Polmone

Radioterapia stereotassica

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The ***Lung*** is a main side of metastatic disease for most solid tumors and local treatments have an emerging role in combination with systemic therapies

Surgery *vs.* stereotactic radiotherapy (SBRT) in the lung oligometastases

Surgery for the management of oligometastatic disease is now standard practice in several settings, improving local control and overal survival.

OS rates of 70% at 2 years and 36% at 5 years.

Casiraghi et al. 2011, Kaifi et al. 2010, Simmonds et al. 2006, van Geel et al. 2002

Surgery *vs.* stereotactic radiotherapy (SBRT) in the lung oligometastases

Stereotactic body radiotherapy, an emerging alternative to surgery, gives high local control rates and good survival outcomes with a good toxicity profile.

High doses in one to 5 fractions must be delivered.

Rusthoven, 2009, Onishi, 2004, Siva 2010, Norihisa 2008

Selection criteria for *lung* SBRT in treating oligometastatic cancer according to "available" **literature**

- ✓ Limited number of metastases (from 1 to 5)
- ✓ Limited tumor diameter (<5 cm)
- ✓ Limited metastatic disease (oligometastasis or oligo-recurrence)
- ✓ Good performance status
- ✓ Favorable histology (?)
- ✓ Metachronous appearance of metastases (?)

Rubin 2006, Norihisa 2008, Nagata 2011

Selection criteria for *lung* SBRT in treating oligometastatic cancer in **general clinical practice**

Patients for whom surgery is not feasible because of their **age**, **comorbidity** or **PS** and because of previous treatment with multiple lines of systemic therapy, when the toxicity of local treatment should be minimized.

J Thorac Oncol. 2010

STATE OF THE ART: CONCISE REVIEW

Stereotactic Radiotherapy for Pulmonary Oligometastases

A Systematic Review

Shankar Siva, MBBS, Michael MacManus, MD, MRCP, FRCR, FRANZCR, and David Ball, MD, MBBS, FRANZCR

A wide range of techniques, doses, and dose fractionation schedules were found. **334** patients with **564** target were reported in **SBRT series**. The 2-year weighted **local control** was **77,9%**. The corresponding 2-year weighted **overall survival** was **53,7%**, with a **4%** rate of **grade 3** or higher radiation toxicities.

154 patients with **174** targets were treated in the **SRS series**. The 2-year weighted **local control** was **78,6%**. The corresponding 2-year weighted **overall survival** was **50,3%**, with a **2,6%** rate of **grade 3** or higher toxicities

Review and Uses of Stereotactic Body Radiation Therapy for Oligometastases

The Oncologist 2013

FILIPPO ALONGI,[a] STEFANO ARCANGELI,[a] ANDREA RICCARDO FILIPPI,[b] UMBERTO RICARDI,[b] MARTA SCORSETTI[a]

LUNG

Study	*n* of patients	Median dose/*n* of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 48% 2-yr, 21%	Grade 3, 1 (3.7%)
Yoon et al. [71]	53	30 Gy/3; 40 Gy/4; 48 Gy/4	14 (4–56)	7 **70-100%** y, 1	1-yr, 89%; 2-yr, 51%	**G3 in 2-4%**
Okunieff et al. [18]	50	50 Gy/10; 48 Gy/6; 57 Gy/3	18.7 (3.7–60.9)	3	2-yr, 50%	Grade 3, 2%
Norihisa et al. [6]	34	48 Gy/4; 60 Gy/5	27 (10–80)	2-yr, 90%	2-yr, 84%	Grade 2, 4 (12%) Grade 3, 1 (3%)
Brown et al. [72]	35	5 Gy/1 to 60 Gy/4	18 (2–41)	Crude, 77%	2-yr, 72.5%	Grade 3–4, 1 (2.8%)
Rusthoven et al. [14]	38	60 Gy/3	15.4 (6–48)	2-yr, 96%	2-yr, 39%	No grade 4 Grade 3, 3 (8%)
Ricardi et al. [17]	61	45 Gy/3; 26 Gy/1	20.4 (3–77)	2-yr, 89%	2-yr, 66.5	Grade 3, 1 (1.6%)

Lung Cancer 2012

Stereotactic body radiation therapy for lung metastases

Umberto Ricardi et al.

Introduction: Stereotactic body radiation therapy (SBRT) has an emerging role in patients affected with pulmonary metastases. Purpose of this study was to evaluate efficacy and tolerability of SBRT in a cohort of patients treated between 2003 and 2009 at our institution.
Methods: A total of 61 patients with oligometastatic lung tumors (single pulmonary nodules in 73.7%) were included in the study. SBRT was performed with a stereotactic body frame and a 3D-conformal technique. Fifty-one patients received 26 Gy in 1 fraction, 22 a dose of 45 Gy in 3 fractions and 3 a dose of 36 Gy in 4 fractions. Primary tumor was lung cancer in 45.7% of patients, colorectal cancer in 21.3% and a variety of other origins in 33%. The primary endpoint was local control, secondary endpoints were survival and toxicity.
Results: After a median follow-up interval of 20.4 months, local control rates at 2 and 3 years were 89% and 83.5%, overall survival 66.5% and 52.5%, cancer-specific survival 75.4% and 67%, progression-free survival 32.4% and 22.3%. Tumor volume was significantly associated to survival, with highest rates in patients with single small tumors. Median survival time was 42.8 months, while median progression-free survival time was 11.9 months. Toxicity profiles were good, with just one case of grade III toxicity (pneumonitis).
Conclusion: This study shows that SBRT is an effective and safe local treatment option for patients with lung metastases. Definitive results are strictly correlated to clinical selection of patients.

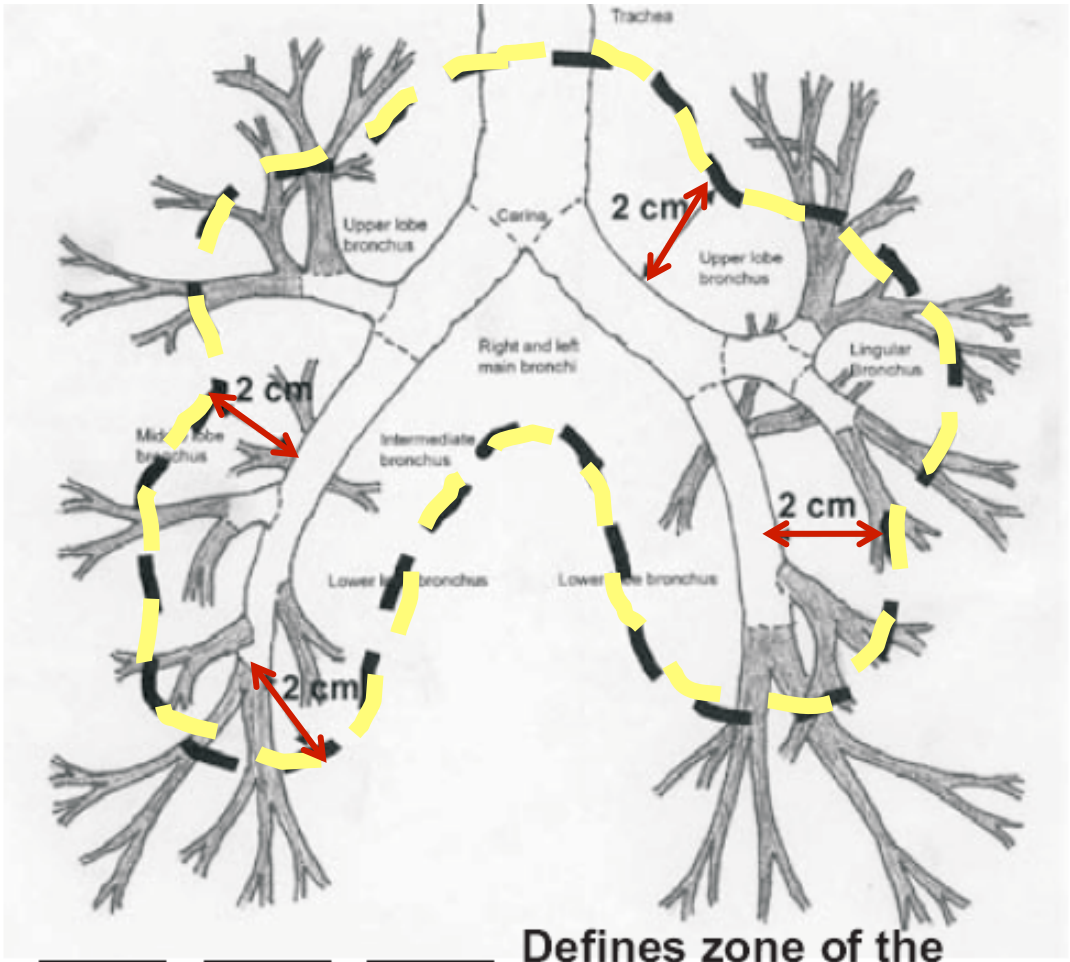
NCCN National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2012
Non-Small Cell Lung Cancer

PRINCIPLES OF RADIATION THERAPY

Table 2. Commonly Used Doses for SABR

Nominal 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, esp. > 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



National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2012
Non-Small Cell Lung Cancer

Table 5. Normal Tissue Dose Volume Constraints for SBRT*

OAR	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/ Large Bronchus	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	40 Gy (8 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	31.2 Gy (7.8 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

frontiers in ONCOLOGY

REVIEW ARTICLE
published: 08 April 2013

Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results

*Akash Bijlani[1], Giovanni Aguzzi[2], David W. Schaal[1] and Pantaleo Romanelli[2]**

Clinical outcomes and costs of SRS and SBRT were comparate to other therapies for treatment of cancer in the brain, spine, *lung*, prostate and, pancreas.

Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results

2013

*Akash Bijlani[1], Giovanni Aguzzi[2], David W. Schaal[1] and Pantaleo Romanelli[2]**

Lung publication characteristics, estimated costs, and effectiveness.

Reference	Country	Type of study	Procedures compared	Perspective	Cost types	Local currency	Procedures cost per patient	Effectiveness	ICER/ICUR/Cost analysis results
Lanni et al. (2011) **Medically inoperable NSCLC**	USA	Cost-effectiveness	SBRT 3DCRT IMRT	Service provider	Direct	USD	SBRT: $52,471 3DCRT: $55,705 IMRT: $136,570	SBRT 36-month overall survival: 71% 3DCRT 36-month overall survival: 42% IMRT 36-month overall survival: n.a.	SBRT dominates
Sher et al. (2011) **65-year-old men with medically inoperable NSCLC**	USA	Cost-utility	SBRT 3DCRT RFA	Service provider	Direct	USD	SBRT: $51,133 3DCRT: $48,842 RFA: $44,648	SBRT: 1.91 QALY 3DCRT: 1.53 QALY RFA: 1.45 QALY	SBRT vs. 3DCRT: $6,000/QALY SBRT vs. RFA: $14,100/QALY
Puri et al. (2012) **Stage I NSCLC**	USA	Cost-effectiveness	SBRT Surgery	Healthcare payer	Direct	USD	SBRT: $14,153 Surgery: $17,629	SBRT overall survival: 2.94 years Surgery overall survival: 3.39 years	Surgery vs. SBRT: $7,753/LYS

SBRT, stereotactic body radiation therapy; EBRT, external beam radiation therapy; 3DCRT, 3-dimensional conventional radiation therapy; IMRT, intensity modulated radiation therapy; RFA, radiofrequency ablation; USD, United States dollar; LY/LYS, life years/life year saved; QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio.

…from a **patient perspective**, SRS and SBRT provide patients a clinically effective treatment option, while from the **payer and provider perspective**, it demonstrate cost savings.

Our experience on lung SBRT

Patient selection

- ✓ 1-2 lung metastases
- ✓ Maximum tumor diameter smaller than 50mm
- ✓ Absent or controlled extra-thoracic disease
- ✓ Adequate pulmonary function
  (FEV1> 40% and DLCO >40% predicted)
- ✓ PS 0-1

Lung SBRT doses

Equivalent total dose in 2 Gy fraction (EQD2)	* 8 Gy x 5	* 10 Gy x 5	12 Gy x 5
$\alpha/\beta = 3$ (LUNG)	88 Gy	130 Gy	170 Gy
$\alpha/\beta = 10$ (TUMOR)	60 Gy	84 Gy	110 Gy

** suboptimal outcome for BED ≤ 100 Gy*

Prevention of toxicity:

Dose-volume constraints for normal tissues

NORMAL TISSUE COMPLICATION PROBABILITY: ≤ 5% at 5 years

Lung SBRT:our experience

(May 2003 – december 2012)

Total	
patients	120
lesions	134
M/F	96/24
Median age	70 years (range, 36-87)
Karnofsky PS	100 (70-100)

Primary tumors:	N. **83** (62%)
Metastatic tumors:	**N. 51 (38%)/41 pts**

Metastatic tumors:

51 lesions

PRIMARY:	**Colon:**	**14 (27%)**
	Lung:	**21(40%)**
	Sarcomas:	**4 (7%)**
	Breast:	**6 (11%)**
	Other:	**8(15%)**

DOSES/LESIONS

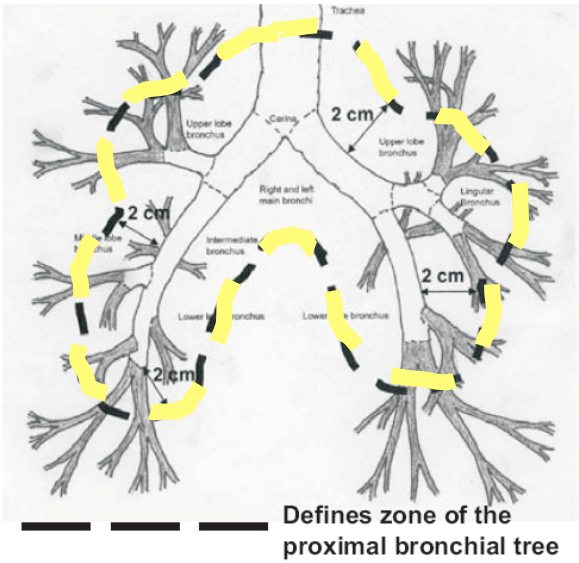
Doses	N. of lesions (%)
10Gy x 5	**13 (25)**
8Gy x 5	**28 (55)**
9Gy x 5	3 (6)
7Gy x 5	7 (14)

80%

Median planned target volume:

35 cc (range,5 -240 cc)

Tumor site:	
PERIFERICAL	**33/51 (65%)**
CENTRAL	**18/51 (35%)**



MEDIAN FOLLOW UP : 33 months (range, 5-90)

CR	17 (33%)
PR	16 (31%)
S	15 (29%)
P	3 (7%)

93%

Median time to progression: 11 months (range, 3-72)

Toxicity profile

Symptomatic ACUTE TOXICITY (2%)

- ***1*** **dysphagia**

Radiological LATE TOXICITY (5%)

- ***2*** **fibrosis**

Re-irradiation with SBRT after prior lung 3D-CRT or SBRT

In case of **relapse or second tumor after thoracic irradiation** patients generally receive chemotherapy with low response rates

Re-irradiation with 3D-CRT has been explored by multiple groups using several techniques, doses and fractionations resulting in good palliation with acceptable toxicity

Okamoto et al 2002, Tada et al 2005

Recently published study of **re-irradiation with SBRT** after prior 3D-CRT showed promising results with good local control and acceptable toxicity

Poltinnikov et al 2005, Kelly et al 2010

Study of re-irradiation with SBRT after 3D-CRT

Clinical trial	*Poltinnikov et al.*	*Kelly et al.*
No. patients/treatment	17/17	36/36
Dose 1st RT course	≥ 50 Gy	median 61.5 Gy (range, 30–79.2 Gy)
Interval (median)	n/s	22.0 months (range, 0–92 months)
Total re-irradiation dose	median 32Gy (17.5 – 42.0)	50 Gy (72%) 40 Gy (17%) Other (11%)
Single fraction dose	median 4Gy (2.5 – 4.2)	12.5 Gy (72%) 10Gy (17%) Other (11%)
Technology	SBF	SBF, 4D-CT, FDG-PET
Target size	median field size 95cm^2 (30–189)	Tumor size (median) 1.7cm (range, 0.6–3.8 cm)
Symptom relief	11/13	n/s
Median follow-up (range)	n/s	15 months (4–45)
Local control	5/17 responders	92%
Median Overall survival (range)	5.5 months (2.5–30)	59% @ 2a
Toxicity	G2 esophagitis n=4 G2 pneumonits n=1	At least one G3 in 33% of patients

from Mantel et al. Radiation Oncology 2013

In case of **relapse or second tumor after thoracic irradiation** patients generally receive chemotherapy with low response rates

Reirradiation with 3D-CRT has been explored by multiple groups using several techniques, doses and fractionations resulting in good palliation with acceptable toxicity

Okamoto et al 2002, Tada et al 2005

Recently published study of **re-irradiation with SBRT** after prior 3D-CRT showed promising results with good local control and acceptable toxicity

Poltinnikov et al 2005, Kelly et al 2010

Re-irradiation with SBRT after prior lung SBRT

Radiotherapy and Oncology 101 (2011) 260–266

Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy

Heike Peulen [d], Kristin Karlsson [b,c], Karin Lindberg [a,c], Owe Tullgren [a,c], Pia Baumann [a,c], Ingmar Lax [b], Rolf Lewensohn [a,c], Peter Wersäll [a,c,*]

[a] *Department of Oncology, Karolinska University Hospital, Radiumhemmet, Sweden;* [b] *Department of Hospital Physics, Karolinska University Hospital, Sweden;* [c] *The Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden;* [d] *Department of Radiation Oncology, MAASTRO Clinic, Maastricht, The Netherlands*

A B S T R A C T

Purpose: To assess toxicity and feasibility of reirradiation with stereotactic body radiotherapy (SBRT) after prior lung SBRT for primary lung cancer or lung metastases.

Patients and materials: Twenty-nine patients reirradiated with SBRT on 32 lung lesions (11 central, 21 peripheral) were retrospectively reviewed. Median follow-up time was 12 months (range 1–97). The primary endpoint was toxicity, secondary endpoints were local control and overall survival time. Toxicity was scored according to the NCI-CTCAE version 3.

Results: Grade 3–4 toxicity was scored 14 times in eight patients. Three patients died because of massive bleeding (grade 5). Larger clinical target volumes (CTV) and central tumour localization were associated with more severe toxicity. There was no correlation between mean lung dose (MLD) and lung toxicity. Local control at 5 months after reirradiation was 52%, as assessed by CT-scan ($n = 12$) or X-thorax ($n = 3$). A larger CTV was associated with poorer local control. Kaplan–Meier estimated 1- and 2-year survival rates were 59% and 43%, respectively.

Conclusions: Reirradiation with SBRT is feasible although increased risk of toxicity was reported in centrally located tumours. Further research is warranted for more accurate selection of patients suitable for reirradiation with SBRT.

Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy

Peulen et al.

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

Central $n = 11$					
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
2	2	–	–	–	Atelectasis
1	1	3	–	–	Cough
1	1	1	–	–	Dyspnoea
–	1	1	–	–	Pneumonitis
–	–	1	–	–	Stenosis of airway
–	–	–	–	3	Bleeding
–	2	–	–	–	Pleural effusion
2	2	–	–	–	Pulmonary fibrosis
–	–	–	–	–	Fracture
–	1	–	–	–	Dermatitis
1	–	x	x	x	Hyperpigmentation
–	–	1	–	–	Pain
–	1	–	2	–	**Fistula, stenosis**

PTV second treatment ($n = 32$)	76
PTV third treatment ($n = 3$)	64
PTV fourth treatment ($n = 1$)	277

Cumulative **EQD_2** ($\alpha/\beta=3$) in grade 4-5 toxicity:

Maximum 492 Gy

Interval between first SBRT and reirradiation (months)	14

Matherials and Methods

11 pts
17 lung lesions (LL)
M/F ratio: 9/2
Median age: 66 years (range,40-71)
Median KPS: 100 (range,90-100)

First SBRT

LR of primary NSCLC→ 3 pts

Lung metastases from NSCLC→ 8 pts
colon-rectal → 2 pts
sarcoma→ 1 pt

Reirradiation in the same lung for **out-field (5 pts), in-field (4 pts)** or both **in and out-field (2 pts)** relapse.

In-field when more than 95% of the recurrence volume was within the original 50% isodose

Comunicazione orale A.I.R.O 2012

-**GTV** was defined as the radiologically visible tumor using lung windowing

-**CTV** =**GTV**

-**PTV** was **GTV/CTV** + **8-10 mm** in the craniocaudal and

4-5 mm in the axial directions.

After dosimetric and physic calculations, the GTV/CTV was re-contoured in the image slices obtained with a verification CT.

Results

I° SBRT doses	N. of LL (%)	EQD_2 (α/β=3)
5 x 10 Gy	11 (65)	130 Gy
5 x 8 Gy	6 (35)	88 Gy

Reirradiation doses	N. of LL (%)	EQD_2 (α/β=3)	Max cumulative EQD_2 (α/β=3)
5 x 8 Gy	6 (35)	88 Gy	218 Gy
5 x 10 Gy	4 (23)	130 Gy	260 Gy
5 x 6 Gy	3 (18)	54 Gy	184 Gy
5 x 5 Gy	3 (18)	40 Gy	170 Gy
5 x 4 Gy	1 (6)	28 Gy	158 Gy

Time between first SBRT and Reirradiation: Median 22 months (range, 6 -36)

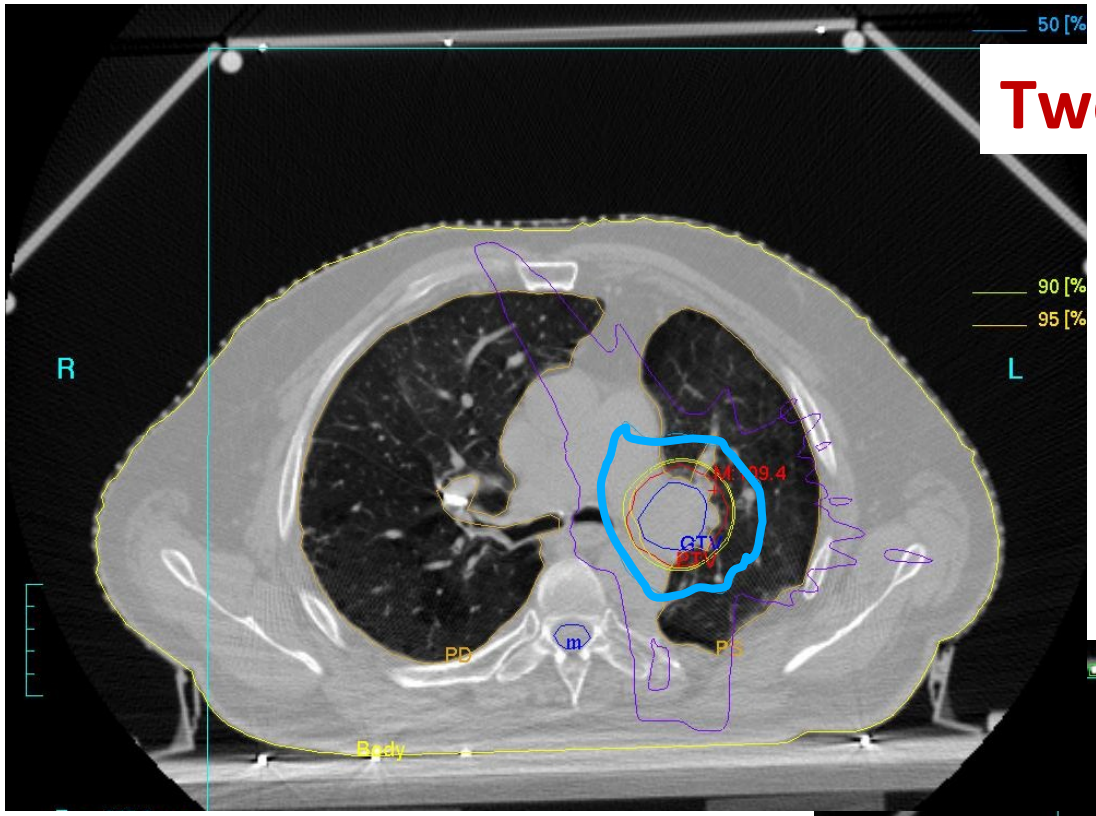
Median number of retreated LL: 1 (range, 1-4), → **10 central**
→ **7 peripheral**

Median PTV: 17 cc (range, 9-55); ∅ 32 mm

Two lesions in the same lobe

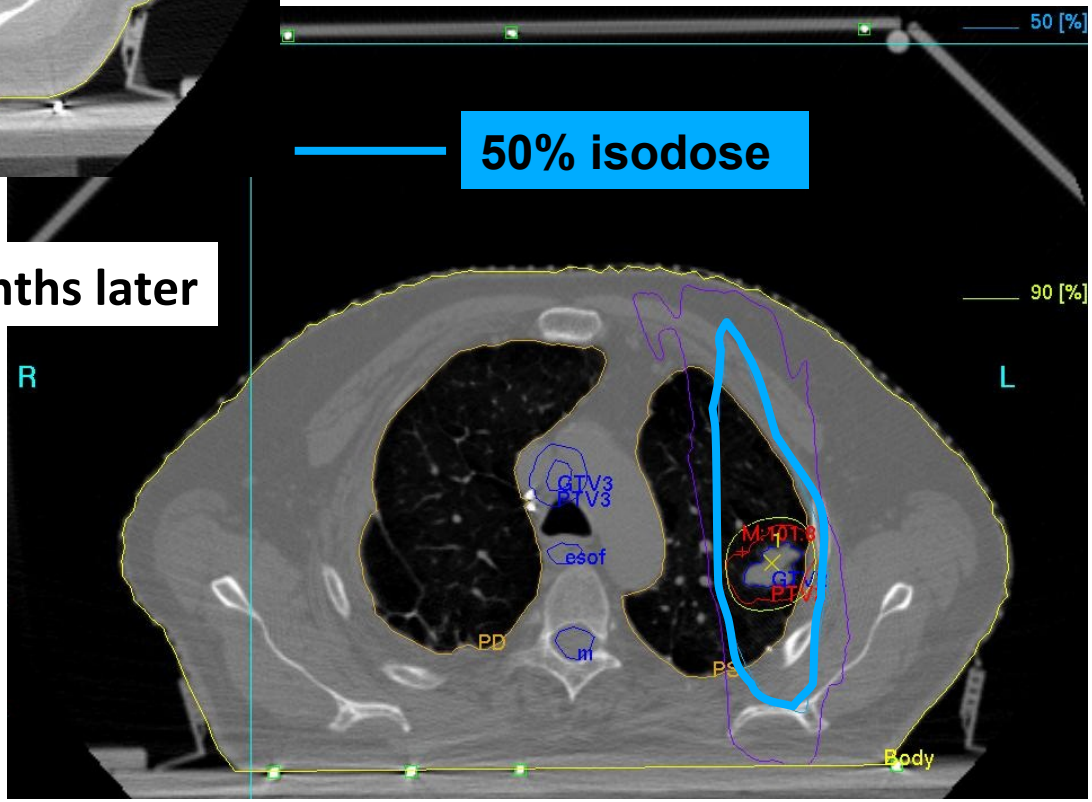
Out-field relapse

5x10 Gy



11 months later

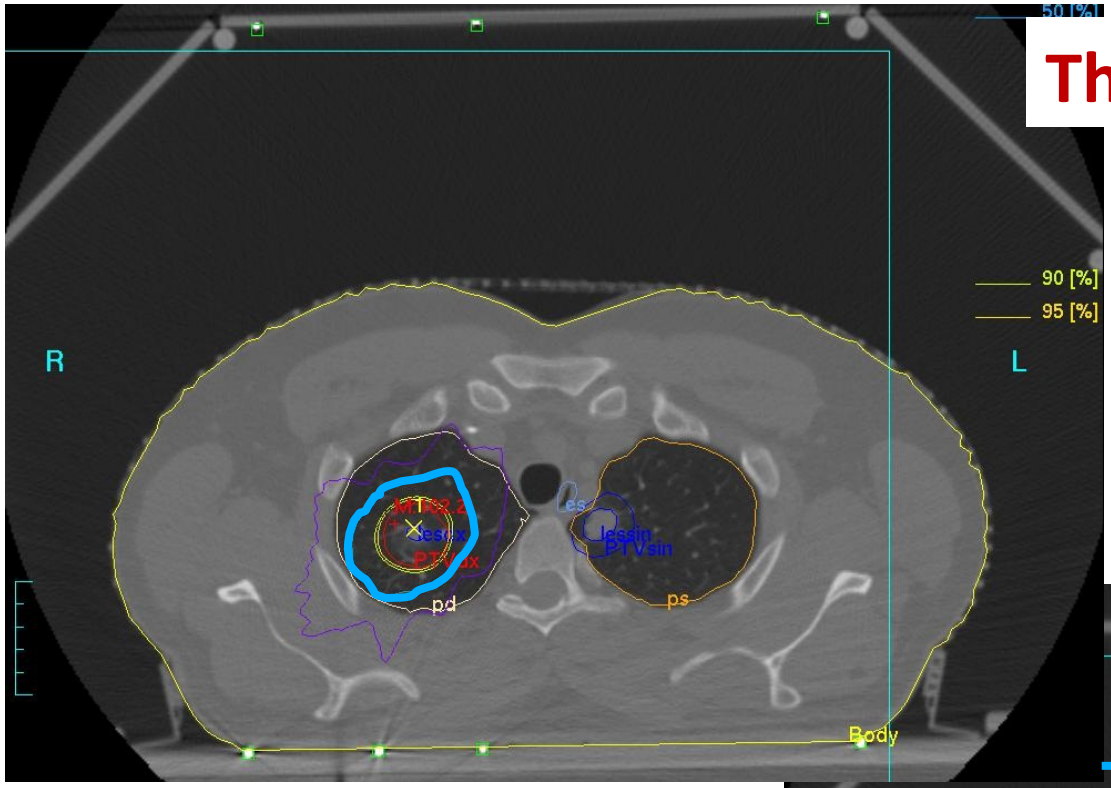
5x8Gy



The same peripheral lesion

In-field relapse

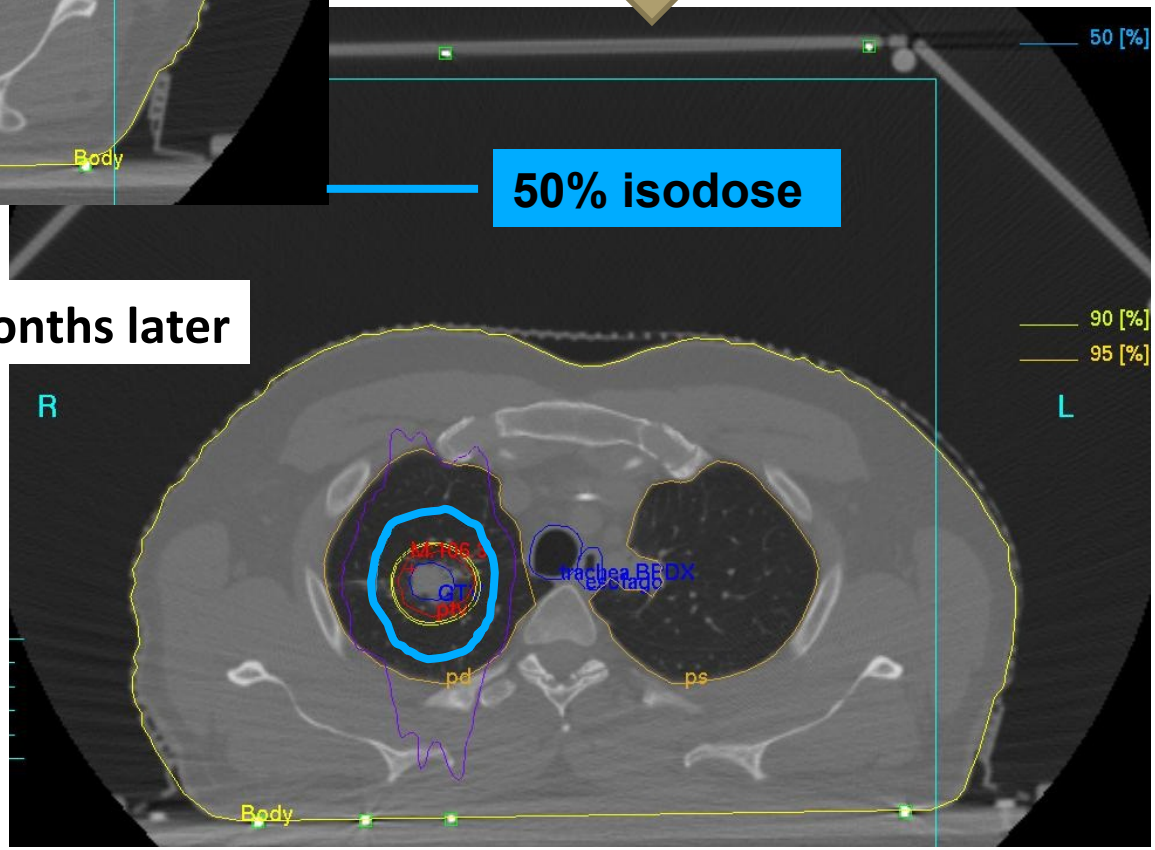
5x8Gy



50% isodose

24 months later

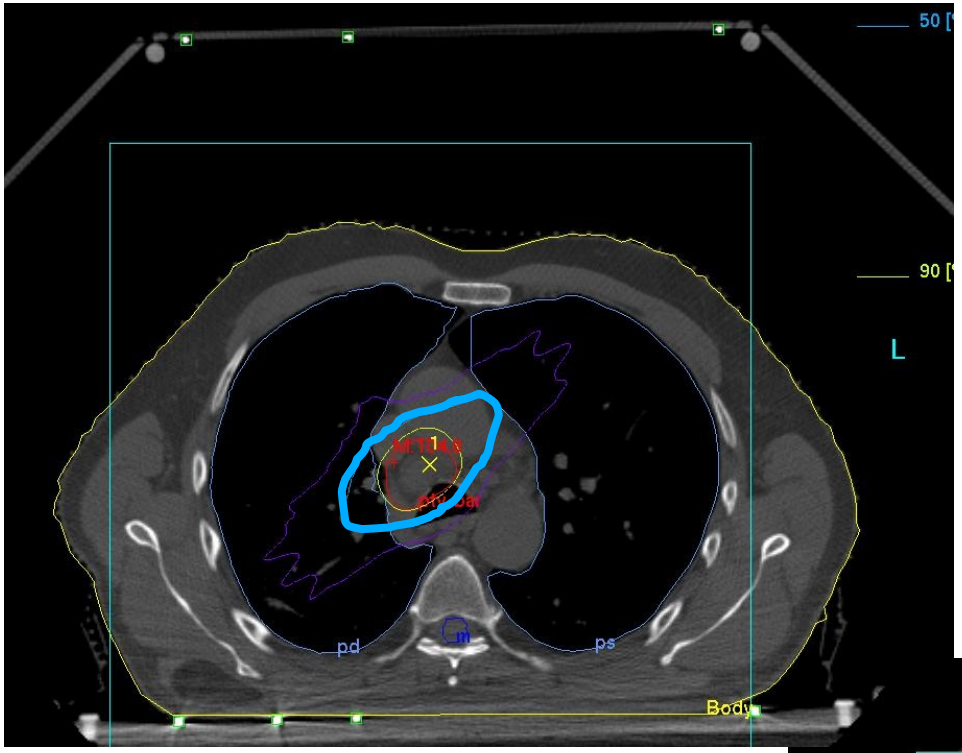
5x10Gy



The same central lesion

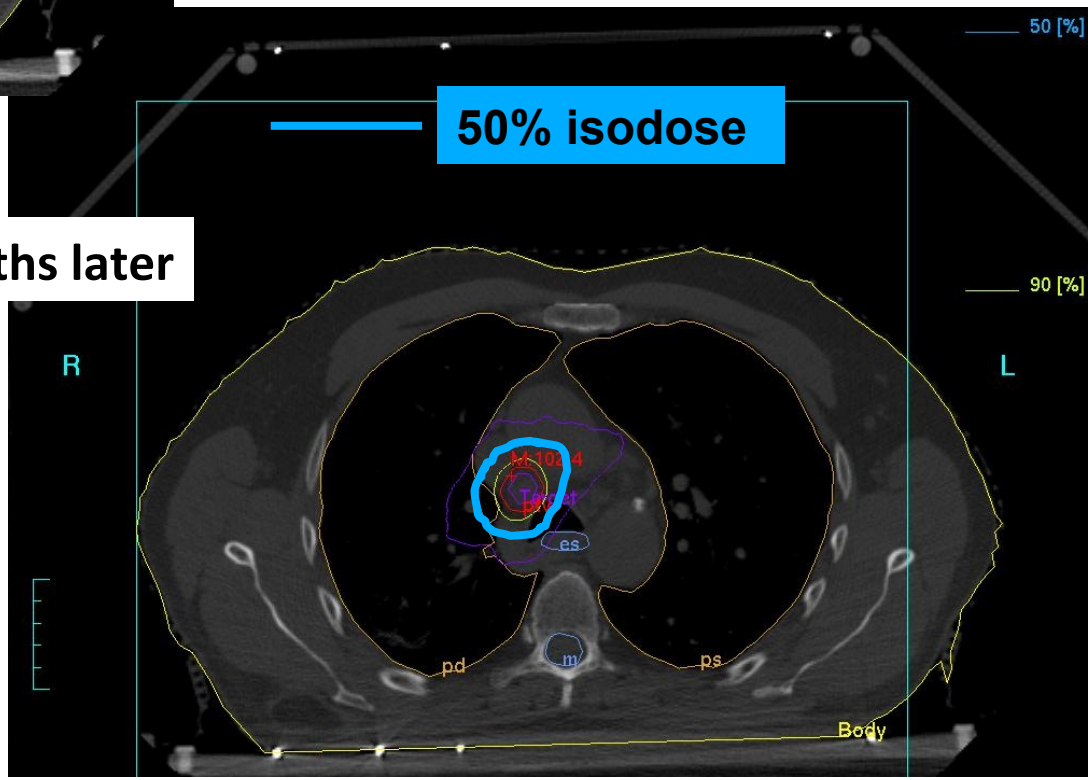
In-field relapse

5x5Gy



13 months later

5x8Gy



Response

Local Control in 100% of LL

	n. of LL	%
CR	7	41
PR	2	12
SD	8	47

RECIST criteria

Toxicity

No acute and late grade 3-5

n. of pts	Site of relapse	n. of treated LL	n. of reirradiation	Type of toxicity
1	out	2	2	Asymptomatic pneumonia (*grade 2*)
2	in & out	1	3 & 4	Thoracic pain (*grade 1-2*)
2	in	1	1	Dyspnea and dysphagia (*grade 2*)
1*	in	1	1	Rib fracture (*grade 2*)

*** pt treated with 5x10Gy SBRT for a peripheral metastases and retreated with 5x8Gy SBRT for an in-field-relapse, 13 months after reirradiation.**

Peulen experience

PTV second treatment ($n = 32$)	~ 70cc	76
PTV third treatment ($n = 3$)		64
PTV fourth treatment ($n = 1$)		277

Cumulative **EQD_2** ($\alpha/\beta=3$) in grade 4-5 toxicity:

Maximum **492 Gy**

Interval between first SBRT and reirradiation (months)	**14**

Our experience

17cc (9-55)

Maximum: 260 Gy

Median 22 months

Conclusions

✓ Few studies exist on SBRT for lung mets.

However,

✓ Lung SBRT and lung re-irradiation with SBRT are feasible with a high local control rate and satisfying survival outcome.

Unfortunately,

✓Surgery is often the treatment preferred in clinical practice

Worth of note,

✓ an accurate patient selection and

✓ an appropriate interval between prior SBRT and re-irradiation are necessary


Grazie per l’attenzione e buona estate!