SIMPOSIO AIRO - SIRM

Diagnostica per Immagini e trattamenti non chirurgici del nodulo polmonare solitario

Radioterapia Stereotassica

Andrea R. Filippi

Early stage NSCLC

EDITORIAL

Treatment of Choice for Stage I Non-small Cell Lung Cancer: Surgery or Radiotherapy?

Hisao Asamura, MD

Journal of Thoracic Oncology • Volume 1, Number 8, October 2006

- The treatment of choice for early-stage NSCLC is anatomic surgical resection
- Certain patients can be considered medically or functionally not amenable with surgery
- For these patients, radiotherapy is the alternative treatment, although with considerably worse outcome

Early stage NSCLC

The effect of tumor size on curability of stage I NSCLC (7620 resected pts)

Survival rates @ 12 yrs

5-15 mm	69%
16-25 mm	63%
26-35 mm	58%
36-45 mm	53%
>45 mm	43%

Wisnivesky JP et al., Chest, 2004

Radiation therapy for the treatment of unresected stage I NSCLC

(3842 pts who did not receive surgical resection)

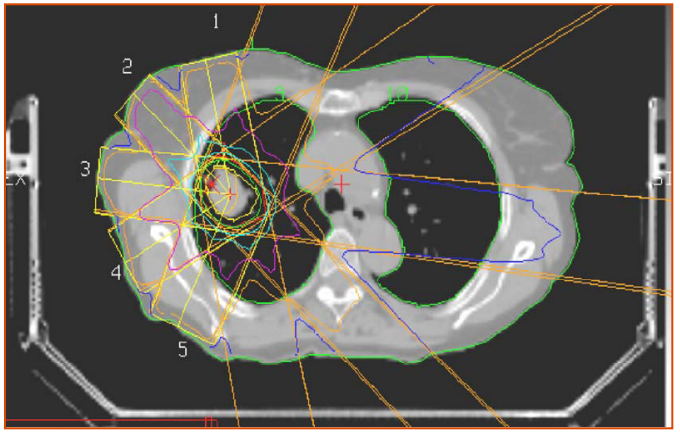
5 yrs survival rate: 15%

(local failure rates ranging from 30% to 70%)

Wisnivesky JP et al., Chest, 2005

Stereotactc Body Radiation Therapy (SBRT)

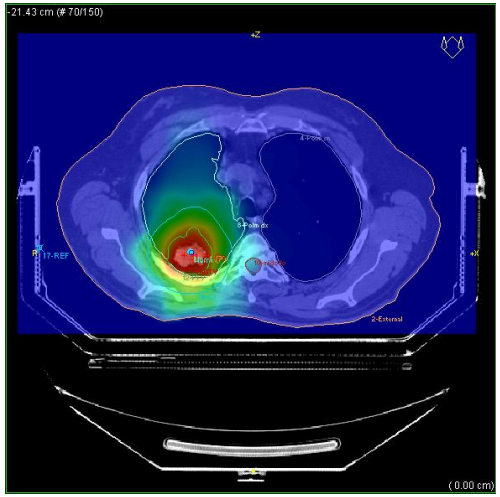
An external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of large fractions



- *Specialized treatment planning results in high target dose and steep dose gradients beyond the target*

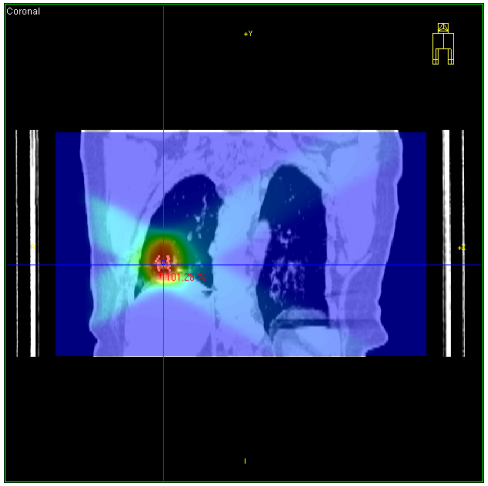
- *The challenge is to hit the entire extent of the tumor with extremely potent and biologically damaging therapy, while simultaneously avoiding surrounding normal tissue (tumor ablation and normal tissues sparing)*

SBRT in early stage lung tumors



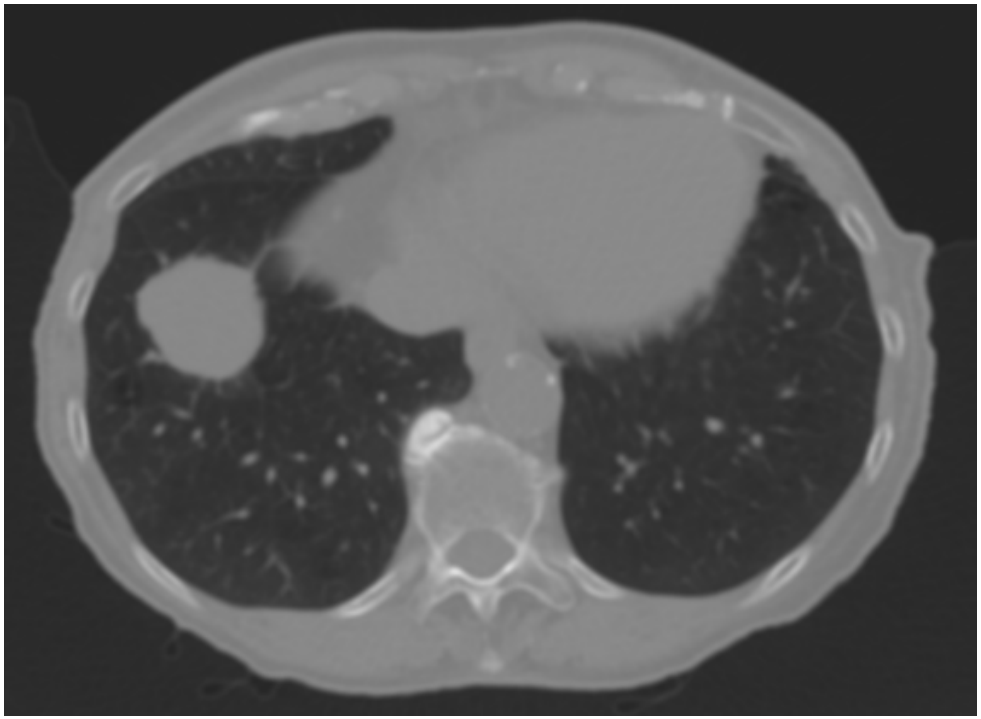
Early stage NSCLC

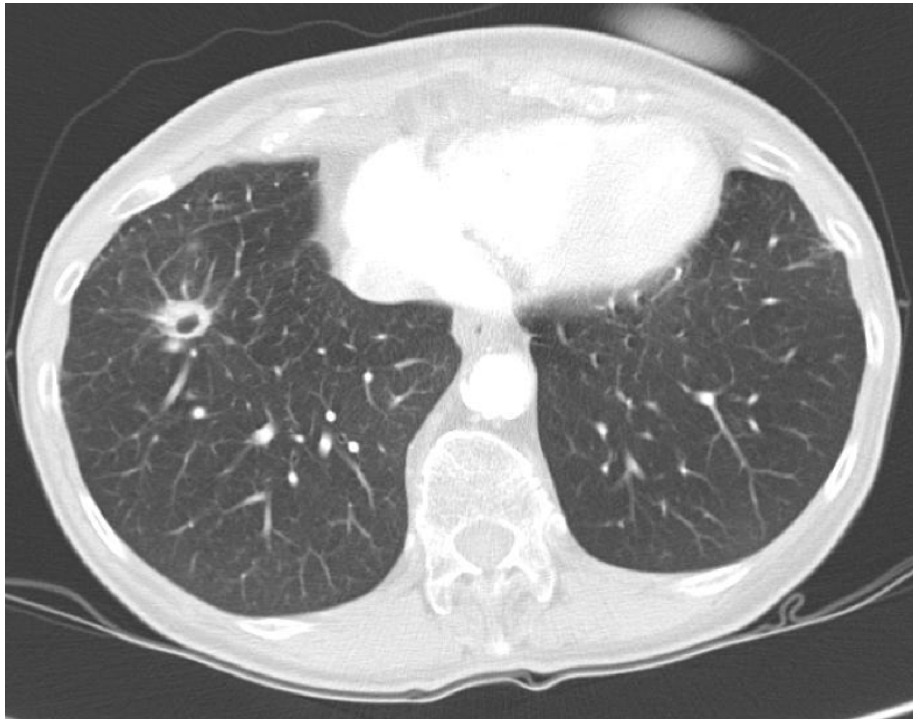
- Small volume
- Peripheral location



SBRT → Dose escalation

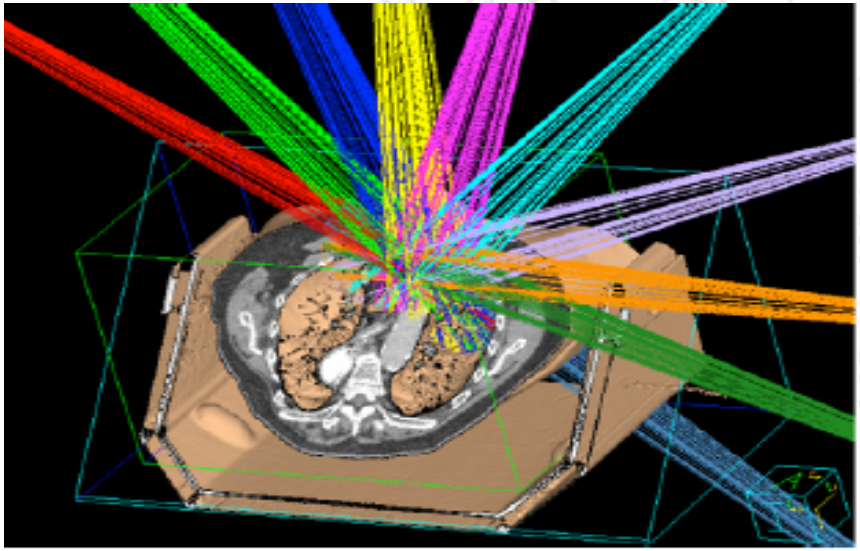
From SBRT to SABR
(Stereotactic ABlative Radiotherapy)

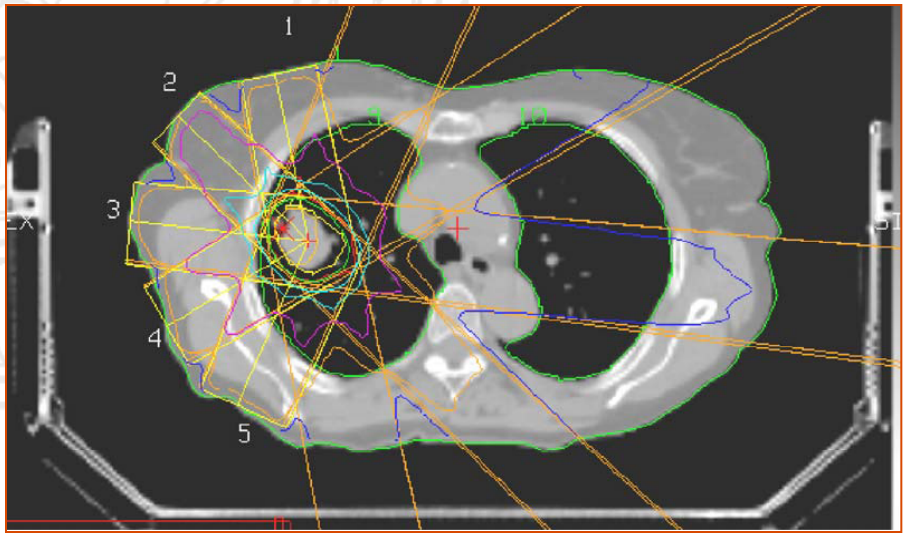




SBRT for lung cancer @ University of Torino

- Standard treatment for early stage NSCLC since May, 2003
- Patients medically or functionally unfit for surgery, or Sx refusal
- Roughly 200 pts have been treated @ University of Torino





Prospective Phase II trial of SBRT

Eligibility Criteria

Histological confirmation or clinical proof of NSCLC

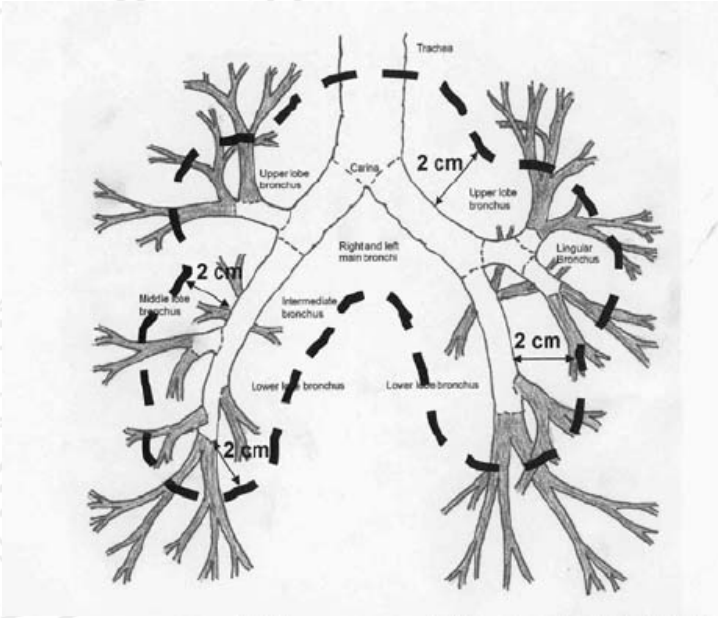
Stage IA or IB (T2aN0)

Contra-indication to surgery or refusal

Performance status ECOG 0-2

^{18}FDG CT-PET scan (mandatory)

Written informed consent



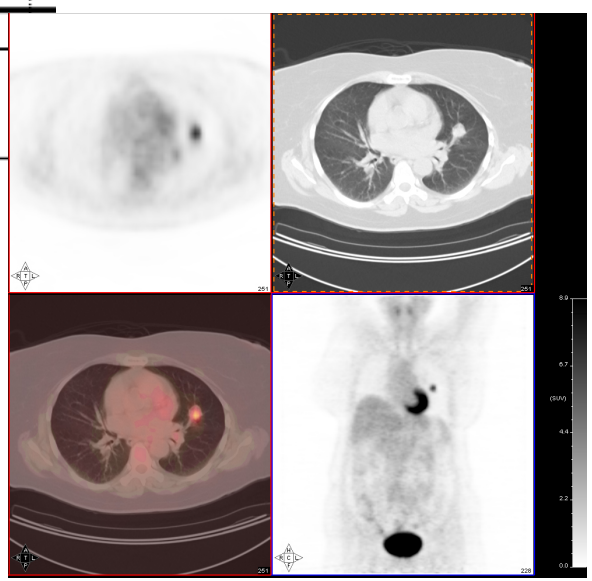
Exclusion criteria

Lesions located less than 2 cm away from airways or less than 1 cm away from major blood vessels

Clinical proof of malignancy

Probability of malignancy SPN (Gould 2007)

Diameter	5mm	10mm	15mm	20mm	25mm	30mm	35mm	40mm
50 years								
Current smoker	13	21	32	45	59	71	81	88
Never smoked	2	3	6	9	15	24	36	49
60 years								
Current smoker	25	37	50	64	76	84	90	94
Never smoked	4	7	11	18	28	41	55	68
70 years								
Current smoker	42	56	69	79	87	92	95	97
Never smoked	8	14	22	33	46	60	72	82
80 years								
Current smoker	61	73	83	89	94	96	98	99
Never smoked	17	26	38	52	65	77	85	91



Clinical proof of malignancy

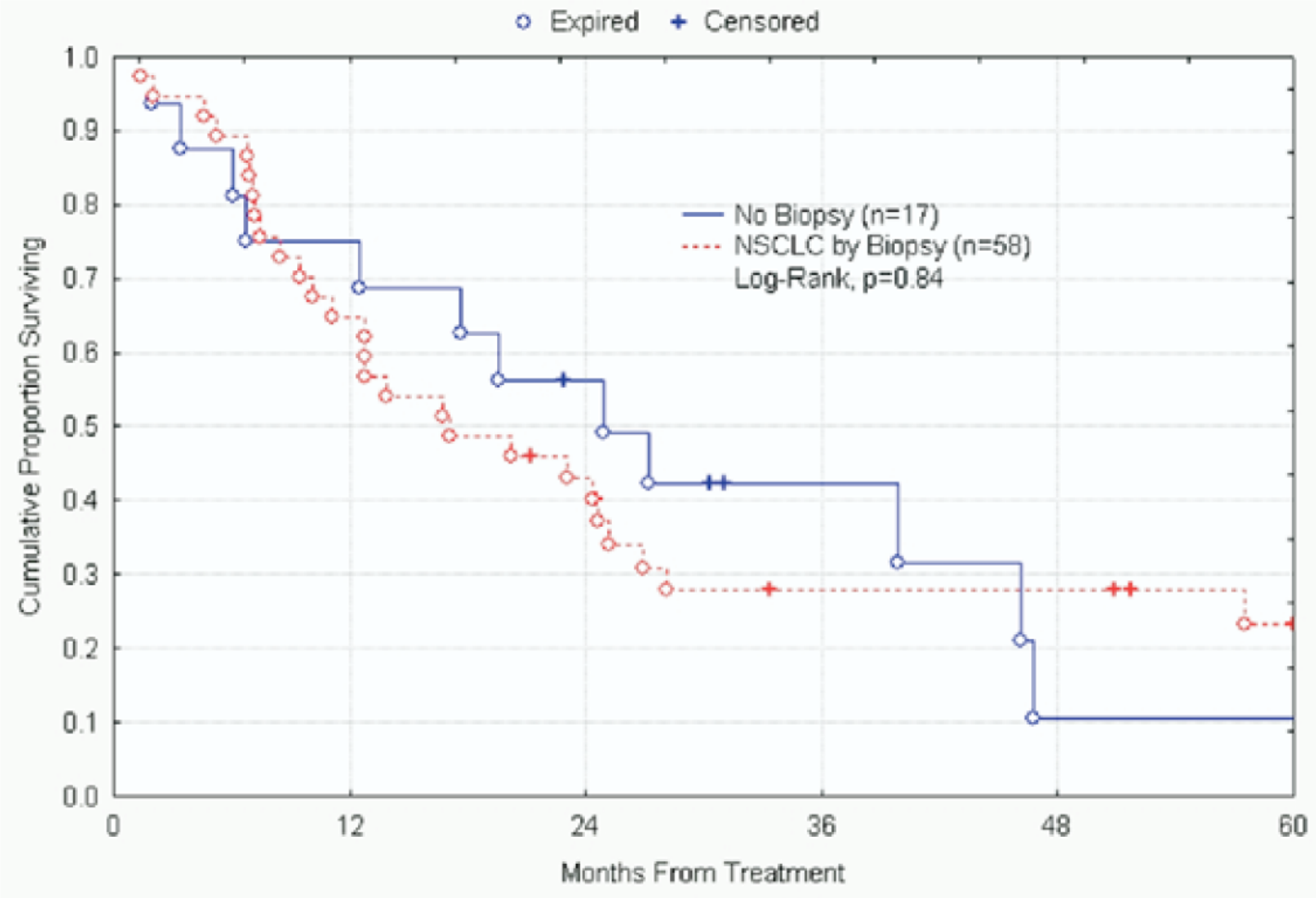
Lagerwaard (2008)

Baumann (2009)

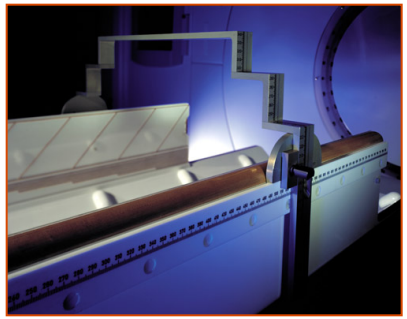
Nyman (2006)

Wulf (2004)

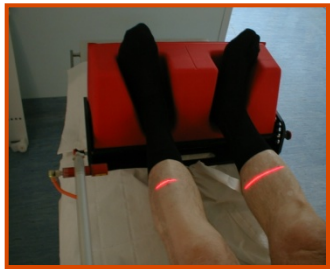
Beitler (2006)



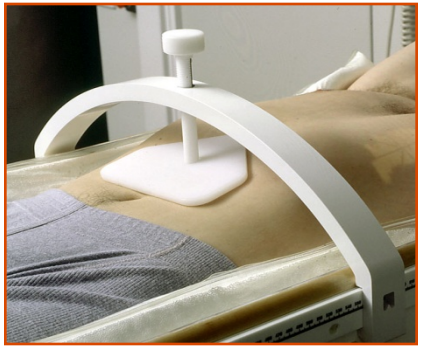
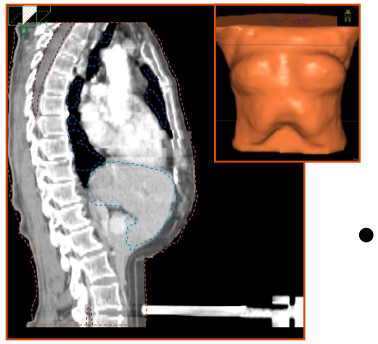
Patient fixation - Stereotactic Elekta® Body Frame

- Individually fitted vacuum pillow


- Laser system for tattoos

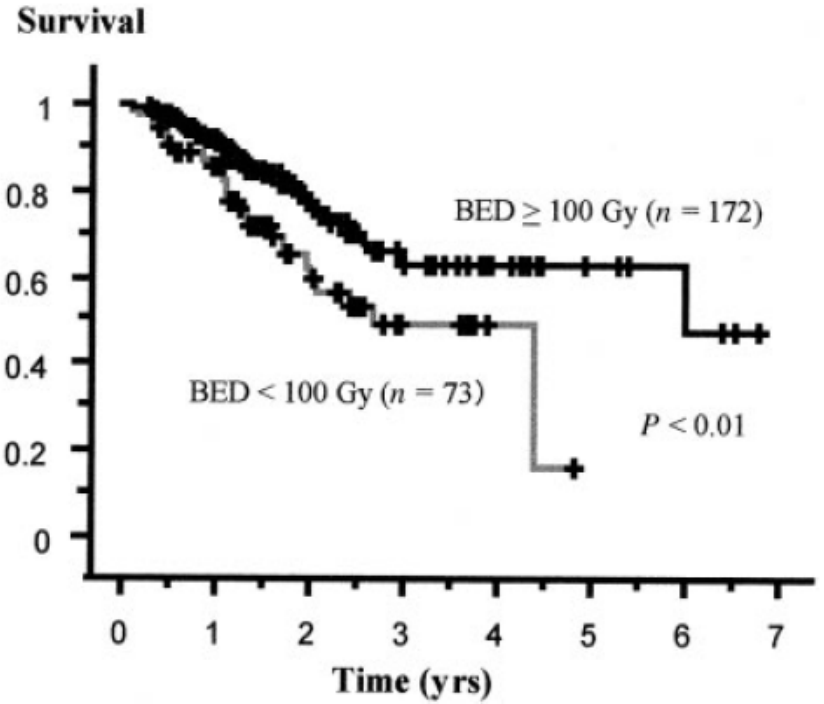



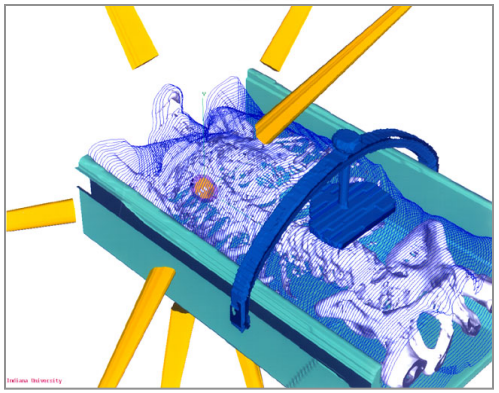
- Device for diaphragm compression

(breathing tumor movements >10 mm at fluoroscopy)

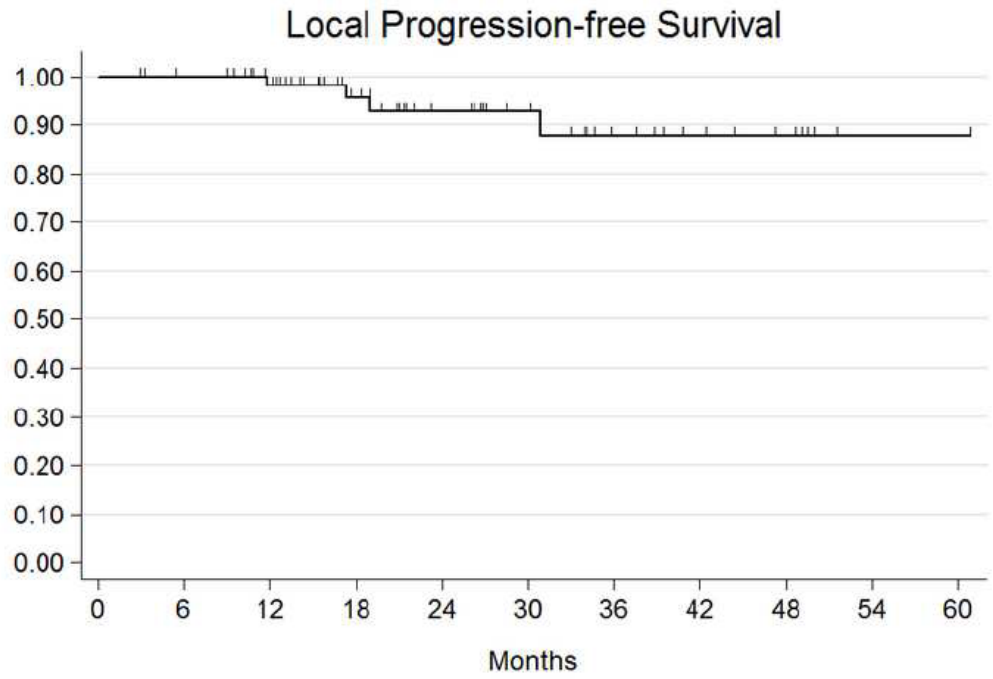
Treatment Planning & Delivery

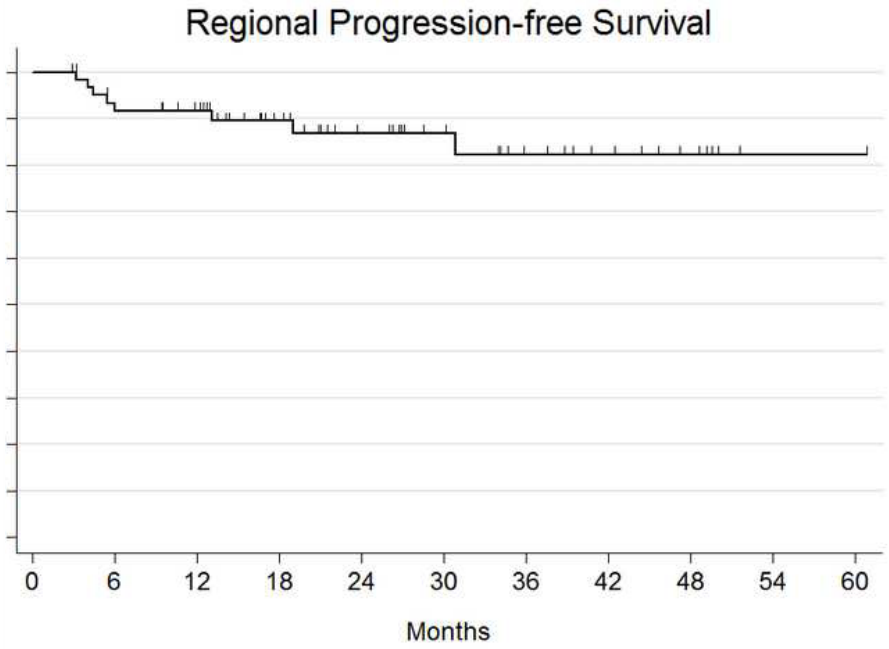
Authors	Dose	BED
Standard RT	2 Gy x 30-33	60-66 Gy
Nagata	12 Gy x 4	88 Gy
Timmerman	20 Gy x 3	150 Gy
Onimaru	7.5 Gy x 8	87 Gy
Hara	30 Gy x 1	100 Gy
	15 Gy x 3	**112.5 Gy**





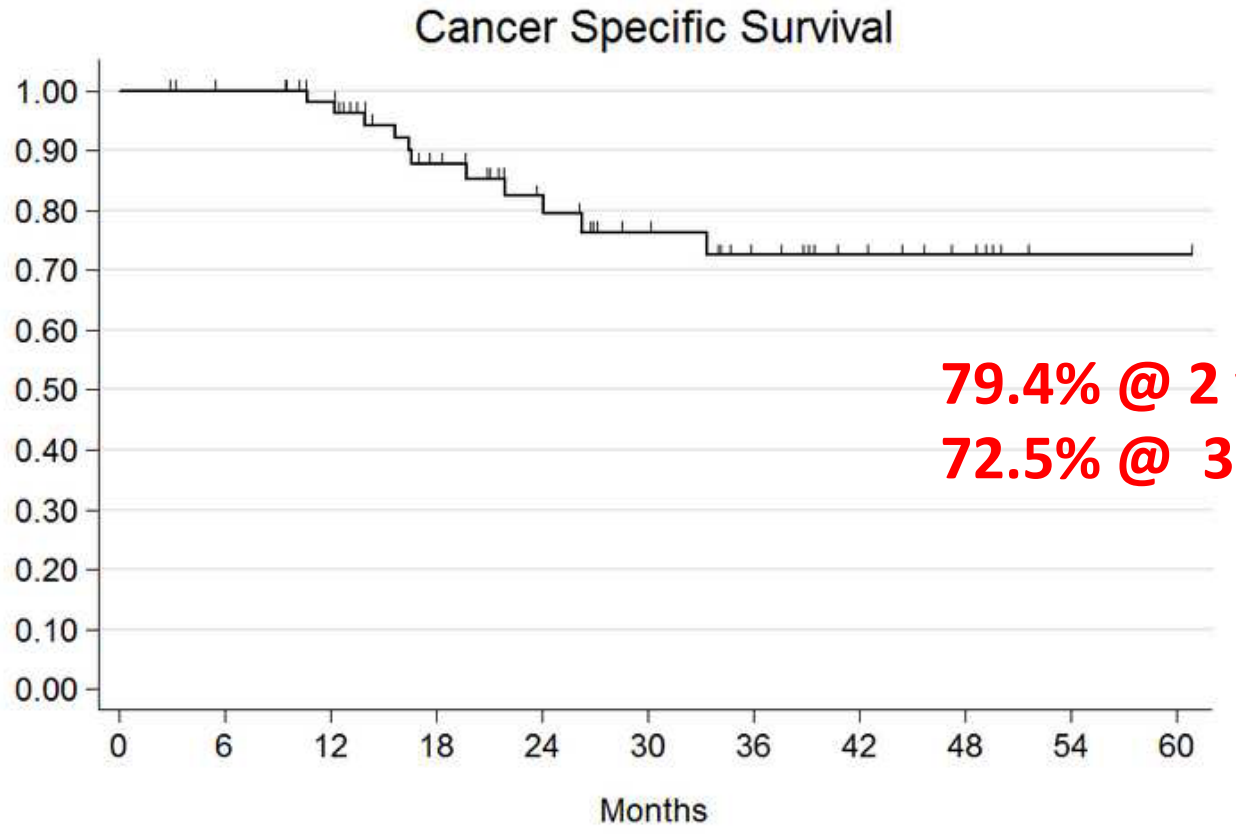
Progression-free Survival





Ricardi, Lung Cancer 2010

Cancer-specific Survival

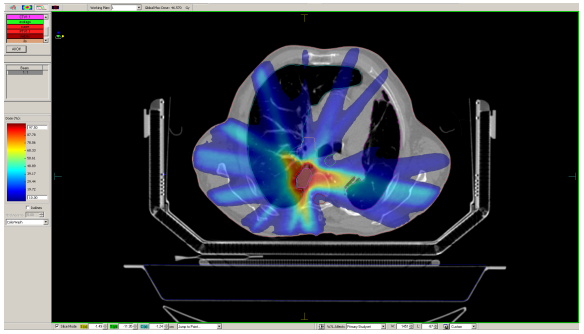


79.4% @ 2 yrs

72.5% @ 3 yrs

Ricardi et al, Lung Cancer 2010

Clinical Research



DISCOVERY MEDICINE

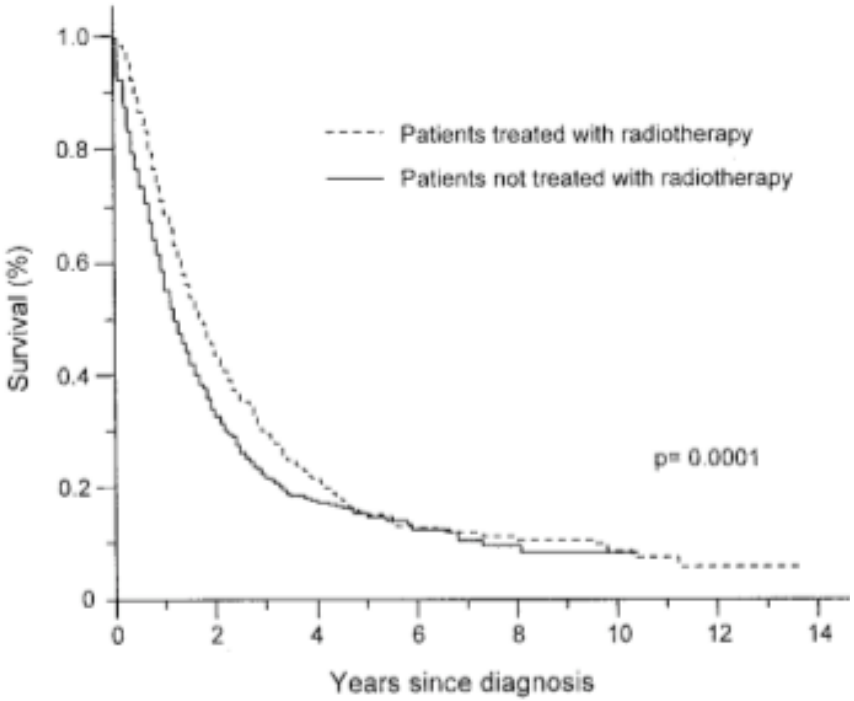
Table 1. Summary of Results of Recently Reported Prospective Trials of SBRT for Stage I NSCLC

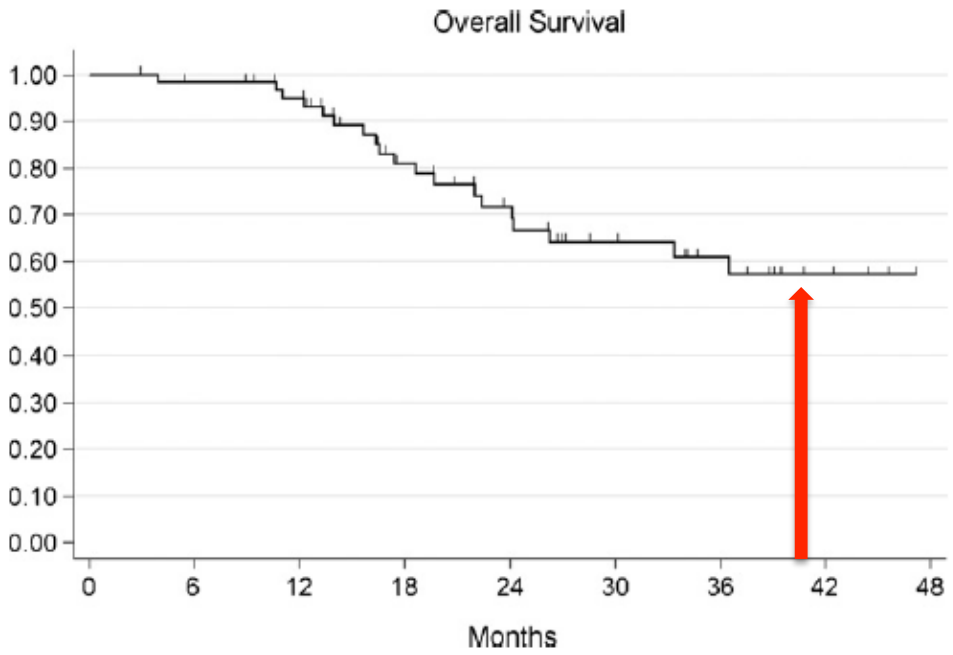
Author (Year)	Type/Stage	No. of Patients	Dose	Median Follow-up	Outcomes
Fakiris (Fakiris et al., 2009)	Phase II/Medically inoperable T1-2N0M0 NSCLC	70	T1: 20 Gy x 3 T2: 22 Gy x 3	50.2 months	3-year LC: 88.1% 3-year OS: 42.7% 3-year CaSS: 81.7%
Baumann (Baumann et al., 2009)	Phase II/Medically inoperable stage I NSCLC	57	15 Gy x 3 to 67%	35 months	3-year LC: 92% 1-, 2-, and 3-year OS: 86%, 65%, and 60% 1-, 2-, and 3-year CaSS: 93%, 88%, and 88% 3-year PFS: 52%
Koto (Koto et al., 2007)	Phase II/Stage I NSCLC	31	15 Gy x 3 (45 Gy) and 7.5 Gy x 8 (60 Gy)	32 months	3-year LC: 77.9% for T1 and 40% for T2 3-year OS: 71.7% 3-year CSS: 83.5%
Ricardi (Ricardi et al., 2010)	Phase II/Stage I NSCLC	62	15 Gy x 3	28 months	3-year LC: 87.8% 3-year CSS: 72.5% 3-year OS: 57.1%
Timmerman (Timmerman et al., 2010)	RTOG Phase II/ Medically inoperable T1-2N0M0 NSCLC (peripherally located)	55	18 Gy x 3	34.4 months	3-year LC: 97.6% 3-year DFS: 48.3% 3-year OS: 55.8%

Abbreviations: LC, local control; OS, overall survival; CSS, cause-specific survival; CaSS, cancer-specific survival; DFS, disease-free survival.

Discovery Medicine, 2011

Comparison between historical RT series and SBRT





Pattern of Failure

STEREOTACTIC BODY RADIATION THERAPY FOR EARLY-STAGE NON–SMALL-CELL LUNG CANCER: THE PATTERN OF FAILURE IS DISTANT

JEFFREY D. BRADLEY, M.D.,* ISSAM EL NAQA, PH.D.,* ROBERT E. DRZYMALA, PH.D.,* MARCO TROVO, M.D.,† GRIFFIN JONES,* AND MARY DEE DENNING, R.N.*

Table 2. Patterns of failure among study patients

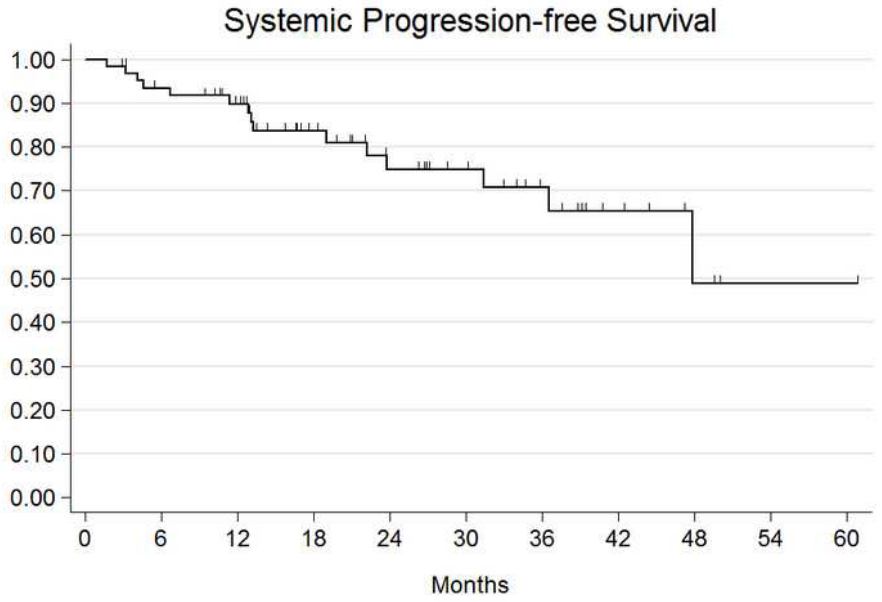
Local	7
Local only	3
Local and nodal	2
Local and distant	1
Local, nodal, and distant	1
Nodal	7
Nodal only	1
Nodal and distant	3
Distant	19
Distant only	10
Metachronous lung	15

Table 4. Overall survival among study patients

Prognostic factor	Univariate (p value)	Multivariate (p value)
Age	0.2858	NS
Sex	0.1148	NS
Performance status	0.0766	NS
Biopsy	0.4030	NS
Location (peripheral/central)	0.4285	NS
Tumor dimension	0.1526	NS
T stage	0.2797	NS
Poor lung function	0.5956	NS
Fraction size	0.6609	NS
Total Rx dose	0.7822	NS
GTV volume	0.9376	NS
PTV volume	0.4856	NS
Maximum dose (Dmax)	0.9450	NS
Secondary cancer	0.4325	NS
Distant metastasis	0.001	0.0043 (n = 72)

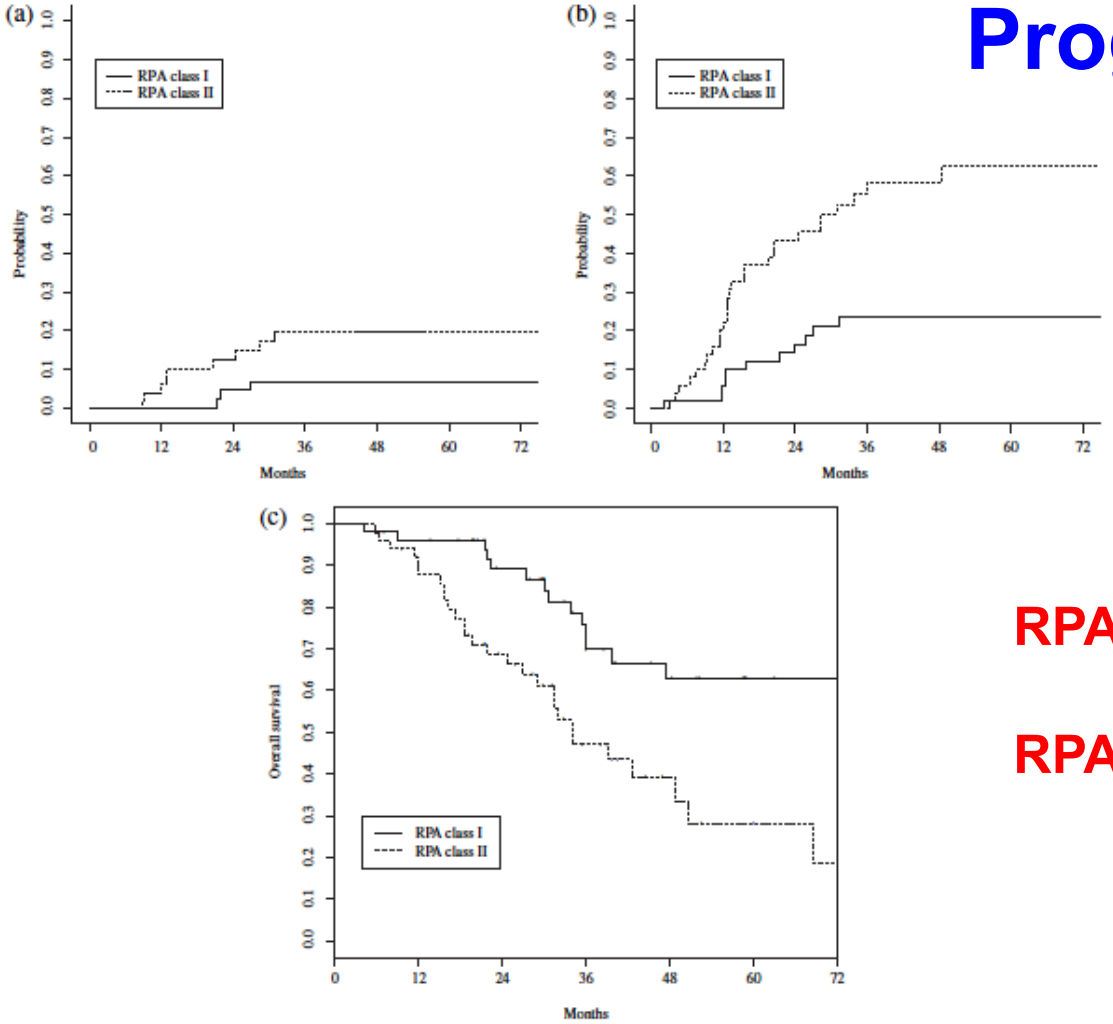
Stereotactic body radiation therapy for early stage non-small cell lung cancer: Results of a prospective trial

Umberto Ricardi[a,*], Andrea Riccardo Filippi[a], Alessia Guarneri[a], Francesca Romana Giglioli[b], Patrizia Ciammella[a], Pierfrancesco Franco[a], Cristina Mantovani[a], Piero Borasio[c], Giorgio Vittorio Scagliotti[d], Riccardo Ragona[a]



PROGNOSTIC FACTORS IN STEREOTACTIC BODY RADIOTHERAPY FOR NON–SMALL-CELL LUNG CANCER

Yukinori Matsuo, M.D., Ph.D.,* Keiko Shibuya, M.D., Ph.D.,* Yasushi Nagata, M.D., Ph.D.,†
Kenji Takayama, M.D.,* Yoshiki Norihisa, M.D.,* Takashi Mizowaki, M.D. Ph.D.,*
Masaru Narabayashi, M.D.,* Katsuyuki Sakanaka, M.D.,* and Masahiro Hiraoka, M.D., Ph.D.*



Prognostic Factors

RPA Class I: Female or T1a

RPA class II: Male T1b-T2a

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 4, pp. 1104–1111, 2011

Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 4, pp. 1033–1039, 2010

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.09.081

CLINICAL INVESTIGATION **Lung**

MAXIMUM STANDARDIZED UPTAKE VALUE FROM STAGING FDG-PET/CT DOES NOT PREDICT TREATMENT OUTCOME FOR EARLY-STAGE NON–SMALL-CELL LUNG CANCER TREATED WITH STEREOTACTIC BODY RADIOTHERAPY

Michael J. Burdick, M.D.,* Kevin L. Stephans, M.D.,* Chandana A. Reddy, M.S.,* Toufik Djemil, Ph.D.,* Shyam M. Srinivas, M.D., Ph.D.,† and Gregory M. M. Videtic, M.D.*

Departments of *Radiation Oncology and †Nuclear Medicine, Cleveland Clinic, Cleveland, OH

Prognostic Factors

Lung Cancer (2007) 56, 229–234

available at www.sciencedirect.com

ScienceDirect

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

FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer

David J. Hoopes[a], Mark Tann[b], James W. Fletcher[b], Jeffrey A. Forquer[a], Pei-Fen Lin[b], Simon S. Lo[a], Robert D. Timmerman[c], Ronald C. McGarry[a,*]

Pre-SBRT FDG-PET SUV did not predict 3-year overall survival or local control.

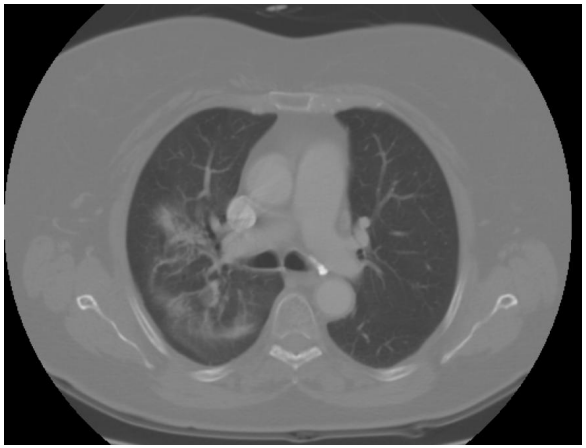
Conclusions: Pretreatment PET SUV_{max} did not predict for MF, DM, or OS in patients treated with SBRT for early-stage NSCLC. © 2010 Elsevier Inc.

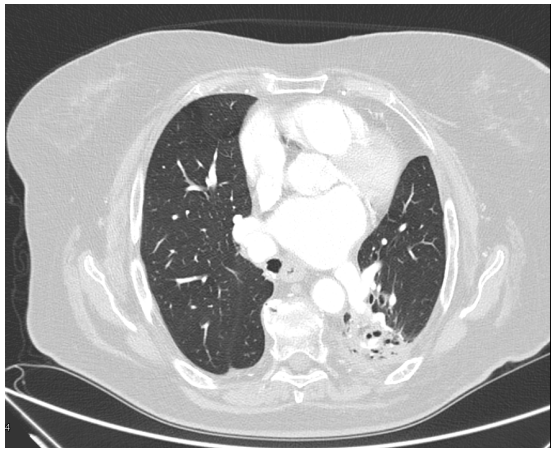
Both negative

TOXICITY

Acute radiological changes after SBRT: 60-80% (Ikezoe classification)

- Diffuse consolidation 20-30%
  (consolidation more than 5 cm in largest dimension)
- Patchy consolidation 8-22%
  (consolidation less than 5 cm in largest dimension)
- Diffuse ground glass opacities 4-8%
  (more than 5 cm of GGO)
- Patchy ground glass opacities 10-15%
  (less than 5 cm of GGO)
- No evidence of increased density 20-40%



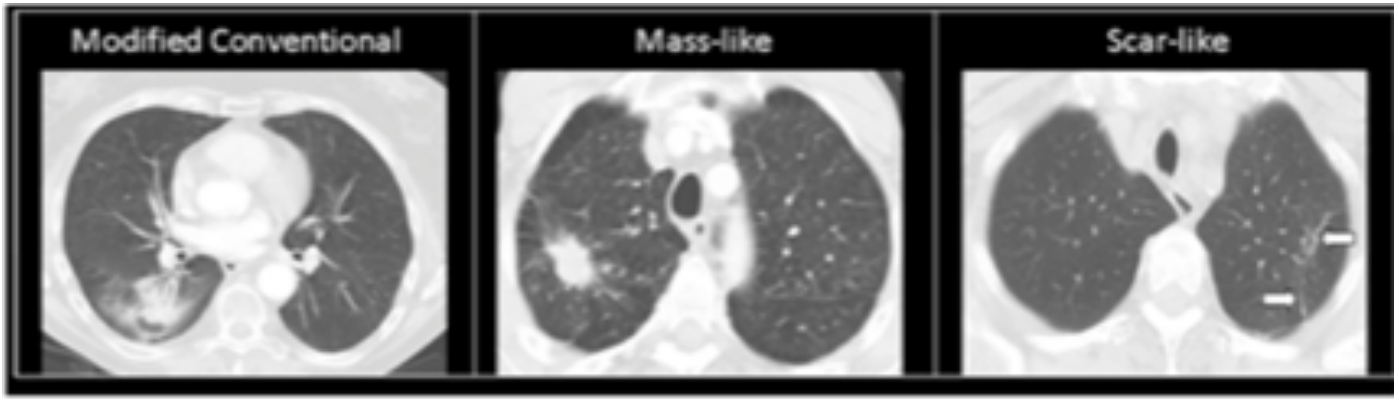


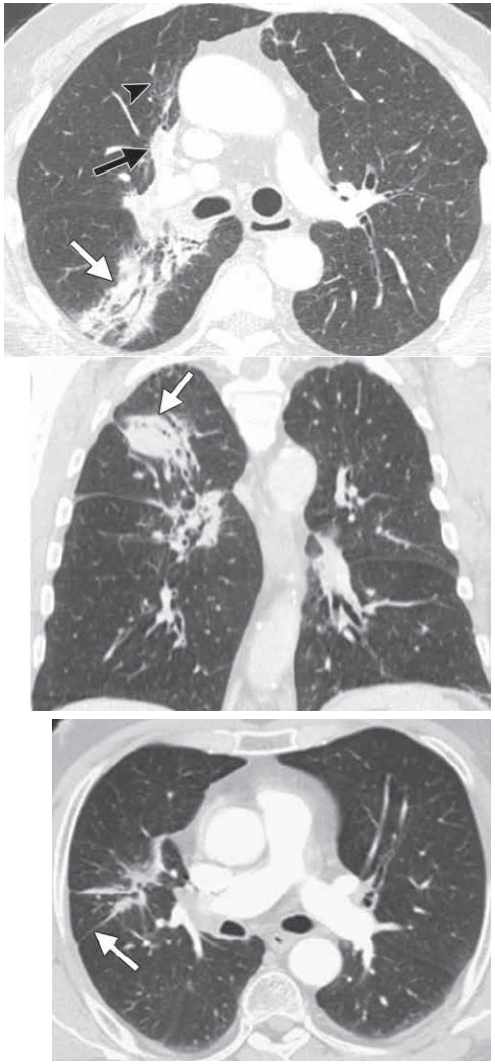
TOXICITY

Late radiological changes after SBRT

Radiation fibrosis (later than 6 months) (Koenig's classification, AJR 2002):

- Modified conventional pattern
- Mass-like pattern
- Scar-like pattern





Severe Pulmonary Toxicity

	No Pts	Dose	Grade 3+ Toxicity
Uematsu	66	30-76 Gy 5-15 fx	0%
Nakagawa	22	15-24 Gy 1 fx	0%
Nagata	40	40-48 Gy 4 fx	0%
Wulf	61	26-37.4 Gy 1-3 fx	3%
Hara	23	20-30 Gy 1 fx	4%
Hof	10	19-26 Gy 1 fx	0%
Onimaru	57	48-60 Gy 8 fx	2%
Whyte	23	15 Gy 1 fx	0%
Blomgren	17	30 Gy 2-3 fx	6%
Ricardi	**62**	**45 Gy/3fx or 26 Gy/1fx**	**3%**

Acta Oncologica, 2009; 48: 571–577

Dosimetric predictors of radiation-induced lung injury in stereotactic body radiation therapy

Table IV. Logistic regression analysis (correlation with RTOG grade 2-3 pulmonary toxicity)

	Odds Ratio	Std. Err.	z	p	95% Confidence Interval	
MLD_2	**1.52**	0.24	2.66	**0.008**	1.12	2.08
Primary/ Metastatic	3.03	3.98	0.84	0.399	0.23	39.79
Central/Peripheral	0.54	0.70	−0.48	0.634	0.04	6.75
Superior/Median/Inferior Lobe	1.53	0.89	0.73	0.464	0.49	4.79
PTV	1.03	0.03	1.05	0.293	0.98	1.08

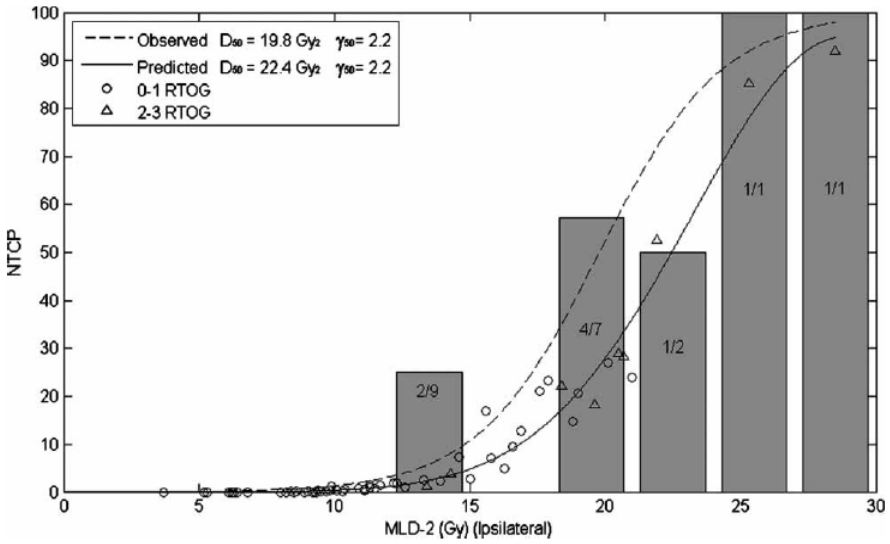


Table III. MLD_2 and NTCP mean values according to RTOG lung toxicity score

	Grade 0-1	Grade 2-3
MLD_2	**11.2 Gy** (95% CI 10.1-12.3 Gy)	**20.3 Gy** (95% CI 16.6-23.9 Gy)
NTCP	**4%** (95% CI 2-5.9%)	**37%** (95% CI 11.6-62.3%)

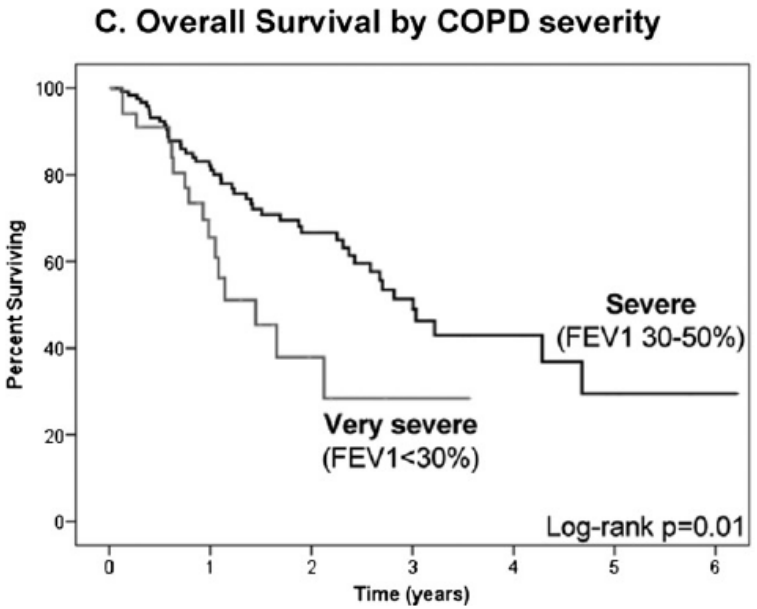
Ricardi U et al, 2009

CLINICAL INVESTIGATION

CURATIVE TREATMENT OF STAGE I NON–SMALL-CELL LUNG CANCER IN PATIENTS WITH SEVERE COPD: STEREOTACTIC RADIOTHERAPY OUTCOMES AND SYSTEMATIC REVIEW

DAVID PALMA, M.D., M.SC., F.R.C.P.C.,*† FRANK LAGERWAARD, M.D., PH.D.,*
GEORGE RODRIGUES, M.D., M.SC., F.R.C.P.C.,† CORNELIS HAASBEEK, M.D., PH.D.,*
AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.*

*VU University Medical Center, Amsterdam, Netherlands; †Division of Radiation Oncology, London Regional Cancer Program, London, Ontario, Canada



133 patients with severe and 43 with very severe COPD treated with SBRT

Table 3. Thirty-day mortality and complications associated with treatment of stage I NSCLC in patients with poor ventilatory function

First author	30-day mortality	Complications
Surgery		
Magdeleinat (26)	8%*	>90% admitted to ICU >45% with complications (pneumonia, air leak, and arrhythmia most common)
Lau (19)	25% after open lobectomy* 7% for open segmentectomy or VATS procedure*	Median hospital stay 8–12 days <10% admitted to ICU
SBRT		
Henderson (27)	0%*	>69% with Grade 1 or 2 toxicity of some kind†
Stephans (28)	0%*	No Grade 3 or higher pneumonitis
Palma (current study)	0%	6 patients (3%) with Grade 3 toxicity

DIFFERENCES IN PULMONARY FUNCTION BEFORE VS. 1 YEAR AFTER HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR SMALL PERIPHERAL LUNG TUMORS

Toshio Ohashi, M.D.,* Atsuya Takeda, M.D.,*† Naoyuki Shigematsu, M.D.,* Etsuo Kunieda, M.D.,* Akitoshi Ishizaka, M.D.,‡ Junichi Fukada, M.D.,* Hossain M. Deloar, Ph.D.,* Osamu Kawaguchi, M.D.,* Toshiaki Takeda, M.D.,† Kazuhiko Takemasa, M.D.,† Kouichi Isobe, M.D.,§ and Atsushi Kubo, M.D.*

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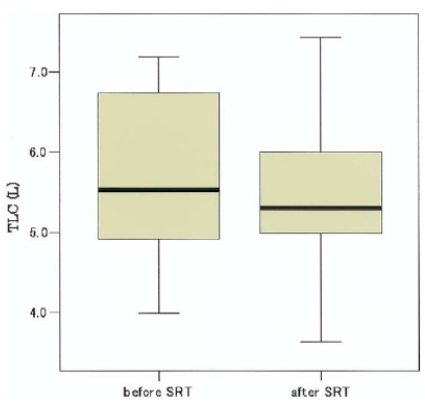
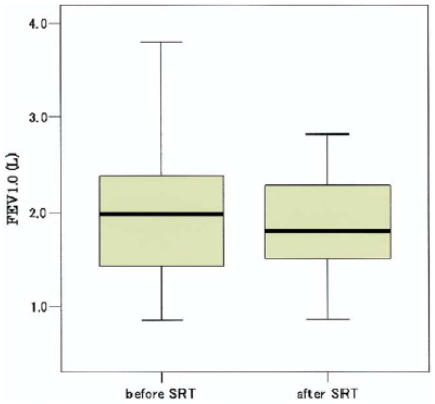
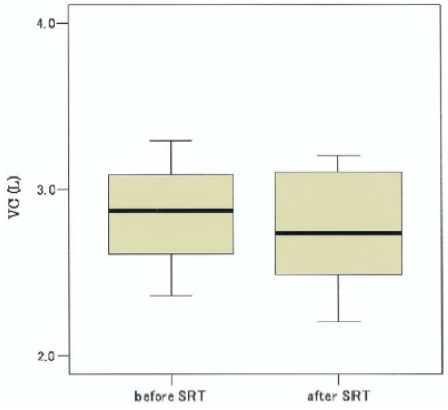
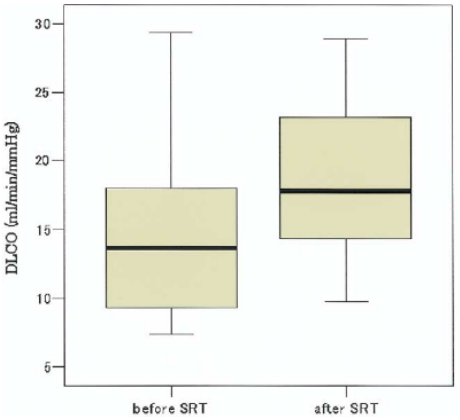








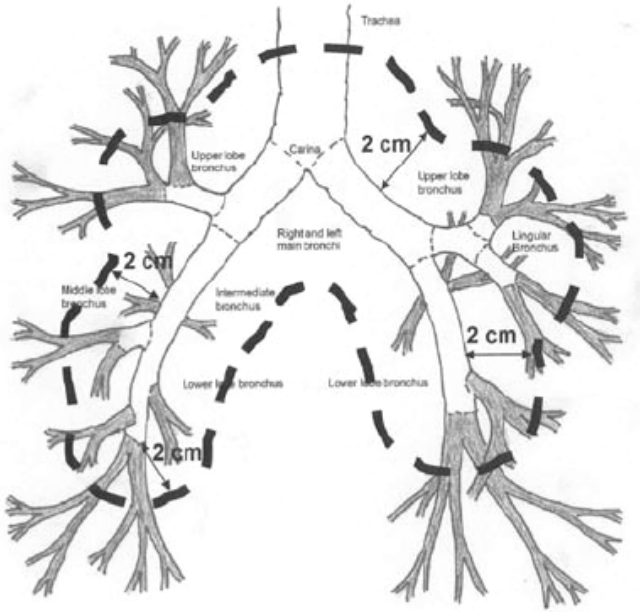
There were no significant changes in TLC, VC, or FEV1 before vs. after SBRT

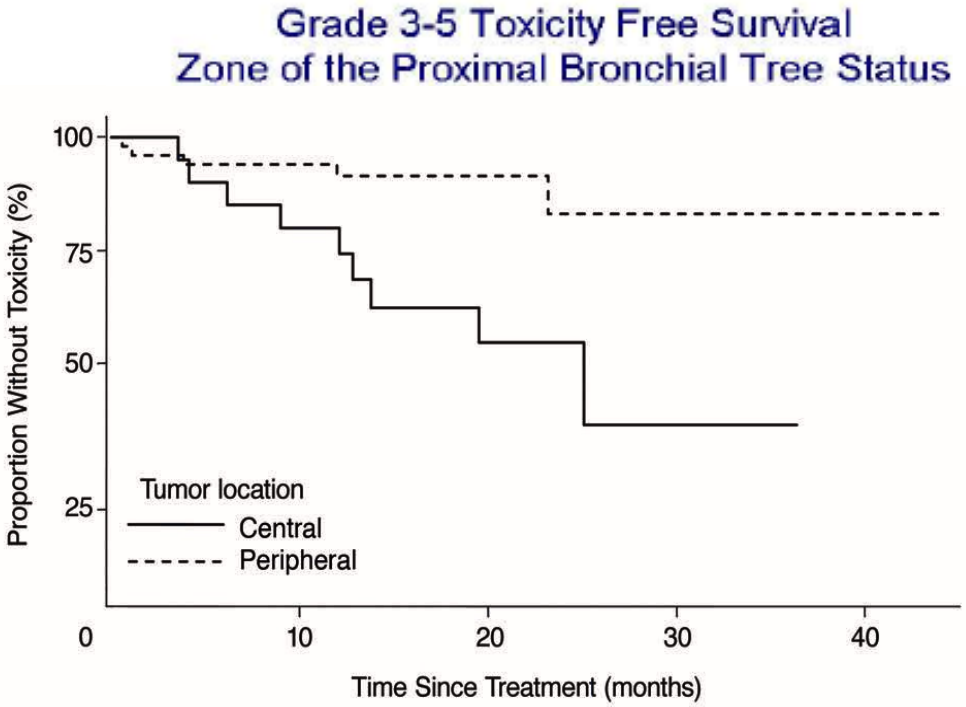
These results are more favorable than those obtained with surgical procedures, including lobectomy, segmentectomy, and VATS.

Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 1003–1008, 2005

J Clin Oncol 24:4833-4839. © 2006 by American Society of Clinical Oncology

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





Location

___inside ----outside p=0.004

Timmerman R et al, 2006

T1 tumors:

20 Gy x 3 fractions (60 Gy total)

T2 tumors:

22 Gy x 3 fractions (66 Gy total)

Original article

Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy

Michael T. Milano *, Yuhchyau Chen, Alan W. Katz, Abraham Philip, Michael C. Schell, Paul Okunieff

Department of Radiation Oncology, University of Rochester Medical Center, NY, USA

Institution	Patient population	Prescribed dose (Gy)	Fraction dose (Gy)	BED2 (Gy)	Toxicity
IndianaU.	Stage I NSCLC	60-66	20-22	219-258	11-Fold increase risk of severe-fatal toxicity
Hokkaido U	NSCLC and Mts	48	6	64	1 of 9 with severe toxicity
U. Texas, San Antonio	NSCLC and Mts	36	6-12	86-126	1 of 9 – asymptomatic airway collapse
Air Force General Hospital	Stage I-II NSCLC	60-70 40-50	6-7 4-5	120-167	No severe toxicity
VU Amsterdam	Stage I NSCLC	60	7.5	88	No severe toxicity
Technical U.	NSCLC and Mts	35	7	105	No severe toxicity

Moderately hypofractionated SBRT to central thoracic lesions is effective with respect to local control and toxicity.

Radiother Oncol, 2009

Use of “risk-adapted” SBRT protocol

- **Peripheral lesions (T1a-T1b):**

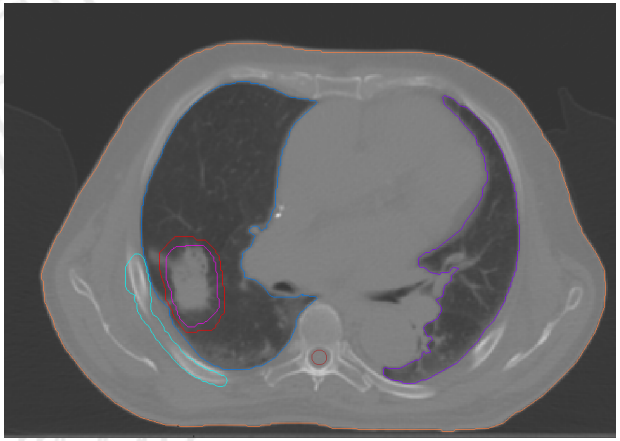
- 54 Gy/ 3 fractions

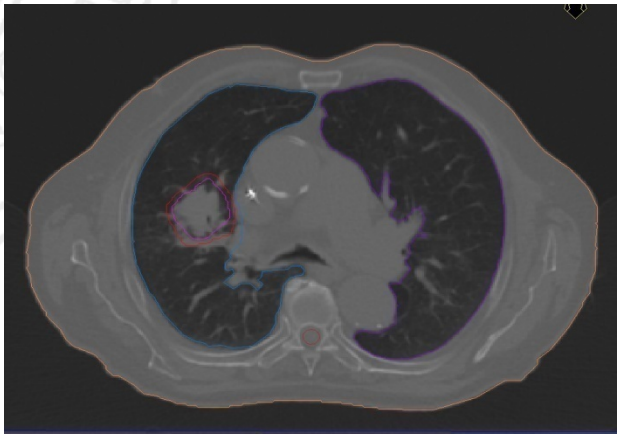
- **Peripheral lesions, with extensive contact with the chest wall, or larger tumors (T2a):**

- 55 Gy/ 5 fractions

- **Central lesions:**

- 60 Gy/ 8 fractions



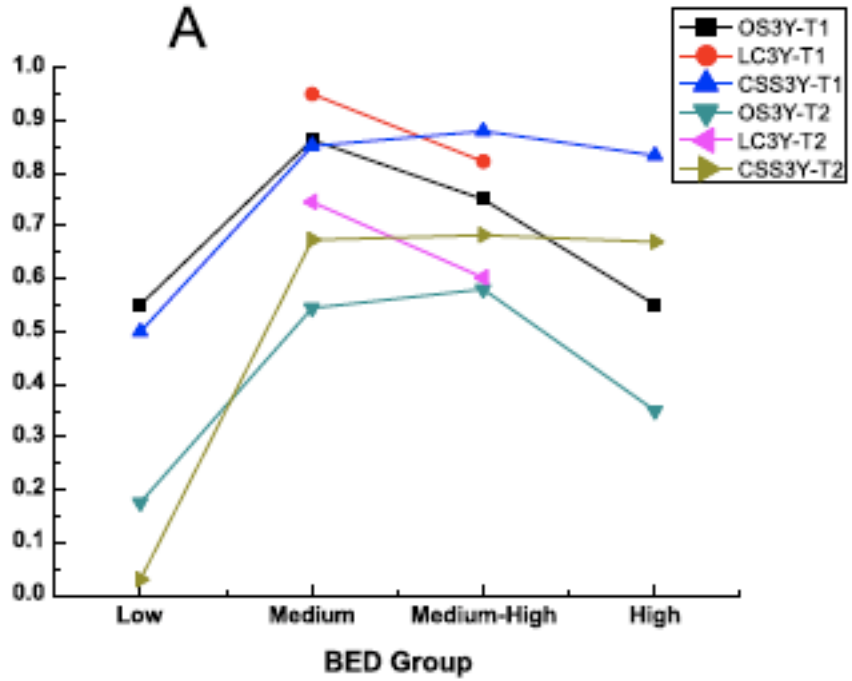


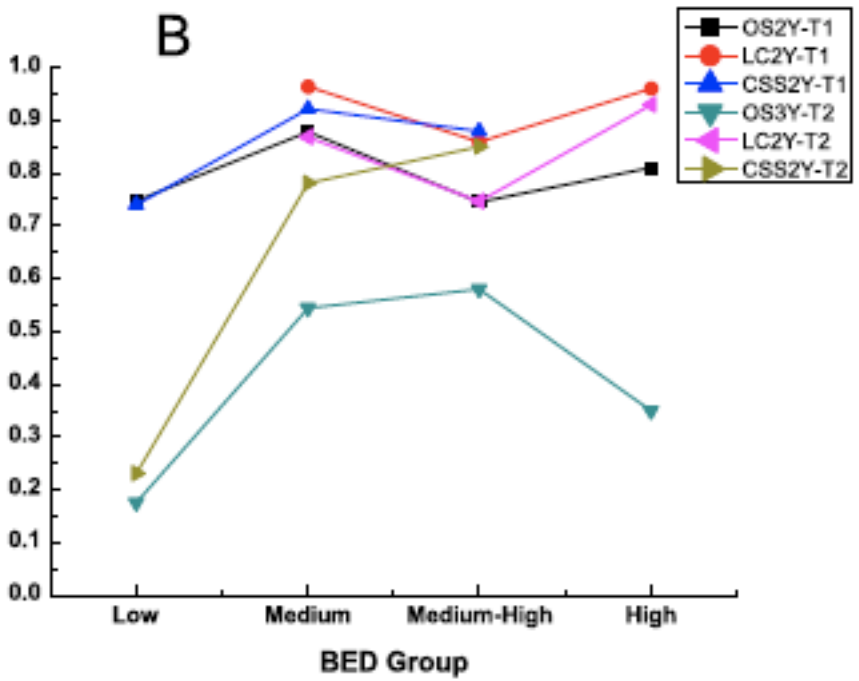
How to improve clinical outcome?

- Lower survival for larger tumors→ dose escalation?
- Lower survival due to high rate of distant metastases: systemic therapy?
- Patients selection (prognostic index?)

WHICH IS THE OPTIMAL BIOLOGICALLY EFFECTIVE DOSE OF STEREOTACTIC BODY RADIOTHERAPY FOR STAGE I NON–SMALL-CELL LUNG CANCER? A META-ANALYSIS

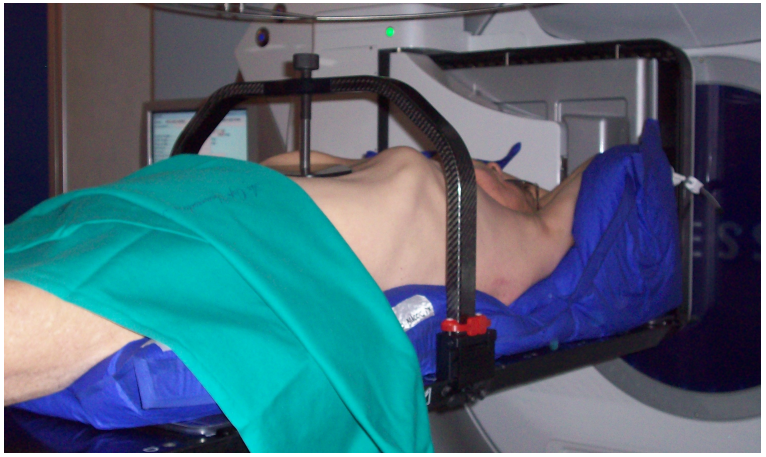
JIAN ZHANG, PH.D.,*†§ FUJUN YANG, M.D.,*†§ BAOSHENG LI, M.D., PH.D.,†§ HONGSHENG LI, PH.D.,†§ JING LIU, PH.D.,‡ WEI HUANG, M.D.,†§ DONGQING WANG, M.D.,†§ YAN YI, M.D.,†§ AND JUAN WANG, M.D.†§

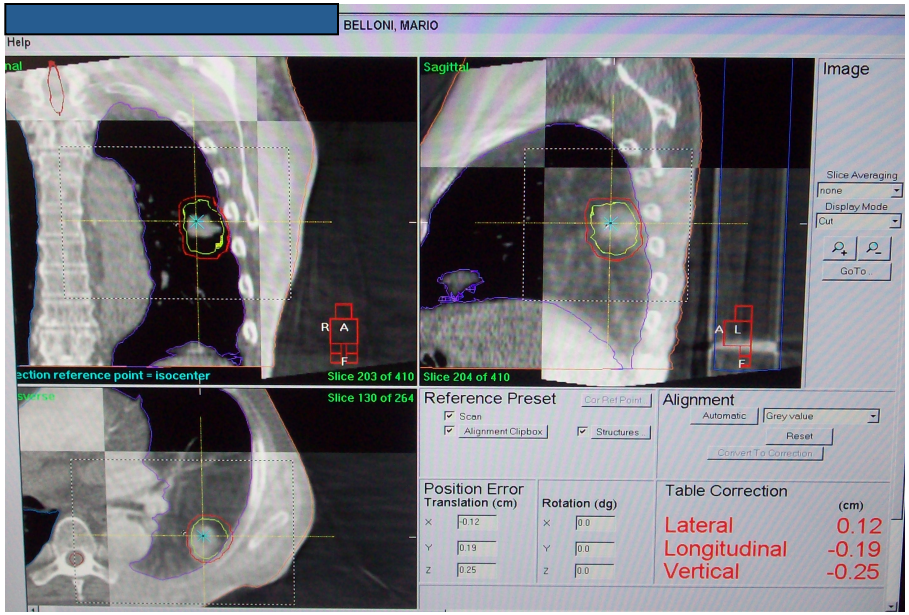




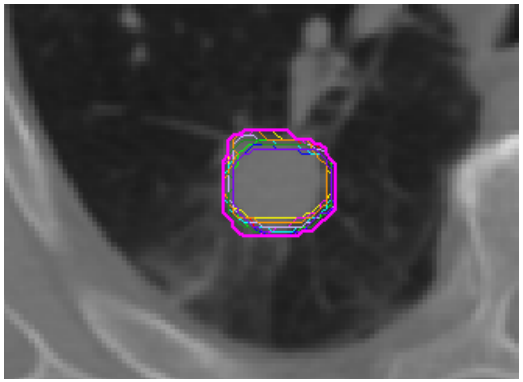
IJROBP 2011

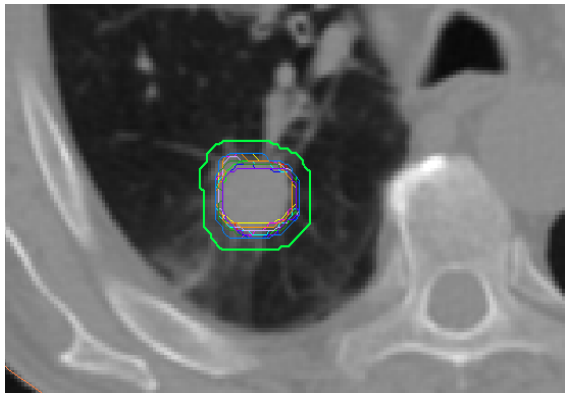
Frameless SBRT/SABR

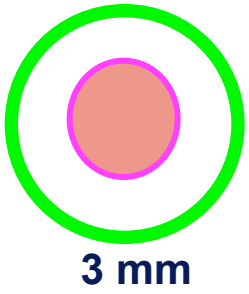




4D-CT Target Definition



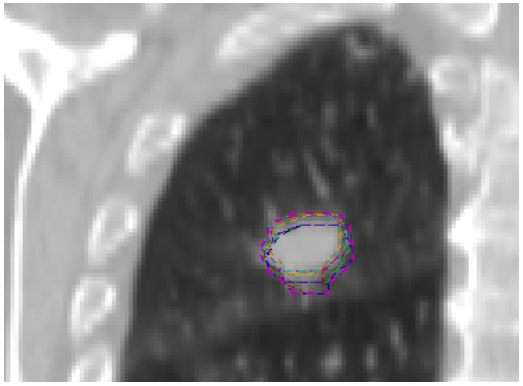


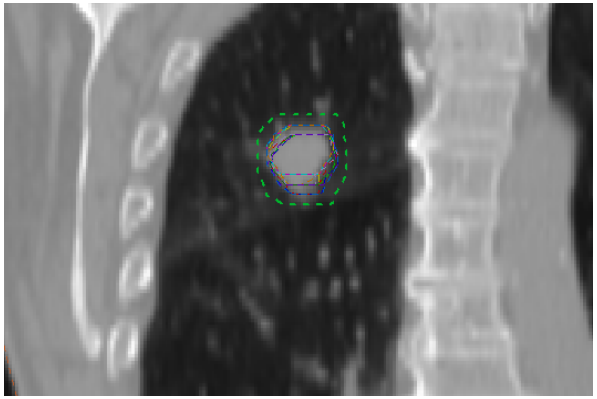


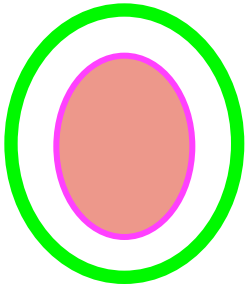
CTV = GTV

ITV_{10} phases= ITV derived from contouring of all 10 phases of the 4DCT (CTV_1, CTV_2…CTV_{10})

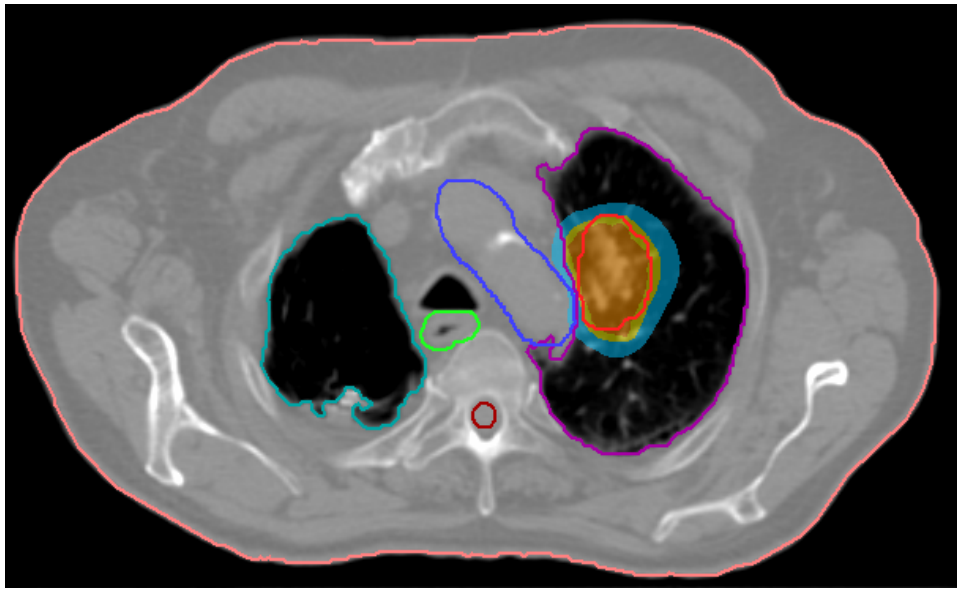
PTV = ITV + 3 mm isotropic

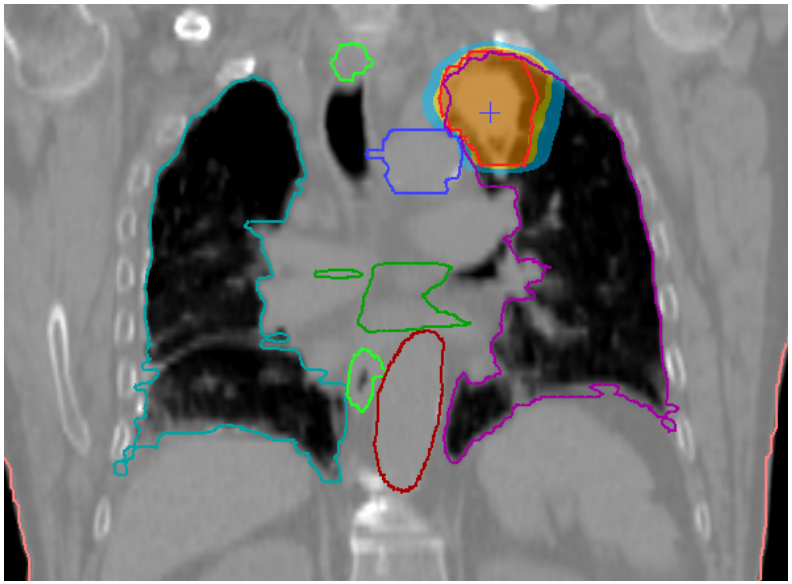






Volumetric Modulated Arc Therapy





Stereotactic radiation therapy: changing treatment paradigms for stage I NSCLC

- In patients with stage I NSCLC where surgery is contraindicated, SBRT achieves superior survival as compared to conventionally fractionated RT
- In patients identified to be at high risk for surgical complications, SBRT appears to provide an effective alternative with low risks of hospitalization and 30-day mortality
- The role of SBRT in operable patients remains to be defined within randomized trials
- Future treatment algorithms should include individualized assessment of surgical risks, and the consideration of SBRT for high-risk patients, in order to develop a personalized treatment approach

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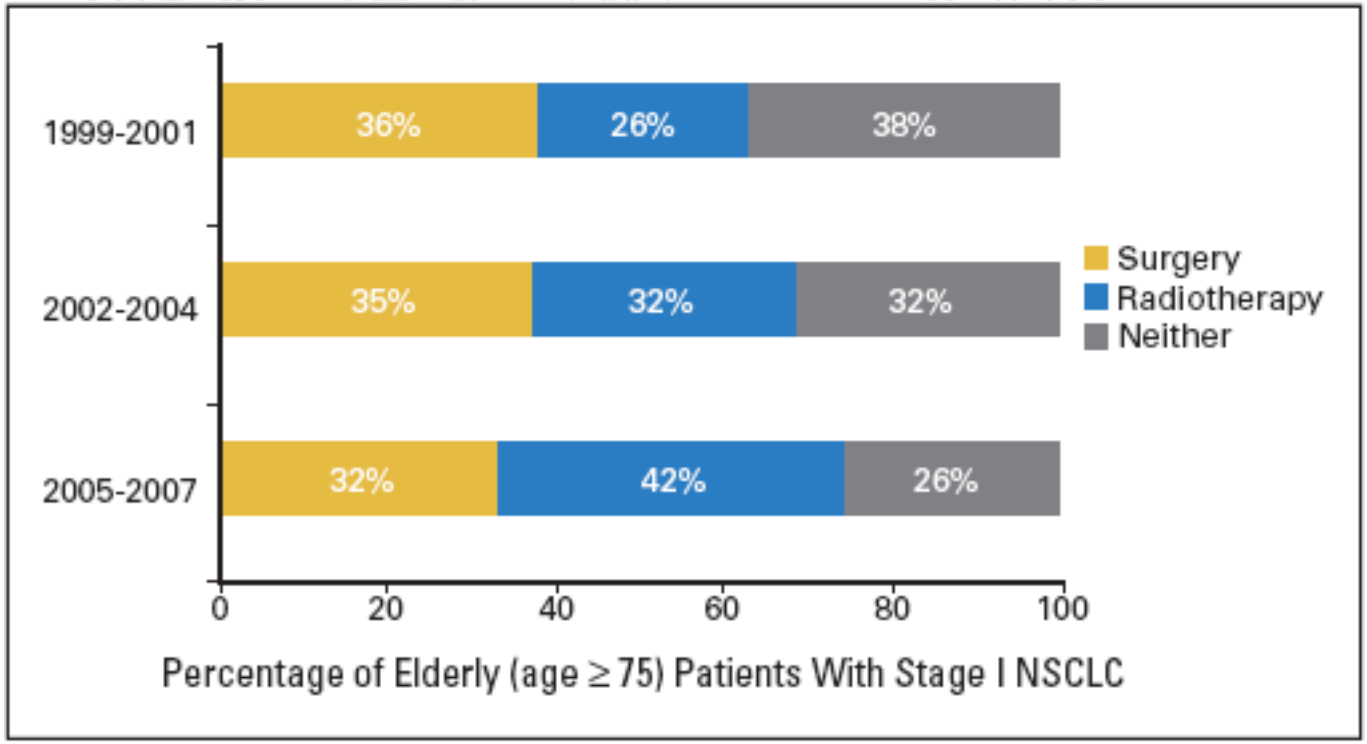
ORIGINAL REPORT

Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non–Small-Cell Lung Cancer: A Population-Based Time-Trend Analysis

David Palma, Otto Visser, Frank J. Lagerwaard, Jose Belderbos, Ben J. Slotman, and Suresh Senan



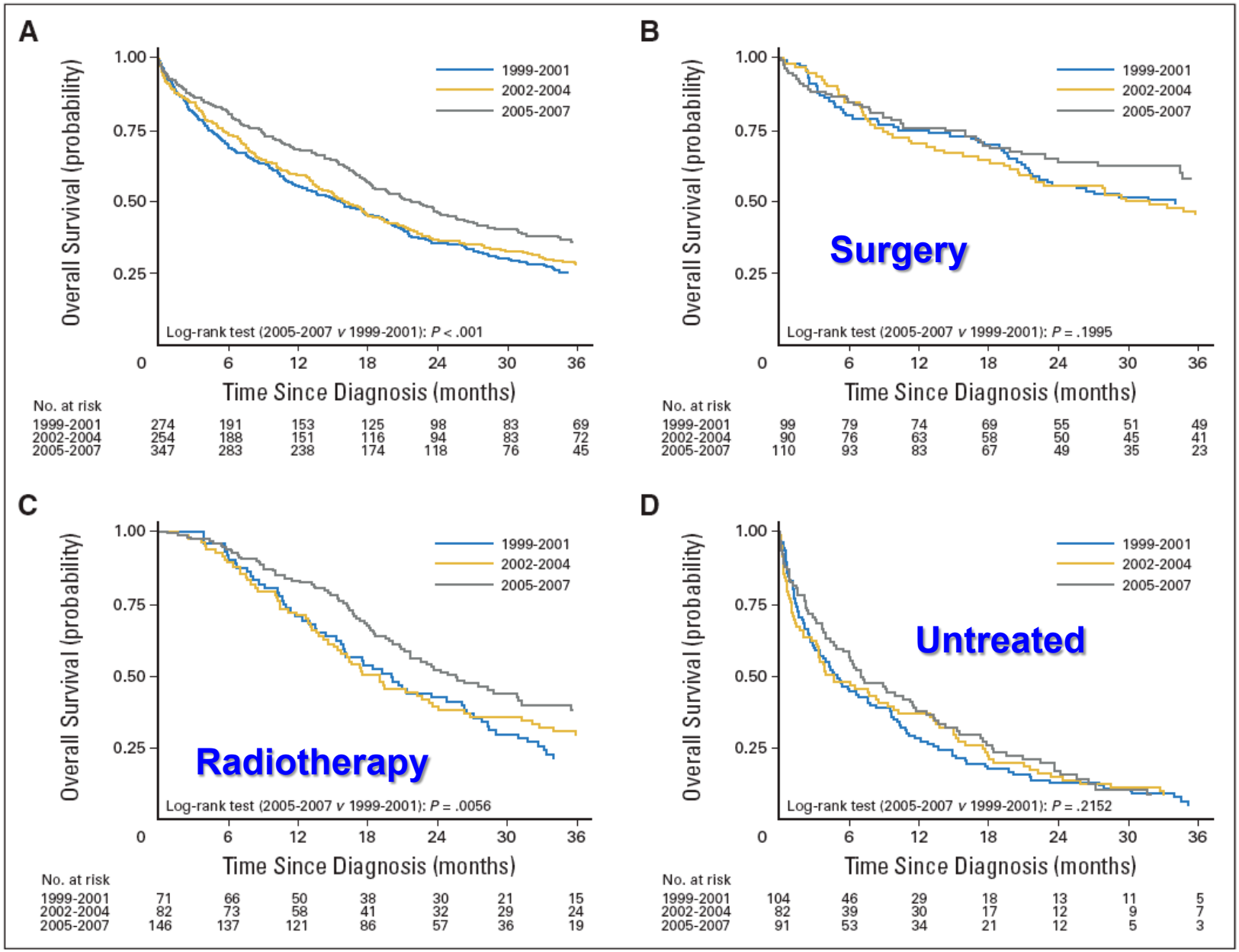


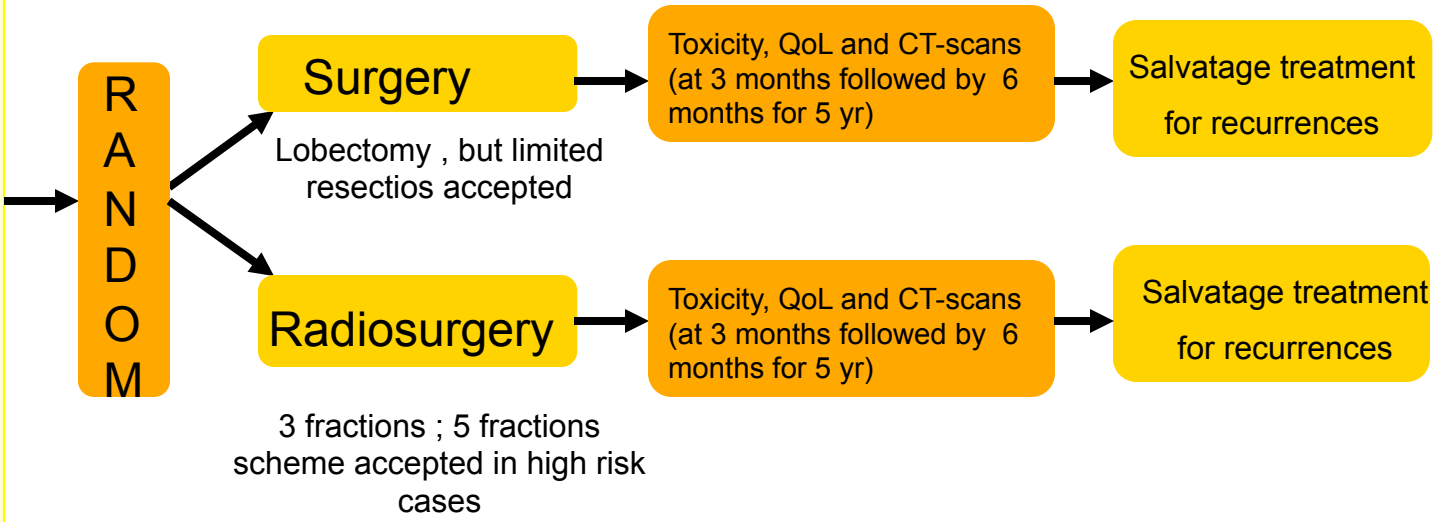
Fig 3. Overall survival for elderly (age ≥ 75 years) patients with stage I non–small-cell lung cancer by time period. (A) All patients; (B) patients treated with surgery; (C) patients treated with radiotherapy; (D) untreated patients.

Dutch ROSEL Study

Radiosurgery **O**r **S**urgery in operable **E**arly stage non small cell **L**ung cancer

Patients

- Stage IA NSCLC
- Diagnosis based
  - cyto-pathology
  - clinical proof of malignancy



TERMINATED (poor recruitment)

SBRT Program

Umberto Ricardi
Andrea Filippi
Alessia Guarneri
Cristina Mantovani

Christian Fiandra
Francesca Romana Giglioli
Riccardo Ragona