Evidenze cliniche della SBRT: NSCLC in stadio iniziale e malattia oligometastatica

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DICHIARAZIONE

Relatore: Filippo Alongi

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Speaker Honoraria: AUGMENIX, ASTELLAS)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(JANSEEN)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

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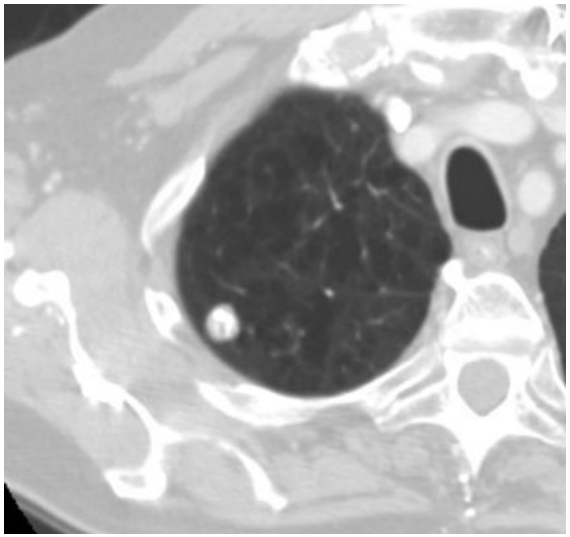
EARLY STAGE LUNG NSCLC:
AN INCREASING POPULATION



- CT screening of patients at high risk can reduce cancer mortality.
- With such screening, ***NSCLC will likely be identified more often and in earlier stages*** than in the past.

Aberle DR, et al . *N Engl J Med 2013*

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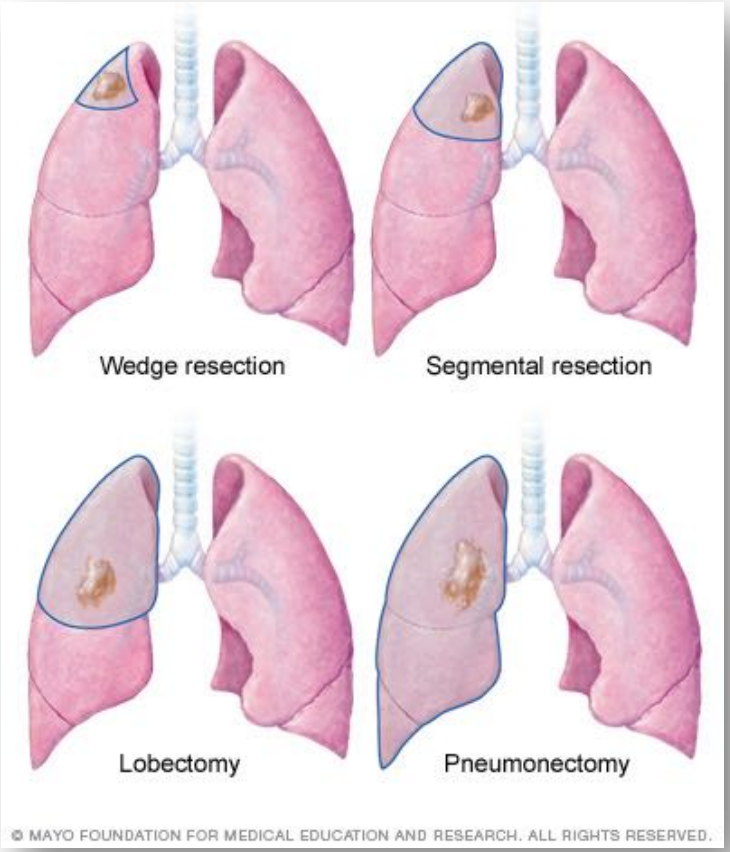
EARLY STAGE LUNG NSCLC:
TREATMENT OPTIONS

- **Surgery is still the preferred definitive treatment** for early stage NSCLC, with **overall survival of 60–70%**.

- Surgical lobectomy may be associated with significant morbidity and mortality, **and up to 25% of** the patients **cannot be operated** due to a poor pulmonary function or comorbidities.

- With **the wait and see policy**, the overall median survival of these patients is only **9 months**.



Roach MC, et al. JTO 2015

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EARLY STAGE LUNG NSCLC:
TREATMENT OPTIONS

For patients **with comorbidities or who refuse invasive treatments, SBRT** has emerged over the past decade **as the standard of care** for the medically inoperable patient with early stage lung cancer.

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

- The non-surgical treatment of choice for stage I NSCLC is stereotactic ablative radiotherapy (SABR). The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose [III, A].

2°ESMO Consenus Conference on Lung cancer
Vansteenkiste et al, Annals of Oncology 2014

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EARLY STAGE LUNG NSCLC: SABR

1. EFFECTIVENESS
2. SAFETY
3. OPERABLE PATIENTS
4. UNRESOLVED ISSUES

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EARLY STAGE LUNG NSCLC:

1. EFFECTIVENESS
2. SAFETY
3. OPERABLE PATIENTS
4. UNRESOLVED ISSUES

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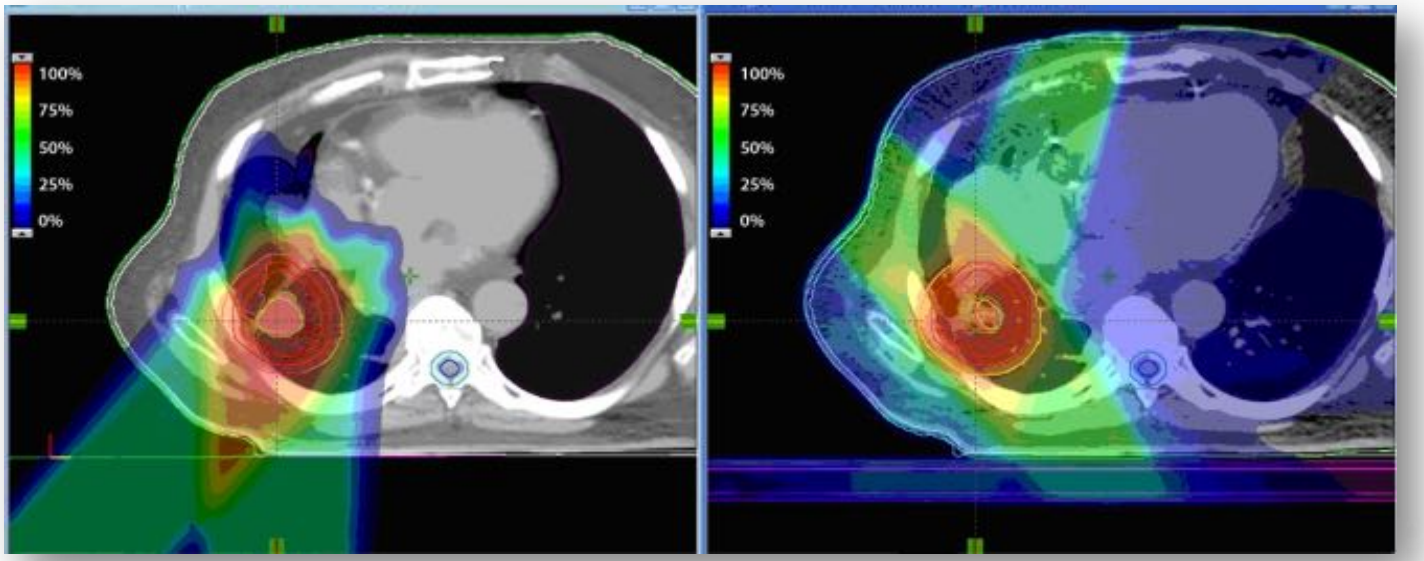
EARLY STAGE LUNG NSCLC:
TREATMENT OPTIONS

➢Until recently, for non operable stage I NSCLC, conventional RT (**3D-CRT**) has been the treatment of choice reaching **local recurrence of 30-50%** and specific survival of 39% at 3 years

➢Therefore, 3DCRT could not meet the demand to replace surgery



Wisnivesky JP, et al. *Chest 2005*.

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EARLY STAGE LUNG NSCLC:
HOW SABR IS EFFECTIVE?

SPACE Trial

SBRT (66Gy /3 fr) vs **3D-CRT** (70Gy/7wks)

Nyman WCLC 2015

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Trial record **46 of 12888** for: radiotherapy
◂ Previous Study | Return to List | Next Study ▸

Stereotactic Body Radiotherapy Versus Conventional Radiotherapy in Medically-Inoperable Non-Small Lung Cancer Patients (LUSTRE)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by Ontario Clinical Oncology Group (OCOG)

Sponsor:
Ontario Clinical Oncology Group (OCOG)

Collaborator:
Canadian Cancer Society Research Institute (CCSRI)

Information provided by (Responsible Party):
Ontario Clinical Oncology Group (OCOG)

ClinicalTrials.gov Identifier:
NCT01968941

First received: October 21, 2013
Last updated: August 24, 2015
Last verified: August 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

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EARLY STAGE LUNG NSCLC:

HOW SABR IS EFFECTIVE? PROSPECTIVE TRIALS

Table 1. Prospective trials of SBRT for stage I lung cancer

Author (yr)	Type/Stage	No. of patients	Dose	Median follow-up (mo)	Outcomes
Timmerman et al. [6] (2003) McGarry et al. [12] (2005)	Phase I/Stage I NSCLC	47	8 Gy × 3 to 20 Gy × 3	19.1–27.4	1-yr LC: 64.7% 3-yr OS: 64%
Hoyer et al. [13] (2006)	Prospective/Stage I NSCLC	40	15 Gy × 3	28.8	2-yr LC: 85% 2-yr CSS: 62% 2-yr OS: 48%
Baumann et al. [14] (2009)	Phase II/Stage I NSCLC	70	15 Gy × 3 to 67%	35	3-yr LC: 92% 3-yr CSS: 88% 3-yr OS: 60%
Timmerman et al. [15] (2010)	RTOG Phase II/T1-2N0M0 NSCLC (peripherally located)	55	18 Gy × 3	34.4	3-yr LC: 97.6% 3-yr DFS: 48.3% 3-yr OS: 55.8%
Ricardi et al. [16] (2010)	Phase II/Stage I NSCLC	62	15 Gy × 3	28	3-yr LC: 87.8% 3-yr CSS: 72.5% 3-yr OS: 57.1%
Bral et al. [17] (2011)	Phase II/T1-3N0M0	40	20 Gy × 3 15 Gy × 4	16	2-yr LC: 84% 2-yr CSS: 64% 2-yr OS: 52%

SBRT, stereotactic body radiotherapy; NSCLC, non-small cell lung cancer; LC, local control; CSS, cancer-specific survival; OS, overall survival; DFS, disease-free survival; RTOG, Radiation Therapy Oncology Group.

- Total doses :45-66 Gy in 3 or 4 fr,
- 2–3 years LC: 84%–98%
- 1–3 years OS 43%– 72%

Ricardi et al, ROJ 2015

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HOW ABLATIVE SBRT IS EFFECTIVE?

LOCAL CONTROL AND DOSE FACTOR

SBRT produced **LC in excess of 90%** for patients with early stage NSCLC when the biological effective **dose (BED)** to the planning target volume (PTV) is **greater than 100 Gy**.

- Lagerwaard FJ, et al. *Int J Radiat Oncol Biol Phys 2008.*
- Timmerman R, et al. *JAMA 2010*
- Chang JY, et al. *Radiat Oncol 2012.*
- Taremi M, et al. *Int J Radiat Oncol Biol Phys 2012.*

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HOW ABLATIVE SBRT IS EFFECTIVE?

LOCAL CONTROL AND DOSE FACTOR

BED ESCALATION IS NECESSARY BETTER??

➢*Onishi et al*: LC was significantly improved with **BED greater than 100 Gy** (prescription dose at isocenter), with 5-year LC rate of 84% for BED10 > 100 Gy vs. 37% for BED10 < 100 Gy ($p < 0.001$).

➢*Kestin et al* : a significant correlation between **BED10 > 105 Gy** (prescription to the edge of the PTV, with 60%–90% of the isocenter dose) and higher local control.

➢*Zhang et al*: based on the BED quartiles (low, medium, medium–high, and high), **outcome got worse for BED below 83.2 Gy and for BED exceeding 146 Gy.**

➢*Koshy et al*: T2 tumors treated with **a BED10 > 150 Gy** (roughly equal to 54 Gy in 3 fractions) **had a significantly improved survival** compared with patients treated with a BED10 < 150 Gy [22].

Onishi H, et al. Cancer 2004.
Kestin L, et al. Radiother Oncol 2014.
Zhang J, et al. Int J Radiat Oncol Biol Phys 2011.
Koshy, et al Int J Radiat Oncol Biol Phys 2015

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EARLY STAGE LUNG NSCLC:

TREATMENT HABITS .. *WIND IS CHANGING*

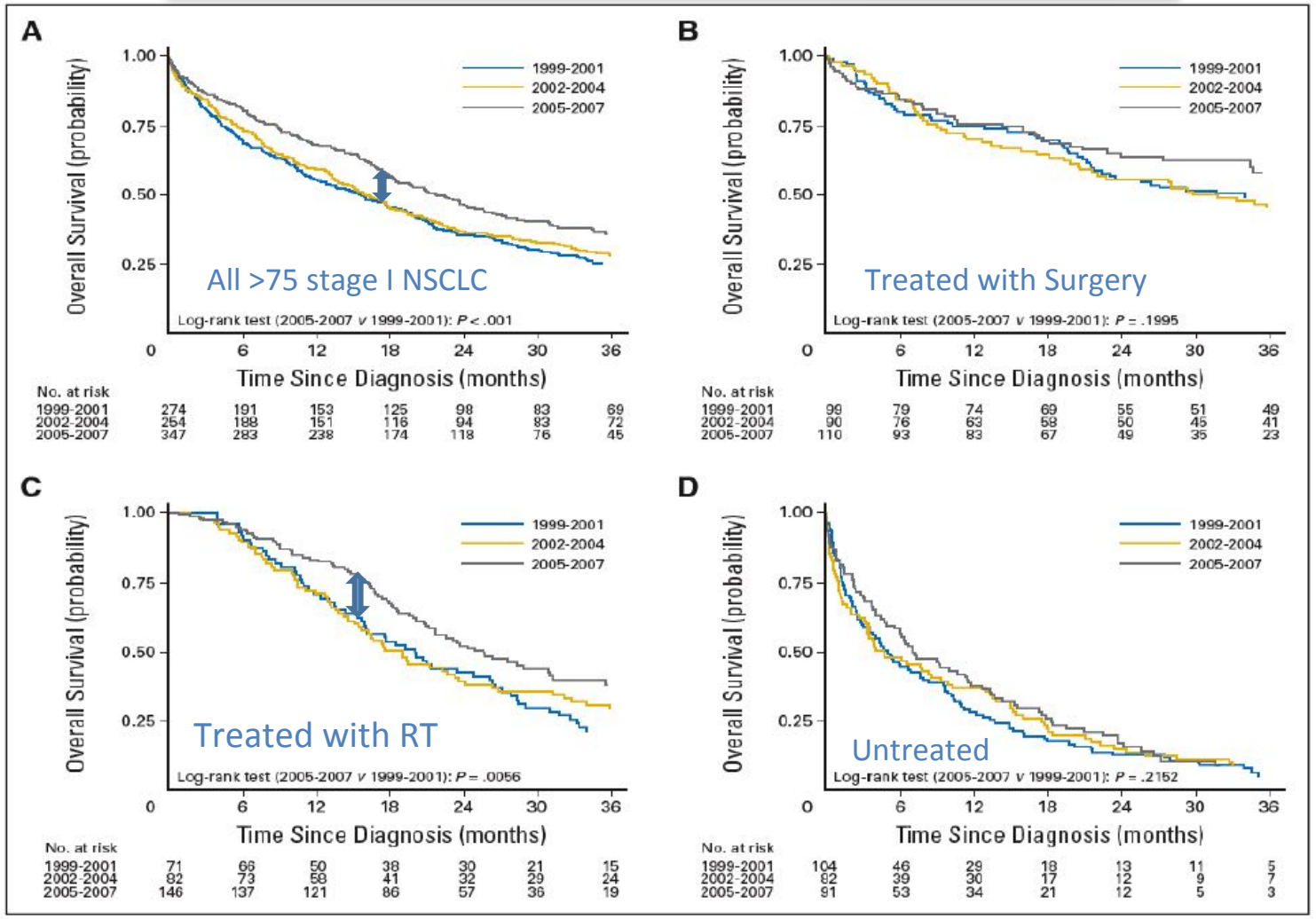

Fig 3. Overall survival for elderly (age ≥ 75 years) patients with stage I non–small-cell lung cancer by time period. (A) All patients; (B) patients treated with surgery; (C) patients treated with radiotherapy; (D) untreated patients.

Palma, et al. *JCO 2010*.

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EARLY STAGE LUNG NSCLC:
SABR

1. EFFECTIVENESS
2. SAFETY
3. OPERABLE PATIENTS
4. UNRESOLVED ISSUES

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EARLY STAGE LUNG NSCLC:
SAFETY SABR

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 457–462, 2012

A DOSE–VOLUME ANALYSIS OF RADIATION PNEUMONITIS IN NON–SMALL CELL LUNG CANCER PATIENTS TREATED WITH STEREOTACTIC BODY RADIATION THERAPY

~2% Grade 3 Pneumonitis

Author	SBRT dosing schema		Scoring criteria
Barriger	Multiple (Table 1)	9.4% 7% Grade 2 2% Grade 3 0.4% Grade 4	CTC v2
McGarry Phase I trial	8 Gy × 3 = 24 Gy 10 Gy × 3 = 30 Gy 12 Gy × 3 = 36 Gy 14 Gy × 3 = 42 Gy 16 Gy × 3 = 48 Gy 18 Gy × 3 = 54 Gy 20 Gy × 3 = 60 Gy 22 Gy × 3 = 66 Gy 24 Gy × 3 = 72 Gy	8.4% 2% Grade 2 6.4% Grade 3	CTC v2
Onishi	Various 18–75 Gy in 1–25 fractions*†	6.5 % 4.1% Grade 2 1.2% Grade 3 1.2% Grade 4	CTC v2
Nagata	12 Gy × 4 = 48 Gy*	4% No Grade 3–4	CTC v2
Ricardi	15 Gy × 3 = 45 Gy	3.2% Grade 3 (Required steroids or intermittent oxygen)	RTOG
Stephans	20 Gy × 3 = 60 Gy 10 Gy × 5 = 50 Gy	2/86 Grade 2 (Required steroids)	Not stated in paper
Grills	12 Gy × 4 = 48 Gy 12 Gy × 5 = 60 Gy	11% 9% Grade 2 2% Grade 3	CTC v3
Timmerman RTOG 0236	20 Gy × 3 (without heterogeneity corrections) 18 Gy × 3 (with heterogeneity corrections)	3.6% Grade 3	CTC v3

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EARLY STAGE LUNG NSCLC:
SAFETY SABR

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

Journal of Thoracic Oncology • Volume 7, Number 3, March 2012

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

TABLE 6. Literature Review of Studies Reporting Changes of Pulmonary Function Test (PFT) after SBRT for Stage I NSCLC

Study	No. of Patients	Time to Post-SBRT PFT	PFT	Median Pretreatment PF	Median Posttreatment/ Change of PF
Henderson (2008)	70	12	FEV1 (L)	1.05	NS
			DLCO (ml/min/mmHg)	10.06	−1.11[a]
Stephans (2009)	92	10	FEV1 (L)	1.21	1.15
			DLCO% (%)	56.5	53.9
Bral (2010)	40	NS	FEV1	NS	−3%
			DLCO	NS	−3%
Collins	24	12	FEV1% (%)	61	NS
			DLCO% (%)	61	51[a]
Miyamota (2007)	50	12	FEV1 (L)	1.48	1.42[a]
			DLCO (ml/min/mmHg)	9.92	9.25
Fritz (2008)	40	36	FEV1 (L)	1.4	1.4
Baumann (2008)	60	14	FEV1% (%)	49	52.5
Ohashi	15	12	FEV1 (L)	1.99	1.8
			DLCO (ml/min/mmHg)	13.65	17.85[a]

[a] Statistically significant.

SBRT, stereotactic body radiotherapy; NSCLC, non-small cell lung cancer; PF, pulmonary function; FEV1, forced expiratory volume in 1 sec; DLCO, diffusing capacity for carbon monoxide.

SABR is safe even for patients with a poor pulmonary function

EARLY STAGE LUNG NSCLC:
TOXICITY SABR

Chest wall pain (5-10%)
Rib fracture(<5%)

DOSE–VOLUME PARAMETERS PREDICT FOR THE DEVELOPMENT OF CHEST WALL PAIN AFTER STEREOTACTIC BODY RADIATION FOR LUNG CANCER

Int J Radiat Oncol Biol Phys. 2012 April 1; 82(5): 1783–1790.

Robert W. Mutter, M.D.[*], **Fan Liu, Ph.D.**[†], **Andres Abreu, B.S.**[‡], **Ellen Yorke, Ph.D.**[†], **Andrew Jackson, Ph.D.**[†], and **Kenneth E. Rosenzweig, M.D.**[§]

[*]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

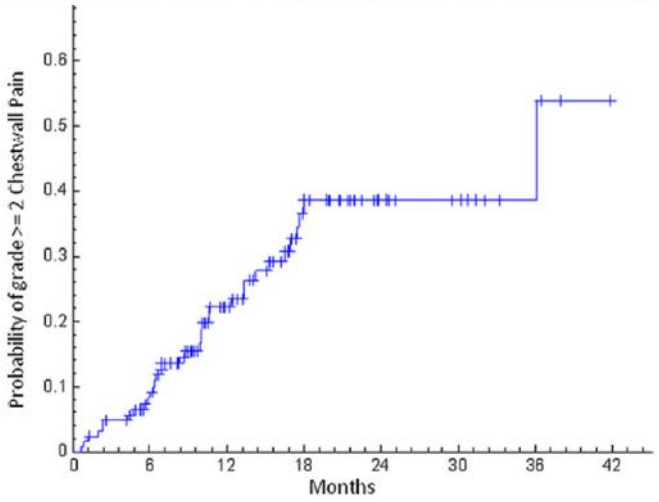
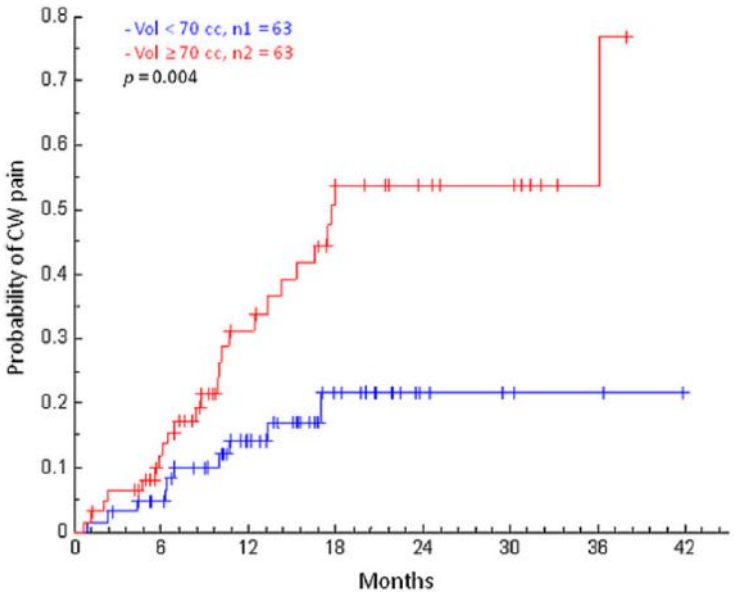


Fig. 3.
Kaplan-Meier curve describing cumulative incidence of developing Grade ≥ 2 chest wall pain.



EARLY STAGE LUNG NSCLC:
TOXICITY SABR

Chest wall pain (5-10%)
Rib fracture(<5%)

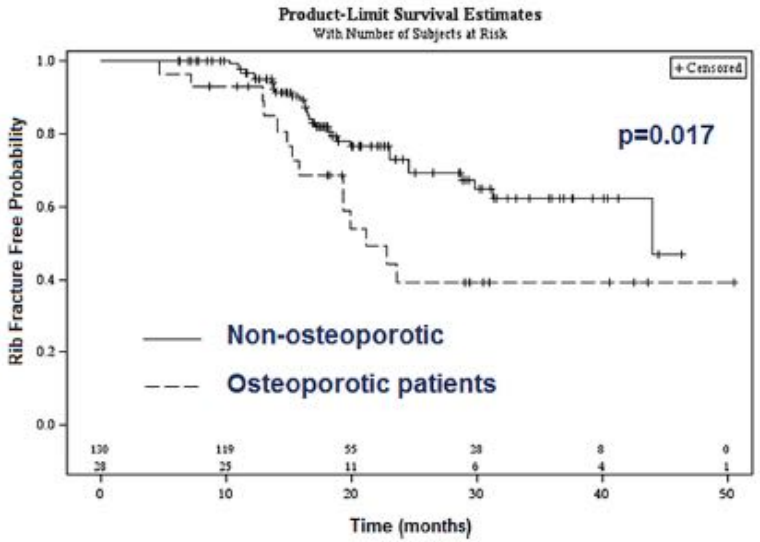
Original Article

Predictors of Chest Wall Toxicity after Lung Stereotactic Ablative Radiotherapy☆

Clinical Oncology xxx (2015) 1–8

I. Thibault *, A. Chiang *, D. Erler *, L. Yeung †, I. Poon *, A. Kim *, B. Keller *, F. Lochray *, S. Jain ‡, H. Soliman *, P. Cheung *

- Increased risk for rib fracture in case of osteoporosis



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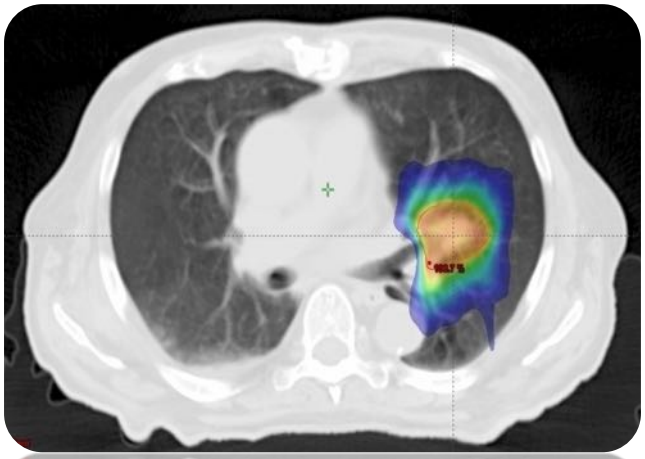
EARLY STAGE LUNG NSCLC:
IS SABR REALLY SAFE?



The use of SABR for lesions that are **centrally located** and thus close to critical normal structures within the thorax is controversial.

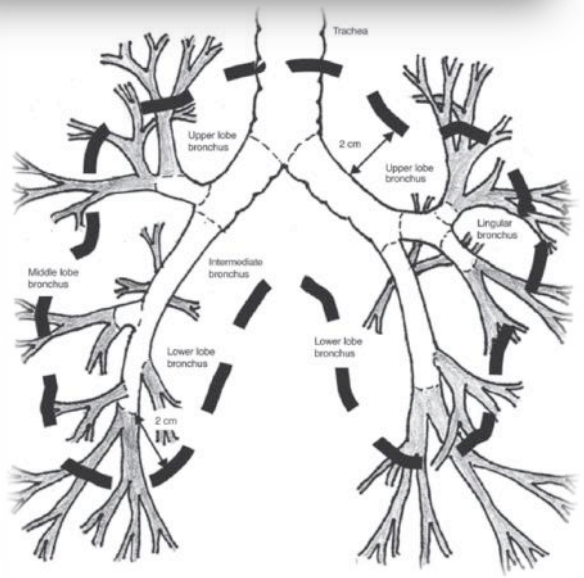
- Timmerman R. *J Clin Oncol* 2006.
- Chang JY, et al. *Int J Radiat Oncol Biol Phys 2008*
- Milano MT, et al. *Radiother Oncol 2009.*
- Song SY, et al. *Lung Cancer 2009.*
- Haasbeek CJ, et al. *JThorac Oncol 2011.*
- Rowe BP, et al. *J Thorac Oncol* 2012;7:1394–1399.
- Nuyttens JJ, et al. *Radiother Oncol 2012.*

EARLY STAGE LUNG NSCLC:
IS SABR REALLY SAFE?

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

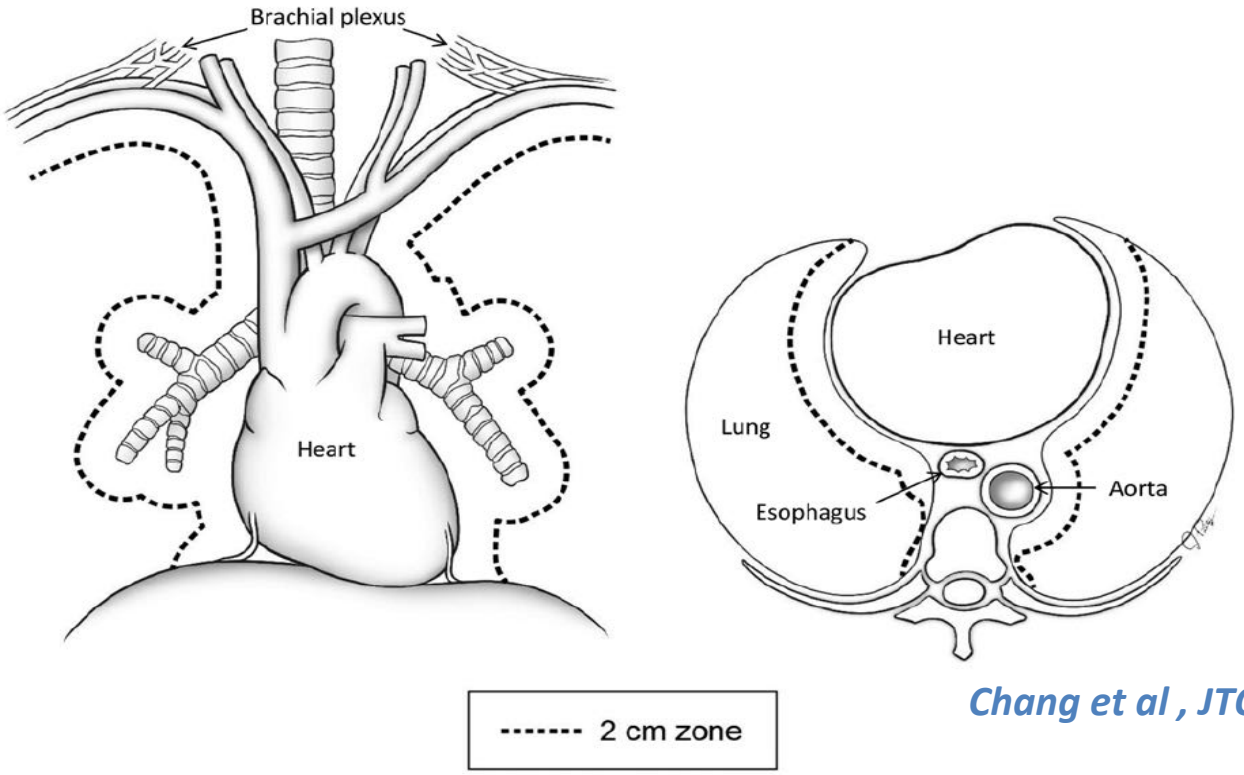
Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Both univariate and multivariate analysis showed that **tumor location (hilar/pericentral *v* peripheral)** was a strong predictor of toxicity (*P* .004).



Timmerman R, JCO 2008; 24:4833-4839

EARLY STAGE LUNG NSCLC:
IS SABR REALLY SAFE?



Chang et al , JTO 2015

Thus, delivery of ablative doses of radiation to **critical structures** such as bronchial tree, esophagus, major vessels, heart, and the brachial plexus/phrenic nerve could produce severe, potentially lethal toxic effects.

Treatment involving additional fractions should be considered for such lesions

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EARLY STAGE LUNG NSCLC:
IS SABR REALLY SAFE?

➢Appropriate case selection and SABR dose regimens based on target location are crucial to reduce toxicity.

Risk-adapted Dose Prescription:

Contents lists available at ScienceDirect

Radiotherapy and Oncology 2014

journal homepage: www.thegreenjournal.com

ELSEVIER

Original article

Stereotactic ablative radiotherapy (SABR) using 70 Gy in 10 fractions for non-small cell lung cancer: Exploration of clinical indications

Qiaoqiao Li [1], Cameron W. Swanick, Pamela K. Allen, Daniel R. Gomez, James W. Welsh, Zhongxing Liao, Peter A. Balter, Joe Y. Chang *

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States

Conclusions: SABR with 70 Gy in 10 fractions appears to achieve excellent local control and acceptable toxicity for clinically challenging cases with improved tolerance of the chest wall and brachial plexus as compared with 50 Gy in 4 fractions. This regimen may not be suitable in patients with tumor invading critical central structures. More studies are needed to validate our conclusions.

PRINCIPLES OF RADIATION THERAPY (6 of 9)

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25-34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45-60 Gy	3	Peripheral tumors and >1 cm from chest wall
48-50 Gy	4	Central or peripheral tumors <4-5 cm, esp. <1 cm from chest wall
50-55 Gy	5	Central or peripheral tumors, esp. <1 cm from chest wall
60-70 Gy	8-10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal Cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial Plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great Vessels	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
Stomach	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

*Based on constraints used in recent and ongoing RTOG SABR trials (RTOG 0618, 0813, & 0915).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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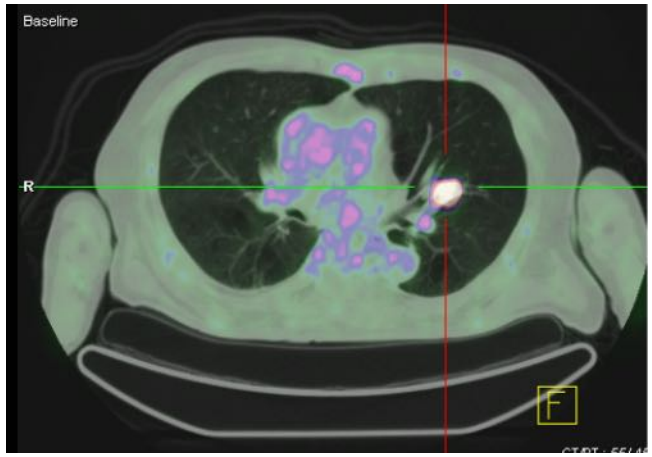
EARLY STAGE LUNG NSCLC:
IS ABLATIVE SBRT REALLY SAFE?

Risk-adapted Dose Prescription:

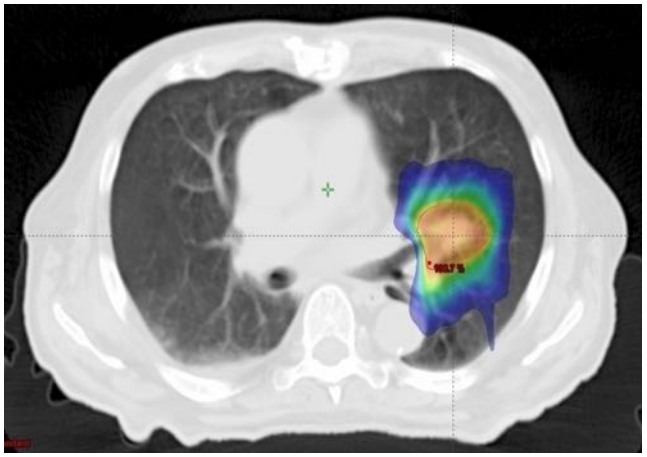
Dose	Topographical Criteria		
	Distance to Chest Wall	Size	Distance to Main Bronchus
54-60 Gy (16-20 Gy/fr x 3 fractions)	> 1 cm	< 2cm	> 2 cm
48-55 Gy (10-12 Gy/fr x 4-5 fractions)	> 1 cm	<2 cm and < 5 cm	> 2 cm
60-70 Gy (7.5 Gy/fr x 8 fractions or 7 X10)	< 1 cm	< 5 cm	> 1 cm and < 2cm

EARLY STAGE LUNG NSCLC:
CAN WE TREAT SAFE?

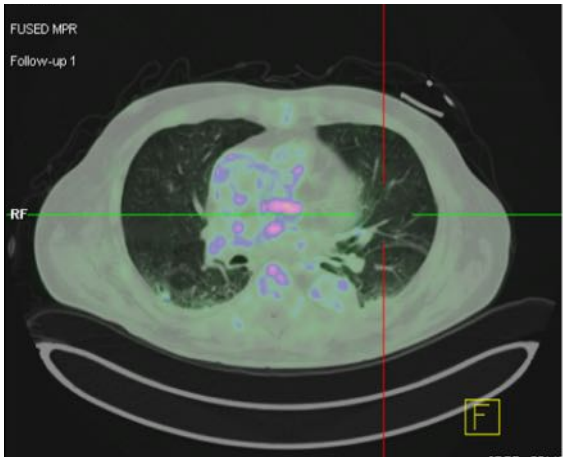
Male 73 y. Ultra-Central NSCLC



CT-PET before SABR



Planning CT



CT-PET after 60 days

CR @ CT-PET after 70 Gy/10 fr. with FFF beams

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ABLATIVE (SB)RT:
A NEW TECHNOLOGY FOR NEW INDICATIONS?

With new technology devices, now is possible to delivery high (when requested also ablative) doses to the target, especially to small volumes

PRECISION DEVISES TO DELIVERY RADIATION

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ABLATIVE (SB)RT:
WHAT IS THE BEST NEW TECHNOLOGY?

35 of the 45 studies covering 91% of the patients used a linear accelerator (Linac) and 11 (14%) a robotic mounted linac (Cyberknife).

There was non survival or local PFS difference with different RT technologies used for SABR

Soldà F, Radiother Oncol 2013.

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EARLY STAGE LUNG NSCLC:
SABR EVIDENCES FOR UNOPERABLE PATIENTS

SABR is effective with dose at least of 100 Gy

✓BED with high local control and Survival rate

SABR could be considered safe

✓Risk adapted dose prescription is suggested for centrally located (or close to OARs)

No evidences of superiority of one delivery **technique** to the other

But what evidences about operable patients????

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EARLY STAGE LUNG NSCLC:
SABR

1. EFFECTIVENESS
2. SAFETY
3. OPERABLE PATIENTS
4. UNRESOLVED ISSUES

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EARLY STAGE LUNG NSCLC:
WHAT ABOUT OPERABLE PATIENTS??

Surgery or stereotactic ablative radiation therapy: how will be treated operable patients with early stage not small cell lung cancer in the next future?

Luca Bertolaccini[1], Alberto Terzi[1], Francesco Ricchetti[2], Filippo Alongi[2]

[1]Thoracic Surgery Unit, [2]Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, 37024 Negrar Verona, Italy

SABR role in pts suitable for curative surgery is yet to be defined.

- To date, the large amount of data of SABR for early stage NSCLC regards populations of *patients excluded from surgery* .
- The absence of randomized trials in this setting does not imply the absence of potential evidence on efficacy of SABR as well as surgery *in early stage operable* NSCLC patients

Bertolaccini, et al. *Anna Transl Med 2015*

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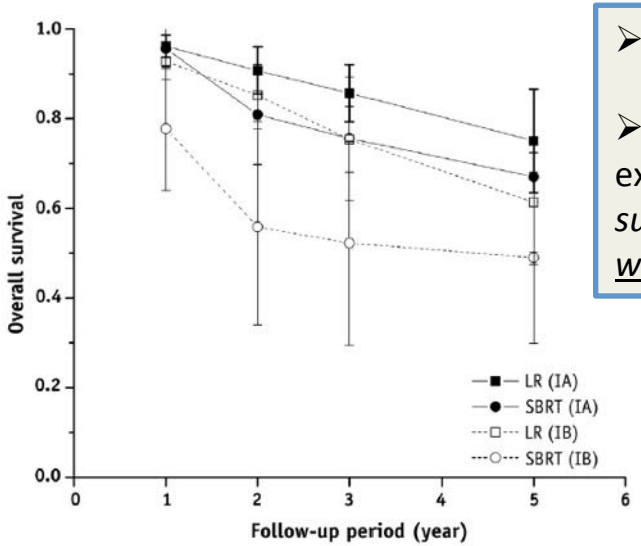
EARLY STAGE LUNG NSCLC:
WHAT ABOUT OPERABLE PATIENTS??

Survival Outcome After Stereotactic Body Radiation Therapy and Surgery for Stage I Non-Small Cell Lung Cancer: A Meta-Analysis

Xiangpeng Zheng, MD, PhD,* Matthew Schipper, PhD,†,‡ Kelley Kidwell, PhD,‡ Jules Lin, MD,§ Rishindra Reddy, MD,§ Yanping Ren, MD,* Andrew Chang, MD,§ Fanzhen Lv, MD,‖ Mark Orringer, MD,§ and Feng-Ming Spring Kong, MD, PhD†

➢A meta-analysis with 40 *SABR studies (4,850 patients) and 23 surgery studies (7,071 patients), published in the same period.*



➢Better treatment outcomes were provided by surgery.

➢Nevertheless, adjusting patient profile differences, extrapolative analysis shows that *SABR produced non-inferior survival outcomes in comparison to surgery, especially in <u>patients with operable</u> stage I NSCLC*

SBRT may be comparable to surgery in patients with operable diseases and favorable physical conditions

Zheng, et al. ***Red J 2015***

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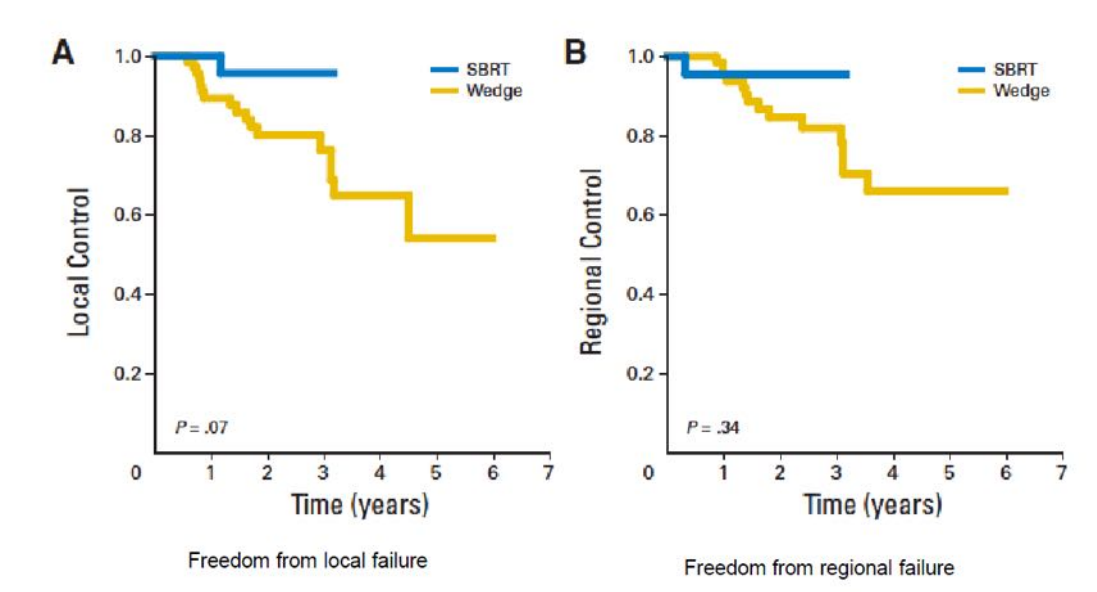
EARLY STAGE LUNG NSCLC:
HOW SABR IS EFFECTIVE? SURVIVAL

Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non–Small-Cell Lung Cancer

Inga S. Grills, Victor S. Mangona, Robert Welsh, Gary Chmielewski, Erika McInerney, Shannon Martin, Jennifer Wloch, Hong Ye, and Larry L. Kestin

➢120 Early Stage NSLCL, not eligible for lobectomy underwent SBRT or Wedge resection



SABR is better than wedge resection

Grills et al JCO 2010.

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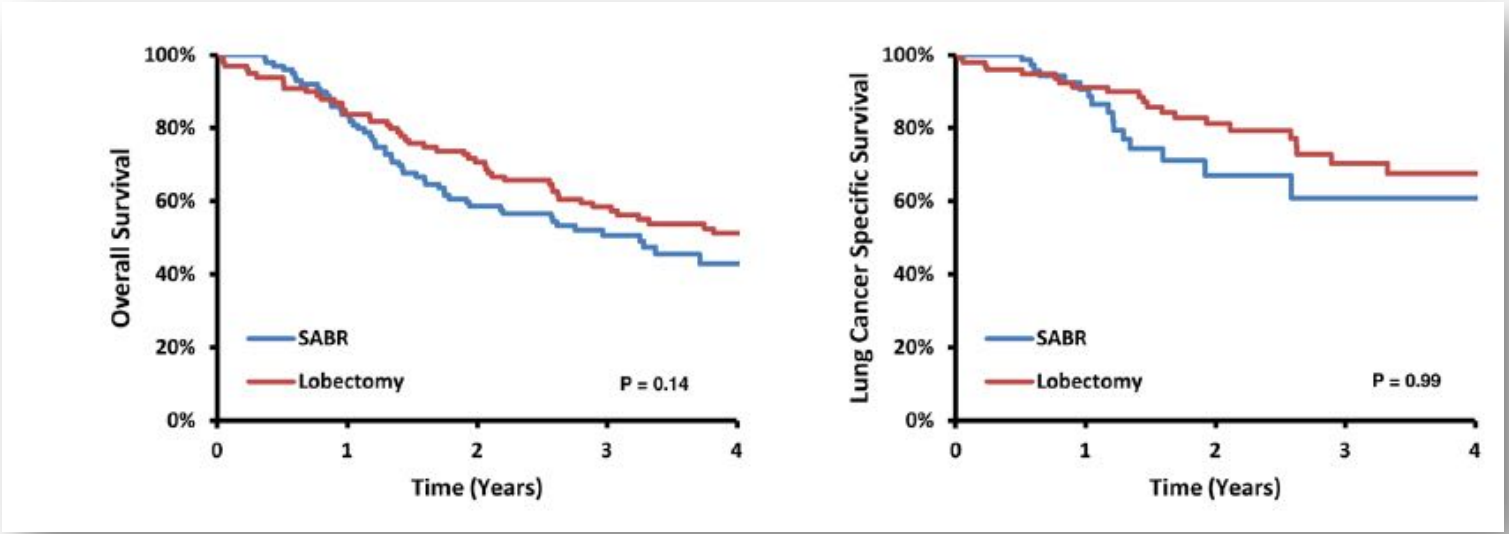
EARLY STAGE LUNG NSCLC:
WHAT ABOUT OPERABLE PATIENTS??

Lobectomy, Sublobar Resection, and Stereotactic Radiation for Early-Stage Non-Small Cell Lung Cancers in the Elderly

Shervin M Shirvani, MD MPH[1,2], Jing Jiang, MS[3], Joe Y. Chang, MD PhD[1], James Welsh, MD[1], Anna Likhacheva, MD MPH[2], Thomas A Buchholz, MD[1], Stephen G. Swisher, MD[4], and Benjamin D Smith, MD[1]

➢ *JAMA Surg 2014.*

9093 elderly patients with early-stage NSCLC, node-negative



Population-based studies and propensity-matched analyses demonstrate that SABR produces overall survival (OS) and disease-specific survival rates similar to those after lobectomy…..

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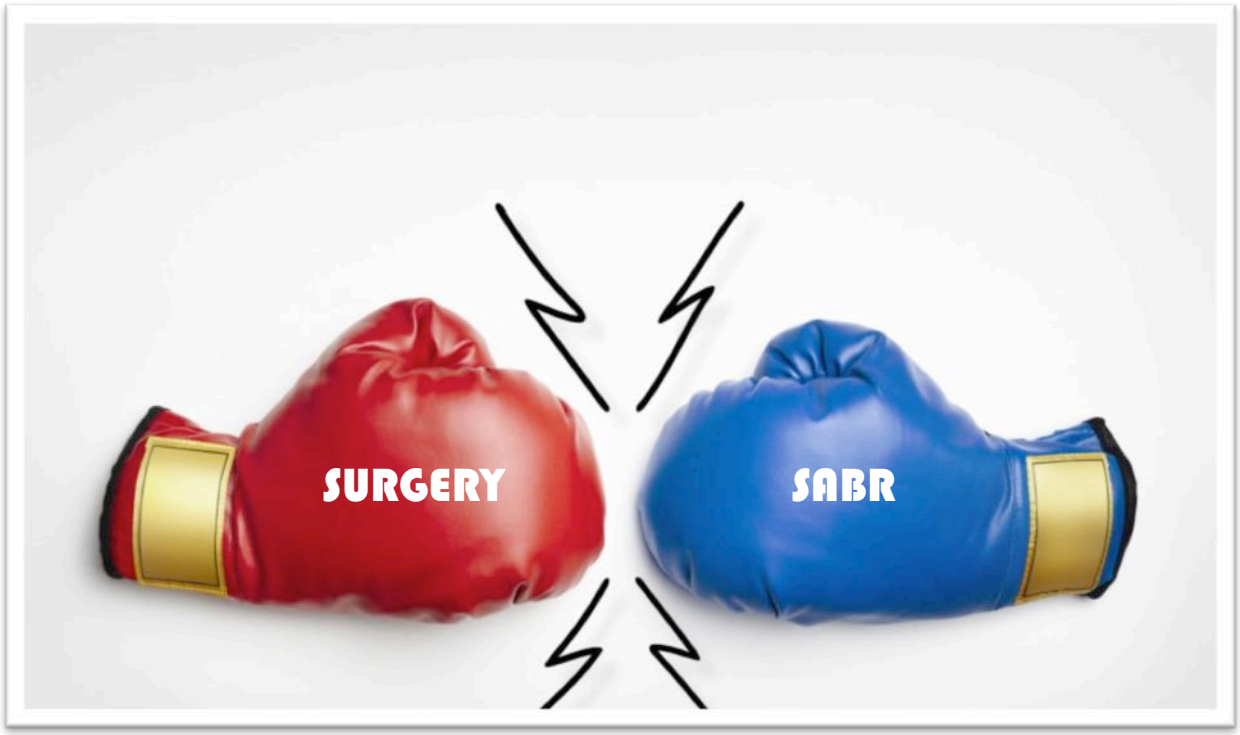
EARLY STAGE LUNG NSCLC:
IS SABR EFFECTIVE AS SURGERY?



➢Unfortunately data on Randomized Trial between SURGERY and SABR are not still available.

However…..

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EARLY STAGE LUNG NSCLC:
IS SABR EFFECTIVE AS SURGERY?

Lancet Oncol 2015

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

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

➢A pooled analysis of the two independent, randomised, **phase 3 trials of SABR in patients with operable** stage I NSCLC (**STARS and ROSEL** closed early due to slow accrual).

Chang et al. ***Lancet Oncol 2015.***

EARLY STAGE LUNG NSCLC:
IS SABR EFFECTIVE AS SURGERY?

Lancet Oncol 2015

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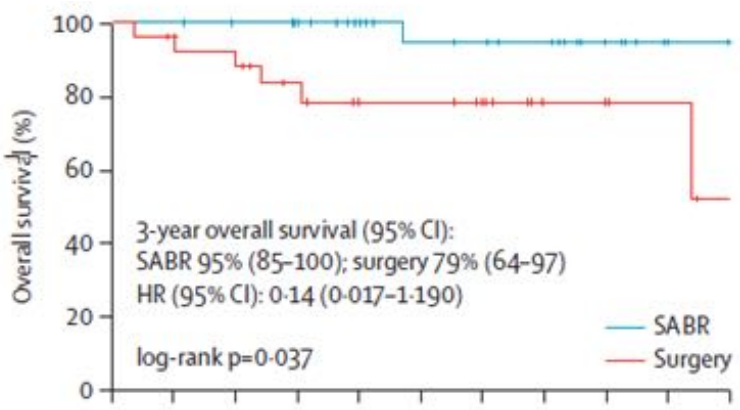

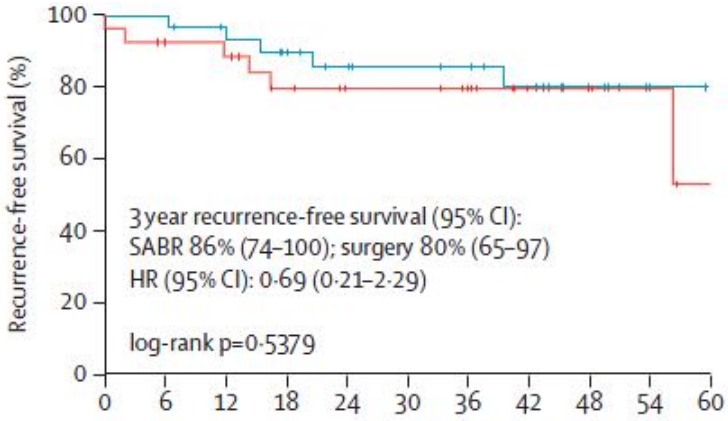

- The difference in **OS** between the two groups was statistically significant **in favour of SABR**.
- No significant differences in of local, regional, or distant metastasis or in RFS between the treatment groups.

Chang et al. ***Lancet Oncol 2015.***

EARLY STAGE LUNG NSCLC:
IS SABR EFFECTIVE AS SURGERY?

Lancet Oncol 2015

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The results of were provocative because in **favor of SABR** with:

✓an **absolute improvement in overall survival (OS)** of 16% at 3y (95% *vs*. 79%, P=0.037)
✓ **a decrease in grade ≥3 toxicity** (10% *vs*. 48%)

Chang et al. ***Lancet Oncol 2015.***

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EARLY STAGE LUNG NSCLC:
IS SABR EFFECTIVE AS SURGERY?

➢Trials comparing SABR and surgery will continue to have difficulty with accrual.

➢Infact the **ACOSOG Z4099/RTOG 1021** randomized phase III trial of sublobar resection with or without brachytherapy versus SABR in high risk patients stage I NSCLC (closed early in 2013 !!) due to lack of accrual and is without publication.

➢However:

1) The **VALOR trial** Surgery versus SABR is scheduled to open in the US within the year.

2) the **SABR Tooth trial** SABR vs surgery for peripheral stage I NSCLC in patients at higher risk of surgical complications is also planned to open in the UK.

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EARLY STAGE LUNG NSCLC:
SABR EVIDENCES FOR OPERABLE PATIENTS

In Conclusion:

✓*Lobectomy is the standard of care for early stage NSCLC*

✓*There is no direct evidence of Its superiority compared to SABR*

✓*Multiple studies using propensity score-matching methods indicate simular outcomes*

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EARLY STAGE LUNG NSCLC:
SABR

1. EFFECTIVENESS
2. SAFETY
3. OPERABLE PATIENTS
4. UNRESOLVED ISSUES

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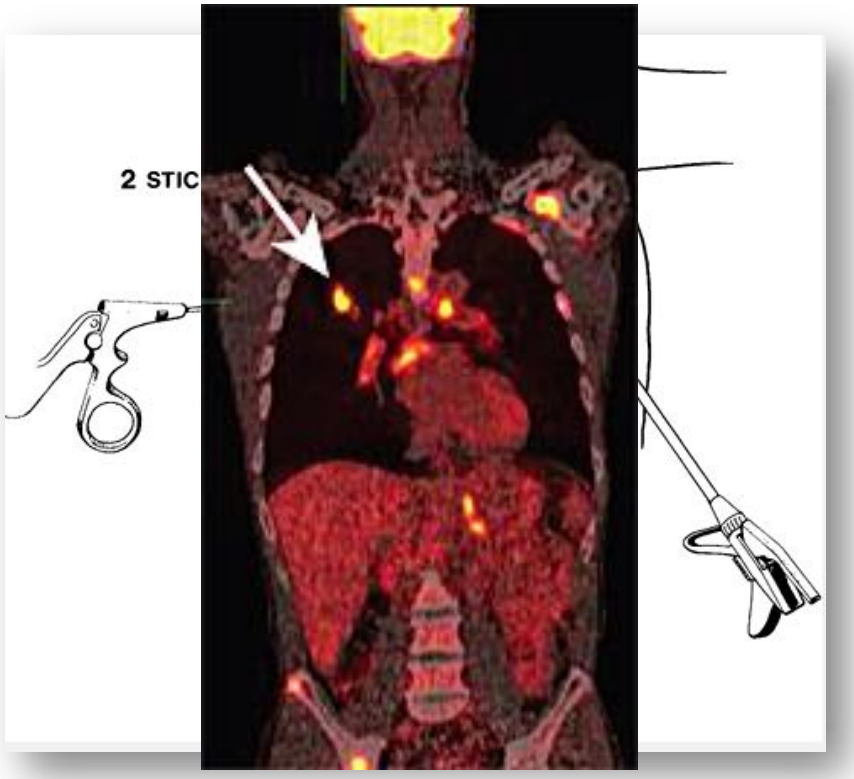
EARLY STAGE LUNG NSCLC:
.. UNRESOLVED ISSUES

NEED FOR A PRETREATMENT PATHOLOGY

A pathological confirmation of malignancy is generally preferred prior any curative-intent therapy for early NSCLC….

…… Many candidates for **SABR have co-morbidities and risks associated with transthoracic biopsy**, or repeated biopsy if the initial attempt is inconclusive.



Use of FDG-PET may perform poorly when used for a clinical diagnosis of stage I NSCLC, in areas where granulomatous disease and other infectious etiologies are endemic

Louie et al. Radiotherapy and Oncology. *2015*

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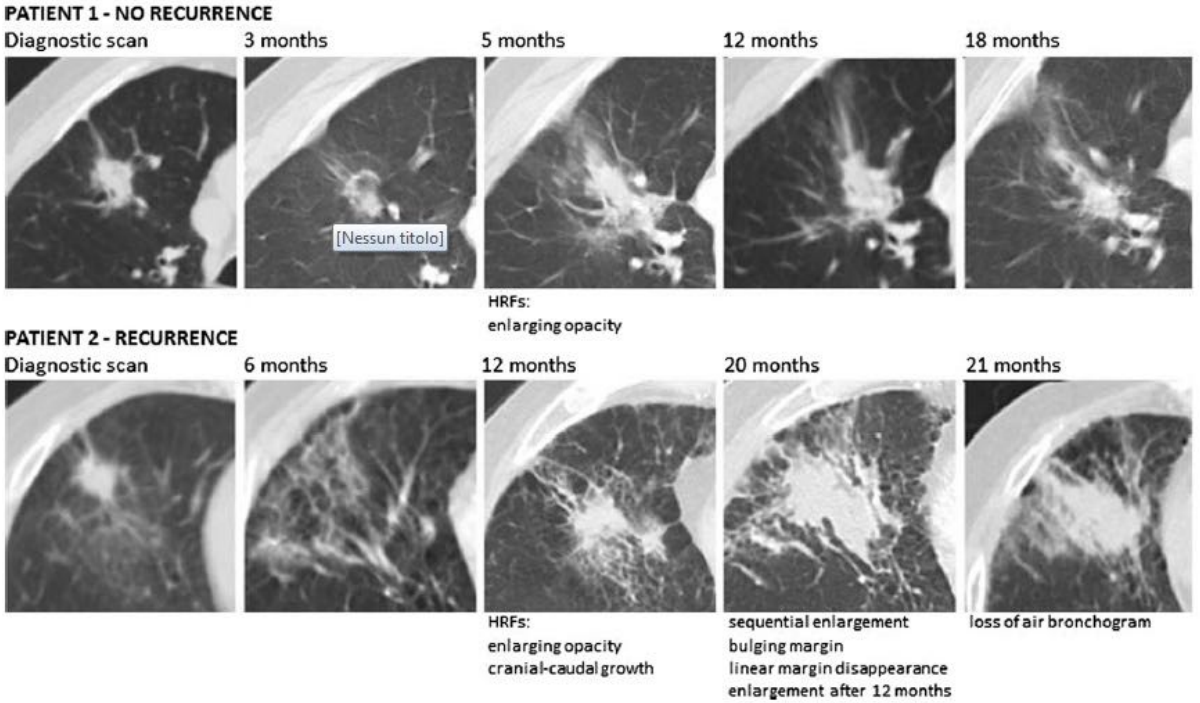
EARLY STAGE LUNG NSCLC:
.. UNRESOLVED ISSUES

RESPONSE EVALUATION



With the increasing using of lung SABR**, distinguishing fibrosis from recurrence is a research priority** for survivorship, as salvage treatment by surgery or repeat SABR while feasible, are not without toxicity

Louie et al. Radiotherapy and Oncology. *2015*

Is the same the effectiveness of SBRT for the oligometastases?

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LUNG OLIGOMETASTASES:
.. THE ROLE OF SABR

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To SABR or Not to SABR? Indications and Contraindications for Stereotactic Ablative Radiotherapy in the Treatment of Early-Stage, Oligometastatic, or Oligoprogressive Non–Small Cell Lung Cancer

David Benjamin Shultz, MD, PhD,[*,†] Maximilian Diehn, MD, PhD,[*,†,‡] and Billy W. Loo Jr, MD, PhD[*,†]

- The concept of Oligomestastatic disease was proposed nearly 20 years ago.
- SABR is quite effective than surgery for controlling pulmunary metastases

Shulz et al. Seminars in Radiat Oncol . *2015*

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LUNG OLIGOMETASTASES:
.. THE ROLE OF SABR

Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD, Andrea Riccardo Filippi, MD,† Juliette Thariat, MD,‡ Francoise Mornex, MD, PhD,‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD†*

Journal of Thoracic Oncology® • Volume 9, Number 10, October 2014

TABLE 1. Clinical Trials of Stereotactic Ablative Radiotherapy for Pulmonary Oligometastatic Disease

Reference	No. of Patients	No. of Targets	Radiation Dose	Median Follow-Up (Months)	Outcomes
Fractionated/Single Fraction SABR					
Onimaru et al.[27]	20	32	48 Gy/8 fx, 60 Gy/8 fx	18	48% 2-yr OS, 69.6% 3-yr LC for 48 Gy, 100% 3-yr LC for 60 Gy
Yoon et al.[26]	53	80	30 Gy/3 fx, 40 Gy/4 fx, 48 Gy/4 fx	14	70% LC for 30 Gy, 77% for 40 Gy, 100% LC for 48 Gy, 51% all 2-yr OS
Okunieff et al.[28]	50	125	50 Gy/10 fx, 48 Gy/6 fx, 57 Gy/3 fx	18.7	91% 3-yr LC, 50% 2-yr OS
Norihisa et al.[18]	34	43	48 Gy/4 fx		90% 2-yr LC, 84% 2-yr OS
Brown et al.[25]	35	69	5 Gy/1 fx		77% crude LC, 72.5% 2-yr OS
Rusthoven et al.[12]	38	63	60 Gy/3 fx		96% 2-yr LC, 39% 2-yr OS
Wulf et al.[24]	41	51	30 Gy/3 fx		80% 1-yr LC, 33% 2-yr OS
Ricardi et al.[23]	61	77	45 Gy/3 fx, 26 Gy/1 fx at 80%	20.4	89% 2-yr LC, 66.5% 2-yr OS
Single Fraction SABR Only					
Hof et al.[30]	61	71	12 to 30 Gy at isocenter	14	65.1% 2-yr OS
Filippi et al.[29]	67	90	26 Gy at 80%	24	88.1% 2-yr LC, 70.5% 2-yr OS

- Total doses :24-60 Gy in 1 or 4 fr,
- 1–3 years LC: 70%–100%
- 1–2 years OS 48%– 84%

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LUNG OLIGOMETASTASES:
.. THE ROLE OF SABR

Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

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Journal of Thoracic Oncology • Volume 9, Number 10, October 2014

TABLE 2. Ongoing Clinical Trials Examining the Role for Surgery or SABR for Oligometastatic Cancer

Study	Design	Eligibility	Intervention	Primary Endpoint
PulMICC[38]	Randomized phase II	Pulmonary metastases from colorectal cancer	Active monitoring vs. pulmonary metastasectomy	Feasibility/survival
SABR-COMET[39]	Randomized phase II	All treatable metastatic sites; maximum of three tumors to any single organ system; controlled primary tumor	Palliative-scheme radiation as clinically indicated vs. stereotactic ablative radiation to multiple sites	Overall survival
SAFRON II[40]	Randomized phase II	A maximum of three metastases to the lung from any nonhematological malignancy	Stereotactic multifraction SABR vs. radiosurgery	Toxicity
NCT01185639[41]	Phase II	NSCLC with ≤5 metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have three mets	SBRT to affected sites, delivered in three or five fractions	Progression-free survival
NCT01725165[72]	Randomized phase II	Three or less metastases from NSCLC	Consolidative radiotherapy and/or surgery vs. systemic therapy or observation	Progression-free survival

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LUNG OLIGOPROGRESSIVE LESIONS:
.. A NEW INDICATION FOR SABR???

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To SABR or Not to SABR? Indications and Contraindications for Stereotactic Ablative Radiotherapy in the Treatment of Early-Stage, Oligometastatic, or Oligoprogressive Non–Small Cell Lung Cancer

David Benjamin Shultz, MD, PhD,[*,†] Maximilian Diehn, MD, PhD,[*,†,‡] and Billy W. Loo Jr, MD, PhD[*,†]

Strahlenther Onkol (2015) 191:453–455
DOI 10.1007/s00066-015-0826-2

LITERATUR KOMMENTIERT

Oligoprogression

Eine innovative Indikation für die Körperstereotaxie bei metastasierten Tumorsituationen

Matthias Guckenberger

Online publiziert: 5. März 2015

Can SABR Be Used to Treat Oligoprogressive Disease Occurring in the Setting of Targeted Therapy?

Patients with NSCLC who were treated with targeted agents eventually develop progression owing to the emergence of drug-resistant clones. Because most cancer may retain a drug-sensitive genotype, it has been hypothesized that, in this clinical scenario, patients should be maintained on the same targeted therapy and that the resistant clones, which are phenotypically distinguished as oligoprogressive tumors, should be treated with surgery, CFRT, or SABR. Studies in which SRS or SABR was used to treat patients with oligoprogressive NSCLC that was either intracranial only[113] or intracranial and systemic [114,115] while being maintained on a targeted agent have been reported. Weickhardt et al reported their retrospective experience of using SABR, CFRT, and surgery with the goal of prolonging the effectiveness of targeted therapy in patients with NSCLC. Overall, 25 patients with *ALK* rearranged or *EGFR* mutation-driven tumors were included in the study, and sites of oligoprogression were classified as being

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LUNG OLIGOPROGRESSIVE LESIONS:
.. A NEW INDICATION FOR SABR???

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David Benjamin Shultz, MD, PhD,[*,†] Maximilian Diehn, MD, PhD,[*,†,‡] and Billy W. Loo Jr, MD, PhD[*,†]

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Table 2 Current or Completed Prospective Trials of Surgery or Radiotherapy for Oligometastatic or Oligoprogressive Non–Small Cell Lung Cancer

Study	Status	Study Type, Location	Modality	Patients Enrolled	Primary Outcome
Endo et al[125]	Pub.	Multi-institutional, Japan	S	20	OS (45% at 5 y)
Downey et al[126]	Pub.	Single institution, United States	S	23	OS (median = 11 mo)
De Ruysscher et al[102]	Pub.	Multi-institutional, Europe	S or R	39	OS (median = 14 mo)
NCT01185639[119]	Rec.	Multi-institutional, United States	R	45*	PFS
NCT01796288[123]	Rec.	Multi-institutional, China	R	200*	PFS
NCT02076477[122†]	Rec.	Multi-institutional, China	R	420*	RR
NCT01725165[124†]	Rec.	Multi-institutional, United States	S or R	94*	PFS
NCT00776100[121†]	Com.	Multi-institutional, United States	R	98	OS
NCT02054819[120]	Rec.	Single institution, United States	R	20*	OS
NCT01573702[117]	Rec.	Single institution, United States	R	40*	PFS

Abbreviations: Com., completed; PFS, progression-free survival; Pub., published; R, radiotherapy; Rec., recruiting; RR, response rate; S, surgery.
*Target enrollment.
†Randomized.

FUTURE OR….COMING SOON IN PRACTICE:

PROTON THERAPY?HEAVY IONS?

BIOLOGICAL PROFILING BEFORE RT?

WHICH INTERACTIONS WITH NEW DRUGS??

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