)	5.6-18.5	
Possible	Fatal lung hemorrhage	5 (3%)	6.5-18.5	
	Multifactorial respiratory failure	1 (1%)	5.6	
Likely	Fatal lung hemorrhage	6 (3%)	5.2-18.2	Two patients also developed G3 RP
	Respiratory failure due to radiation pneumonitis/pneumonia with septicaemia	1 (1%)	7.7	
	Euthanasia performed due to disease progression and dyspnea.	1 (1%)	13.1	Patient also developed G3 RP
	Euthanasia performed after severe dyspnea due to severe COPD, and atelectasis and edema, both arising from bronchial obstruction (main stem/lower lobe bronchus)	1 (1%)	11.3	Patient also developed G3 hemoptysis
Total		**24 (12%)**	**0.2-20.1**	
High grade (occlusion with or without atelectasis) radiographic bronchial toxicity (n = 195)				
	Main stem bronchus	1 (0.5%)	12.2	
	Intermediate bronchus	2 (1%)	6.6-6.9	
	Lobar bronchi	34 (17%)	2.3-38.4	
Total		**36 (18%)**	**2.3-38.4**	

Clinical toxicity outcomes have been previously reported for all patients from institute X, and for a subset of patients from institute XX.[6,9,11] Radiographic toxicity has been previously described for all patients included from institute XX.[24]
Abbreviations: COPD = chronic obstructive pulmonary disease. G3 RP = grade 3 radiation pneumonitis.

ACCEPTED MANUSCRIPT

Radiotherapy and Oncology 124 (2017) 11–17

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESTRO-ACROP consensus guideline

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Matthias Guckenberger[a,*], Nicolaus Andratschke[a], Karin Dieckmann[b], Mischa S. Hoogeman[c], Morten Hoyer[d], Coen Hurkmans[e], Stephanie Tanadini-Lang[a], Eric Lartigau[f], Alejandra Méndez Romero[c], Suresh Senan[g], Dirk Verellen[h]

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Institutions agreed (62.5%–100%) that there are no absolute contraindications for lung SBRT in terms of age, Charlson Comorbidity score, chronic obstructive pulmonary disease (COPD) GOLD classification and pre-treatment pulmonary function.

Although we have addressed aspects of SBRT for centrally located tumors, and despite the fact that SBRT for this indication is currently practiced by the majority of the authors institutions, **we acknowledge the fact that substantially less evidence is available to allow for recommendations to be made**

Table 2: Series reporting results for SBRT for centrally located tumors

Author	N	Central tumors	Dose	Median F/U (mos)	AE ≥ Gr 3	LC	OS
Onimaru, 2003[85]	45	20%	48 Gy in 8 fx (central tumors)	18	N/R	55.1% (3-year, NSCLC only)	41.5% (2-year, stage I only)
Timmerman, 2006[13]	70	100%	60 Gy in 3 fx for T1, 66 Gy in 3 fx for T2	17.5	11%	95% (2-year)	54.7% (2-year)
Chang, 2008[88]	27 (13 stage I)	N/R (All central or superior)	Initially 40 Gy in 4 fx, later increased to 50 Gy in 4 fx	17	N/R	89% (at follow-up)	N/R
Milano, 2009[75]	53 (11 stage I or II)	100%	30-63 Gy in 4-18 fx	10	8%	73% (2-year)	72% (2-year, stage I only)
Song, 2009[76]	32	28%	40-60 Gy in 3-4 fx	26.5	33% (pulmonary toxicity, central tumors only)	88.9% (2-year, central tumors only)	50% (2-year, central tumors only)
Oshiro, 2010[73]	21	100%	25 to 60 Gy in 1-13 fx	20	14.3%	59.6% (2-year)	62.2% (2-year)
Bral, 2011[74]	40	43%	60 Gy in 4 fx (central tumors)	16	20%	94.1% (at follow-up, central tumors only)	52% (2-year)
Rowe, 2012[89]	47 (30 primary tumors)	100%	Most commonly 50 Gy in 4 fx	11.3	11%	94% (2-year)	N/R
Modh, 2014[78]	125 (91 primary tumors)	100%	Most commonly 45 Gy in 5 fx	17.4	8%	79% (2-year, pts with BED10 =/>80 Gy only)	64% (2-year, primary and recurrent tumors only)
Nishimura, 2014[81]	133 (120 primary tumors)	100%	40-60 Gy in 5 fx	33	3.8%	78% (3-year)	54.1% (3-year)
Wu, 2014[77]	125 (91 primary tumors)	100%	Most commonly 45 Gy in 5 fx	14.3	1.6% (esophageal toxicity)	N/R	N/R
Harder, 2015[83]	157 (133 primary tumors)	100%	30-60 Gy in 3-8 fx	28.3	0.6% (esophageal toxicity)	N/R	N/R
Haseltine, 2016[80]	108 (101 primary tumors)	100%	36-60 Gy in 2-5 fx	22.7	12%	77.4% (2-year)	63.9% (2-year)

AE, adverse event; F/U, follow-up; LC, local control; N/R, not reported; OS, overall survival; pts, patients; SBRT, stereotactic body radiation therapy

(J Thorac Oncol. 2011;6: 2036–2043)

ORIGINAL ARTICLE

Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer

Cornelis J. A. Haasbeek, MD, PhD, Frank J. Lagerwaard, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan, MRCP, FRCR, PhD

TABLE 2. Tumor Location

Tumor Location[a]	No. of Patients
Proximal bronchial tree	37
Pericardium	11
Overlap other mediastinal structures	15
Aorta	6
Near esophagus	2
Other	7

[a] Many tumors are near multiple structures. The area with predominant overlap was chosen as primary location.

VU University Medical Center, Amsterdam, The Netherlands.

37 patients

60 Gy in 8 fraction regimen prescribed at the 80% PTV encompassing isodose (BED α/β10 = 105 Gy, BED α/β3 = 210 Gy) At least 99% of the PTV volume was covered by the prescription isodose. Dose reductions of the PTV to spare overlapping critical structures were not used.

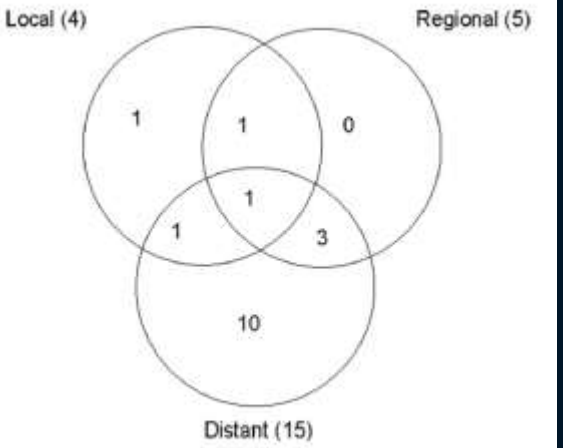

FIGURE 2. Local, regional, and distant failure rates for central early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

Four local failures were observed resulting in actuarial local control rates at 1, 2, and 5 years of **94.8%, 92.6%, and 92.6%,** respectively.

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.

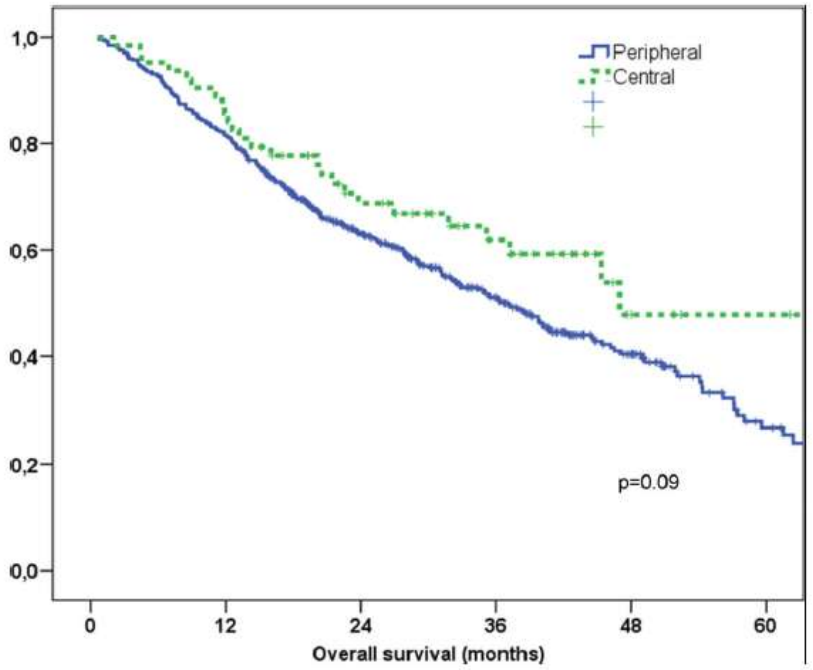

FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

Survival Outcomes

For the 63 patients with central tumors, 1, 2- and 5-year overall survival rates were 85.7%, 69.0%, and 49.5%, respectively

No grade 4 or 5 toxicities were reported, and no dose volume-constraints were provided or suggested.

Radiotherapy and Oncology 117 (2015) 64–70

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer SABR

Stereotactic ablative radiotherapy (SABR) for central lung tumors: Plan quality and long-term clinical outcomes

Hilâl Tekatli, Suresh Senan, Max Dahele, Ben J. Slotman, Wilko F.A.R. Verbakel *

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

Apollo Cancer Institutes

Radiotherapy and Oncology 117 (2015) 64–70

VU University Medical Center, Amsterdam, The Netherlands.2015

80 patients data

•The prescription dose was 60 Gy in 8 fractions.

•Dmax was P60 Gy in 40% of patients for PBT, 26.3% for aorta, 55% for heart, and 1.3% for trachea.

•Esophageal maximum Dmax was 58 Gy.

•

•Mean lung V5Gy/V20Gy was 21%/8%.

• 54 patients (68%) exceeded RTOG0813 Dmax for P1 organ-at-risk (OAR), with 27 exceeding PBT Dmax

•5 of 78 patients (6.4%) with adequate follow-up information had grade 3 toxicity. Grade 4 toxicity was not observed

Treatment-related death was considered **possible (n = 3) or likely (n = 3) in 6 patients (7.5%)**. With median follow-up of 47 months, 3-year survival was 53%, compared with 57% for 252 peripheral tumors treated with 3/5-fractions SABR in the same period (p = 0.369).

Table 3
Details of patients who are considered to have a likely or possible treatment-related death.

Cause of death	Pre-treatment comorbidity	Clinical details	Dosimetric details of index treatment
Likely treatment-related			
RP resulting in respiratory failure	WHO PS 1 Severe ILD	Age 72.3 years, T1bN0M0 Survival 2 months	CL V_{5Gy}: 0% TL V_{5Gy}: 16% TL V_{20Gy}: 9% PBT D0.1 cc: 13.8 Gy
Euthanasia performed due to disease progression and dyspnea	WHO PS 2 COPD GOLD IV	Age 64.8 years, T3N0M0 Patient developed RP grade 3 Survival 13 months	CL V_{5Gy}: 39% TL V_{5Gy}: 45% TL V_{20Gy}: 13% PBT D0.1 cc: 39.7 Gy
Sudden death	WHO PS 2 COPD GOLD II ILD	Age 73.1 years, T2bN0M0 Patient developed RP grade 3 Survival 5 months	Heart D0.5 cc: 56.2 Gy Heart D15 cc: 34.5 Gy CL V_{5Gy}: 51% TL V_{5Gy}: 48% TL V_{20Gy}: 9% PBT D0.1 cc: 71.2 Gy
Possible treatment-related			
Massive lung hemorrhage	WHO PS 1 COPD GOLD II	Age 48.9 years, T2aN0M0 No in-field radiological progression, but possible intrathoracic progression Survival 18 months	PBT D0.1 cc: 79.5 Gy PBT D0.5 cc: 76.1 Gy PBT D4.0 cc: 63.4 Gy
Massive lung hemorrhage	WHO PS 2 COPD GOLD IV	Age 56.9 years, T2aN0M0 Patient developed grade 1 atelectasis Survival 10 months	PBT D0.1 cc: 69.7 Gy PBT D0.5 cc: 63.6 Gy PBT D4.0 cc: 21.3 Gy
Terminal respiratory failure	WHO PS 3 COPD GOLD IV	Age 84.2 years, T2bN0M0 Patient died at a nursing home Survival 3 months	CL V_{5Gy}: 8% TL V_{5Gy}: 24% TL V_{20Gy}: 9% PBT D0.1 cc: 3.9 Gy

Abbreviations: CL = contralateral lung; ILD = interstitial lung disease; PBT = proximal bronchial tree; RP = Radiation Pneumonitis; TL = total lung minus PTV; WHO PS = World Health Organization Performance Status.

Although a substantial proportion of central SABR patients received P60 Gy to OARs, the 3-year survival was no different from peripheral SABR.

ORIGINAL ARTICLE

IASLC

Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk Patients with "Ultracentral" Non-Small Cell Lung Cancer

Hilâl Tekatli, MD,[a] Niels Haasbeek, MD, PhD,[a] Max Dahele, MbChB., PhD, FRCP, FRCR,[a] Patricia De Haan, MD,[a] Wilko Verbakel, PhD,[a] Eva Bongers, MD,[a] Sayed Hashemi, MD,[b] Esther Nossent, MD,[b] Femke Spoelstra, MD, PhD,[a] Adrianus J. de Langen, MD, PhD,[b] Ben Slotman, MD, PhD,[a] Suresh Senan, FRCR, PhD[a,*]

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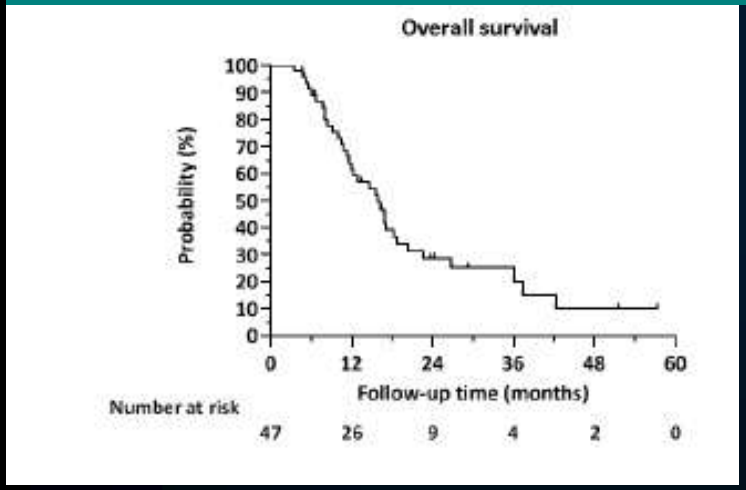
Received 8 February 2016; revised 11 March 2016; accepted 12 March 2016
Available online - 21 March 2016

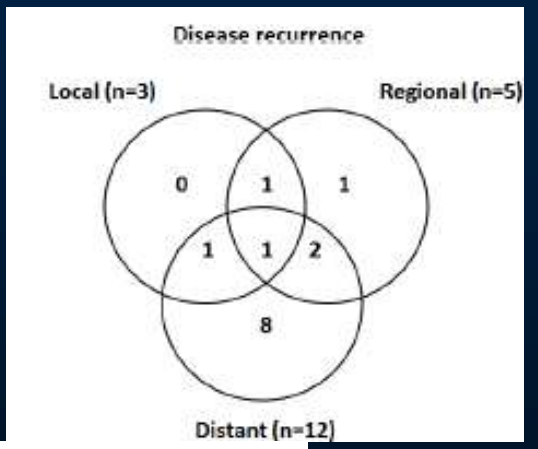
VU University Medical Center, Amsterdam, The Netherlands.2016

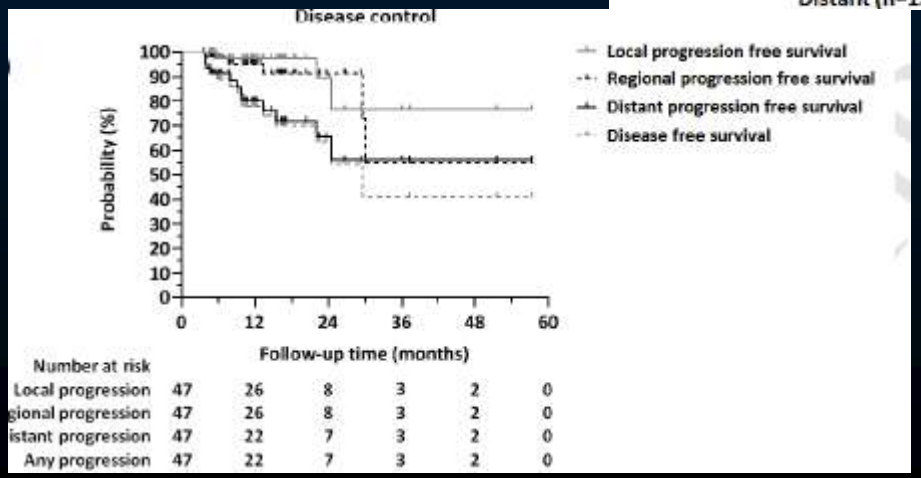
47 patients with single primary or recurrent ultra-central NSCLC treated between 2010-2015
5Gyx12 fractions

Definition of ultra-central :for which a planning target volume (PTV) overlaps the trachea or main bronchi



No isolated local recurrences were observed





At a median follow-up of 29.3 months, median overall survival was 15.9 months, and 3- year survival was 20.1%.

Table 2. Details of Severe (Grade 3 or More) Toxicity

CTCAE v4.03	Adverse Event	No. Patients (%)	First Date after Start of Radiotherapy
Grade ≥3	All	18 (38%)	0.2-41.3 mo
Grade 3		10 (21%)	0.2-41.3 mo
	Radiation pneumonitis	5 (11%)	4.1-14.1 mo
	Dyspnea or cough	3 (6%)	2.9-41.3 mo
	Chest wall pain	2 (4%)	4.1-16.0 mo
	Hemoptysis	2 (4%)	0.2-19.5 mo
Grade 4	Hemoptysis	1 (2%)	20.1 mo
Grade 5		10 (21%)	5.2-18.2 mo
Likely treatment related	Fatal lung hemorrhage	6 (13%)	5.2-18.2 mo
	Euthanasia performed after severe dyspnea arising from bronchial obstruction and COPD	1 (2%)	11.3 mo
	Respiratory failure due to RP/pneumonia with septicaemia	1 (2%)	7.7 mo
Possibly treatment related	Multifactorial respiratory failure	1 (2%)	5.6 mo
	Sudden death, possibly associated with lung hemorrhage	1 (2%)	16.2 mo

COPD, chronic obstructive pulmonary disease; CTCAE, Common Terminology Criteria for Adverse Events; Mo, months; RP, radiation pneumonitis.

Grade ≥3 toxicity was recorded in 38%, with **21%** scored as having a “possible” (n = 2) or “likely” (n = 8) treatment-related death, at between 5.2-18.2 months post-treatment. Fatal pulmonary hemorrhage was observed in **15%** of patients.

Conclusions

Unfit patients with ultra-central tumors treated using this scheme had a high local control and a median survival of 15.9 months. Despite manifesting rates of a fatal lung bleeding comparable to that seen with conventional radiotherapy for endobronchial tumors, **the overall rate of G5 toxicity is of potential concern.** Additional work is needed to identify tumor/treatment factors related to hemorrhage

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 4, pp. 967–971, 2008
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0360-3016/08/$–see front matter

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doi:10.1016/j.ijrobp.2008.08.001

RAPID COMMUNICATION

STEREOTACTIC BODY RADIATION THERAPY IN CENTRALLY AND SUPERIORLY LOCATED STAGE I OR ISOLATED RECURRENT NON–SMALL-CELL LUNG CANCER

Joe Y. Chang, M.D., Ph.D.,* Peter A. Balter, Ph.D.,† Lei Dong, Ph.D.,† Qiuan Yang, M.D.,* Zhongxing Liao, M.D.,* Melenda Jeter, M.D., M.P.H.,* M. Kara Bucci, M.D.,* Mary F. McAleer, M.D., Ph.D.,* Reza J. Mehran, M.D.,§ Jack A. Roth, M.D.,§ and Ritsuko Komaki, M.D.*

Departments of *Radiation Oncology, †Radiation Physics, and §Thoracic and Cardiovascular Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX

MDACC 2008

27 patients

The prescribed dose of 40 Gy (n = 7) to the planning target volume was escalated to 50 Gy (n = 20) in 4 consecutive days

Median follow-up of 17 months

When **50 Gy in 4 fractions** was delivered (BED α/β10 = 112.5 Gy, BED α/β3 = 258 Gy), the local control rate at 2 years was 100% and no fatal toxicity was reported. In contrast, 40 Gy in four fractions was associated with poor local control (57%) 3 of 7 patients had local recurrences when treated using 40 Gy and one patient who had received 40 Gy to the brachial plexus experienced severe brachial plexus neuropathy.

Conclusions: Image-guided SBRTusing **50 Gy** delivered in four fractions is feasible and resulted in excellent local control.

Clinical Investigation: Thoracic Cancer

Stereotactic Ablative Radiation Therapy for Centrally Located Early Stage or Isolated Parenchymal Recurrences of Non-Small Cell Lung Cancer: How to Fly in a "No Fly Zone"

Joe Y. Chang, MD, PhD,* Qiao-Qiao Li, MD,* Qing-Yong Xu, MD,* Pamela K. Allen, PhD,* Neal Rebueno, CMS,* Daniel R. Gomez, MD,* Peter Balter, PhD,† Ritsuko Komaki, MD,* Reza Mehran, MD,‡ Stephen G. Swisher, MD,‡ and Jack A. Roth, MD‡

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Received Dec 10, 2013, and in revised form Jan 7, 2014. Accepted for publication Jan 16, 2014.

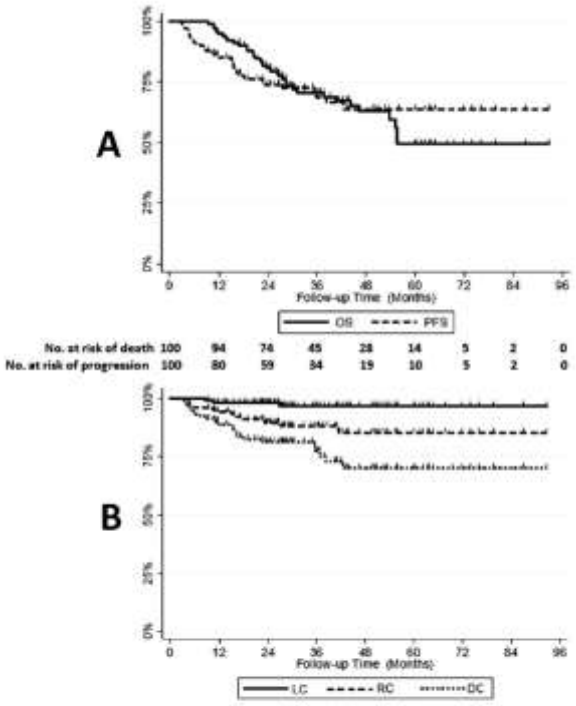

Fig. 1. Kaplan-Meier curves illustrating (A) overall survival (OS) and progression-free survival (PFS) and (B) actuarial local control (LC), regional control (RC), and distant control (DC) over time.

MDACC 2014

100 patients

The tumor within a 2-cm radius of the trachea and bronchial tree has been considered a "no fly zone" (RTOG) protocol 0236

Median survival time (58 months) and local control rates (96% at 2 years) were comparable to those for peripheral lesions treated with SABR to **50 Gy in four fractions**

3-year OS rate was 70.5%. Three-year cumulative actuarial local, regional, and distant control rates were 96.5%, 87.9%, and 77.2%, respectively

Table 4 Previous dose-volume constraints, dosimetric factors associated with radiation toxicity, and recommendations for new dose-volume constraints for patients undergoing stereotactic ablative radiation therapy to 50 Gy in 4 fractions

	Dose-volume constraint	Univariate analysis in current study			
Toxicity and related organs	Previous constraints†	Dosimetric cut-points in current study	No. of patients with specified toxicity (%)	*P*	New recommended dose-volume constraints (ref.)
Radiation pneumonitis (grade ≥2)					
Lung	V_5 <40%	MLD ≤6 Gy	5 of 63 (8)	.016*	MLD ≤6 Gy (preferred)
		MLD >6 Gy	6 of 19 (32)		
		V_5 ≤30%	6 of 73 (8)	.002	V_5 ≤30% (preferred)
		V_5 >30%	5 of 9 (56)		
	V_{10} <30%	V_{10} ≤17%	5 of 58 (9)	.056	V_{10} ≤17% (preferred)
		V_{10} >17%	6 of 24 (25)		
	V_{20} <20%	V_{20} ≤12%	6 of 67 (9)	.025*	V_{20} ≤12% (preferred)
		V_{20} >12%	5 of 15 (33)		
		V_{30} ≤7%	7 of 70 (10)	.051	V_{30} ≤7% (preferred)
		V_{30} >7%	4 of 12 (33)		
		iMLD ≤10 Gy	4 of 55 (7)	.026	iMLD ≤10 Gy (preferred)
		iMLD >10 Gy	7 of 27 (26)		
		iV_{10} ≤35%	4 of 61 (7)	.005	iV_{10} ≤35% (preferred)
		iV_{10} >35%	7 of 21 (33)		
		iV_{20} ≤25%	7 of 69 (10)	.068	iV_{20} ≤25% (preferred)
		iV_{20} >25%	4 of 13 (31)		
		iV_{30} ≤15%	8 of 73 (11)	.097*	iV_{30} ≤15% (preferred)
		iV_{30} >15%	3 of 9 (33)		
Bronchial tree	V_{40} ≤1 cm³	D_{max} ≤38 Gy	8 of 68 (12)	.389	D_{max} ≤38 Gy (preferred)
		D_{max} >38 Gy	3 of 14 (21)		
	V_{35} ≤10 cm³	V_{35} ≤1 cm³	10 of 78 (13)	.444	V_{35} ≤1 cm³
		V_{35} >1 cm³	1 of 4 (25)		
Hilar major vessels	V_{40} ≤1 cm³	D_{max} ≤56 Gy	8 of 72 (11)	.128	D_{max} ≤56 Gy
	V_{35} ≤10 cm³	D_{max} >56 Gy	3 of 10 (30)		
		V_{40} ≤1 cm³	7 of 68 (10)	.087	V_{40} ≤1 cm³
		V_{40} >1 cm³	4 of 14 (29)		
Trachea	V_{35} ≤1 cm³		1 tracheal V_{35} >1 cm³ (no related toxicity)		V_{35} ≤1 cm³
	V_{30} ≤10 cm³				
Esophagitis (grade ≥2)					
Esophagus	V_{35} ≤1 cm³	D_{max} ≤35 Gy	1 of 78 (1)	.005	D_{max} ≤35 Gy
		D_{max} >35 Gy	2 of 4 (50)		
	V_{30} ≤10 cm³	V_{30} ≤1 cm³	1 of 78 (1)	.005	V_{30} ≤1 cm³
		V_{30} >1 cm³	2 of 4 (50)		
Brachial plexopathy (grade ≥2)					
Brachial plexus	D_{max} <40 Gy	D_{max} ≤35 Gy	0 of 73	.001	D_{max} ≤35 Gy
		D_{max} >35 Gy	3 of 9 (33)		
	V_{35} ≤1 cm³	V_{30} ≤0.2 cm³	0 of 75	.000	V_{30} ≤0.2 cm³
	V_{30} ≤10 cm³	V_{30} >0.2 cm³	3 of 7 (43)		
Arrhythmia (grade ≥1)					
Heart	V_{40} ≤1 cm³	D_{max} ≤45 Gy	1 of 75 (1)	.018	D_{max} ≤45 Gy (preferred)
	V_{35} ≤10 cm³	D_{max} <45 Gy	2 of 7 (29)		
		V_{40} ≤ 1 cm³	1 of 77 (1)	.009	V_{40} ≤1 cm³
		V_{40} >1 cm³	2 of 5 (40)		V_{20} ≤5 cm³ (24)
Spinal cord	No patient experienced spinal cord toxicity in current study				
Spinal cord	V_{20} ≤1 cm³		11 D_{max} >20 Gy 2 D_{max} >25 Gy 3 V_{20} >1 cm³		D_{max} <25 Gy
	V15 ≤10 cm³				V_{20} ≤1 cm³
Skin toxicity (grade 1 or 2)					
Skin	V_{40} ≤1 cm³ (within 5 mm from skin)		4 grade 2 skin		V_{30} <50 cm³ for skin toxicity (preferred) (21)
	V_{35} ≤10 cm³ (within 5 mm from skin)				
Chest wall pain	NA		18 grade 1 chest-wall pain		V_{30} <30 cm³ for chest-wall pain (preferred) (21)
			13 grade 2 chest-wall pain		

Abbreviations: D_{max} = maximum dose; iV_{20} = ipsilateral volume exposed to 20 Gy or more; MLD = mean lung dose; NA = not apply; V_5 = volume exposed to 5 Gy or more.

* Also significant in multivariate analyses.

† See ref. (8).

No grade 4 or 5 toxicities were reported

Patients in whom these dose-volume constraints could not be met were treated with 70 Gy in 10 fractions (BED α/β10 = 119 Gy, BED α/β3 = 233 Gy), which led to similar local control with tolerable toxicity

One patient with a tumour invading the hilum treated with 70 Gy in 10 fractions (hilar Dmax = 83 Gy) developed fatal haemoptysis, which led to the recommendation that **tumours that invade central structures should not be treated with high-BED schedules**

Conclusions: SABR for centrally located lesions produces clinical outcomes similar to those for peripheral lesions when normal tissue constraints are respected.

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors

Aadel A. Chaudhuri[a], Chad Tang[a], Michael S. Binkley[a], Michelle Jin[a], Jacob F. Wynne[a], Rie von Eyben[a], Wendy Y. Hara[a,b], Nicholas Trakul[a], Billy W. Loo Jr.[a,b,**], Maximilian Diehn[a,b,c,*]

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The Stanford group 2015

68 patients
Central =34
Ultra-central= 7

The Stanford group reported data of **68 patients with peripheral (n=34), central (n=34)** and sub-classifiedcertain central tumors as “ultra-central” if their GTV directly abut-ted the proximal bronchial tree or trachea. **(n=7)**

Dose 50 Gy in 4–5 fractions

Ultra-central”, defined to mean tumors within the zone of the trachea or proximal bronchial tree whose GTVs directly abutted one of the major airways

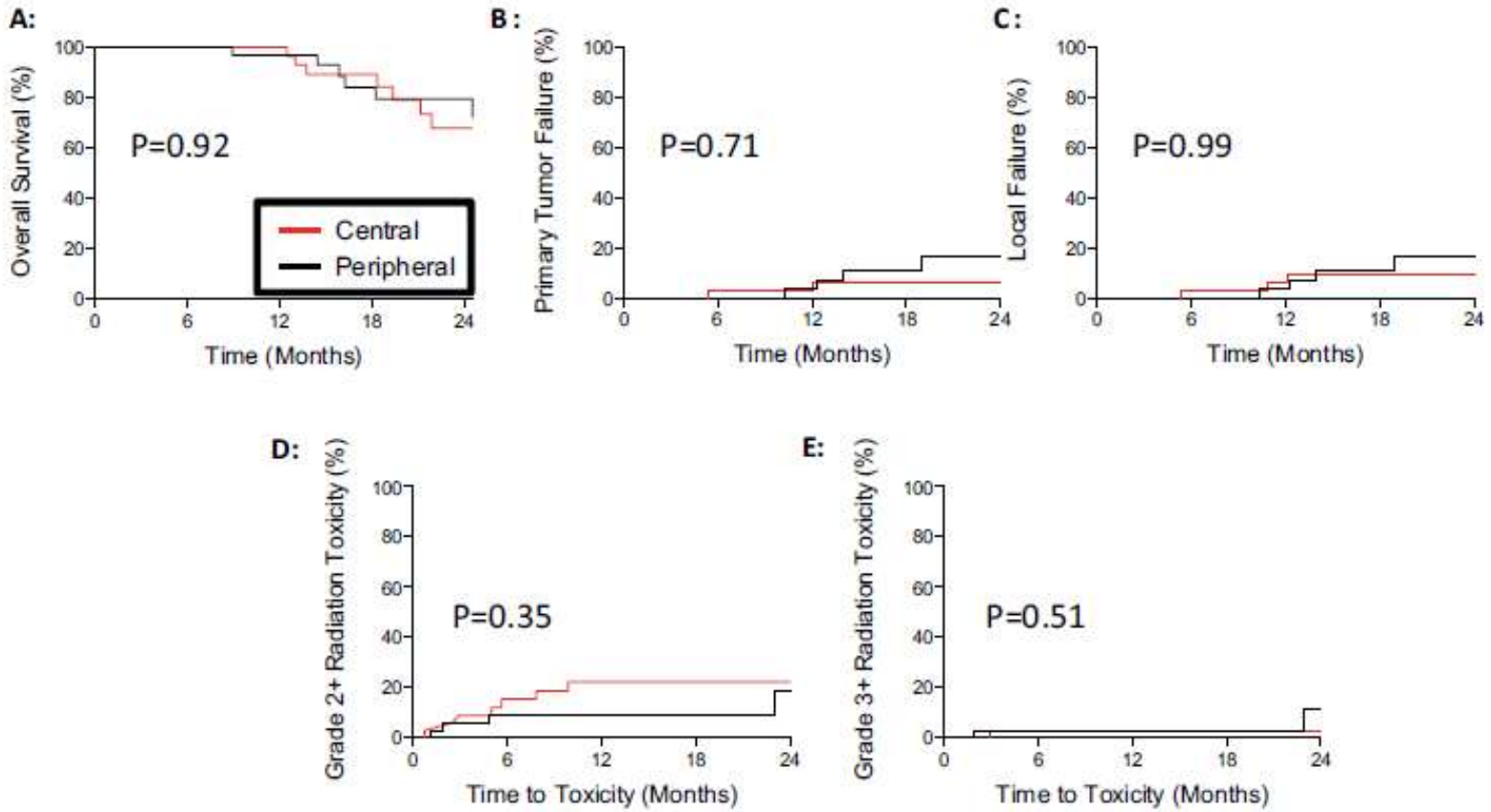


Fig. 1. Lung SABR outcomes and toxicities. Kaplan–Meier curves for (A) overall survival, and competing-risks curves for (B) primary tumor failure, (C) local failure, (D) grade ≥2 toxicity, and (E) grade ≥3 toxicity in central tumor patients compared to peripheral tumor patients. Red lines represent central and black lines represent peripheral.

With a median follow-up time of **18.4 months**, 2-year overall survival and local failure was similar in all the groups. Reported toxicity rates were low and comparable between the three groups, with only two cases of grade 3 toxicity (chest wall pain), and one case of grade 4 toxicity (pneumonitis) observed. **There were no symptomatic toxicities reported in treated patients with ultra-central tumours**

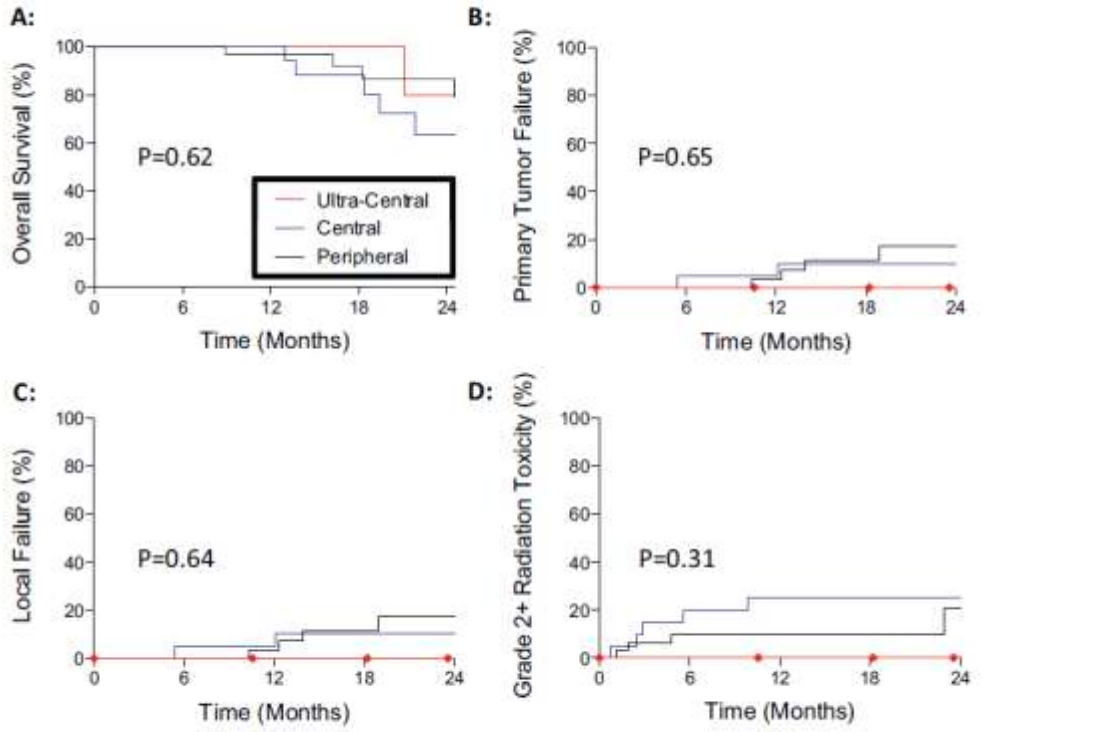


Fig. 4. Ultra-central lung SABR outcomes. Kaplan–Meier curves for (A) overall survival in NSCLC patients. Competing-risks curves for (B) primary tumor failure, (C) local failure, and (D) grade ≥2 toxicity in NSCLC patients. Red lines represent ultra-central, blue lines represent central (not including ultra-central), and black lines represent peripheral.

2-year OS was 80.0% for ultra-central NSCLC patients, com-pared to 63.2% for the remaining central NSCLC patients, and 86.6%for peripheral NSCLC patients (p = 0.62) . Two-year primary tumor control and local control in the ultra-central NSCLC patients were 100%, also with no significant difference compared to the remaining central or peripheral NSCLC patients

Conclusion: Patients with central and ultra-central lung tumors treated with SABR (50 Gy in 4–5 fractions)experienced few toxicities and good outcomes, similar to patients with peripheral lung tumors.

Clinical Investigation

Local Control and Toxicity in a Large Cohort of Central Lung Tumors Treated With Stereotactic Body Radiation Therapy

Ankit Modh, MD,* Andreas Rimner, MD,* Eric Williams, PhD,† Amanda Foster, MS,* Mihir Shah, BS,* Weiji Shi, MS,† Zhigang Zhang, PhD,† Daphna Y. Gelblum, MD,* Kenneth E. Rosenzweig, MD,† Ellen D. Yorke, PhD,† Andrew Jackson, PhD,† and Abraham J. Wu, MD*

*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York;

The Memorial Sloan Kettering group 2014.

108 patients treated with SABR (mostly **45 Gy in five fractions** (**α/β10 = 85.5 Gy**, BED α/β3 = 180 Gy);

local control rate at 2 years was 79% .

However, severe oesophageal toxicity, including fistula in a patient with an oesophageal Dmax of 46 Gy, was reported.

Six of 12 patients for whom the median oesophageal Dmax was 30 Gy developed grade ≥ 2 oesophagitis when the PTV overlapped the oesophagus. Two patients developed fatal haemoptysis, one with tumour involving the hilum and a maximum dose to the right bronchial tree of 47 Gy in five fractions, and the other with tumour encasing the left superior segmental bronchus with a maximum bronchial tree dose of 48 Gy in five fractions

Conclusions: Using moderate doses, SBRT for central lung tumors achieves acceptable local control with low rates of severe toxicity. Dosimetric analysis showed no significant correlation between dose to the lungs, heart, or NFZ(no-fly zone) and severe pulmonary toxicity**. Esophageal toxicity may be an underappreciated risk, particularly when PTV overlaps the esophagus**

Brussels, Belgium 2010

CLINICAL INVESTIGATION Lung

PROSPECTIVE, RISK-ADAPTED STRATEGY OF STEREOTACTIC BODY RADIOTHERAPY FOR EARLY-STAGE NON–SMALL-CELL LUNG CANCER: RESULTS OF A PHASE II TRIAL

Samuel Bral, M.D.,* Thierry Gevaert, M.Sc.,* Nadine Linthout, Ph.D.,* Harijati Versmessen, M.D.,* Christine Collen, M.D.,* Benedikt Engels, M.D.,* Douwe Verdries, M.D.,† Hendrik Everaert, Ph.D.,† Nicolas Christian, M.D.,* Mark De Ridder, Ph.D.,* and Guy Storme, Ph.D.*

Departments of *Radiotherapy, †Nuclear Medicine, and ‡Radiology of the University Hospital Brussels, Brussels, Belgium

Cleveland Clinic 2014

Clinical Investigation

Esophageal Dose Tolerance to Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors for Late Toxicity

Kevin L. Stephans, MD,* Toufik Djemil, PhD,* Claudiu Diaconu, MD,† Chandana A. Reddy, MS,* Ping Xia, PhD,* Neil M. Woody, MD,* John Greskovich, MD,* Vinit Makkar, MD,† and Gregory M.M. Videtic, MD, CM, FRCPC*

*Department of Radiation Oncology, Cleveland Clinic, Taussig Cancer Center, Cleveland, Ohio; †Cleveland Clinic Learner College of Medicine, Cleveland, Ohio; and ‡Department of Medical Oncology,

Japan 2014

ORIGINAL ARTICLE

Toxicities of Organs at Risk in the Mediastinal and Hilar Regions Following Stereotactic Body Radiotherapy for Centrally Located Lung Tumors

Shuichi Nishimura, MD, Atsuya Takeda, MD, PhD,* Naoko Sanuki, MD,* Satoshi Ishikura, MD, PhD,† Yohei Oku, PhD,* Yousuke Aoki, BMSc,* Etsuo Kunieda, MD, PhD,‡ and Naoyuki Shigematsu, MD, PhD§*

Others have reported with similar doses (40–60 Gy in five fractions) fatal haemoptysis when a Dmax of greater than 50 Gy was delivered to the pulmonary artery and bronchus

The Cleveland Clinic group also reported a case of oesophageal fistula when the oesophageal point dose exceeded 51 Gy and the V48 was >1 cm3.

Bral et al reported grade 5 toxicity in 1 out of 17 patients with central tumours after treatment with 60 Gy in 4 fractions

OA24.05

The Nordic HILUS-Trial - First Report of a Phase II Trial of SBRT of Centrally Located Lung Tumors

Karin Lindberg,[1] Per Bergström,[2] Odd Terje Brustugun,[3] Silke Engelholm,[4] Vitali Grozman,[5] Morten Hoyer,[6] Kristin Karlsson,[5] Azza Khalil,[6] Charlotte Kristiansen,[7] Ingmar Lax,[5] Britta Löden,[8] Jan Nyman,[9] Gitte Persson,[10] Lotte Rogg,[11] Peter Wersäll,[5] Rolf Lewensohn[1]

[1]*Oncology and Pathology, Karolinska Institutet, Stockholm/Sweden,* [2]*Norrlands University Hospital,*

42 patients with tumours close to a main stem bronchus (group A), and 31 patients with tumours close to a lobar bronchus (group B

Patients were treated with 60 Gy in 8 fractions prescribed to the 65-70% isodose line

Dose limits were mandatory for the spinal cord, trachea and contralateral main bronchus (Dmax, EQD = 89 Gy). However, dose guidelines to the ipsilateral main stem bronchus were recommended but not mandated (Dmax, EQD = 112 Gy).

Severe toxicity of grade 3 or higher was reported in 28% of patients, and grade 4 and 5 toxicity occurred in 19% of patients in group A and 3% in group B

Six out of the 7 grade 5 events were due to fatal lung haemorrhage.

PTV overlap with main stem bronchus or trachea was found to be significantly correlated with both grade 3 or higher clinical toxicity and high grade radiographic toxicity. A PTV overlap was present in 33% of all patients, and in 70% of patients who developed grade 3 or higher pulmonary bleeding.

Conclusion: SBRT of centrally located tumors may be afflicted with high risk of serious toxicity and further evaluation of clinical and dose-volume dependent risk factors are highly warranted.

LBA 10

Primary Study Endpoint Analysis for NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Non-Small Cell Lung Cancer (NSCLC)

A. Bezjak,[1] R. Paulus,[2] L.E. Gaspar,[3] R.D. Timmerman,[4] W.L. Straube,[5]

120 pts were accrued February 2009 to September 2013 from 43 participating centers

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

The dose was escalated from 50 Gy to 60 Gy, in five fractions delivered every other day (except over weekends), with at least 40 hours between treatments

Grade 3 or higher toxicity was 16% in the 5x11.5 Gy group and 21% in the 5x12 Gy group. Moreover, **grade 5 pulmonary bleeding occurred in 4%,** with three out of four patients being treated in the highest dose groups of 11.5 and 12 Gy per fraction

Phase I data analysis revealed that maximum tolerated dose was the highest dose level allowed on the study, 12 Gy/fr x 5 fractions.

Efficacy and Toxicity Analysis of NRG Oncology/RTOG 0813 Trial of Stereotactic Body Radiation Therapy (SBRT) for Centrally Located Non-Small Cell Lung Cancer (NSCLC)

A. Bezjak,[1] R. Paulus,[2] L.E. Gaspar,[3] R.D. Timmerman,[4] W.L. Straube,[5] W.F. Ryan,[6] Y. Garces,[7] A.T. Pu,[8] A.K. Singh,[9] G.M. Videtic,[10] R.C. McGarry,[11] P. Iyengar,[4] J.R. Pantarotto,[12] J.J. Urbanic,[13] A. Sun,[14] M.E. Daly,[15] I.S. Grills,[16] D.P. Normolle,[17] J.D. Bradley,[5] and H. Choy[18];

[1]Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2]NRG Oncology, Philadelphia, PA, [3]Department of

71 patients

33 eligible pts were treated with 12 Gy/fx, and another **38** pts were treated on the preceding dose level of 11.5 Gy/fr; this is the report of efficacy based on patients in those two cohorts.

5 fraction SBRT schedule ranging from 10-12 Gy/fraction (fr) delivered over 1.5-2 weeks.

Median follow-up was 33 months (mo) for the 11.5 Gy/fr cohort and 29.8 mo for the 12 Gy/fr cohort (49 and 31.8 mo for the surviving pts, respectively)

Late toxicities grade 3 or greater (G3+) attributed to SBRT were 2 G5 toxicities in the 11.5 Gy/fr cohort, and in the 12 Gy/fr cohort 3 G3 (2 respiratory, 1 cardiac), 1 G4 (esophageal perforation), and 1 G5 (pulmonary hemorrhage) toxicities

Abstract 16; Table 1

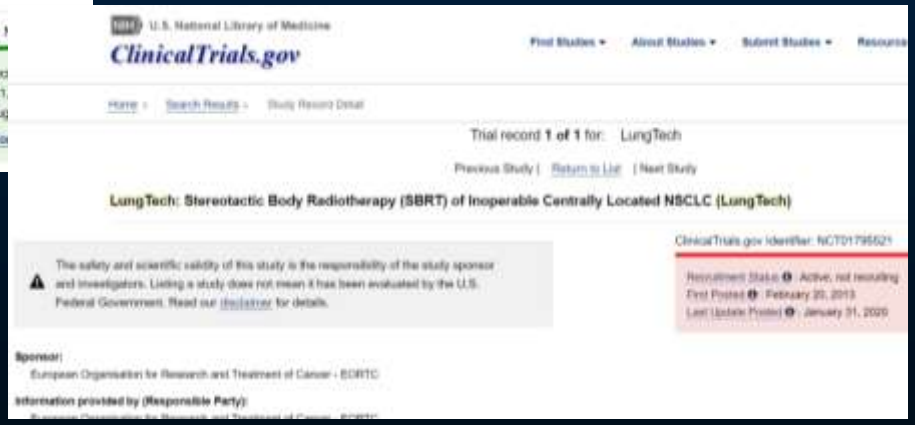
Dose level	11.5 Gy x 5fr	12 Gy x 5fr
Number (n) of eligible patients	38	33
Pts w Toxicity G3+ (at any time)	6	7
Pts w Early Toxicity G3+ (within 1st yr)	5	4
Pts with Late Toxicity G3+ (beyond 1st yr)	2	5
Pts with primary tumor failure	4	6
Pts with involved lobe failure	2	2
Pts with regional (lymph node) failure	2	4
Pts with distant failure	6	5
2-year local control	89.4% (81.6-97.4%)*	87.7% (78.3-97%)*
2-yr progression free survival	52.2% (35.3-66.6%)*	54.5% (36.3-69.6%)*
2-year overall survival (OS)	70.2% (52.6-82.3%)*	72.7% (54.1-84.8%)*

*90% confidence interval.

Conclusion: Observed local control at 2 yrs in 71 pts treated with the two highest doses levels (11.5-12 Gy/fr x 5 fr) in this multicenter trial was high, and G3+ toxicity rates were acceptable. Two-year OS rates of 70% in this medically inoperable group of elderly pts with comorbidities were comparable to pts with peripheral early stage tumors.

The **EORTC LungTech trial NTC01795521** has recently closed to recruitment and will be reporting shortly

Relevant trails that are recruiting include **SUNSET (*NCT03306680)***
and a phase II randomized clinical trial comparing proton versus photon-based SABR for centrally located or recurrent lung parenchymal early stage NSCLC is currently ongoing (NCT01511081)



Primary Outcome Measures :Maximally tolerated dose (MTD) Time Frame: Occurring within 2 years of treatment]MTD of radiotherapy for ultracentral tumors. The MTD is the dose of radiotherapy associated with a <30% rate of grade 3-5 toxicity occurring within 2 years of treatment.

LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective

[1,2]S ADEBAHR, [3]S COLLETTE, [3]E SHASH, [4]M LAMBRECHT, [5]C LE PECHOUX, [6]C FAIVRE-FINN, [7]D DE RUYSSCHER, [8]H PEULEN, [8]J BELDERBOS, [9]R DZIADZIUSZKO, [10]C FINK, [11]M GUCKENBERGER, [4]C HURKMANS and [1,2]U NESTLE

[1]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany
[2]German Cancer Consortium (DKTK), Heidelberg, Partner Site Freiburg, Germany
[3]EORTC Headquarters, Brussels, Belgium

Table 3. EORTC 221133 LungTech trial: dose constraints for organs at risk (OARs)

OAR	α/β (Gy)	D_{max} (Gy)	EqD2 (Gy)	Acceptable variation (Gy)	Acceptable variation EqD2 (Gy)	Unacceptable variation (Gy)	Unacceptable variation EqD2 (Gy)
Trachea/main bronchus	3	$8 \times 5.5 = 44$	74.8	$<8 \times 5.81 = 46.68$	<81.9	$\geq 8 \times 5.81 = 46.68$	>81.9
Heart[a]	3						
Great vessels[a]	3						
Oesophagus	3	$8 \times 5 = 40$	64	$<8 \times 5.44 = 43.52$	<73.6	$\geq 8 \times 5.44 = 43.52$	≥73.6
Spinal cord[b]	2	$8 \times 4 = 32$	48			$>8 \times 4 = 32$	>48
Brachial plexus[b]	3	$8 \times 4.75 = 38$	58.9	$<8 \times 5.17 = 41.36$	<67.7	$\geq 8 \times 5.17 = 41.36$	≥67.7
Body-PTV[b]	3	$8 \times 7.5 = 60$	126	$<8 \times 7.785 = 62.28$	<134.2	$\geq 8 \times 7.785 = 62.28$	≥134.2
Lung-CTV[a]	3						
Chest wall[a]	3						

CTV, clinical target volume; DVH, dose–volume histogram; EORTC, European Organization for Research and Treatment of Cancer; EqD2, equivalent dose in 2 Gy fractions; PTV, planning target volume.
Source: EORTC 22113-0813-LungTech radiation therapy quality assurance guidelines.
[a]No restrictions are provided but recording of DVH data for toxicity evaluation is required.
[b]For $<0.5\,cm^3$.

Practical Radiation Oncology (2017)

practical radiation oncology
pro

Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline

Key Question 2: When is stereotactic body radiation therapy appropriate for medically inoperable patients with T1-2, N0 non-small cell lung cancer:

- **With centrally located tumors**
- With tumors >5 cm in diameter
- Lacking tissue confirmation
- With synchronous primary or multifocal tumors
- Who underwent pneumonectomy and now have a new primary tumor in their remaining lung?

Practical Radiation Oncology (2017)

Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline

For patients with centrally located tumors?

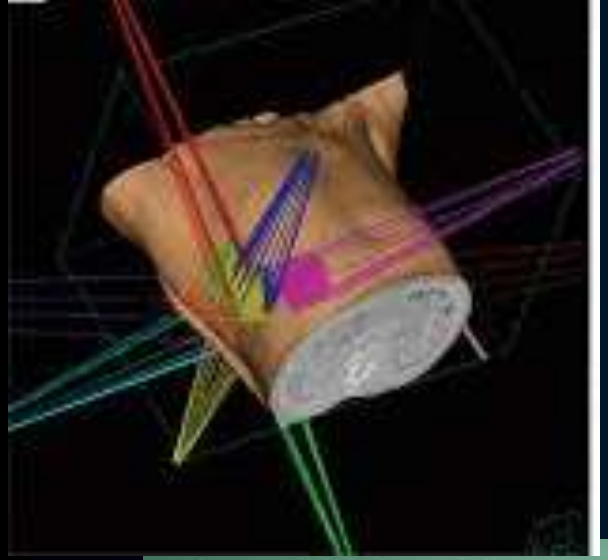
Statement KQ2A: SBRT directed towards centrally located lung tumors carries unique and significant risks when compared to treatment directed at peripherally located tumors. The use of 3 fraction regimens should be avoided in this setting.

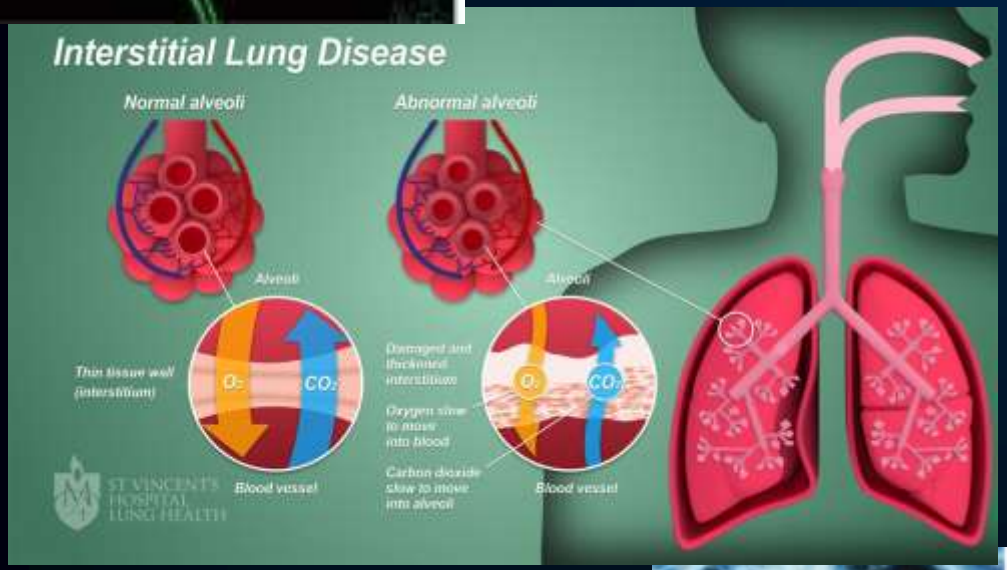
- **Recommendation strength**: Strong
- **Quality of evidence**: High
- **Consensus**: 94%

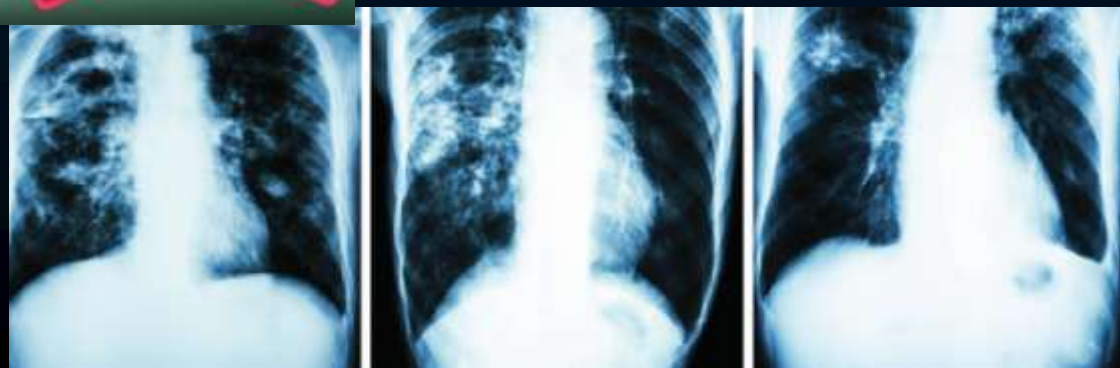
Statement KQ2B: SBRT directed at central lung tumors should be delivered in 4 or 5 fractions. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment. For central tumors for which SBRT is deemed too high-risk, hypofractionated radiation therapy utilizing 6-15 fractions can be considered.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Moderate
- **Consensus**: 94%

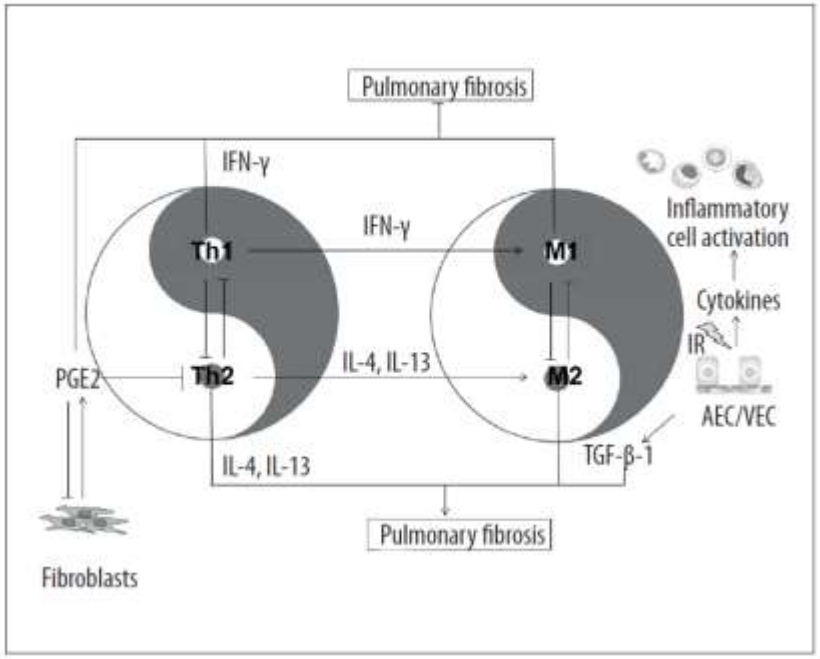
SABR with ILD

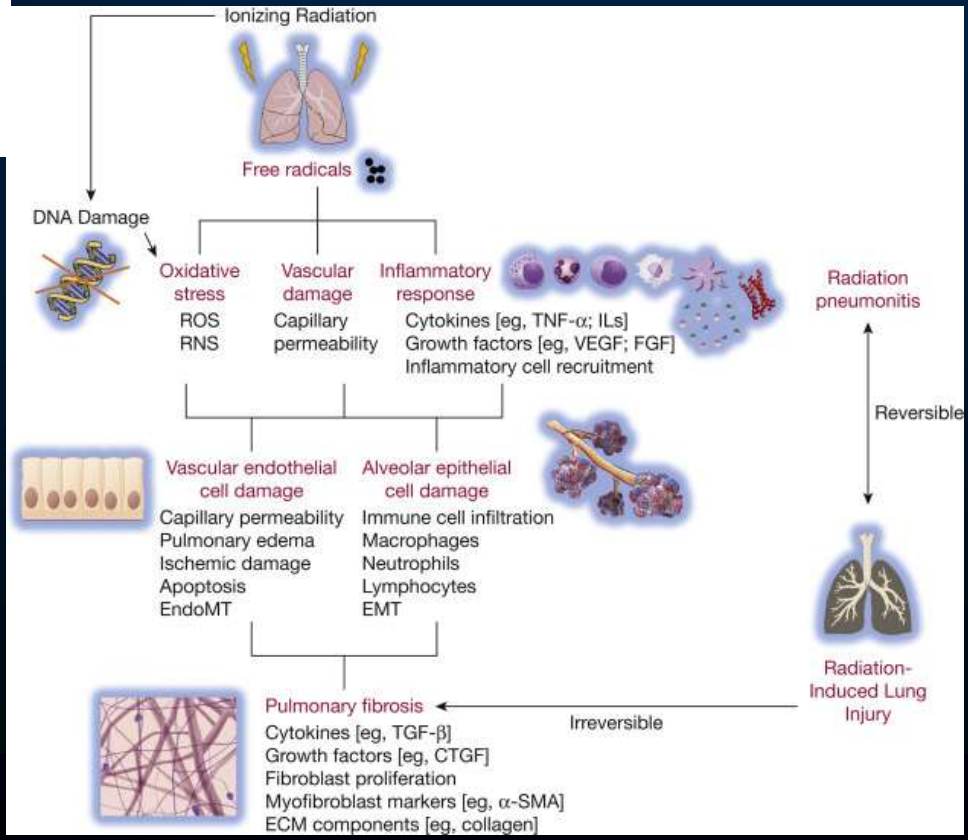






Mechanism of Lung injury by radiation





SABR with ILD

Treatment-Related Toxicity in Patients with Early-Stage Non-Small Cell Lung Cancer and Co-Existing Interstitial Lung Disease: A Systematic Review

Hanbo Chen, MD, Suresh Senan, MRCP, FRCR, PhD, Esther J. Nossent, MD, R. Gabriel Boldt, RLIS, Andrew Warner, MSc, David A. Palma, MD, PhD, FRCPC, Alexander V. Louie, MD, PhD, FRCPC

PII: S0360-3016(17)30670-3

DOI: 10.1016/j.ijrobp.2017.03.010

Although rates of clinically significant lung toxicity following SABR are low there is growing evidence that patients with underlying lung fibrosis at baseline are at increased risk

The weighted proportions for treatment-related mortality and ILD-specific toxicity were 15.5% and 25%, respectively

Table 1. Summary of study characteristics and results.

	Stereotactic Ablative Radiation Therapy (SABR)	Particle Beam Therapy	Radiofrequency Ablation (RFA)	Surgery
No. of studies (N)	N = 13	N = 4	N = 3	N = 30
% Studies retrospective	92% (N = 12/13)	50% (N = 2/4)	100%	93% (N = 28/30)
No. of patients (n)	n = 122	n = 23	n = 46	n = 1709
Stage distribution				
I only	54% (N = 7/13)	75% (N = 3/4)	67% (N = 2/3)	90% (N = 27/30)
I/II	46% (N = 6/13)	25% (N = 1/4)	33% (N = 1/3)	10% (N = 3/30)
Oligometastases included	15% (N = 2/13)	25% (N = 1/4)	33% (N = 1/3)	0%
Medically operable patients included	(N = 7 reporting) 29% (N = 2/7)	25% (N = 1/4)	0%	100%
ILD diagnoses	IPF only: 31% (N = 4/13) Others: 69% (N = 9/13)	IPF only: 50% (N = 2/4) Others: 50% (N = 2/4)	IPF only: 33% (N = 1/3) Others: 67% (N = 2/3)	IPF only: 40% (N = 12/30) Others: 60% (N = 18/30)
Treatment-related mortality (median [Q1-Q3])*	(N = 9 reporting) 16.7% (6.2%-20%)	(N = 2 reporting) 3.1% (-)	(N = 2 reporting) 20.2% (-)	(N = 15 reporting) 0% (0%-3.7%)
Weighted proportion	**15.6%** (n = 19/122)	**4.3%** (n = 1/23)	**8.7%** (n = 4/46)	**2.2%** (n = 34/1507)
Treatment-related ILD-specific toxicity (median [Q1-Q3])*	(N = 7 reporting) 18.8% (13.4%-46.4%)	(N = 2 reporting) 16.2% (-)	(N = 1 reporting) 33.3% (-)	(N = 15 reporting) 7% (2.2%-17%)
Weighted proportion	**25%** (n = 28/112)	**18.2%** (n = 4/22)	**25%** (n =1/4)	**12%** (n = 38/316)

SABR: stereotactic ablative radiotherapy; RFA: radiofrequency ablation; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis

* Studies with a sample size of one were excluded. Q1-Q3 range was not reported for particle beam therapy or RFA due to low number of studies.

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Table 2. Radiation dose and dosimetric parameters.

	Modality	BED_{10} (Gy_{10})[a]	PTV (mL)[a]	V20 (%)[a]	MLD (Gy)[a]	Comments
Hara 2015	SABR	72-132	85.4 (18.1-116)	3.5 (1.2-7.8)	3.32 (1.64-5.11)	
Yoshitake 2015	SABR	106[b]		6.0 ± 1.9[b] (mean ± SD)	4.0 ± 1.0[b] (mean ± SD)	• V5 > 18%, V10 > 12% and MLD > 4 Gy were predictors of grade ≥ 2 RP in the ILD patient group on univariate analysis.
Jung 2015	SABR	106-180	37.9 (6.4–137.8) (mean [range])			
Ueki 2015	SABR	105-134[b]	39.9 (12.6–74.3)[b]			• V5 was shown to be predictive of grade ≥ 2 RP and V20 for grade ≥ 3 RP on multivariate analysis for all patients in the cohort including non-ILD patients. Values for dosimetric parameters not directly reported
Shintani 2014	SABR	96-106				
Bahig 2014	SABR	72-180	82 (21-95)[b]	15 (6-21)[b]	8 (5-11)[b]	• Dosimetric values reported for patients who suffered grade 5 RP only
Thibault 2014	SABR	106[b]			4.27/6.18[b]	• MLD represents values from two treatments in contralateral lungs
Aibe 2014	SABR	100[b]	27.5 (10.1-120.8)[b]	5.0 (2.0-13.9)[b]	4.1 (1.9-8.7)[b]	• PTV and V5 appeared higher in patients with grade 5 RP but this was not statistically significant.
Yamaguchi 2013	SABR	60-120		9.5 (3.0-11.6)[b]	5.3 (2.2-6.8)[b]	• Dosimetric parameters reported for patients with grade ≥ 3 RP only. • V5/V20/MLD was significantly higher in patients with grade ≥ 2 RP compared to patients with grade 0-1 RP when all patients were taken into account including non-ILD patients.
Takeda 2012	SABR	72-100	35.4 (12.8-65.8)			
Yamashita 2010	SABR	106[b]	29.4 (20.9-120.9)[b]	6.7 (3.7-11.2)[b]	4.92 (2.88-9.38)[b]	• Dosimetric parameters reported for patients with ILD and Grade 4 or 5 RP. • PTV/V20/MLD were not predictors for Grade ≥ 4 RP on statistical analysis that included all patients including non-IP patients.
Takeda 2008	SABR	100[b]		6[b]	6.11[b]	
Timmerman 2003	SABR	43-180				
Ono 2016	PBT	106-110 (RBE)		7.7 (2.9-17.9)[b]	4.45 (0.9-10.6)[b]	• Dosimetric parameters (MLD, V5/10/15/20/25/30) were not significantly different between patients with Grade ≥ 3 RP and Grade ≤ 2 RP
Westover 2013	PBT	>100 (RBE)		9.5 (2-27)	5.12 (1.37-12.56)	
Nakayama 2009	PBT	97-110 (RBE)				
Miyamoto 2002	CIBT	79-149 (RBE)	81.2 (4.8–467.4)			

ACCEPTED MANUSCRIPT

For particle beam therapy, 23 patients across 4 studies were identified, including 3 proton beam therapy and 1 carbon-ion beam therapy studies. One proton beam therapy study included a minority of medically-operable patients. Overall, particle beam therapy-related mortality and ILD-specific toxicity were 4.3% and 18.2%, respectively

In conclusion, consistently high levels of treatment-related toxicity and ILD-specific toxicity was observed in pooled data for ES-NSCLC patients with co-existing ILD undergoing definitive treatment with SABR, particle beam therapy or RFA. A cautious approach for active treatment of ES-NSCLC in patients with co-existing ILD is still indicated, though patients should be actively counselled on the pros and cons of proceeding with curative treatment versus best supportive care in this clinical dilemma. Future studies on ES-NSCLC should aim to establish

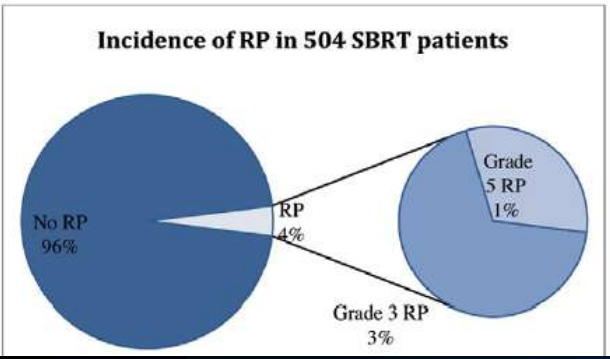
Original Article

Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease

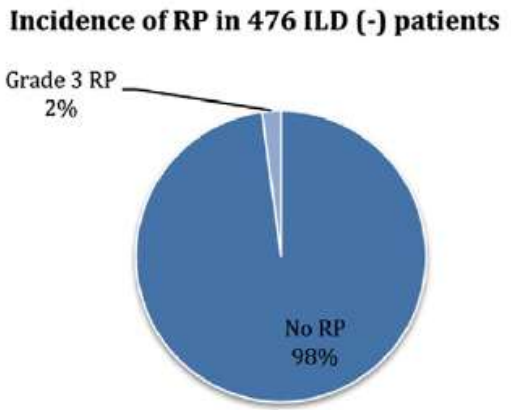
Houda Bahig MD [a], Edith Filion MD [a], Toni Vu MD [a], Jean Chalaoui MD [b], Louise Lambert MD [a], David Roberge MD [a], Michel Gagnon MD [c], Bernard Fortin MD, MSc [d], Dominic Béliveau-Nadeau MSc [a], Dominique Mathieu MSc [a], Marie-Pierre Campeau MD [a,*]

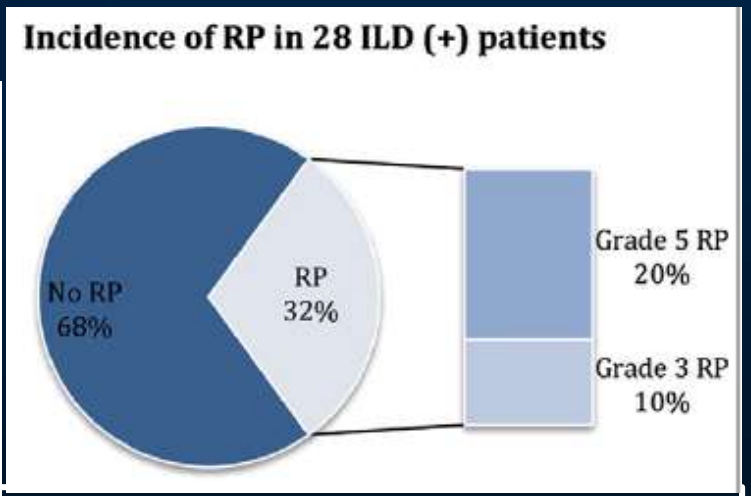
[a]Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

Canada 2016



Practical Radiation Oncology (2016)





Bahig et al reported that pre-existing radiological interstitial lung disease (ILD) was identified in 6% of 504 patients treated with SABR for Stage 1 lung cancer . A 4% rate of ≥ grade 3 radiation pneumonitis was observed in the entire cohort.
ILD was associated with increased risk of ≥ grade 3 radiation pneumonitis (**32% in patients with ILD vs 2% in those with no ILD, P <0 .001**).

Five patients (21%) with ILD developed grade 5 radiation pneumonitis.

Table 3 Predictive factors of grade ≥3 radiation pneumonitis.

	RP		No RP		Univariate	Multivariate
	Mean	95% CI	Mean	95% CI	*P*	*P*
Age	74	69-78	78	72-83	NS	
Charlson	5	4-5	5	4-5	NS	
BED (Gy10)	136	112-164	148	131-164	NS	
PTV (mL)	41	22-60	29	20-38	NS	
V5 (%)	28%	21-42	18	14-22	.05	
V20 (%)	10	6-15	6	4-8	NS	
MLD (Gy)	7	5-9	4	3-5	.03	NS
FEV1 (%)	76	66-85	93%	85-100	.017	.04
FVC (%)	85	76-95	101	95-108	.016	
FEV1/FVC	0.9	0.8-1.0	0.9	0.8-1.0	NS	
DLCO (%)	39	28-47	56	48-65	.02	NS
ILD grade	RP ≥3					
Mild	27%					
Moderate	11%					
Severe	100%				.001	
Active smoker						
Yes	38%					
No	30%				NS	
Emphysema						
Yes	47%					
No	0%				0.038	
Oxygen dependence						
Yes	100%					
No	21%				0.045	
SABR technique						
Tracking	33%					
ITV	31%				NS	

BED, biologically effective dose; CI, confidence interval; DLCO, diffusing lung capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; ITV, internal target volume; M, mean; MLD, mean lung dose; NS, nonsignificant; PTV, planning target volume; RP, radiation pneumonitis; SABR, stereotactic ablative radiation therapy.

Lung Cancer 82 (2013) 260–265

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Stereotactic body radiotherapy for lung tumors in patients with subclinical interstitial lung disease: The potential risk of extensive radiation pneumonitis

Shinsaku Yamaguchi[a], Takayuki Ohguri[a,*], Satoru Ide[a], Takatoshi Aoki[a], Hajime Imada[b], Katsuya Yahara[a], Hiroyuki Narisada[b], Yukunori Korogi[a]

[a] Department of Radiology, University of Occupational and Environmental Health, Kitakyushu, Japan
[b] Department of Cancer Therapy Center, Tobata Kyoritsu Hospital, Kitakyushu, Japan

Japan 2013

124 Patients

48 Gy in four fractions

Subclinical ILD was recognized in 16 (16%) of 100 patients

No significant differences were seen in either overall survival or local control rates between the patients with ILD and those without ILD

Conclusions: Subclinical ILD was not found to be a significant factor for Grade 2–5 RP or clinical outcomes in the current study; however, uncommon extensive RP can occur in patients with subclinical ILD

Impact of Pretreatment Interstitial Lung Disease on Radiation Pneumonitis and Survival after Stereotactic Body Radiation Therapy for Lung Cancer

Nami Ueki, MD, Yukinori Matsuo, MD, PhD,* Yosuke Togashi, MD,†‡ Takeshi Kubo, MD,§ Keiko Shibuya, MD, PhD,‖ Yusuke Iizuka, MD,* Takashi Mizowaki, MD, PhD,* Kaori Togashi, MD, PhD,§ Michiaki Mishima, MD, PhD,‡ and Masahiro Hiraoka, MD, PhD**

Japan J Thorac Oncol. 2015

Pre-existing ILD was retrospectively identified in **20 of 157** patients treated with SABR in a Japanese series reported by Ueki et al.

The incidence of ≥ grade 2 or ≥ 3 pneumonitis was significantly higher in those with ILD than those without (**55% vs 13.3% and 10% vs 1.5% respectively**)

.

On multivariate analysis the presence of ILD and volume of irradiated lung was as risk factor for ≥ grade 2 or ≥ 3 pneumonitis. Despite no difference being observed in the disease progression or local progression rates, **the overall survival rate tended to be worse in patients with ILD than without (3-year OS, 53.8% versus 70.8%; p = 0.28).**

TABLE 2. Numbers and Rates of Worst Radiation Pneumonitis Grade

RP Grade	All	ILD(+)	ILD(−)
No. of Patients (%)	***n* = 157**	***n* = 20**	***n* = 137**
None	19 (12.1%)	1 (5.0%)	18 (13.1%)
Grade 1	109 (69.4%)	8 (40.0%)	101 (73.7%)
Grade 2	25 (15.9%)	9 (45.0%)	16 (11.7%)
Grade 3	1 (0.6%)	1 (5.0%)	0 (0%)
Grade 4	2 (1.3%)	1 (5.0%)	1 (0.7%)
Grade 5	1 (0.6%)	0 (0%)	1 (0.7%)

ILD, interstitial lung disease; RP, radiation pneumonitis.

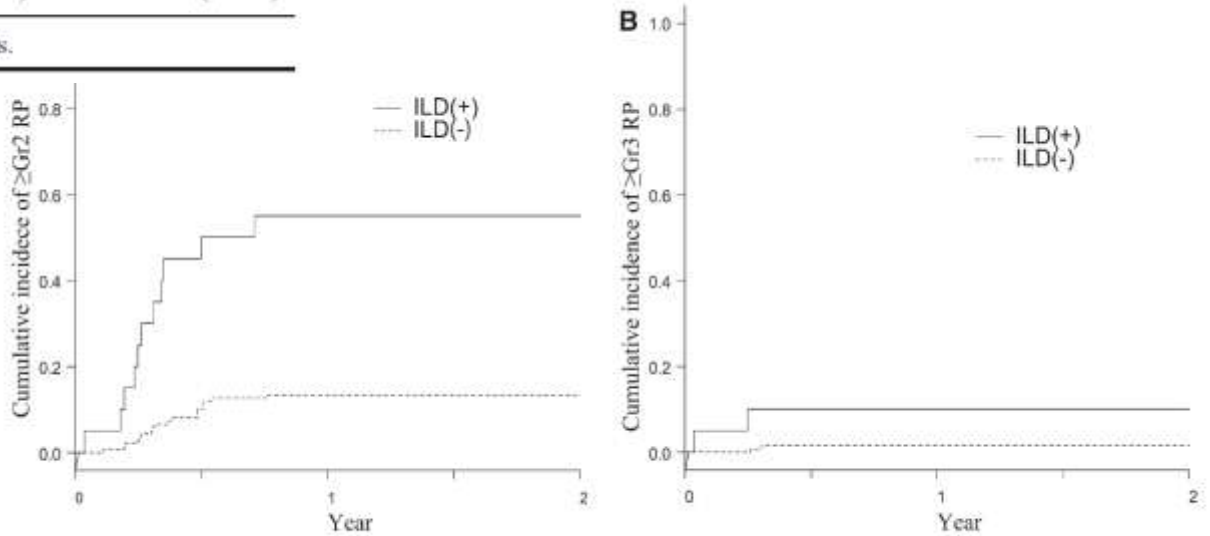


FIGURE 1. Cumulative incidence of radiation pneumonitis worse than grade 2 (≥Gr2 RP) (*A*), and worse than grade 3 (≥ Gr3 RP), (*B*), are shown in those with ILD (ILD[+]) and those without ILD (ILD[−]).ILD, interstitial lung disease.

CONCLUSIONS

Pre-existing ILD was a significant risk factor for symptomatic and severe RP. In addition, ILD tended to be a poor prognostic factor for survival. Prescreening for ILD findings is important for determining the radiation pneumonitis risk and selecting candidates for SBRT

FULL PAPER

Predicting risk factors for radiation pneumonitis after stereotactic body radiation therapy for primary or metastatic lung tumours

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Department of Radiology, Tokyo Medical University Hospital, Tokyo, Japan

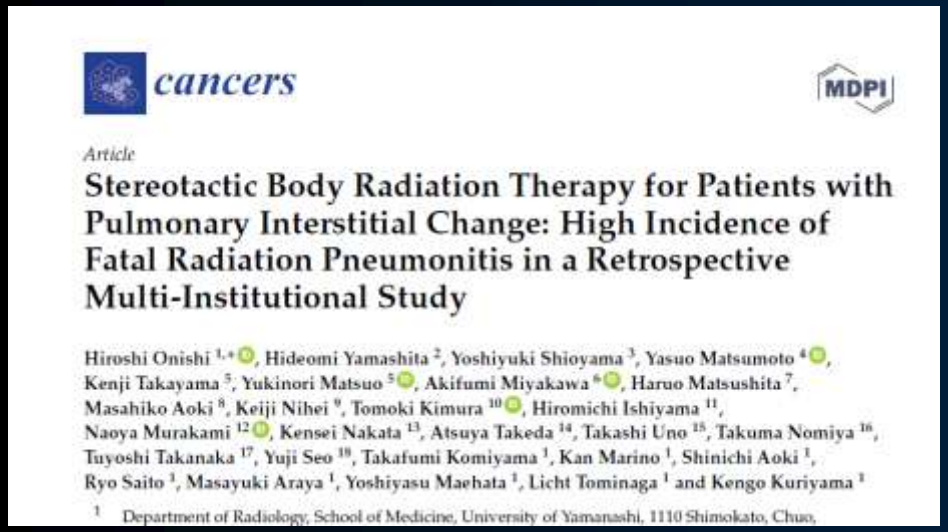
Japan
Br J Radiol 2017

Table 2. Clinical factors associated with radiation-induced pneumonitis (RP)

	RP		Univariate
	Grade 2–5, $n = 6$	p-value	Hazard ratio (95% confidence interval)
Age (<80 years *vs* ≥80 years)	4/35 *vs* 2/36	0.429	0.456 (0.078–2.665)
Sex (male *vs* female)	5/46 *vs* 1/25	0.414	0.342 (0.038–3.1)
PS (0 *vs* ≥1)	5/58 *vs* 1/13	>0.999	0.883 (0.094–8.269)
Operability (yes *vs* no)	1/25 *vs* 5/46	0.414	2.927 (0.323–26.556)
Number of SBRT (once *vs* twice)	6/66 *vs* 0/5	>0.999	Acalculia
Respiratory gating (yes *vs* no)	4/34 *vs* 2/37	0.417	2.333 (0.399–13.645)
Pulmonary emphysema (yes *vs* no)	3/28 *vs* 3/43	0.674	1.600 (0.299–8.555)
Tumour location (upper/middle *vs* lower)	4/49 *vs* 2/22	>0.999	1.125 (0.190-6.653)
Subclinical ILD (yes *vs* no)	5/11 vs 1/60	<0.001	49.167 (4.903–463.078)

ILD, interstitial lung disease; PS, performance status; SBRT, stereotactic body radiotherapy.

In a further series of **71 primary** or metastatic lung tumours, **subclinical ILD was the only factor significantly associated with the occurrence of radiation pneumonitis ≥ grade 2 ($p < 0.001$). 2 patients with grade 5 radiation pneumonitis had ILD with honeycombing visible on imaging**



cancers

MDPI

Article

Stereotactic Body Radiation Therapy for Patients with Pulmonary Interstitial Change: High Incidence of Fatal Radiation Pneumonitis in a Retrospective Multi-Institutional Study

Hiroshi Onishi [1,*], Hideomi Yamashita [2], Yoshiyuki Shioyama [3], Yasuo Matsumoto [4], Kenji Takayama [5], Yukinori Matsuo [5], Akifumi Miyakawa [6], Haruo Matsushita [7], Masahiko Aoki [8], Keiji Nihei [9], Tomoki Kimura [10], Hiromichi Ishiyama [11], Naoya Murakami [12], Kensei Nakata [13], Atsuya Takeda [14], Takashi Uno [15], Takuma Nomiya [16], Tuyoshi Takanaka [17], Yuji Seo [18], Takafumi Komiyama [1], Kan Marino [1], Shinichi Aoki [1], Ryo Saito [1], Masayuki Araya [1], Yoshiyasu Maehata [1], Licht Tominaga [1] and Kengo Kuriyama [1]

[1] Department of Radiology, School of Medicine, University of Yamanashi, 1110 Shimokato, Chuo,

Japan Cancers 2018,
242 patients

❖A total dose of 40–70 Gy is administered in 4 to 10 fractions during a 4-to-25 day period.

❖One, two, and three-year overall survival (OS) rates are 82.1%, 57.1%, and 42.6%,

❖Fatal RP is identified in 6.9% of all patients.

❖The percent vital capacity <70%, mean percentage normal lung volume receiving more than 20 Gy (>10%), performance status of 2–4, presence of squamous cell carcinoma, clinical T2 stage, regular use of steroid before SBRT, and percentage predicting forced expiratory volume in one second (<70%) are associated with worse prognoses for OS.

❖**Results indicate that fatal RP frequently occurs after SBRT for stage I lung cancer in patients with PIC**.

Table 2. Univariate * and multivariate ** analysis for OS (p value).

Variables (If Significant, Left Was Better)	Univariate	Multivariate
Female vs. Male	0.26	0.03
Age <80 years vs. ≥80 years	0.69	0.88
Performance status 0,1 vs. 2,3,4	0.50	0.03
Adeno ca vs. Squamous cell ca	0.07	<0.01
T1 vs. T2	0.22	0.01
Medical operable vs inoperable	0.44	0.92
Smoking history (−) vs. (+)	0.33	0.10
Pulmonary emphysema (−) vs. (+)	0.24	0.13
Steroid administration before SBRT (−) vs. (+)	0.49	<0.01
% vital capacity (% VC) ≥70% vs. <70%	0.02	0.60
FEV1.0% *** ≥70% vs. <70%	0.98	<0.01
Biological effective dose ≥100 Gy vs. <100 Gy	0.13	0.90
V20 **** <10% vs. ≥10%	0.03	0.13

* Calculated using the Kaplan Meier's method and log-rank test; ** Calculated using the Cox's proportional hazard model; *** FEV1.0%: percentage of predicted forced expiratory volume in one second; **** V20: rate of the volume irradiated with 20 Gy or more to the normal lung volume. (+): present; (−): absent.

Table 3. Incidence of severe radiation pneumonitis according to patient backgrounds.

Patient Factors	Grade 3–5	Grade 5
Female vs. Male	12.1% vs. 15.4%	11.5% vs. 6.3%
Age <80 years vs. ≥80 years	13.2% vs. 11.2%	6.9% vs. 6.7%
Performance status 0,1 vs. 2,3,4	10.7% vs. 25.0%	6.8% vs. 5.0%
Adeno ca vs. Squamous cell ca	14.9% vs. 11.0%	9.5% vs. 5.5%
T1 vs. T2	11.6% vs. 10.7%	6.2% vs. 5.3%
Medical operable vs. inoperable	5.7% vs. 15.5%	5.7% vs. 7.7%
Smoking history (−) vs. (+)	13.0% vs. 12.8%	8.7% vs. 6.1%
Pulmonary emphysema (−) vs. (+)	11.5% vs. 16.7%	7.1% vs. 9.5%
Steroid administration before SBRT (−) vs. (+)	12.6% vs. 21.1%	7.8% vs. 5.3%
% vital capacity (%VC) ≥70% vs. <70%	5.3% vs. 12.0%	5.3% vs. 5.3%
FEV1.0% * ≥70% vs. <70%	9.9% vs. 13.4%	4.2% vs. 6.0%
Biological effective dose ≥100 Gy vs. <100 Gy	11.8% vs. 16.7%	6.9% vs. 6.7%
V20 ** < 10% vs. ≥10%	11.1% vs. 29.4%	6.0% vs. 28.6%

* FEV1.0%: percentage of predicted forced expiratory volume in one second; ** V20: rate of the volume irradiated with 20 Gy or more to the normal lung volume. (+): present; (−): absent.

Table 4. Frequency of radiation pneumonitis post SBRT for lung cancer according to presence of pulmonary interstitial change.

Pulmonary Interstitial Change	Author [Ref.]	Study Design	Patient Number	Dose/Fraction	Grade of Radiation Pneumonitis	Frequency	Risk Factor
No pulmonary interstitial change	Yamaguchi [3]	Retrospective	86	48 Gy/4 fr	4–5	0.00%	
	Ueki N [4]	Retrospective	137	48–60 Gy/4–8 fr	3–5	1.40%	
	Yoshitake [5]	Retrospective	242	48 Gy/4 fr	3 4–5	1.20% 0.00%	
	Matsuo Y [6]	Retrospective	74	48 Gy/4 fr	3 4	10.80% 1.90%	V25
	Nagata Y [7]	Prospective	104 (inoperable) 65 (operable)	48 Gy/4 fr 48 Gy/4 fr	3 3	6.20% 3.60%	
With pulmonary interstitial change	Yamaguchi [3]	Retrospective	16	48 Gy/4 fr	3 4 5	6.30% 6.30% 6.30%	V5–25, MLD
	Ueki N [4]	Retrospective	20	40–60 Gy/4–8 fr	3–5	10.00%	
	Yoshitake [5]	Retrospective	18	48 Gy/4 fr	3 4–5	16.70% 22.30%	KL-6, V5, V10, MLD
	This study	Retrospective	242	Various (mainly 48 Gy/4 fr)	3–5 5	12.40% 6.90%	% VC, FEV1.0 (%), Squamous cell ca., V20, PS, T stage, steroid before SBRT

Vx: rate of the volume irradiated with x Gy or more to the normal lung volume; MLD: mean dose of normal lung.

Stereotactic Ablative Body Radiation Therapy (SABR): A Resource

UK SABR Consortium

Although SABR may be used for peripherally located early lung cancers in patients with underlying ILD, patients must be appropriately counseled regarding the potential risks including fulminant pneumonitis which may be fatal. In addition, patients with subclinical ILD should be carefully monitored for the occurrence of severe radiation pneumonitis after SABR.

SABR as Re-radiation

JCRT2013

9 patients

Original Article

Repeat stereotactic body radiation therapy for patients with pulmonary malignancies who had previously received SBRT to the same or an adjacent tumor site

Vladimir Valakh, Curtis Miyamoto, Bizhan Micaily, Philip Chan, Toni Neicu, Shidong Li

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CONCLUSION

Repeat image-guided SBRT for patients with small peripheral lung tumors was feasible and life-threatening toxicity was not observed for these nine patients. Additional studies are needed to evaluate safety and efficacy of lung reirradiation using a second SBRT course.

Table 2: List of patients, radiotherapy regimens and outcomes

Patient	Indication for reirradiation	1st tumor size, cm	1st SBRT	2nd tumor size, cm	2nd SBRT	Oncologic outcome	Toxicity, grade≥2	History of additional chest radiotherapy
1	New mass 3.0 cm away from prior SBRT site	1.8	20 Gy×3	1.3	20 Gy×3	Distant recurrence (contralateral lung) at 23 m, alive	G3 dyspnea at 7 m; G2 CWP at 6 m; G2 brachial plexopathy at 14 m	Previous SBRT to remote ipsilateral lung
2	New mass 3.5 cm away from prior SBRT site	1.3	12 Gy×5	1.8	10 Gy×4	Alive and NED at 22 m	G3 CWP at 14 m; G2 dyspnea at 4 m	
3	Isolated in-field relapse	3.1	14 Gy×4	1.8	12 Gy×5	Alive and NED at 40 m	None	
4	Isolated in-field relapse	3.0	10 Gy×3	NR	10 Gy×4	In-field progression at 6 m, subsequent distant metastases and death at 22 m	G2 CWP at 2 m	Conventional radiotherapy to 70 Gy/35 fx to ipsilateral lung prior to 1st SBRT; prior ipsilateral whole breast irradiation
5	Isolated in-field relapse	3.0	12 Gy×5	4.2	20 Gy×3	In-field progression at 9 m simultaneously with nodal and distant metastases; death at 14 m	None	Previous SBRT to contralateral lung
6	New mass 3.5 cm away from prior SBRT site	3.0	10 Gy×3	NR	10 Gy×3	Alive and NED at 40 m	G3 dyspnea at 29 m	Conventional radiotherapy to 45 Gy/25 fx to the primary mass before 1st SBRT
7	Progressive second mass 3.5 cm away from prior SBRT site	2.7	12 Gy×5	1.7	12 Gy×5	Alive and NED at 17 m	G2 pneumonitis at 3 m	
8	New mass 2.0 cm away from prior SBRT site	2.2	20 Gy×3	NR	12 Gy×4	Alive and NED at 4 m	None	
9	New mass 2.0 cm away from prior SBRT site	1.4	20 Gy×3	1.1	20 Gy×3	Alive and NED at 12 m	G2 pneumonitis at 11 m	

SBRT=Stereotactic body radiation therapy, F/U=Follow-up duration, m=Months, G=Grade, CWP=Chest wall pain, NR=Not recorded, FX=Fractions

Radiotherapy and Oncology 110 (2014) 505–510

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

SBRT re-irradiation

Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment

Jeremy M. Kilburn [a,*], Jeffrey G. Kuremsky [a], A. William Blackstock [a], Michael T. Munley [a], William T. Kearns [a], William H. Hinson [a], James F. Lovato [c], Antonius A. Miller [b], William J. Petty [b], James J. Urbanic [a]

[a] Department of Radiation Oncology; [b] Department of Hematology and Oncology; and [c] Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, USA

2014 USA

Table 2
Treatment details.

Treatment courses	*n* (%)
EBRT then SBRT	23 (70)
SBRT then SBRT	7 (21)
SBRT then EBRT	3 (9)
Median interval between courses (range)	18 months (6–61)
Data for first XRT course	
All patients (*n* = 33)	
Median dose all patients (range)	60 Gy (22.5–80.5 Gy)
Median number of fractions (range)	30 (1–37)
Patients treated initially with SBRT (*n* = 10, 30%)	
Median dose (range)	50 Gy (22.5–60 Gy)
Median number of fractions (range)	5 (1–5)
Fractionation schemes (dose/fraction)	*n* (%)
54 Gy in 3 fractions (18 Gy)	3 (30)
50 Gy in 5 fractions (10 Gy)	3 (30)
40 Gy in 5 fractions (8 Gy)	1 (10)
60 Gy in 3 fractions (20 Gy)	1 (10)
22.5 Gy in a single fraction	2 (20)
Patients treated initially with EBRT (*n* = 23, 70%)	
Median dose (range)	66 Gy (45–80.5 Gy)
Median number of fractions (range)	33 (28–37)
Chemotherapy	16 (70% of EBRT group)
Concurrent	14 (61% of EBRT group
Sequential	2 (29% of EBRT group)
Data for retreatment course	
All patients (*n* = 33)	
Median dose all patients (range)	50 Gy (20–70.2 Gy)
Median number of fractions (range)	10 (1–35)
Patients retreated with SBRT (*n* = 30, 91%)	
Median dose (range)	50 Gy (20–54 Gy)
Median number of fractions (range)	5 (1–10)
Fractionation schemes (dose/fraction)	*n* (% of SBRT patients)
50 Gy in 10 fractions (5 Gy)	14 (47)
40 Gy in 5 fractions (8 Gy)	3 (10)
54 Gy in 3 fractions (18 Gy)	2 (7)
50 Gy in 5 fractions (10 Gy)	2 (7)
36 Gy in 2 fractions (18 Gy)	2 (7)
35 Gy in 5 fractions (7 Gy)	1 (3)
26 Gy in 2 fractions (13 Gy)	1 (3)
20–22.5 Gy in a single fraction	5 (17)
Patients retreated with EBRT (*n* = 3, 9%)	
Doses for all 3 patients	66 Gy – 70 Gy – 70.2 Gy
Number of fractions	33 – 35 – 26

Six patients suffered a local failure after re-irradiation with a median follow-up of 17 months. Local control on Kaplan–Meier analysis was 67% at 2 years (95% CI 38–85%)

Excluding the eight patients with oligo-metastatic disease, distant failures were noted in 9 of the remaining 25 patients. Distant metastatic free survival was 58% at 2 years

Four patients suffered a regional failure with a 2 year regional control rate of 83% (95% CI 59–93).

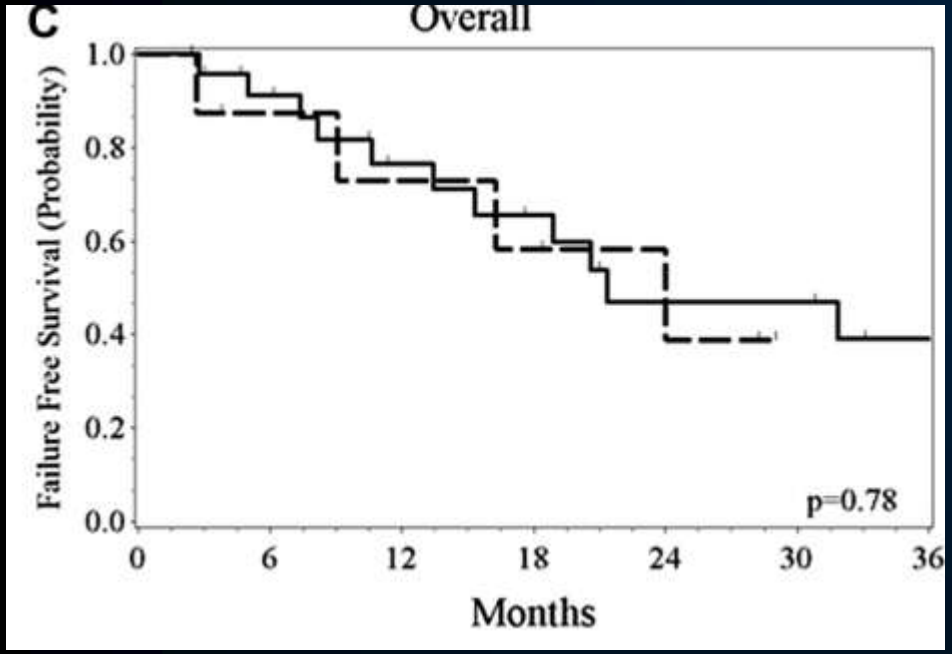
Incidence of relevant toxicity in published series of re-irradiation with SBRT.

Toxicity	MDACC series [12]	Karolinska Univ series [13]	Stanford series [14]	Current study
Patients with in-field recurrence or second primary	$n = 11$	$n = 29$	$n = 15$	$n = 33$
	n (%)	n (%)	n (%)	n (%)
Chest wall pain requiring narcotics	3 (27)	5 (17)	1 (7)	6 (18)
Pneumonitis				
Grade 2	5 (45)	3 (10)	0	2 (6)
Grade 3	0	1 (3)	0	1 (3)
Esophageal injury				
Esophagitis*	0	0	1 (7)	0
Stricture leading to dilatation	1 (9)	0	0	0
Aorta-esophageal fistula resulting in Grade 5 toxicity	0	0	0	1 (3)†
Vascular injury and death	0	3(10%)	0	1(3)†

* A single patient suffered esophagitis with no Grade defined.

† A single patient in the current series died of massive hemoptysis and was scored as both vascular and esophageal injury.

At the time of this analysis, 12 of the 25 patients without metastatic disease had not progressed. Median PFS for these patients was 16 months (95% CI 6.6–NR).



Among the entire group, 17 of the 33 patients have died. Median overall survival was 21 months (95% CI 15–51 months). One and 2 year overall survival was 76% and 45%. Cause of death was related to cancer in 14 of the 17 deaths with distant disease noted at time of death in 13 of 17 patients

Re-irradiation after EBRT with SBRT for patients with local recurrences or tumors in the high dose region of prior treatment offers an option for patients not candidates for surgical resection, and offers **control rates far greater than systemic chemotherapy**

STEREOTACTIC BODY RADIATION THERAPY FOR PATIENTS WITH LUNG CANCER PREVIOUSLY TREATED WITH THORACIC RADIATION

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MDACC data 2010

36 Cases

SBRT provided in-field local control for 92% of patients; at 2 years, the actuarial overall survival rate was 59%, and the actuarial progression-free survival rate was 26%, with the primary site of failure being intrathoracic relapse. Radiographic response to radiation was seen in all patients

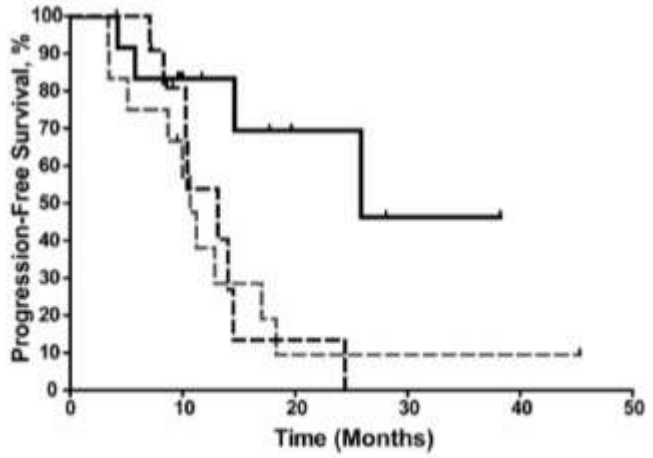

Fig. 3.
Kaplan-Meier analysis of progression-free survival for patients with in-field relapse (black dashed line), isolated out-of-field relapse (solid black line), and disseminated disease (gray dashed line). Progression-free survival was significantly better among patients with isolated recurrence outside the previous treatment field ($p = 0.04$ by log-rank test).

Patients treated for isolated out-of-field relapses who had no evidence of metastatic disease had significantly longer progression-free survival time than did patients treated for in-field relapses or patients treated for out-of-field relapses with known metastatic disease or multiple foci of intrathoracic disease ($p = 0.04$)

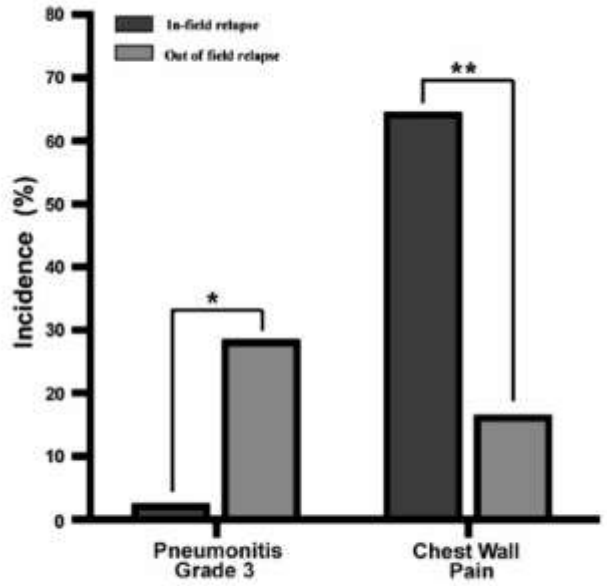

Fig. 4.
Grade 3 pneumonitis and chest wall pain stratified by in-field relapse or out-of-field relapse. *$p = 0.03$, **$p = 0.02$ by Fisher's exact test.

Incidence of Grade 2 and 3 toxicity by group

	In-field relapse (n = 11)	Out-of-field relapse (n = 25)	Total (n = 36)
	n (%)	n (%)	n (%)
Cough			
Grade 2	0	3 (12%)	3 (8%)
Grade 3	0	1 (4%)	1 (3%)
Pneumonitis			
Grade 2	5 (45%)	6 (24%)	11 (36%)
Grade 3	0	7 (28%)	7 (28%)
Esophagitis			
Grade 2	1 (9%)	1 (4%)	2 (6%)
Grade 3	1 (9%)	2 * (8%)	3 (8%)
Skin			
Grade 2	1 (9%)	0	1 (3%)
Grade 3	2 (18%)	0	2 (6%)
Chest Wall Pain			
Not requiring narcotic	4 (36%)	1 (4%)	5 (14%)
Requiring narcotic	3 (27%)	3 (12%)	6 (17%)

No Grade 4 or 5 toxicity was seen.

* In addition, one patient developed esophageal stricture requiring dilation.

Conclusions—SBRT can provide excellent in-field tumor control in patients who have received prior radiation therapy. Toxicity was significant but manageable. The high rate of intra thoracic failure indicates the need for further study to identify patients who would derive the most benefit from SBRT for this purpose

Stereotactic Ablative Radiotherapy for Reirradiation of Locally Recurrent Lung Tumors

Nicholas Trakul, MD, PhD, Jeremy P. Harris, BS, MPhil,* Quynh-Thu Le, MD,*† Wendy Y. Hara, MD,*† Peter G. Maxim, PhD,*† Billy W. Loo, Jr, MD, PhD,*† and Maximilian Diehn, MD, PhD*†*

J. Thorac Oncol. 2012

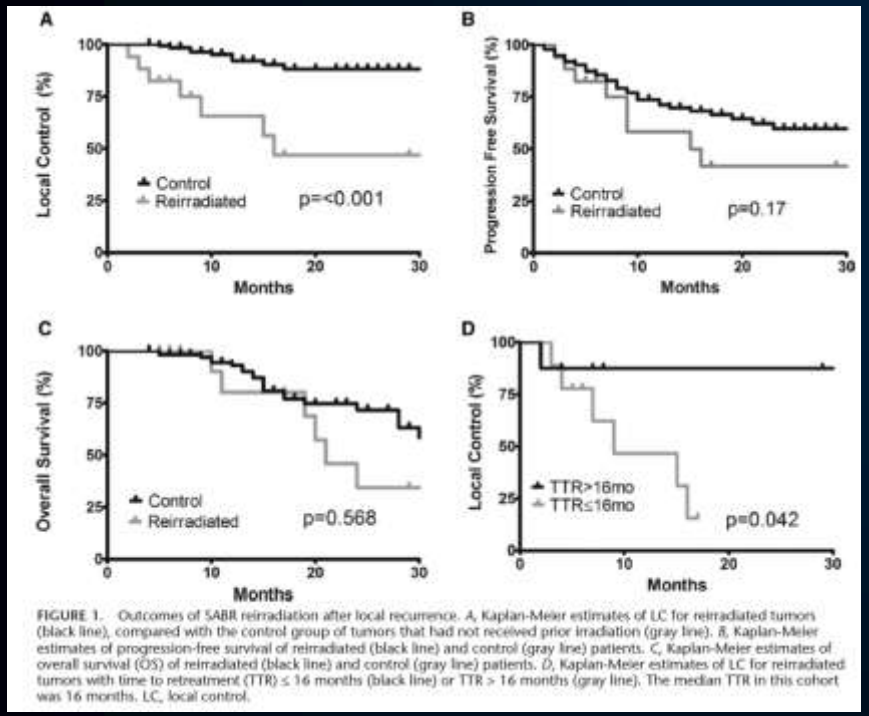

FIGURE 1. Outcomes of SABR reirradiation after local recurrence. *A*, Kaplan-Meier estimates of LC for reirradiated tumors (black line), compared with the control group of tumors that had not received prior irradiation (gray line). *B*, Kaplan-Meier estimates of progression-free survival of reirradiated (black line) and control (gray line) patients. *C*, Kaplan-Meier estimates of overall survival (OS) of reirradiated (black line) and control (gray line) patients. *D*, Kaplan-Meier estimates of LC for reirradiated tumors with time to retreatment (TTR) ≤ 16 months (black line) or TTR > 16 months (gray line). The median TTR in this cohort was 16 months. LC, local control.

Standford data 2012

17 tumours in 15 patients

Results: Twelve-month local control (LC) for retreated tumors was 65.5%, compared with 92.1% for tumors receiving SABR as initial treatment. Twelve-month LC was significantly worse for reirradiated tumors in which the time interval between treatments was 16 months or less (46.7%), compared with those with longer intertreatment intervals (87.5%). SABR reirradiation did not lead to significant increases in treatment-related toxicity.

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Morbidity of lung SBRT

Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy

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Karolinska University Hospital, Sweden 2011

29 patients reirradiated with SBRT on 32 lung lesions (11 central, 21 peripheral)

Table 2
All toxicity according to NCI-CTCAE v3.0 grouped according to localization.

Central $n = 11$						Peripheral $n = 18$				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
2	2	–	–	–	Atelectasis	1	3	–	–	–
1	1	3	–	–	Cough	2	6	–	–	–
1	1	1	–	–	Dyspnoea	–	5	3	–	–
–	1	1	–	–	Pneumonitis	–	2	–	–	–
–	–	1	–	–	Stenosis of airway	–	–	–	–	–
–	–	–	–	3	Bleeding	–	–	–	–	–
–	2	–	–	–	Pleural effusion	1	3	1	–	–
2	2	–	–	–	Pulmonary fibrosis	2	5	–	–	–
–	–	–	–	–	Fracture	1	–	–	–	–
–	1	–	–	–	Dermatitis	–	–	1	–	–
1	–	x	x	x	Hyperpigmentation	–	1	x	x	x
–	–	1	–	–	Pain	2	4	–	–	–
–	1	–	2	–	Other	–	1	–	–	–

n = number of patients, x = non existent. "Other" toxic events were mucus production (grade 2) in one patient. Another patient experienced two grade 4 events: a vena cava superior stenosis and a fistula between trachea and gastric tube.

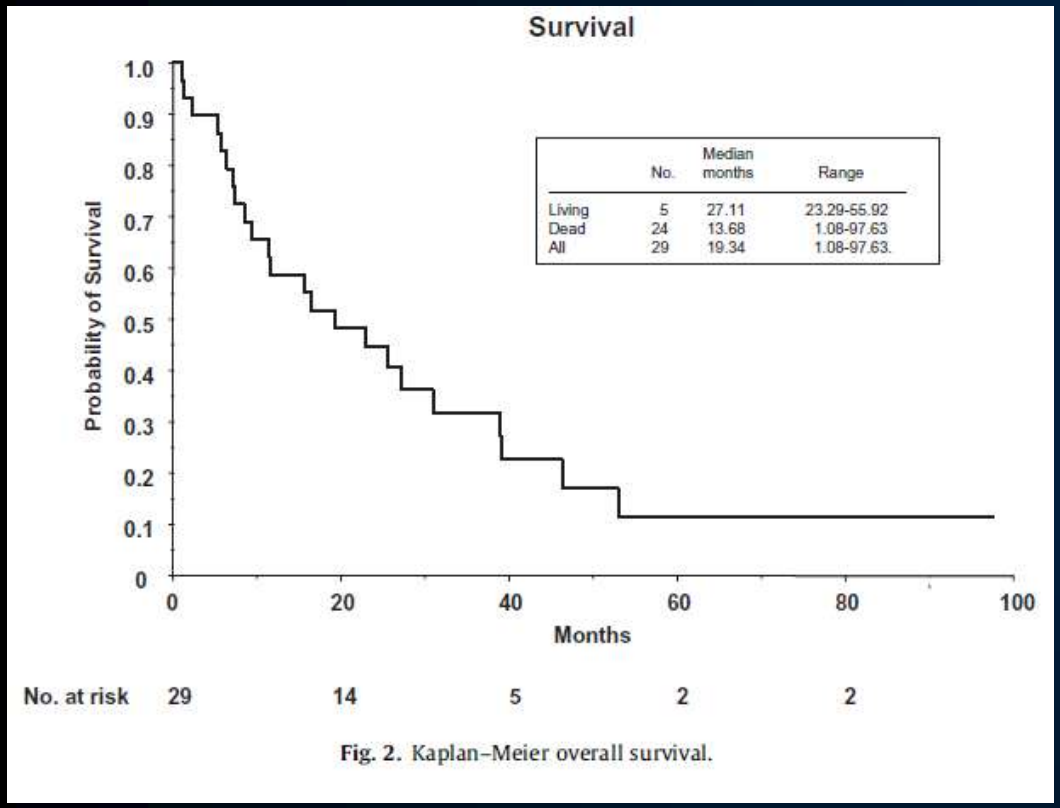

Fig. 2. Kaplan–Meier overall survival.

- Kaplan–Meier estimated median overall survival time after reirradiation was 19.3 months (range 1–98) .

- The 1-, 2- and 3-year survival rates were 59%, 43% and 23%, respectively

Conclusion

Reirradiation with SBRT of pulmonary tumours is justified as a safe and effective procedure for a subpopulation of patients. However, reirradiation of central tumours should only be performed after careful considerations of potential severe toxicity. Prospective studies are needed to specify patient selection criteria and find dose-limiting constraints.

Table 2. Reports on Salvage Radiotherapy for Local Tumor Recurrence After Prior Stereotactic Body Radiotherapy for Primary or Metastatic Lung Tumors.[a]

Author (Year)	Peulen *et al* (2011)[15]	Valakh *et al* (2013)[16]	Yoshitake *et al* (2013)[17]	Hearn *et al* (2014)[18]
No. of patients (lesions)	29 (32)	9 (9)	17[b]	10 (10)
Sex (M:F)	18:11	NR	15:2	5:5
Age, years	65 (18-87)	74 (59-83)	81 (69-88)	72 (51-78)
Tumor type (primary: metastatic)	6:23	8:1	17:0	10:0
Tumor location (central: periphery)	11:21	0:9	NR	2:8
Initial treatment				
Tumor size, cm	PTV, 71 (7-150) (cm^3)	2.39 (1.3-3.1)	2.8 (1.0-5.1)	2.2 (1.0-4.5)
Regimen	SBRT, 20-45 Gy/2-5fx	SBRT, 30-60 Gy/3-5fx	SBRT, 48-60 Gy/4-10fx	SBRT, 30-50 Gy/1-5fx
EQD2 [Gy_{10}]	CTV mean, 109 (49-163)	110.0 (50.0-150.0)	88.0 (80.0-88.0)	83.3 (83.3-124.7)
Time to salvage treatment, mo	14 (5-54)	11 (1-25)	12.4 (6.3-35.5)	14.8(9.9-26.3)
Salvage treatment				
Tumor size, cm	PTV, 76 (16-355) (cm^3)	1.98 (1.1-4.2)	4.1 (1.9-7.7)	3.4 (1.7-4.8)
Regimen	SBRT, 20-45 Gy/1-5fx	SBRT, 30-60 Gy/3-5fx	CFRT, 60-70 Gy/30-35fx	SBRT, 50-60 Gy/3-5fx
EQD2 [Gy_{10}]	CTV mean, 109 (79-163)	110.0 (50.0-150.0)	60.0 (60.0-70.0)	83.3 (83.3-150.0)
Use of concurrent chemotherapy	12 (41%)	NR	4 (23.5%)	NR
Follow-up from the salvage, mo	12 (1-97)	22 (4-40)	12.6 (4.3-31.1)	13.8 (5.3-43.5)
Local control	52% at 5 mo	75% at 2 years	LPFS 33.8% at 1 year	60%
Survival	59% at 1 year, 43% at 2 years	68.6% at 2 years	74.7% at 1 year	3 NED
Toxicity				
Grade 2	12 (RP, pleural effusion, etc)	3 (CWP, RP, BrP)	1 (rib fracture)	(3 Gr1-2 fatigue, 5 Gr1-2 CWP)
Grade 3	5 (RP, dermatitis, CWP, etc)	3 (dyspnea, CWP)	none	none
Grade 4	1 (SVC occlusion, tracheal fistula)	none	none	none
Grade 5	3 (bleeding)	none	none	none

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CTV, clinical target volume; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; LPFS, local progression-free survival; mo, months; NED, alive with no evidence of disease; NR, not reported; PTV, planning target volume; RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; SVC, superior vena cava.

[a]Values are shown in median (range), if unspecified.

[b]Including 4 patients who had regional or distant metastasis in addition to local recurrence.

Table 3. Reports on Salvage Radiotherapy for Local Tumor Recurrence After Prior Radiotherapy for Primary or Metastatic Lung Tumor.[a]

Author (Year)	Trakul *et al* (2012)[19]	Meijneke *et al* (2013)[20]	Ester *et al* (2013)[21]	Kilburn *et al* (2014)[22]	Patel *et al* (2015)[23]	Binkley *et al* (2016)[24]	Ceylan *et al* (2017)[25]
No. of patients (lesions)	15 (17)	20 (20)	12 (13)	33	26 (29)	38 (44)	28 (34)
Sex (M:F)	7:10	14:6	8:4	19:14	19:7	23:15	25:3
Age, years	66 (49-92)	71 (50-80)	67.9 (45.9-86.7)	66 (45-80)	68 (42-87)	66 (35-94)	64 (48-90)
Tumor type (primary:metastatic)	12:5	17:3	11:1	29:4	26:0	31:7	28:0
Tumor location (central:peripheral)	6:11	NR	4:9	17:16	NR	26:12	16:18
Initial treatment							
GTV, cm^3	NR	26.5 (0.2-240)	NR	NR	NR	31.4 (0.8-248.5)	NR
Regimen	SBRT (n = 4), 25-50 Gy/1-4fx; CFRT (n = 11)	SBRT (n = 14), 30-60 Gy/1-6Fx; CFRT (n = 8), 45-60 Gy/15-25fx	SBRT (n = 2); CFRT (n = 10), 61.2 Gy (12-70 Gy)	SBRT (n = 10), 22.5-60 Gy/1-5fx; CFRT (n = 23), 45-80.5 Gy/28-37fx	SBRT (n = 3); CFRT (n = 23), 61.2 Gy (30-74 Gy)	SBRT (n = 21), 25-54 Gy; CFRT (n = 17), 45-71.6 Gy	SBRT (n = 1), 60 Gy; CFRT (n = 27), 59.4 Gy (47.5-66 Gy)
EQD2 [Gy_{10}]	72.9 (50-93.8)	133 (44-150)	NR	SBRT: 83.3; CFRT: 66	NR	72.9 (43.1-126)	NR
Time to salvage treatment, mo	16 (5-80)	17 (2-33)	19.7 (4.7-84.7)	18 (6-61)	8 (3-26)	16 (1-71)	14 (4-56)
Salvage treatment							
GTV, cm^3	14.2 (2-57.7)	20 (0.2-589)	4.6 (1.0-28.4)	2.5 (0.6-5.4) (cm)	3.2 (1.2-9.5) (cm)	9.1 (0.5-87.5)	24.2 (2.3-156.3)
Regimen	SBRT, 20-50 Gy/1-5fx	SBRT (n = 18), 32-60 Gy/3-6fx; CFRT (n = 2), 20-30 Gy/5-10fx	SBRT, 45-50 Gy/5fx	SBRT (n = 30), 20-54 Gy/1-10fx; CFRT (n = 3), 60-70.2 Gy/26-35fx	SBRT, 15-50 Gy/3-5fx	SBRT (n = 30), 25-50 Gy; CFRT (n = 14), 60-72 Gy	SBRT, 20-60 Gy/3-9fx
EQD2 [Gy_{10}]	66.7 (50.0-93.8)	83 (23-150)	71.3 (71.3-83.3)	SBRT: 83.3; CFRT: 70	40 (16.3-93.8)	72.9 (50.0-93.8)	46.9 (23.3-150.0)
Use of concurrent chemotherapy	NR	None	None	NR	NR	9 (24%)	16 (57%)
Follow-up from the salvage, mo	15 (4-65)	12 (2-52)	11.4 (1.6-38.3)	17		17 (3-57)	9 (3-93)
Local control	65.5% at 1 year	75% at 1 year; 50% at 2 years	92%	67% at 2 years	78.6% at 1 year; 65.5% at 2 years	88.3% at 1 year; 83.5% at 2 years	69% at 1 year; 37% at 2 years
Survival	80% at 1 year	67% at 1 year; 33% at 2 years	80% at 1 year; 36% at 2 years	76% at 1 year; 45% at 2 years	52.3% at 1 year; 37.0% at 2 years	79.6% at 1 year; 57.3% at 2 years	71% at 1 year; 42% at 2 years
Toxicity							
Grade 2	2 (CWP, VCP)	(4 dyspnea, 2 CWP, 2 dysphagia)	1 (atelectasis)	10 (6 CWP, 3 dyspnea, 1 esophagitis)	2 (cough, RP)	8 (lung, esophagitis, CWP)	1 (RP)
Grade 3		None	1 (RP)		None	6 (esophagitis, CWP, Horner syn., VCP, BrP)	None
Grade 4	None	None	None	None	None	None	None
Grade 5	None	None	None	1 (aortaesophageal fistula)	None	None	None

Abbreviations: BrP, brachial plexopathy; CFRT, conventionally fractionated radiotherapy; CWP, chest wall pain; EQD2, equivalent dose in 2-Gy fractions; fx, fractions; GTV, gross tumor volume; NR, not reported; SBRT, stereotactic body radiotherapy; SVC, superior vena cava; syn., syndrome; RP, radiation pneumonitis; VCP, vocal cord paralysis.

[a]Values are shown in median (range), if unspecified.

CLINICAL INVESTIGATION

Lung reirradiation with stereotactic body radiotherapy (SBRT)

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(Received: March 30, 2013; Accepted: May 30, 2013)

Prior thoracic RT	
CF	9 (75.0%)
HF	1 (8.3%)
SBRT	2 (16.7%)

Retreatment SBRT Rx	
9 Gy x 5	8 (61.5%)
10 Gy x 5	5 (38.5%)

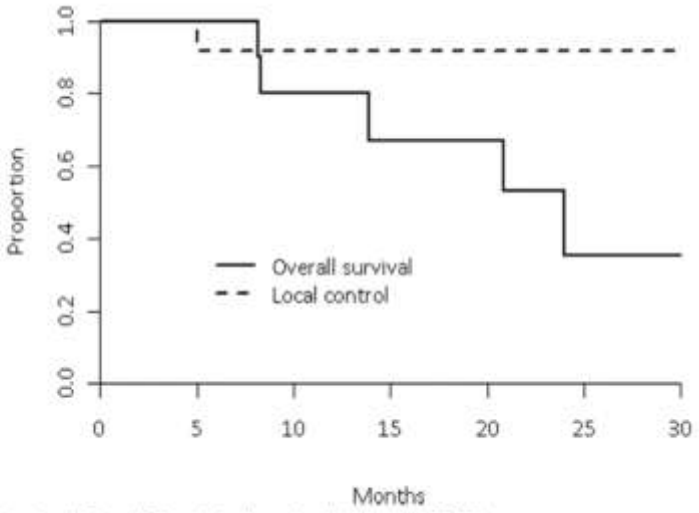

Figure1. Local Control and Overall Survival after reirradiation with SBRT.

Overall local control of the retreated tumors was 92%. The sole local recurrence occurred following 4500 cGy in 5 fractions

The estimated median survival time is 24 months (95% CI: 8-38 months). 1- and 2-year overall survival are 80% (95% CI: 41%-95%) and 36% (95% CI: 6%-68%) respectively

Table 5. Reirradiation of lung cancer with Stereotactic Body Radiation Therapy (SBRT)/ Stereotactic Ablative Radiotherapy (SABR). A summary of published reports.

Institution	n	Number tumors	Most common regimens (Gy/Fx)	Median F/u (mo)	LC (%)	Median OS (mo)	1y OS (%)	2y OS (%)	3 y OS (%)	Grade 3 toxicity (%)	Grade 4-5 toxicity (%)
MDA Kelly *et al.*	36	36	40/4, 50/4	15	92			59		33	0
Oregon Seung *et al.*	8	8	48/4, 50/5 40/5, 60/3	18	86					0	0
European Peulen *et al.*	29	32	30/2, 45/3 40/4	12	52	19.3	59	43	23	24	14
Stanford Trakul *et al.*	15	17	20-25/1, 30/3 40/4	15	65.5		80			0	0
U of MN	12	13	45/5, 50/5	11.4	92	24	80	36		8	0

Lung reirradiation with stereotactic body radiotherapy

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(Received: February 2, 2015; Accepted: March 28, 2015)

Italy 2015
18 patients

Peripherally located lesions received 5 fractions of 8-10 Gy, while centrally ones lower doses (5 fractions of 5-8 Gy). Cumulative EQD2 did not exceed 198 Gy10 and reirradiated volumes were rather small (median 18 cc). Local control was obtained for all patients except one and lasted medially 43 months. Median overall survival was 40 months from reirradiation. Only acute grade 1 toxicity was recorded.

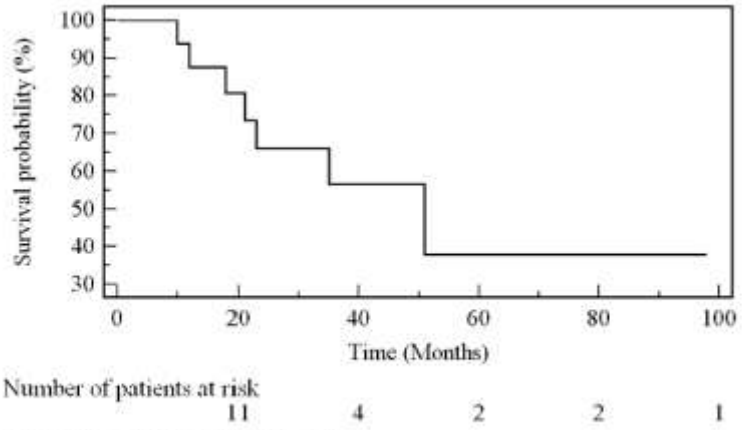

Figure 1. Overall survival probability from reirradiation.

Conclusions: Reirradiation of LRLs with SBRT was feasible and effective. It is important to appropriately select patient and to adopt organ at risk constrains considering cumulative doses.

Ogawa et al. Radiation Oncology (2018) 13:136
https://doi.org/10.1186/s13014-018-1080-4

Radiation Oncology

RESEARCH Open Access

Repeat stereotactic body radiotherapy (SBRT) for local recurrence of non-small cell lung cancer and lung metastasis after first SBRT

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Japan 2018

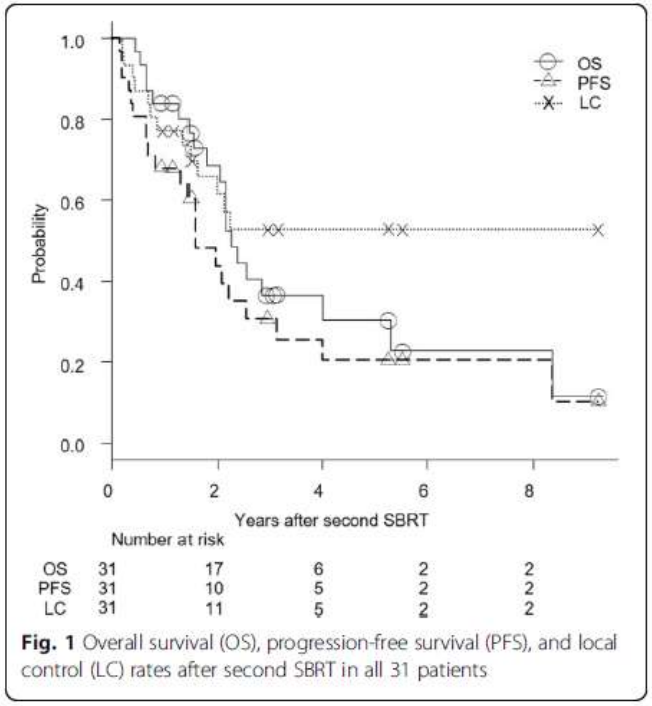

Fig. 1 Overall survival (OS), progression-free survival (PFS), and local control (LC) rates after second SBRT in all 31 patients

31 patients with in-field local relapse of NSCLC (n = 23) or lung metastasis (n = 8) underwent repeat SBRT

At 3 years, overall survival and local control rates were 36 and 53%, respectively, for all 31 patients. Four patients showed no further recurrence for > 5 years (63–111 months) after the second SBRT. Radiation pneumonitis after the second SBRT was grade 2 in 4 patients, and no grade 3 pneumonitis was observed.

Practical Radiation Oncology (2017)

pro

Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer: an ASTRO Evidence-Based Guideline

Key Question 4: In medically inoperable patients, what is the role of SBRT as salvage therapy for early stage lung cancer that recurs:

- **After conventionally fractionated radiation therapy,**
- **After SBRT,**
- **After sublobar resection?**

After SBRT?

Statement KQ4D: Patient selection for salvage SBRT after previous SBRT is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength**: Strong
- **Quality of evidence**: Low
- **Consensus**: 100%

After sublobar resection?

Statement KQ4E: Patient selection for salvage SBRT after prior sublobar resection is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength**: Strong
- **Quality of evidence**: Low
- **Consensus**: 94%

Practical Radiation Oncology (2017)

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After conventionally fractionated radiation therapy?

Statement KQ4A: The use of salvage SBRT after primary conventionally fractionated radiation may be offered to selected patients due to reported favorable local control and survival.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low
- **Consensus**: 100%

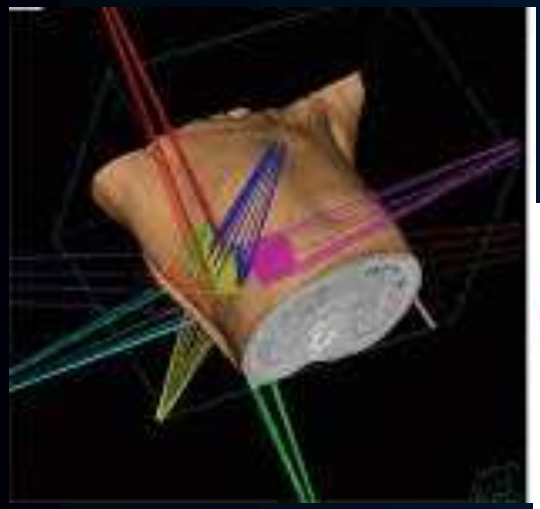
Statement KQ4B: Patients treated with salvage SBRT after primary conventionally fractionated radiation should be informed of significant (including fatal) toxicities.

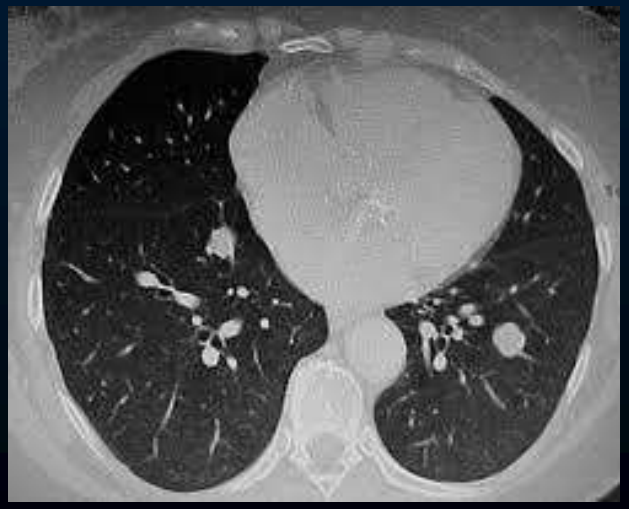
- **Recommendation strength**: Strong
- **Quality of evidence**: Low
- **Consensus**: 100%

Statement KQ4C: Patient selection for salvage SBRT after primary conventionally fractionated radiation is a highly individualized process. Radiation oncologists should assess evidence-based patient, tumor, and treatment factors prior to treatment initiation.

- **Recommendation strength**: Strong
- **Quality of evidence**: Low
- **Consensus**: 94%

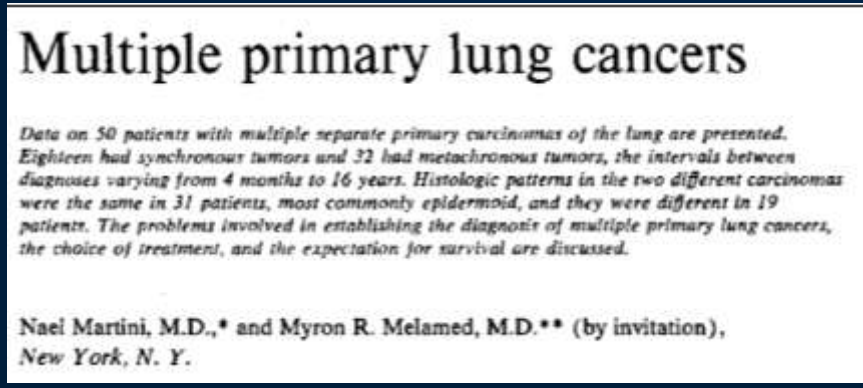
SBRT in Multiple Lung Tumours





Martini and Melamed Criteria

Synchronous tumors
A. Tumor physically distinct and separate
B. Histology
1. Different
2. Same, but different segment, lobe or lung, and
a. Origin from carcinoma in situ
b. No carcinoma in lymphatics common to both
c. No extrapulmonary metastasis at time of diagnosis
Metachronous tumors
A. Different histology
B. Same histology if;
1. Intervals between cancers at least 2 years or
2. Origin from carcinoma in situ or
3. Second cancer in different lobe or lung, but;
a. No carcinoma in lymphatics common to both
b. No extrapulmonary metastasis at time of diagnosis



Multiple primary lung cancers

Data on 50 patients with multiple separate primary carcinomas of the lung are presented. Eighteen had synchronous tumors and 32 had metachronous tumors, the intervals between diagnoses varying from 4 months to 16 years. Histologic patterns in the two different carcinomas were the same in 31 patients, most commonly epidermoid, and they were different in 19 patients. The problems involved in establishing the diagnosis of multiple primary lung cancers, the choice of treatment, and the expectation for survival are discussed.

Nael Martini, M.D.,* and Myron R. Melamed, M.D.** (by invitation),
New York, N. Y.

J Thorac Cardiovasc Surg 1975

Genomic Profiling

ARTICLE

Received 25 Feb 2016 | Accepted 11 Sep 2016 | Published 21 Oct 2016

DOI: 10.1038/ncomms13200 OPEN

Genomic heterogeneity of multiple synchronous lung cancer

- Genomic profiles analyzed from 15 lung adenocarcinomas in 6 patients
- All suggested independent primary tumors (not metastases)
- Lung tumours of the same individuals are no more similar to each other than are lung adenocarcinomas of different patients from TCGA cohort matched for tumour size and smoking status.

Nature Communications 2016

Say goodbye to Martini and Melamed: genomic classification of multiple synchronous lung cancer

Brendon M. Stiles

IASLC – Clinical Criteria

Table 2. Clinical Criteria for Separate versus Related Pulmonary Tumors

Clinical criteria[a]
Tumors may be considered separate primary tumors if
They are clearly of a different histologic type (e.g., squamous carcinoma and adenocarcinoma).
Tumors may be considered to be arising from a single tumor source if
Matching breakpoints are identified by comparative genomic hybridization.
Relative arguments that favor separate tumors:
Different radiographic appearance or metabolic uptake
Different pattern of biomarkers (driver gene mutations)
Different rates of growth (if previous imaging is available)
Absence of nodal or systemic metastases
Relative arguments that favor a single tumor source:
The same radiographic appearance
Similar growth patterns (if previous imaging is available)
Significant nodal or systemic metastases
The same biomarker pattern (and same histotype)

[a]Note that a comprehensive histologic assessment is not included in clinical staging, as it requires that the entire specimen has been resected.

Stereotactic Ablative Radiotherapy

A Potentially Curable Approach to Early Stage Multiple Primary Lung Cancer

Joe Y. Chang, MD, PhD[1]; Yung-Hsien Liu, MD[1†]; Zhengfei Zhu, MD, PhD[1†]; James W. Welsh, MD[1]; Daniel R. Gomez, MD[1]; Ritsuko Komaki, MD[1]; Jack A. Roth, MD[2]; and Stephen G. Swisher, MD[2]

MD Anderson Cancer Center,2013

101 patients,

39 synchronous, 62 metachronous (>6 months apart).

- First lesion: 29 SABR, 25 conventional RT, 42 surgery, *5 surgery + PORT*
- Second lesion: 101 SABR • Treated with 50 Gy in 4 fractions (or 70 Gy in 10 fractions if dose constraints not met)

2-year and 4-year in-field local control rates were 97.4% and 95.7%.

		Treatment for Index Tumor		
Toxicity	All Patients, n = 101	SARB, n = 29	Surgery, n = 42	C-RT, n = 30
Pneumonitis				
Grade 1	70 (69.3)	24 (82.8)	29 (69)	17 (56.7)
Grade 2	20 (19.8)	3 (10.3)	10 (23.8)	7 (23.3)
Grade 3	6 (14.9)	1 (3.4)	1 (2.4)	4 (13.3)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Grade 5	1 (1)	0 (0)	0 (0)	1 (3.3)
Skin toxicity				
Grade 1	19 (18.8)	9 (31)	6 (14.3)	4 (13.3)
Grade 2	9 (8.9)	3 (10.3)	4 (9.5)	2 (6.7)
Grade 3	1 (1)	0 (0)	0 (0)	1 (3.3)
Chest wall pain				
Grade 1	12 (11.9)	6 (20.7)	4 (9.5)	2 (6.7)
Grade 2	22 (21.8)	8 (26.7)	8 (19)	6 (20)
Grade 3	3 (3)	3 (10.3)	0 (0)	0 (0)
Rib fracture				
Grade 1	4 (4)	3 (10.3)	1 (2.4)	0 (0)
Grade 2	20 (19.8)	12 (41.4)	6 (14.3)	2 (6.7)

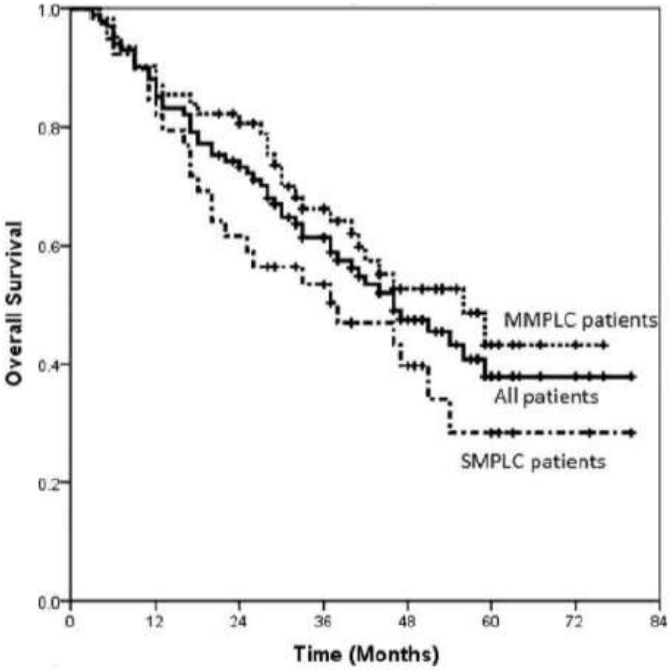


Figure 1. Overall survival is illustrated for all patients, for patients who had metachronous multiple primary lung cancer (MMPLC), and for patients who had synchronous MPLC (SMPLC).

median follow-up interval of 36 months

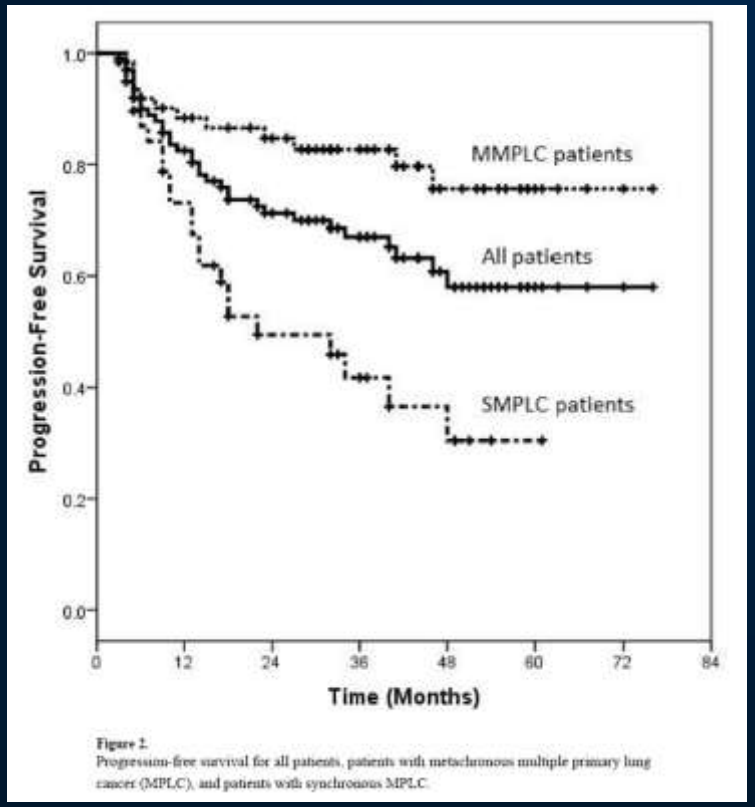


Figure 2.
Progression-free survival for all patients, patients with metachronous multiple primary lung cancer (MPLC), and patients with synchronous MPLC.

Median overall survival of 46 months, 2- and 4-year rates of overall survival (OS) were 73.2% and 47.5% progression-free survival (PFS) were 67.0% and 58.0%. Patients with metachronous tumors had higher OS and PFS than did patients with synchronous tumors (2-year OS 80.6% metachronous vs. 61.5% synchronous; 4-year OS 52.7% vs. 39.7%; p=0.047; 2-year PFS 84.7% vs. 49.4%; 4- year PFS 75.6% vs. 30.4%; p=0.0001)

CONCLUSIONS—SABR achieves promising long- term tumor control, survival and could be a potential curative treatment of early-stage MPLC

Optimizing SABR delivery for synchronous multiple lung tumors using volumetric-modulated arc therapy

Hilâl Tekatli, Shyama U. Tetar, Timothy K. Nguyen, Andrew Warner, Wilko F. Verbakel, David A. Palma, Max Dahele, Stewart Gaede, Cornelis Haasbeek, Femke O. Spoelstra, Patricia F. de Haan, Ben J. Slotman & Suresh Senan

Acta Oncologica 2016

VU University Medical Center, Amsterdam, The Netherlands.2016

London Health Sciences Centre, London, Ontario, Canada

- 84 patients with 188 lesions treated with multiple isocentres, from 2 institutions
- Most patients (97%) with 2-3 lesions.
- Median total PTV size: 52 cc
- Fractionations: 34/1, 54/3, 55/5, 60/8

Table 2. Summary of lung parameters for all patients ($n = 84$), patients with unilateral ($n = 37$), and bilateral lesions ($n = 47$). All doses were reported in EQD_2 values.

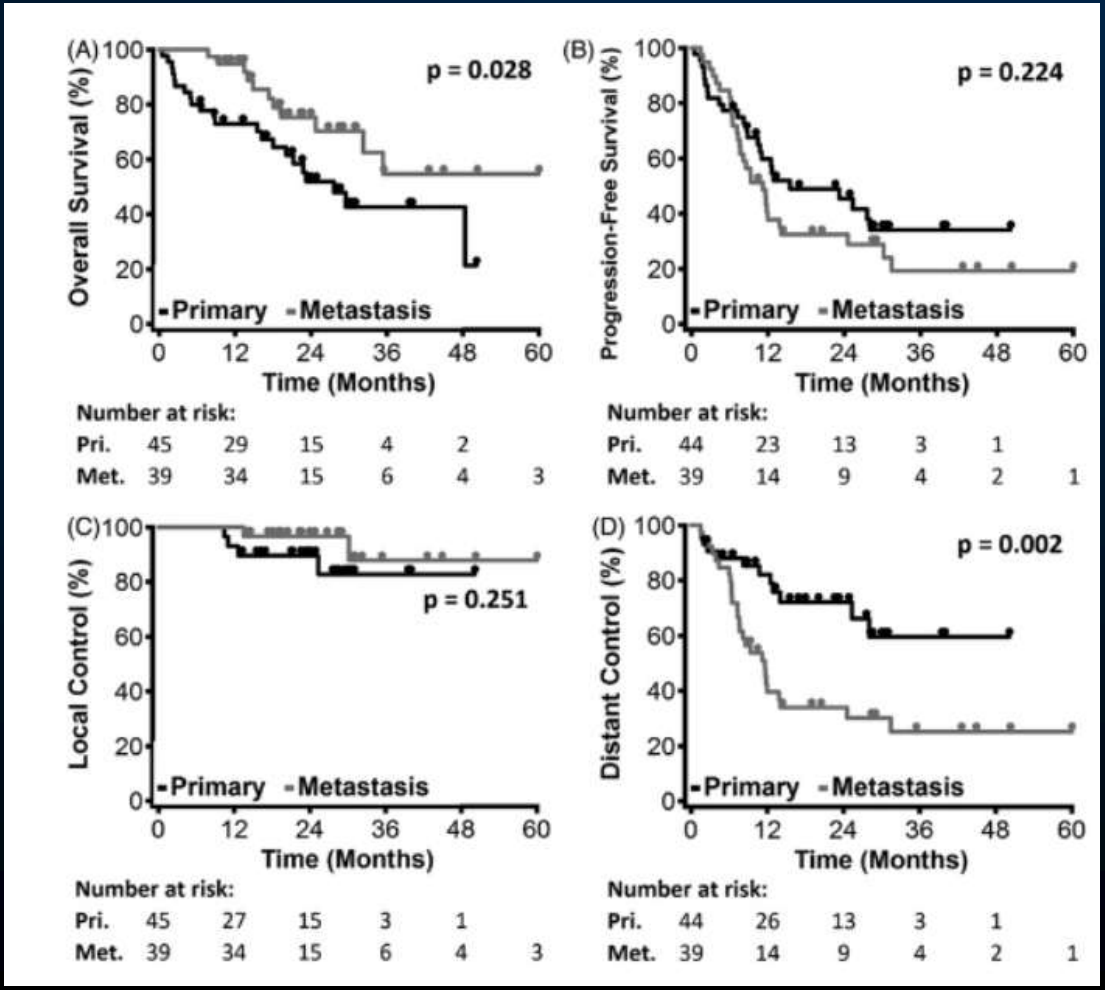
Total lung minus PTV Median (range)	All patients	Patients with unilateral tumors	Patients with bilateral tumors
Minimum lung dose (Gy)	0.1 (0.0, 0.3)	0.1 (0.04, 0.3)	0.1 (0.0, 0.3)
Mean lung dose (Gy)	7.1 (2.3, 16.7)	5.9 (2.3, 16.7)	7.8 (2.5, 16.1)
Maximum lung dose (Gy)	194.0 (72.5, 342.1)	192.5 (143.9, 311.2)	198.5 (72.5, 342.2)
V_{5Gy} (%)	25.3 (8.1, 54.8)	19.7 (8.1, 42.1)	27.5 (9.0, 54.8)
V_{15Gy} (%)	12.1 (2.5, 31.9)	10.0 (2.5, 31.9)	12.7 (2.5, 31.6)
V_{20Gy} (%)	8.9 (1.6, 27.6)	8.2 (1.6, 27.6)	10.5 (1.6, 26.1)
V_{25Gy} (%)	7.2 (1.0, 22.8)	6.9 (1.0, 22.8)	8.1 (1.7, 22.0)
V_{35Gy} (%)	4.9 (0.5, 15.3)	4.7 (0.5, 15.0)	5.3 (1.1, 15.3)
V_{50Gy} (%)	3.1 (0.1, 9.0)	2.6 (0.1, 9.0)	3.3 (0.1, 8.6)

The actuarial local control rates at 1 and 3 years were 96.9% and 84.7%

At a median follow-up of 28.1 months (95% CI 22.6–30.2), median OS for all patients was 35.4 months, with 1- to 5-year survivals being 83.2%, 62.1%, 46.3%, 46.3%, and 38.6%

Median progression-free survival (PFS) was 12.0 months for all patients, 25.3 months for patients with unilateral lesions, and 11.0 months for patients with bilateral lesions (p¼.059)

Patients presenting with primary lung tumors had a median PFS of 15.5 months, while this was 11.2 months in patients with metastatic lesions



Toxicity

- 20% Grade 2+
  - RP (11%), chest wall (6%)
- 2% Grade 3
- 1 patient with possible Grade 5: bilateral pneumonia

Supplemental Table 2. Multivariable Cox proportional hazards regression models of factors predicting overall survival, and multivariable logistic regression models of factors predicting radiation pneumonitis grade ≥ 2 (n = 84).

Dependent Variables	Overall Survival		Radiation Pneumonitis (Grade ≥2)	
Independent Variables	**HR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
WHO Performance Status		0.008		--
1 vs. 0	3.18 (1.04, 9.74)	0.042	--	--
2-3 vs. 0	6.19 (1.94, 19.74)	0.002	--	--
Metastasis vs. Primary Lung	0.31 (0.13, 0.77)	0.011	0.11 (0.01, 0.97)	0.047
Bilateral Lesions	3.42 (1.42, 8.23)	0.006	--	--
Chemotherapy post-SABR	3.47 (1.48, 8.12)	0.004	--	--
SABR after index treatment	--	--	--	--
Total – PTV: V35 ≥ 6.5 vs. < 6.5 %[1]	--	--	10.85 (1.93, 61.05)	0.007

[1] = RPA cut-point. Abbreviations: CI = confidence interval; HR = hazard ratio; WHO = World Health Organization; OR = odds ratio; PTV = planning target volume.

Conclusion: Severe toxicity was uncommon following SABR using VMAT for up to three lung tumors. Further investigations of planning parameters are needed in patients presenting with more lesions.

Multivariable analysis showed that G2 RP was significantly associated with a primary lung tumor (OR 0.11; 95% confidence interval [CI]0.01–0.97; p¼.047) and a total **lung V35Gy of 6.5% (OR 10.85; 95% CI 1.93–61.05; p=0.007**

Critical Volume Concept

International Journal of Radiation Oncology biology • physics
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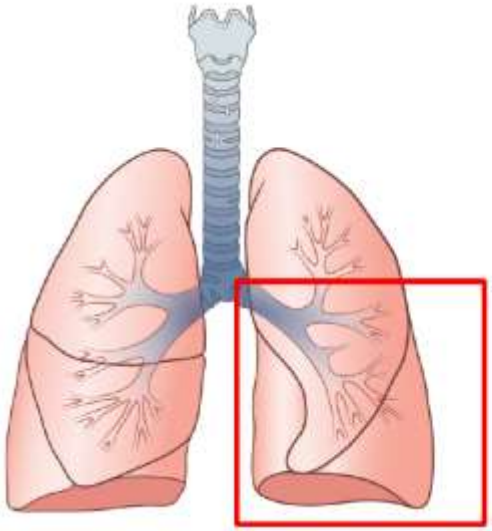
COMMENTARY

Application of Critical Volume-Dose Constraints for Stereotactic Body Radiation Therapy in NRG Radiation Therapy Trials

Timothy A. Ritter, PhD,*,†,†† Martha Matuszak, PhD,†,†† Indrin J. Chetty, PhD,‡,†† Charles S. Mayo, PhD,†,†† Jackie Wu, PhD,§,†† Puneeth Iyengar, MD, PhD,‖,†† Michael Weldon, MS,¶,†† Clifford Robinson, MD,#,†† Ying Xiao, PhD,**,†† and Robert D. Timmerman, MD‖,††



- Rough rule of thumb: For a parallel organ, keep a certain amount of the organ (approximately 1/3) preserved
- NRG protocols, and others, define threshold doses for 1500 cc and 1000 cc of lung

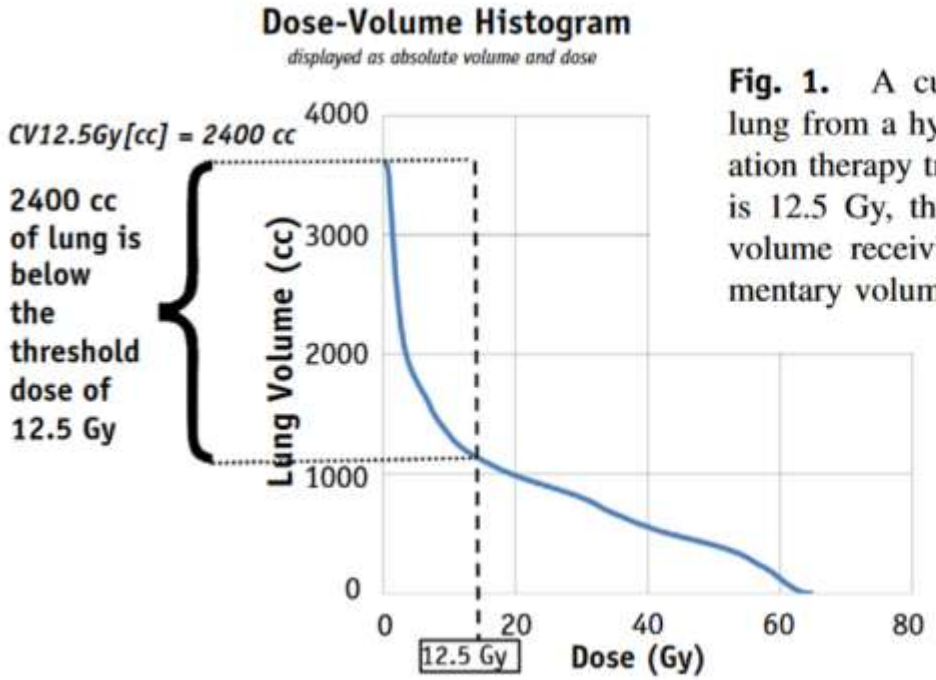


Fig. 1. A cumulative dose-volume histogram for total lung from a hypothetical 5-fraction stereotactic body radiation therapy treatment. In this example the threshold dose is 12.5 Gy, the total lung volume is 3600 cm^3, and the volume receiving $\geq$12.5 Gy is 1200 cm^3. The complementary volume, CV12.5 Gy[cc], is 2400 cm^3.

CV12.5 = volume receiving 12.5 Gy **or less**

5 fractions: 1.5 L receiving <12.5 Gy

Table 6: Series reporting results for SBRT for synchronous MPLC

Author	N	Treatment	Dose	Median F/U (mos)	AE ≥ Gr 3	LC (SBRT)	OS
Sinha, 2006[129]	8	N/R	48-66 Gy in 3-4 fx	18.5	0%	93% (1.5-year)	100% (1.5-year)
Creach, 2012[127]	15	3 surgery + SBRT 12 SBRT x 2	40-54 Gy in 3-5 fx	24	0%	90% (at follow-up)	27.5% (2-year)
Griffioen, 2014[126]	62	56 surgery + SBRT 6 SBRT x 2	54-60 Gy in 3-8 fx	44	4.8%	84% (2-year)	56% (2-year)
Kumar, 2014[130]	26	SBRT x 2	30-60 Gy in 1-8 fx	12	4%	96% (at follow-up)	N/R
Shintani, 2014[128]	18	3 surgery + SBRT 15 SBRT x 2	48-60 Gy in 4-10 fx	34.3	11%	78% (3-year)	69% (3-year)

AE, adverse event; F/U, follow-up; LC, local control; MPLC, multiple primary lung cancer; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

Table 7: Series reporting results for SBRT for metachronous MPLC

Author	N	Median interval (months)	Treatment	Dose	Median F/U (mos)	AE ≥ Gr 3	LC (SBRT)	OS
Creach, 2012[127]	48	N/R	46 surgery + SBRT 2 SBRT x 2	40-54 Gy in 3-5 fx	24	0%	92% (at follow-up)	68% (2-year)
Griffioen, 2014[142]	107	48	98 surgery + SBRT 9 CRT + SBRT	54-60 Gy in 3-8 fx	46	3.7%	89% (3-year)	60% (3-year)
Hayes, 2015[141]	17	115	17 surgery + SBRT	48-60 Gy in 3-8 fx	18.3	N/R	93% (2-year)	88% (2-year)

AE, adverse event; F/U, follow-up; fx, fraction; LC, local control; MPLC, multiple primary lung cancer; N/R, not reported; OS, overall survival; SBRT, stereotactic body radiation therapy

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For patients with synchronous primary or multifocal tumors?

Statement KQ2F: Multiple primary lung cancers (MPLC) can be difficult to differentiate from intrathoracic metastatic lung cancer and pose unique issues for parenchymal preservation, therefore it is recommended that they are evaluated by a multidisciplinary team.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

Statement KQ2G: PET/CT and brain MRI are recommended in patients suspected of having MPLC to help differentiate from intrathoracic metastatic lung cancer. Invasive mediastinal staging should be addressed on a case-by-case basis.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 100%

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Statement KQ2H: SBRT may be considered as a curative treatment option for patients with synchronous MPLC. SBRT for synchronous MPLC has equivalent rates of local control and toxicity but decreased rates of overall survival compared to those with single tumors.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low
- **Consensus**: 94%

Statement KQ2I: SBRT is recommended as a curative treatment option for patients with metachronous MPLC. SBRT for metachronous MPLC has equivalent rates of local control and toxicity and overall survival compared to those with single tumors.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate
- **Consensus**: 94%

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Guidelines

UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy

Table 3: Thoracic Dose Constraints

Description	Constraint	3 Fractions		5 Fractions		8 Fractions	
		Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory
Brachial Plexus	DMax (0.5cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	< 27Gy	< 38Gy
Heart	DMax (0.5cc)	< 24Gy	< 26Gy	< 27Gy	< 29Gy	< 50Gy	< 60Gy
Trachea and bronchus	DMax (0.5cc)	< 30Gy	< 32Gy	< 32Gy	< 35Gy	< 32Gy	< 44Gy
Normal Lungs* (Lungs-GTV)	V20Gy	-	< 10%	-	< 10%	-	< 10%
	V12.5Gy	-	< 15%	-	< 15%	-	< 15%
Chest Wall	DMax (0.5cc)	< 37Gy	-	< 39Gy	-	< 39Gy	-
	D30cc	< 30Gy	-	< 32Gy	-	< 35Gy	-
Great Vessels	DMax (0.5cc)	-	< 45Gy	-	< 53Gy	-	-

Thank you

Acknowledgement :
Dr Kanhu Charan Patro
Department Of Radiation oncology, Apollo Hospitals Hyderabad