Congresso inter-regionale
AIRO Lombardia e AIRO Piemonte-Liguria-Valle d'Aosta

L'INNOVAZIONE TECNOLOGICA
IN RADIOTERAPIA:
NUOVI STANDARD CLINICI
E PROBLEMATICHE GESTIONALI

Gazzada (VA), 29 Novembre 2014

Polmone: lesioni periferiche e centrali

Andrea Riccardo Filippi

Dipartimento di Oncologia

Università di Torino

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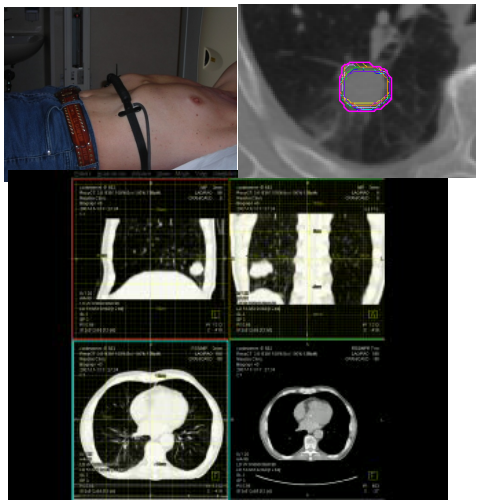
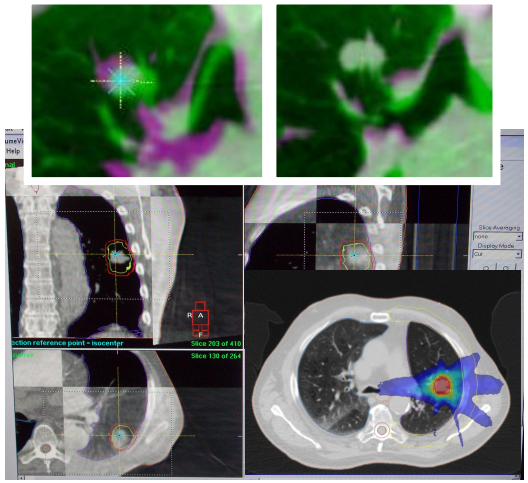
A technique for delivering external beam radiotherapy

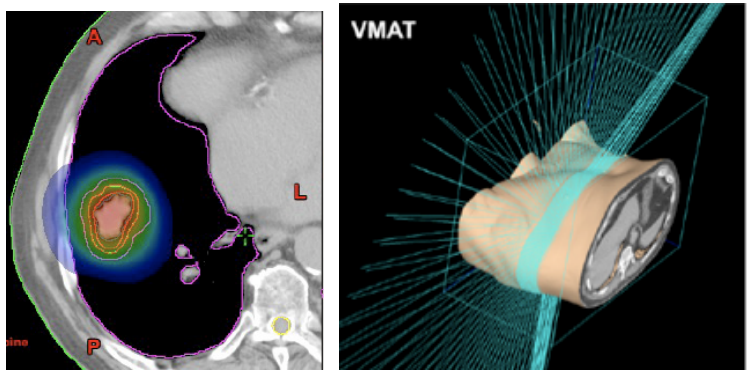
i. with a high degree of accuracy to an extra-cranial target,
ii. using high doses of irradiation,
iii. in 1-8 treatment fractions.



4-D imaging

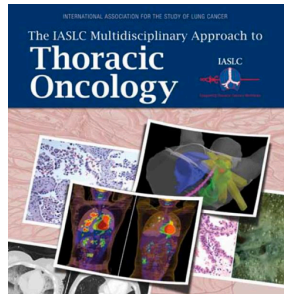


Sophisticated plans
CT scan on treatment couch



Delivery in <4 mins (FFF)

S. Senan, M. Guckemberger, U. Ricardi
Stage I NSCLC and oligometastatic disease
The IASLC Multidisciplinary approach to Thoracic Oncology, 2014

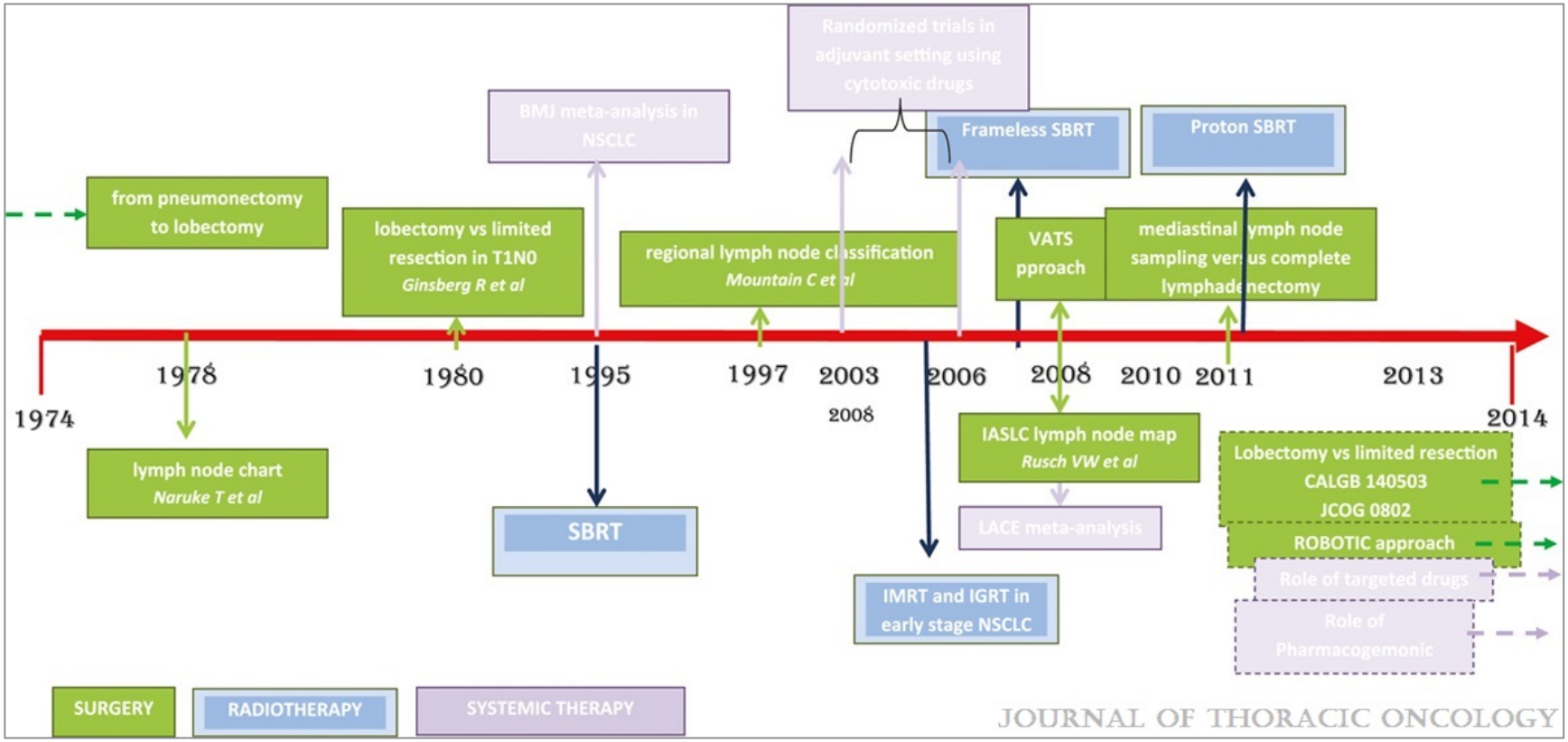


Early-Stage Lung Cancer: 40s Anniversary

Novello, Silvia; Asamura, Hisao; Bazan, Jose; Carbone, David; Goldstraw, Peter; Grunenwald, Dominique; Ricardi, Umberto; Vansteenkiste, Johan

Journal of Thoracic Oncology. 9(10):1434-1442, October 2014.

doi: 10.1097/JTO.0000000000000327



SABR for peripheral lung tumors

- ESMO Clinical Practice Guidelines 2013: SABR is the non surgical treatment of choice (dose to a biologically equivalent tumor dose $\geq$ 100 Gy)

- NCCN guidelines (version 3.2014): non surgical treatment of choice

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SABR for Stage I NSCLC: phase II studies

DISCOVERY MEDICINE

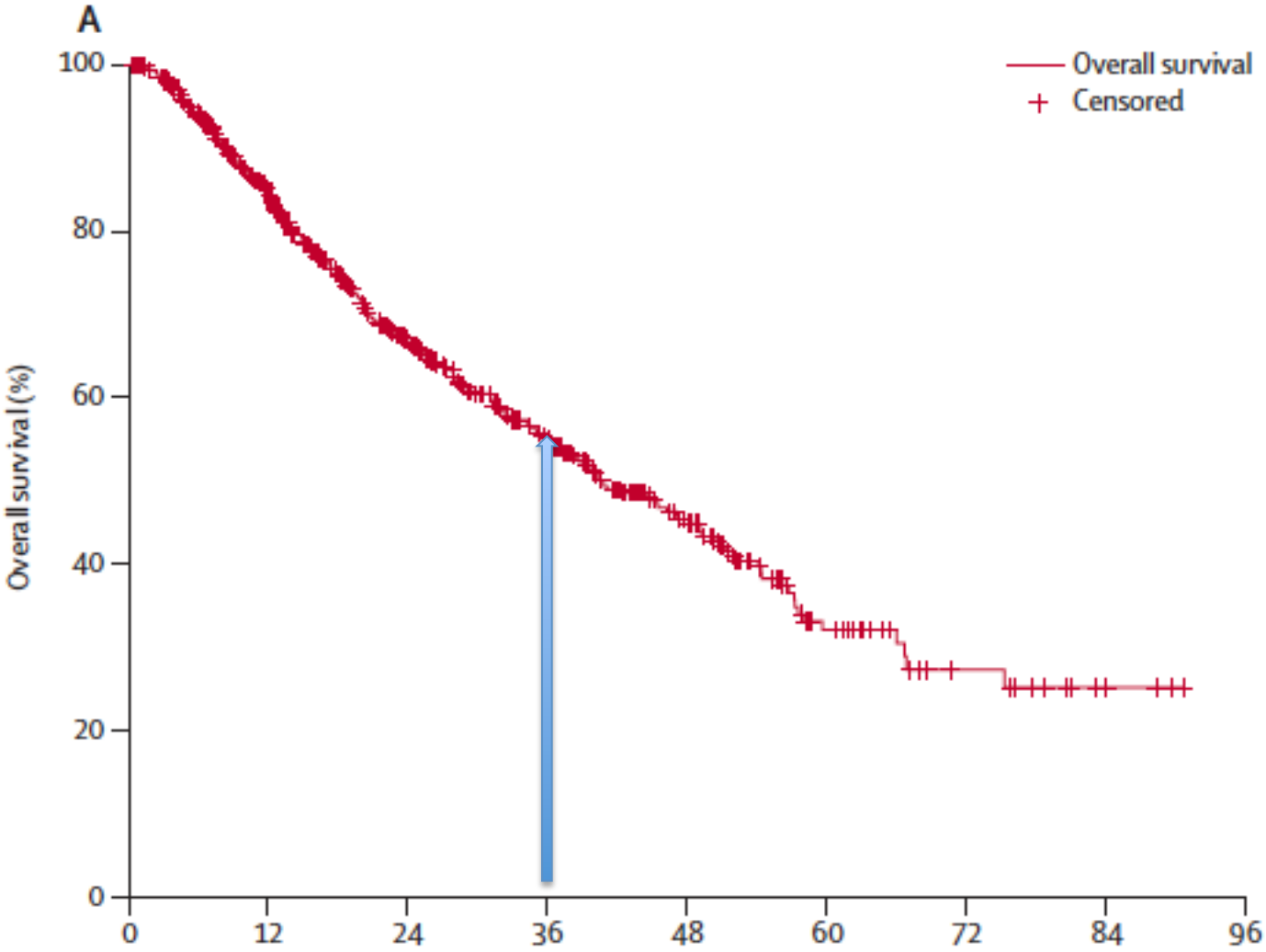
Table 1. Summary of Results of Recently Reported Prospective Trials of SBRT for Stage I NSCLC

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.

Loo et al, Discovery Medicine 2011

Mono-institutional largest study, with/without histological diagnosis



676 patients

Median follow-up time: 32.9 months

et al, Lancet Oncol 2012

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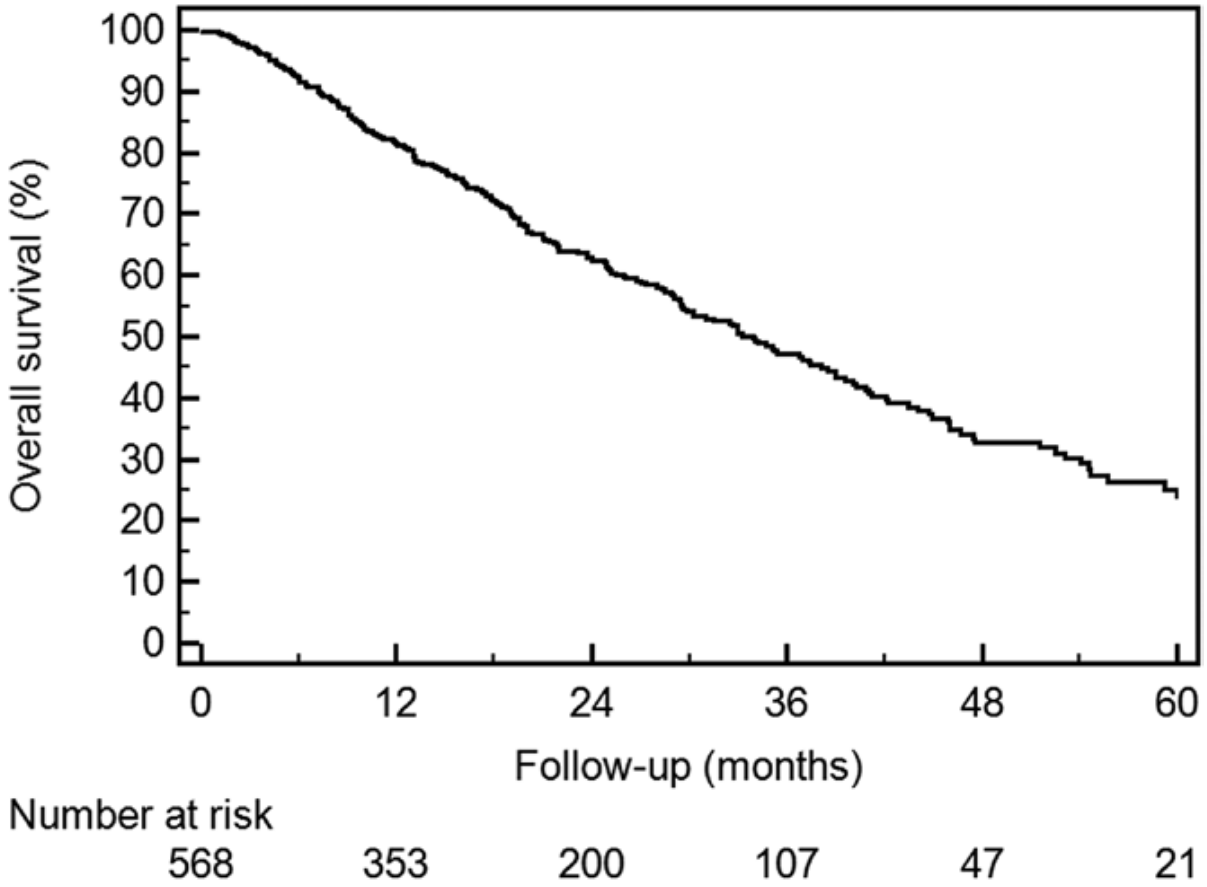
German Society for Radiation Oncology (DEGRO) Observational Multicentric Study



OS @3 years 47.1%

[Guckenberger et al, JTO 2013]

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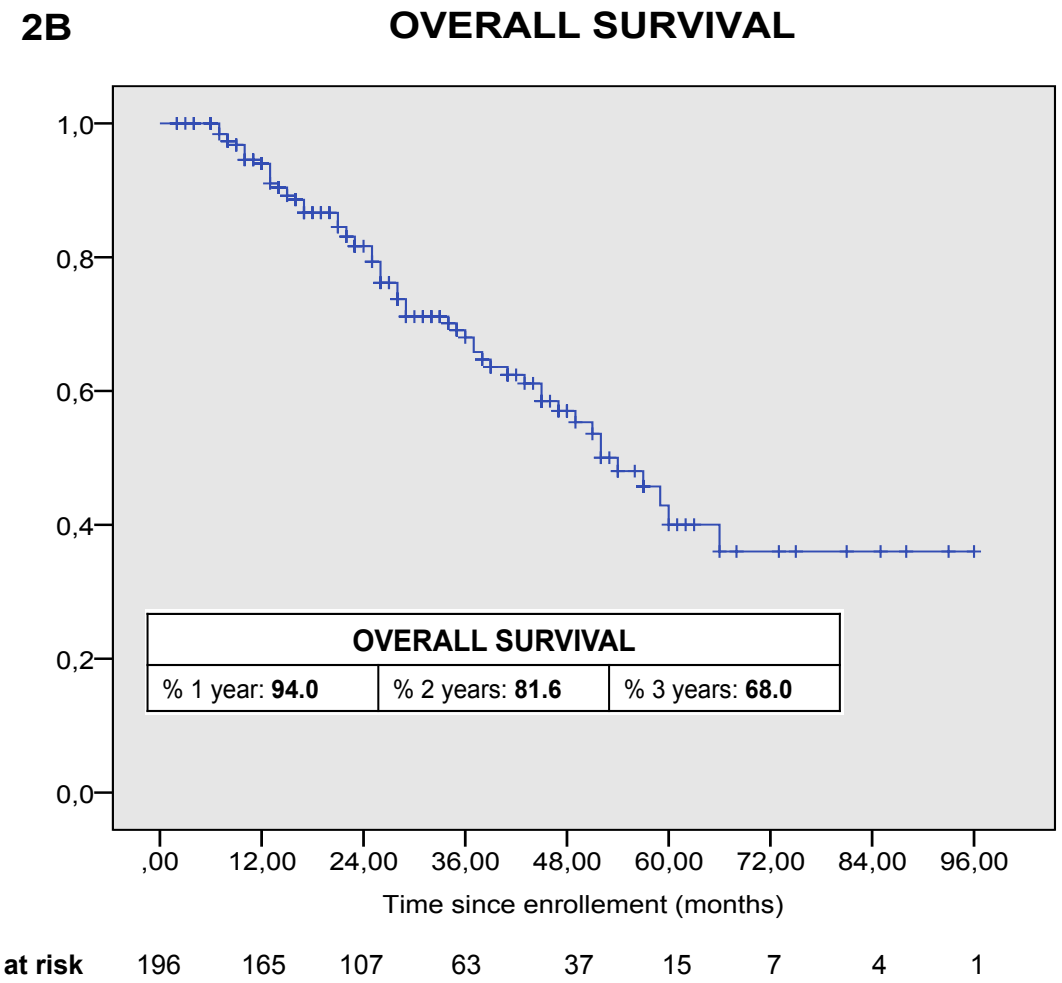
SABR in stage I histologically proven NSCLC: an Italian multicenter observational study



Ricardi et al, Lung Cancer 2014

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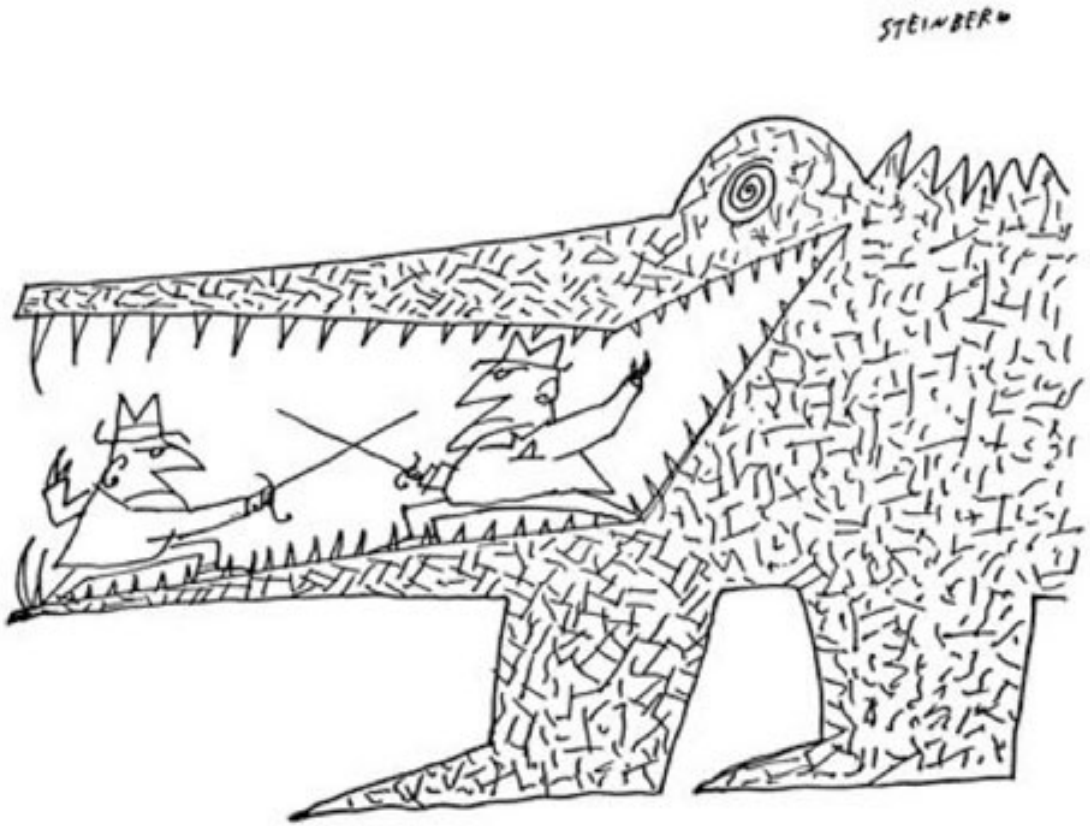
SABR vs SURGERY: randomized trials?



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Trials of surgery versus SABR

Table 1 – Approved Phase III Randomized Trials of Operable Stage I NSCLC Patients (all prematurely terminated due to poor accrual)

Dutch ROSEL trial, NCT00687986, "Randomized Clinical Trial of Stereotactic Radiotherapy or Surgery in Patients with Stage IA Non-Small Cell Lung Cancer who are fit to undergo Primary Resection".

- Sponsored by the The Netherlands Organisation for Health Research and Development.
- Opened at 9 centers
- Opened 2008, Closed 2010
- Enrolled 22 of 960

STARS Trial, NCT00840749, "Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer"

- Sponsored by Accuray©
- Opened at 15 centers
- Opened 2009, Closed 2013
- Enrolled 36 of 1,030 patients

ACOSOG-Z4099/RTOG-1021, NCT01336894, "A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)"

- Sponsored by American College of Surgeons
- Opened at 53 centers
- Opened 2011, Closed 2013
- Enrolled 10 of 420 patients

Morganaki D, unpublished

SABR - surgical viewpoints

- Await results of randomized clinical trials
- **'Late' recurrences may be a problem**
- Upstaging occult nodal disease is beneficial
- SABR is "equivalent to a wedge excision"

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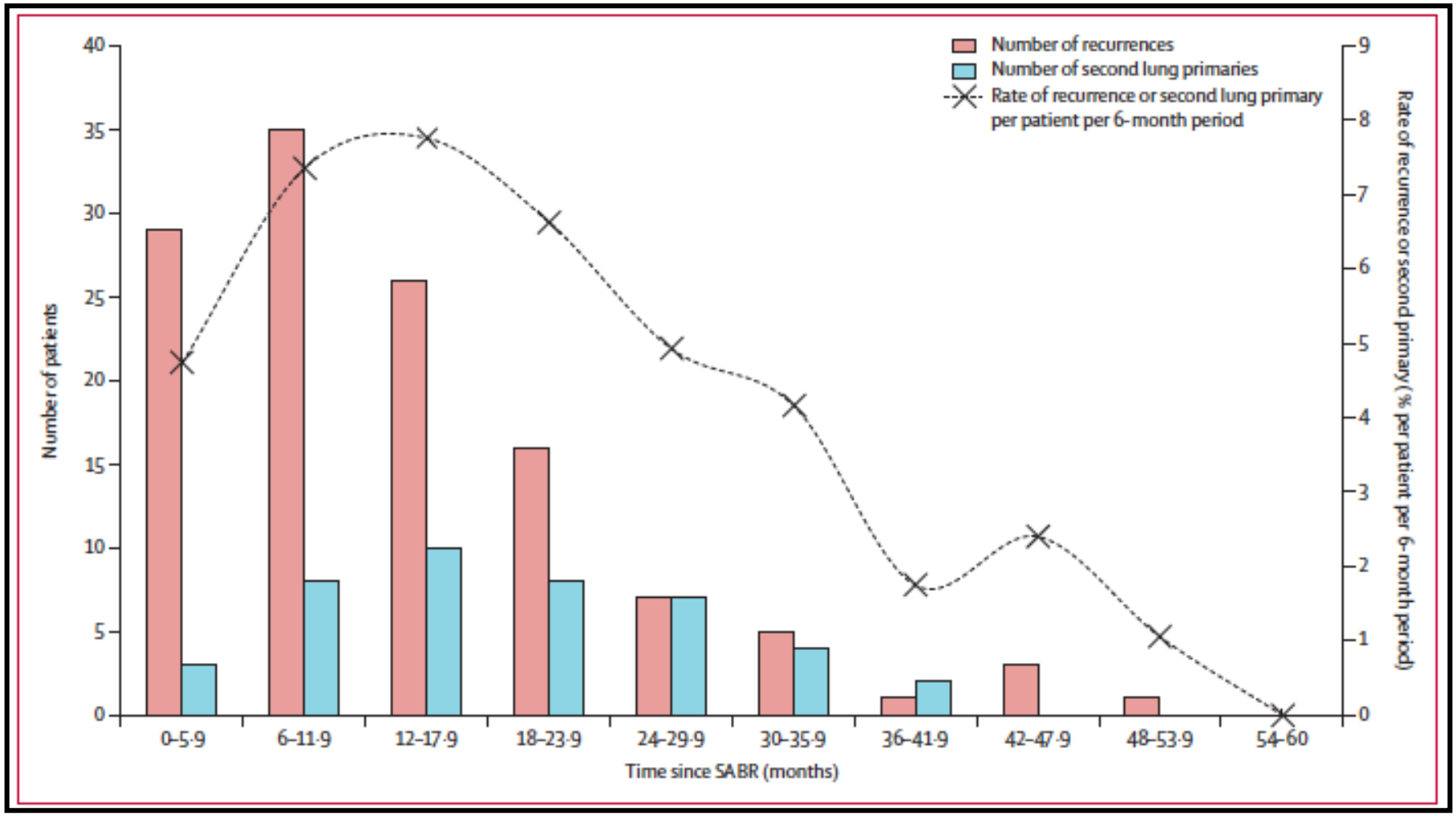
Time to distant failure



Senthi et al, Lancet Oncol 2012

SABR - some surgical viewpoints

- Await results of randomized clinical trials
- ‘Late’ local recurrences may be a problem
- **Upstaging occult nodal disease is beneficial**
- SABR is “equivalent to a wedge excision”

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Stage I NSCLC: Recurrence patterns

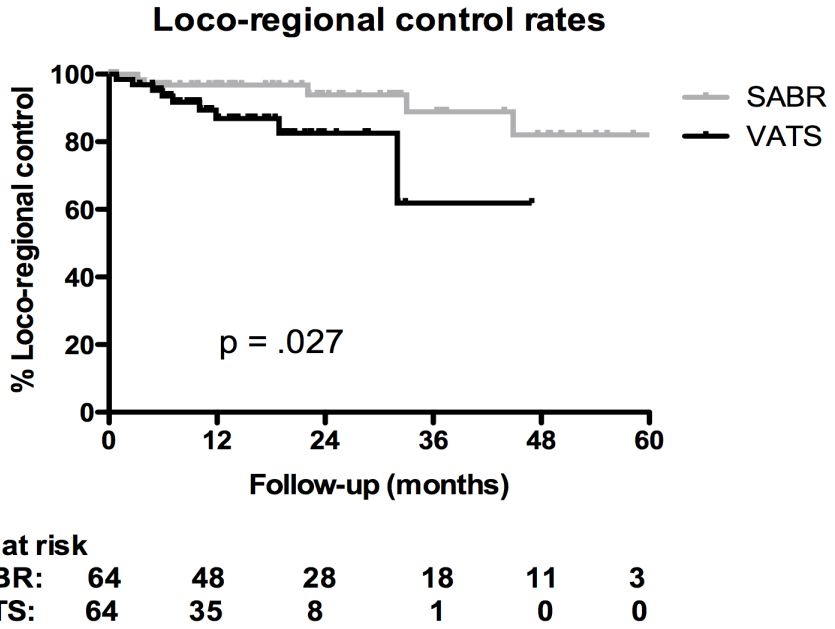
Propensity score-matched analysis of stage I-II NSCLC treated using either SABR or VATS-lobectomy

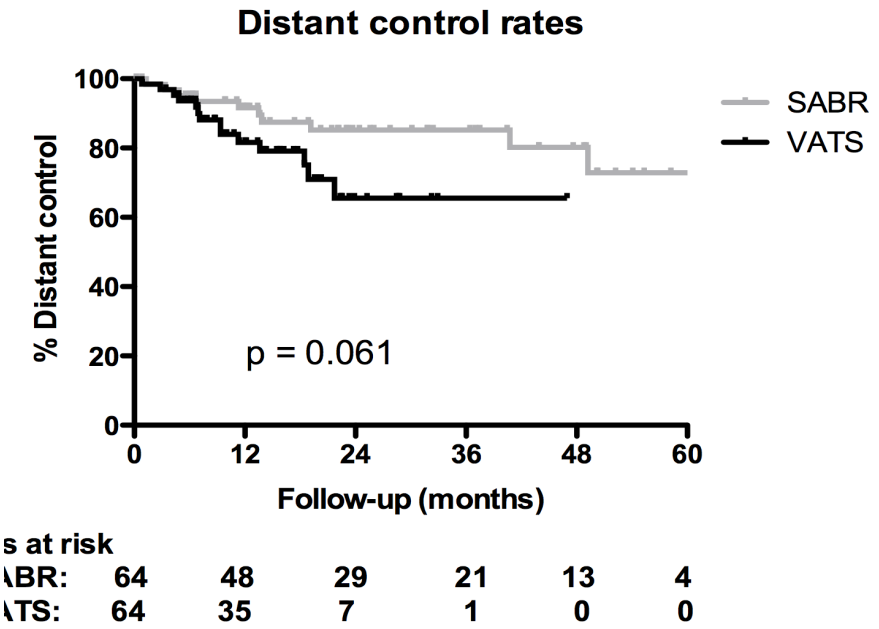
- 86 VATS-lobectomy and 527 SABR patients eligible
- Nodal staging in VATS group in accordance with ESTS guidelines
- Matching covariates:
  - *Gender - Age*
  - *cTNM - Tumor diameter*
  - *Histology - Tumor location*
  - *FEV 1% - WHO score*
  - *Charlson comorbidity*

Verstegen et al, Annals of Oncology 2013

Department of Oncology
University of Turin

Propensity score-matched analysis





Verstegen et al, Annals of Oncology 2013

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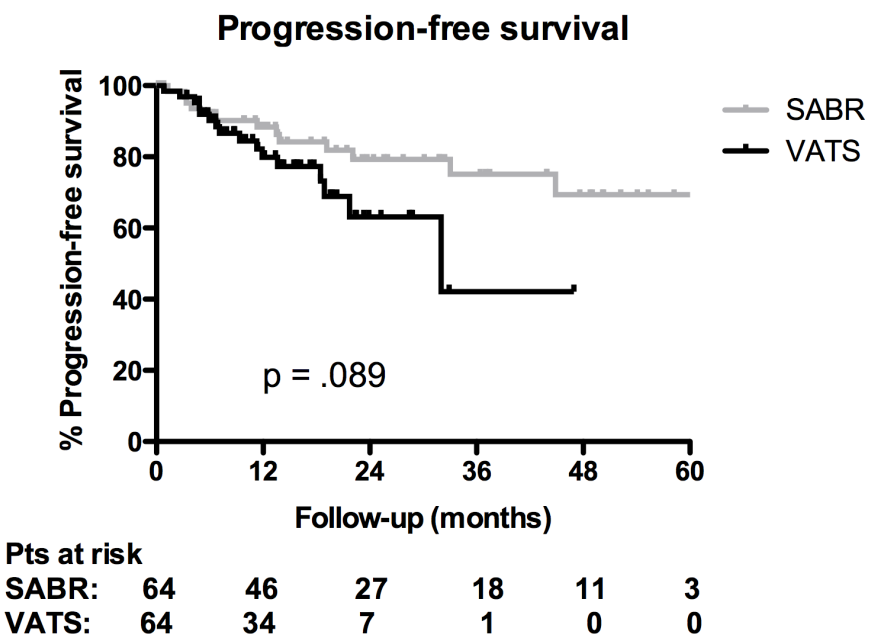
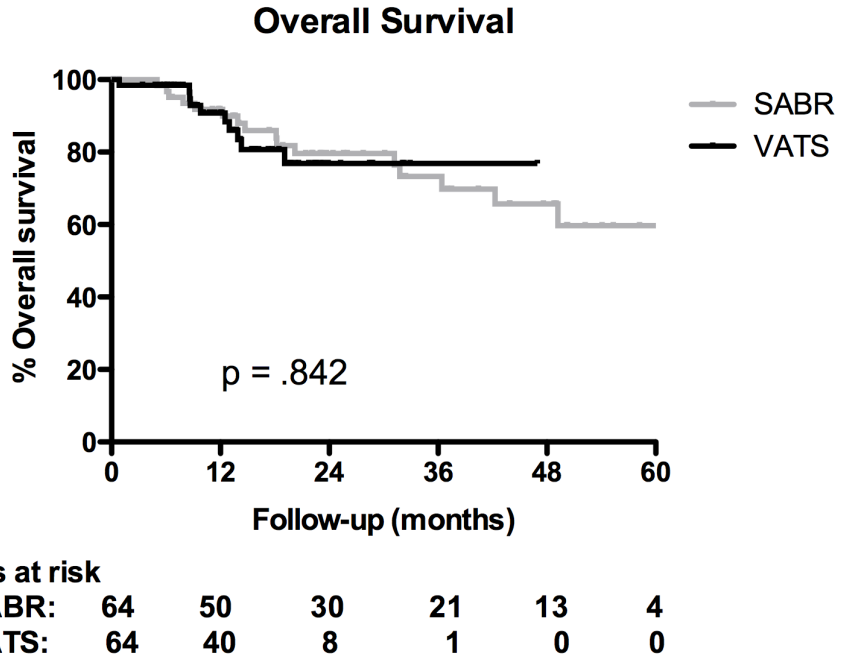
Propensity score-matched analysis





Verstegen et al, Annals of Oncology 2013

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

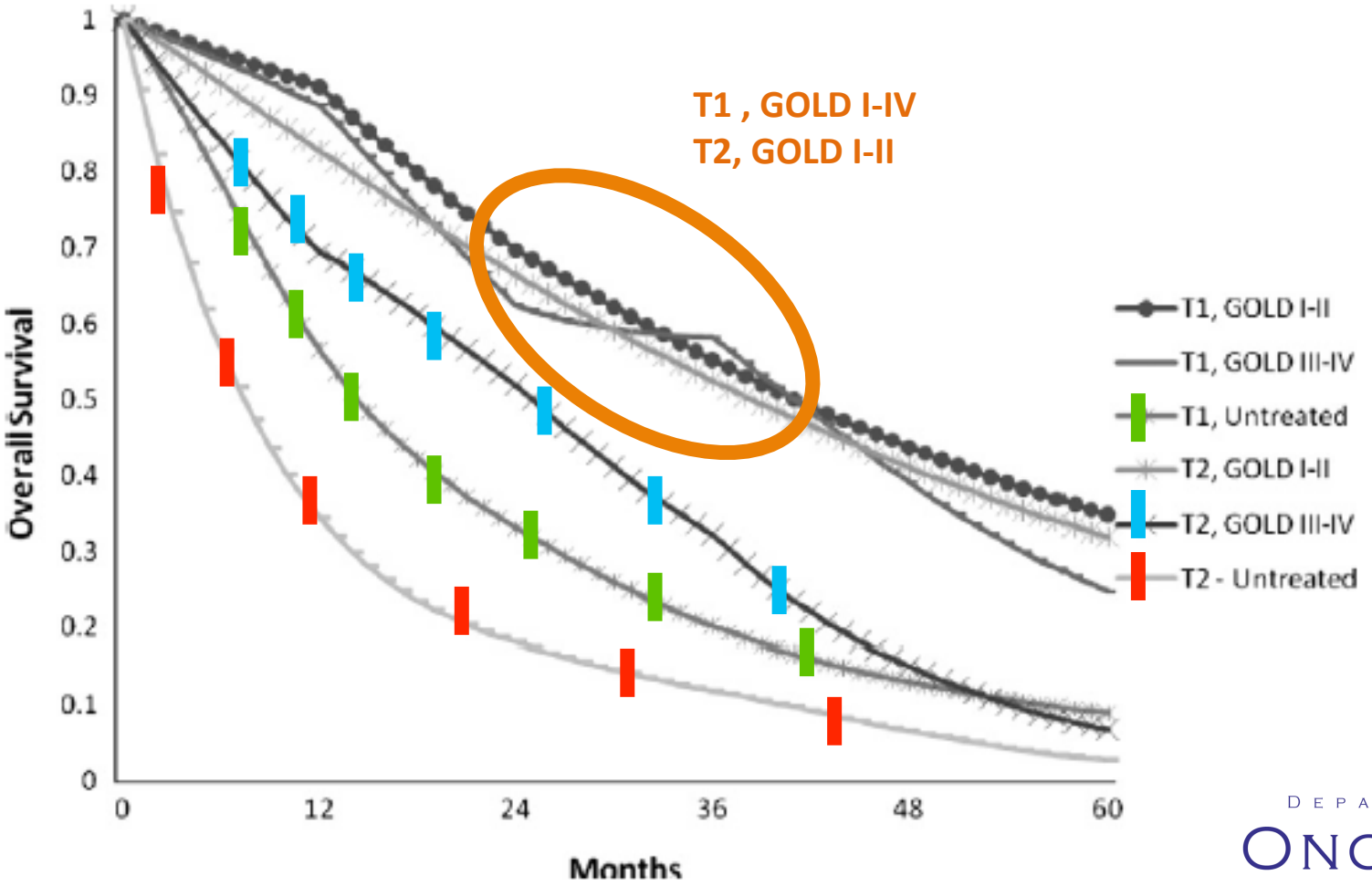
journal homepage: www.thegreenjournal.com

R&O, 2011

SBRT in lung cancer

Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: Outcomes of a markov model analysis

Alexander V. Louie [a], George Rodrigues [a,b,*], Malek Hannouf [b], Frank Lagerwaard [c], David Palma [a,c], Gregory S. Zaric [b,d], Cornelis Haasbeek [c], Suresh Senan [c]



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Stage I-II NSCLC and severe COPD?

Systematic Review: Eligible patients had to have GOLD III-IV or a predicted postoperative FEV_1 of ≤40%

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

Abbreviations: ICU = intensive care unit; VATS = video-assisted thoracoscopic surgery.
* Denotes values measured from Kaplan-Meier curves.
† 8% Grade 3–4 toxicity with some late deaths related to treatment of central tumors in larger Phase II study, but these rates not specified for subgroup with poor pulmonary function.

Palma D et al, IJROBP 2012

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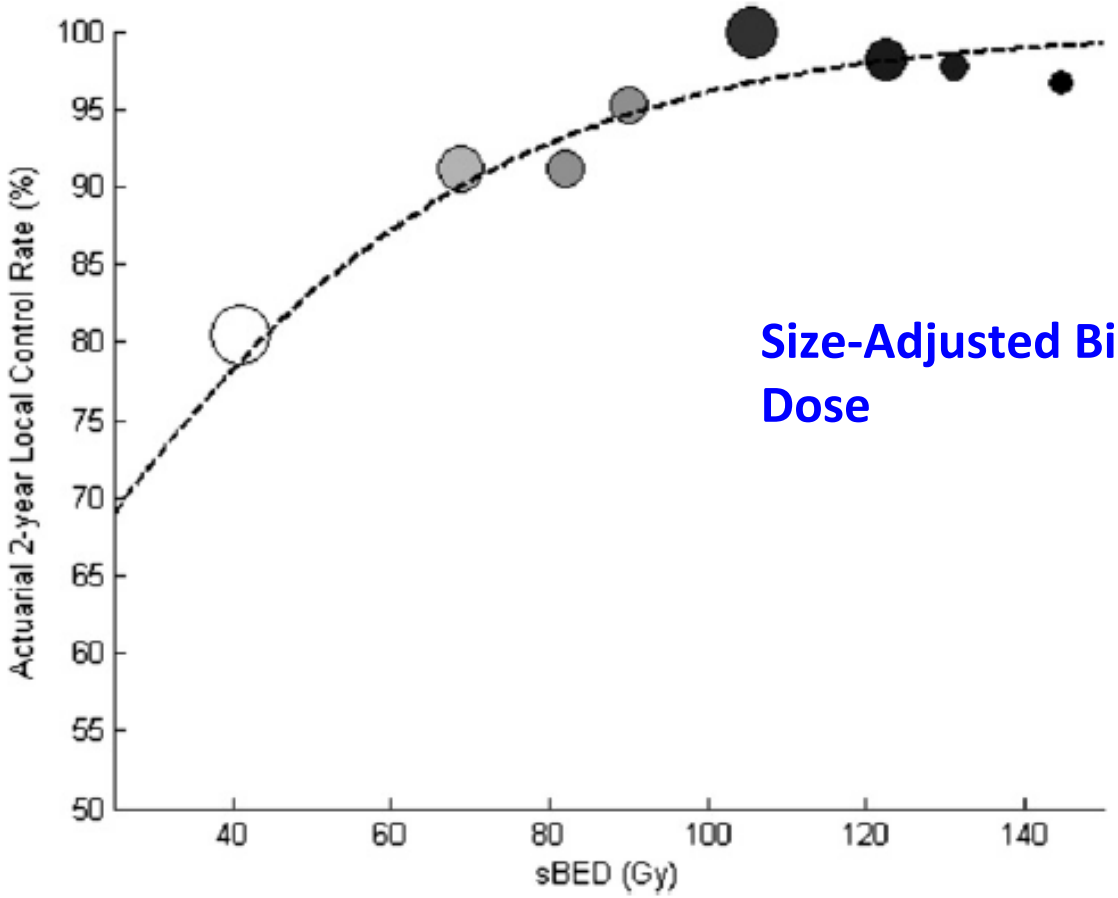
Clinical Investigation: Thoracic Cancer

Modeling Local Control After Hypofractionated Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer: A Report From the Elekta Collaborative Lung Research Group



Size-Adjusted Biologically Effective Dose

Ohri et al, IJROBP 2012

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Dose-response relationship at medium-high doses is essential for central and large tumors

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

Milano et al, Radiother Oncol, 2009

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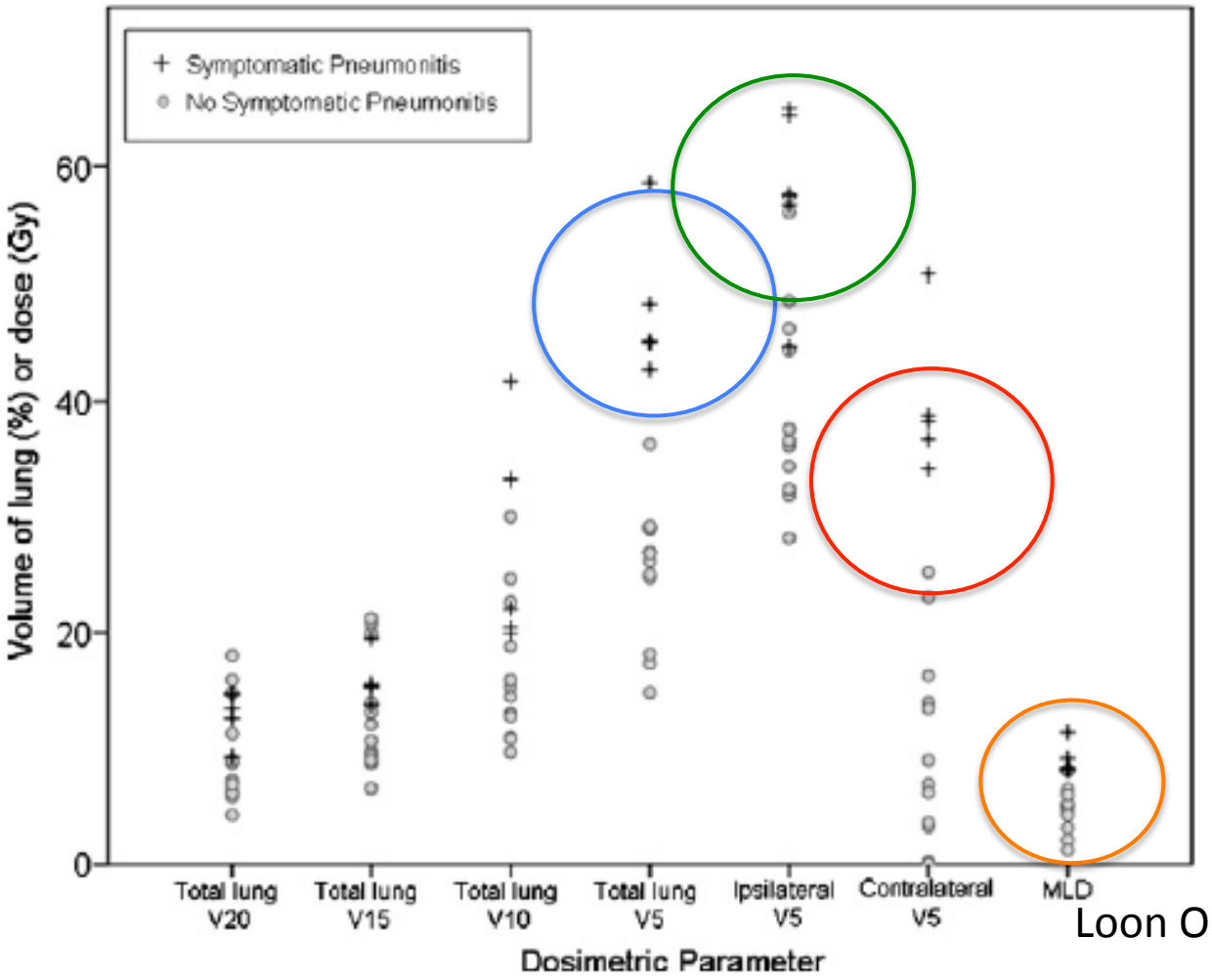
Dose-volume parameters predict toxicity in large tumors



Loon Ong et al, Radiother Oncol 2010

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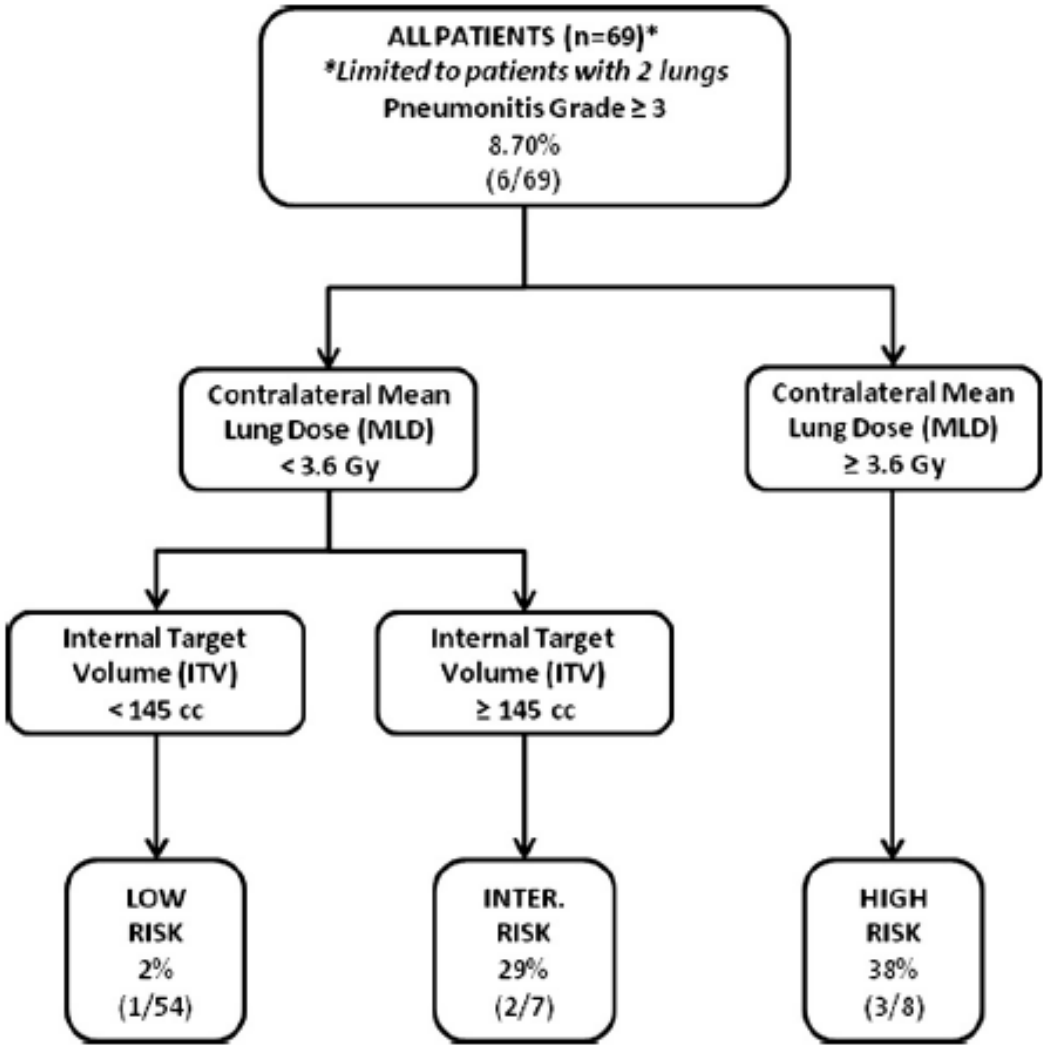
Toxicity is also dependent from contralateral Mean Lung Dose



Bongers et al, Radiother Oncol 2010

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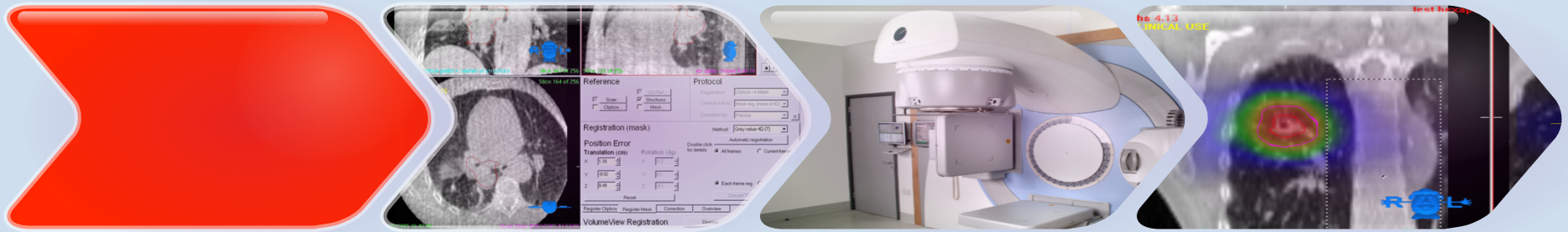
Technical Advances may have an impact on efficacy and toxicity

Planning

4D planning CT | Mid-ventilation | Treatment plan

4D Volume View | 4D image reg. | Patient shift | Delivery



Treatment

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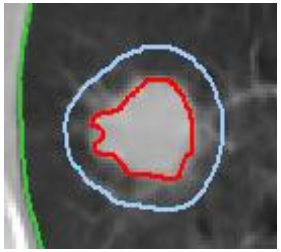
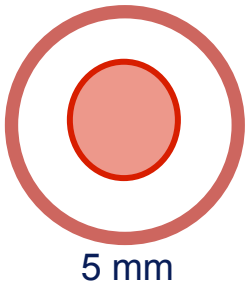
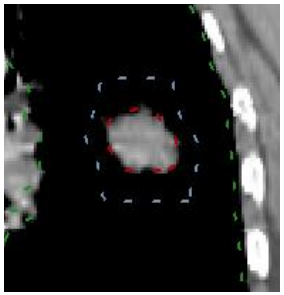
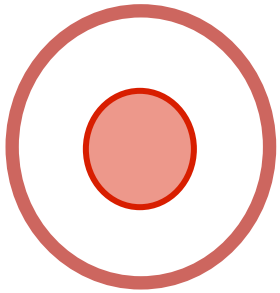
Higher accuracy should translate in less toxicity and better PTV coverage





5 mm

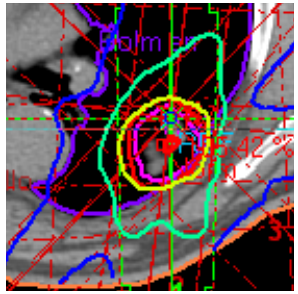


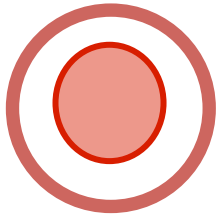


10 mm

GTV=CTV

PTV





3 mm

PTV = ITV + 3 mm isotropic

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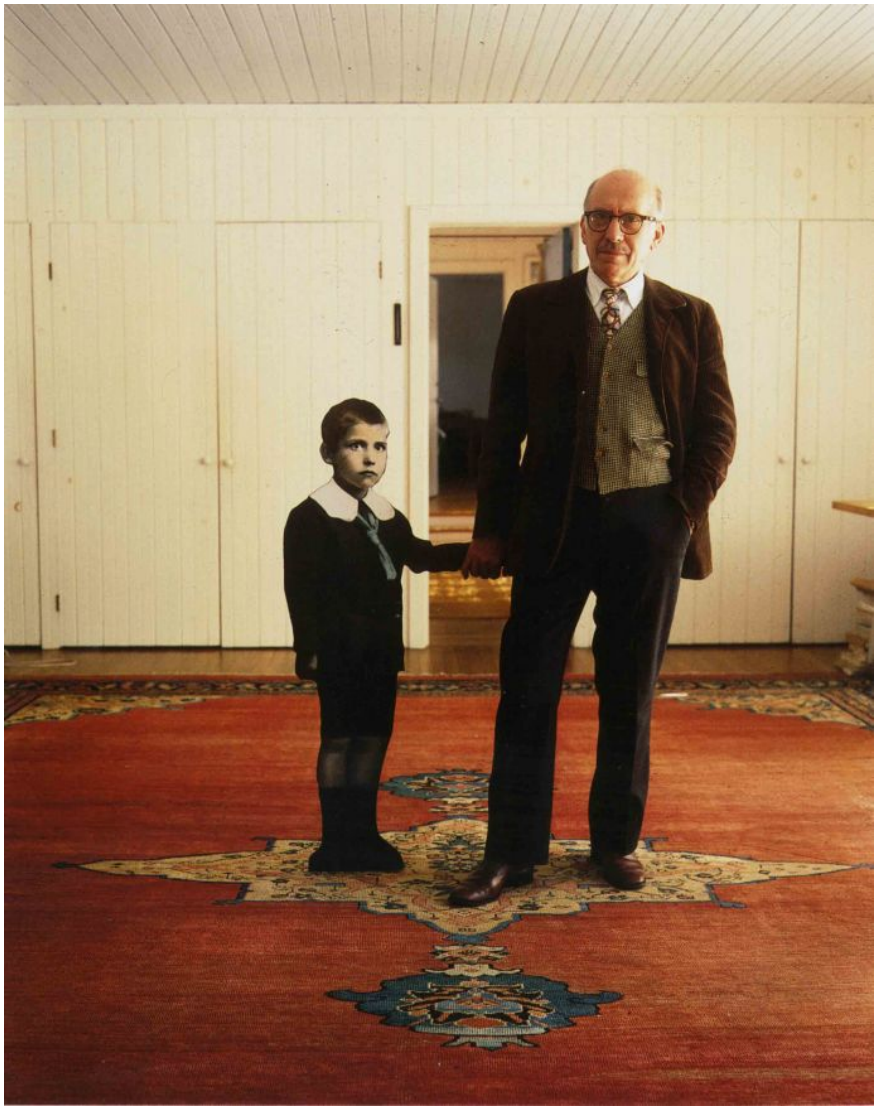


SABR applications in early stage NSCLC: the past as a window for understanding the future

Saul Steinberg holding his eight-year-old self by the hand, 1978

Clinical routine: “risk-adapted” SBRT protocol

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

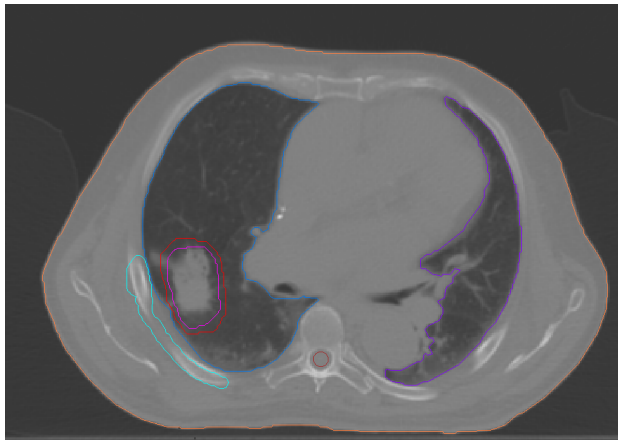
- 45-54 Gy/ 3 fractions

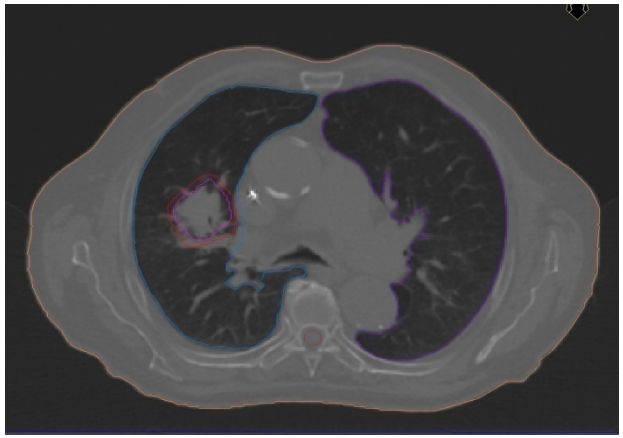
- **Peripheral lesions, with extensive contact with the chest wall, or larger tumors (T2a):**

- 55 Gy/ 5 fractions

- **Central lesions:**

- 60 Gy/ 8 fractions





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Prognostic factors?

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Multivariate analysis form the DEGRO Observational Multicentric Study

TABLE 3. Multivariate Analysis of Factors Influencing OS and FFLP

		OS			FFLP		
Parameter		***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**
Performance status	<80	0.02	1.44	1.05 to 1.97			
Clinical stage	IB	0.007	1.52	1.12 to 2.07	0.08	1.66	0.95 to 2.92
Baseline FEV_1 (%)	Continuous variable	0.07	0.99	0.99 to 1.00			
Biopsy status	No biopsy	0.09	1.49	0.94 to 2.35	0.02	2.53	1.17 to 5.48
Staging FDG-PET	Yes				>0.1		
Histology	SCC				0.03	2.03	1.06 to 3.89
PTV-encompassing dose (Gy BED)	≥106	0.01	0.62	0.43 to 0.90	0.04	0.39	0.16 to 0.93
Dose inhomogeneity (PTV-encompassing dose / maximum dose) (%)	≥ 80				0.06	1.74	0.98 to 3.08
IGRT technology	In-room IGRT				>0.1		
SBRT procedures/institution and year	<9	>0.1			>0.1		

Guckenberger et al, JTO 2013

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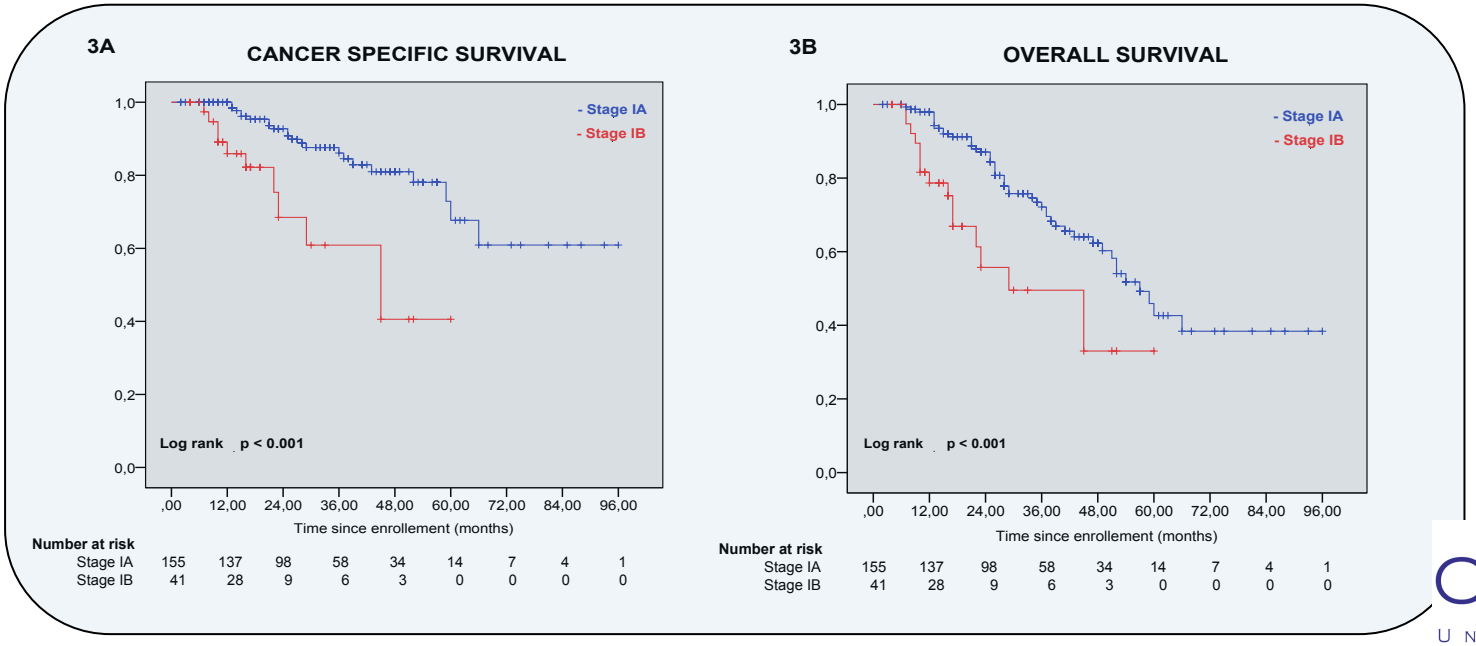
Cox Regression Multivariable Analysis on Histologically Proven NSCLC in Italian observational cohort study

Table 3
Multivariate analysis.

Parameter	LR		DFS		OS		CSS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Stage								
IB vs IA	0.55 (0.03–10.3)	0.69	3.06 (1.62–5.77)	0.001*	2.46 (1.28–4.74)	0.007*	3.47 (1.50–7.98)	0.003*
GTV volume								
>13 cc vs ≤13 cc	4.4 (0.73–26.7)	0.1	1.04 (0.57–1.88)	0.89	1.04 (0.59–1.82)	0.89	1.37 (0.59–3.16)	0.45
Sex								
Male vs Female	0.5 (0.08–3.2)	0.47	1.05 (0.57–1.92)	0.87	0.94 (0.51–1.74)	0.86	0.79 (0.31–1.98)	0.61
Age								
>75 years vs ≤75 years	0.6 (0.15–2.57)	0.52	1.39 (0.83–2.36)	0.21	1.39 (0.83–2.32)	0.2	1.28 (0.63–2.61)	0.49
Histology								
Adenocarcinoma vs others	2.42 (0.39–14.84)	0.34	1.12 (0.64–1.97)	0.68	1.21 (0.68–2.16)	0.8	1.17 (0.52–2.61)	0.69



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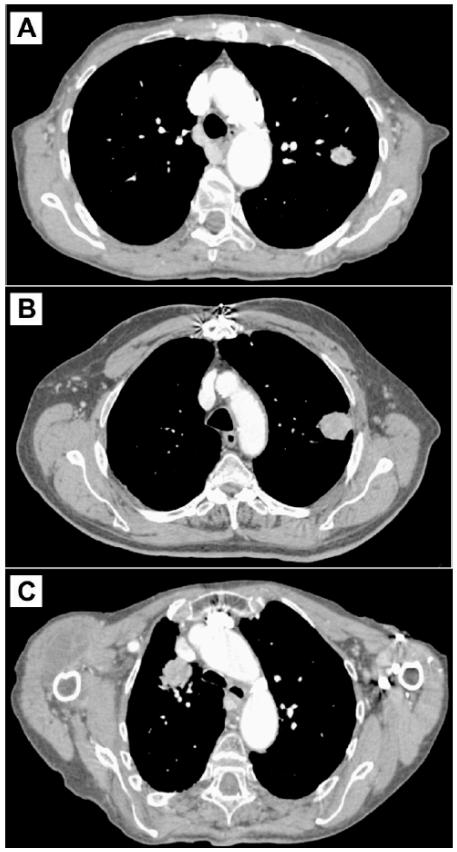
Imaging Features Associated With Disease Progression After Stereotactic Ablative Radiotherapy for Stage I Non–Small-Cell Lung Cancer

David B. Shultz,[1] Nicholas Trakul,[1] Jonathan A. Abelson,[1] James D. Murphy,[1] Peter G. Maxim,[1,2] Quynh-Thu Le,[1,2] Billy W. Loo, Jr,[1,2] Maximilian Diehn[1,2,3]



	Univariate				Multivariate[a]	
Tumor Variable	**FFLP**	**FFRP**	**FFDM**	**OS**	**FFDM**	**OS**
Maximum Tumor Dimension[b]						
	.374	.328	**.037** (HR, 5.33; 95% CI, 1.72-16.47)	.1085	**.014** (HR, 5.26; 95% CI, 1.41-19.70)	
BED_{10}-LQ, Gy						
	.452	.580	.182	**.0353** (HR, 0.99; 95% CI, 0.98-1.0)	—	.427
BED_{10}-LQ-L, Gy						
	.435	.331	.696	.14	—	—
Contact with CWP						
	.361	.676	.091	.804	—	—
Contact with MP						
	.478	.166	**.005** (HR, 4.24; 95% CI, 1.55-11.62)	**.005** (HR, 3.40; 95% CI, 1.70-6.77)	**.001** (HR, 7.51; 95% CI, 2.41-23.42)	**.002** (HR, 3.58; 95% CI, 1.63-7.87)
Central versus Peripheral[c]						
	.430	.302	**.013** (HR, 3.20; 95% CI, 1.27-8.01)	**.044** (HR, 1.89; 95% CI, 1.02-3.94)	—	—
SUVmax						
	.894	.413	**.018** (HR, 1.09; 95% CI, 1.01-1.17)	**.009** (HR, 1.07; 95% CI, 1.02-1.12)	**.053** (HR, 1.08; 95% CI, 1.00-1.16)	**.011** (HR, 1.07; 95% CI, 1.02-1.12)
Arc-Based versus CyberKnife Treatment						
	.038 (HR, 0.238; 95% CI, 0.06-0.92)	.416	.842	.740	—	—
Nonsquamous Histology						
	.866	.136	.435	.656	—	—

Toxicity and Quality of Life

Department of
Oncology
University of Turin

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

- Poor baseline PFT did not predict decreased OS
- FEV1 mean decline 5.8%; DLCO mean decline 6.3% (SS at 6 weeks and 3 months)
- Minimal changes of arterial blood gases and no decline in oxygen saturation

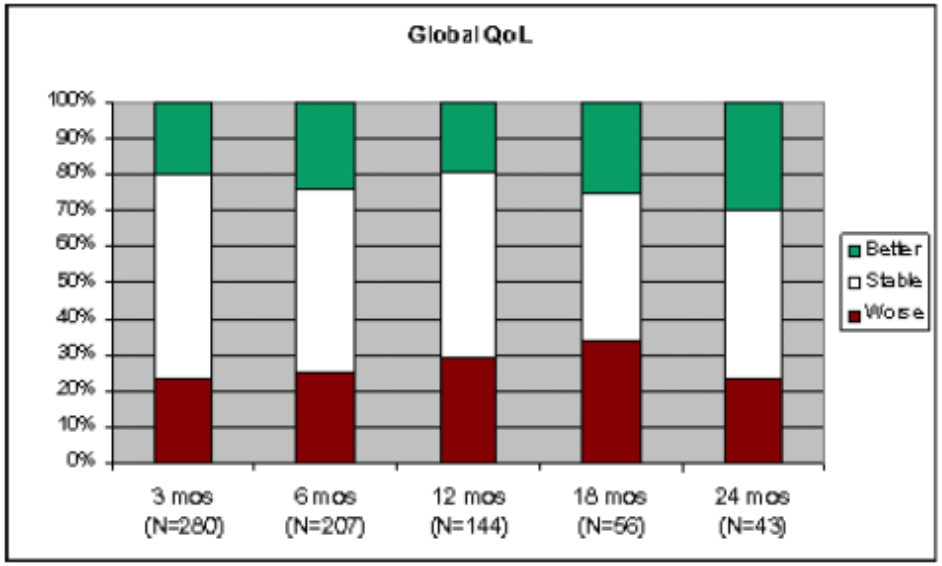
Stanic S et al, IJROBP 2014

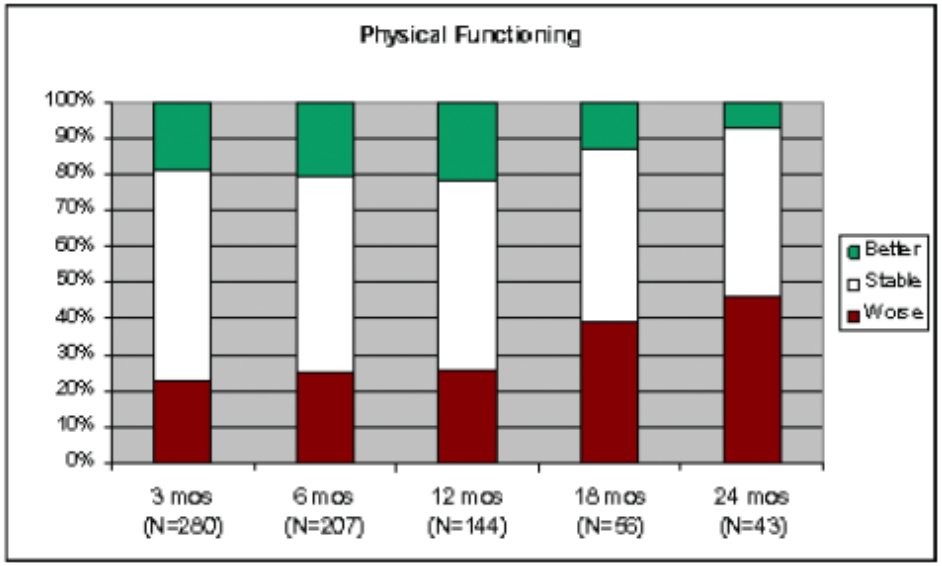
SABR and Quality of Life

No declines in QoL reported after SABR

- *van der Voort van Zyp NC, IJROBP 2010*
- *Widder J, IJROBP 2011*
- *Lagerwaard F, JTO 2012*
- *Videtic GM, Support Care Cancer 2013*

Quality of Life – self assessed





Lagerwaard et al, JTO 2012

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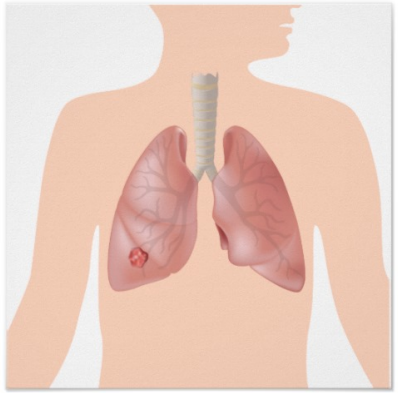
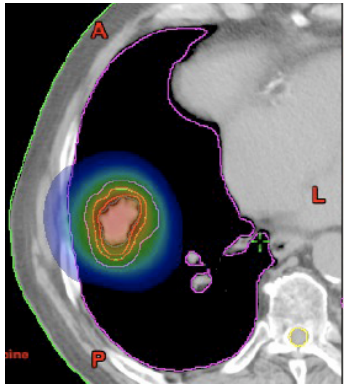
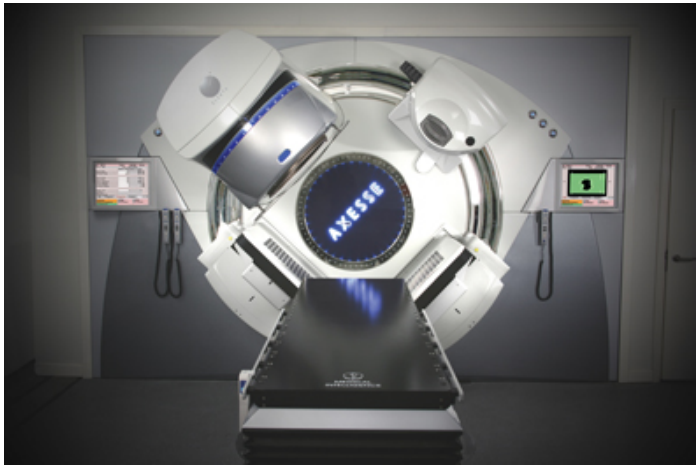
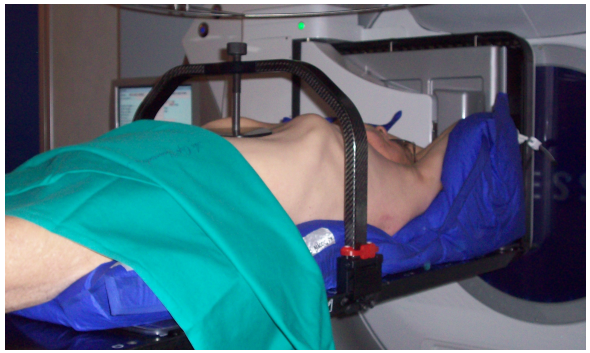
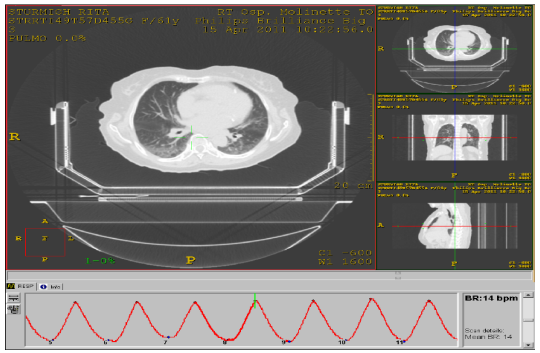
SABR in Lung Mets

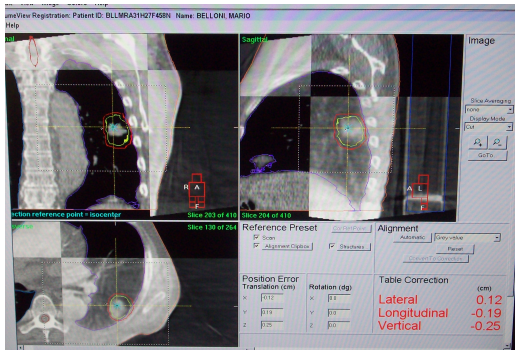












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Clinical Trials on SABR for Lung Oligometastases

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, 60 Gy/5 fx, at isocenter	27	90% 2-yr LC, 84% 2-yr OS
Brown et al.[25]	35	69	5 Gy/1 fx to 60 Gy/4 fx	18	77% crude LC, 72.5% 2-yr OS
Rusthoven et al.[12]	38	63	60 Gy/3 fx at 80%	15.4	96% 2-yr LC, 39% 2-yr OS
Wulf et al.[24]	41	51	30 Gy/3 fx, 36 Gy/3 fx, 26 Gy/1 fx at 100%	13	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

Schulz, Filippi et al, J Thor Oncol 2014

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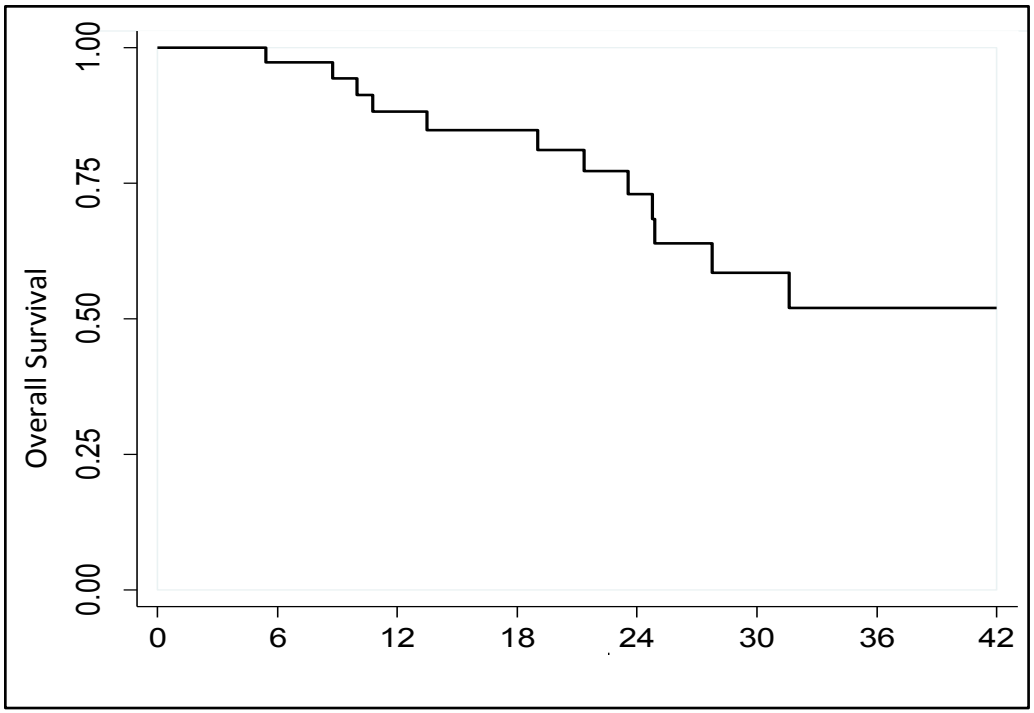
SABR as first local therapy for CRC lung mets: a single institution cohort study on 40 patients



Number at risk Months

40	35	28	23	17	10	6	5

At the time of analysis, 14 patients (35%) were dead

MEDIAN FOLLOW-UP TIME 23 months

Estimated Median Survival Time: 46 months

Filippi, Badellino et al, in press Int J Radiat Oncol Biol Phys 2014

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SABR as first local therapy for CRC lung mets

Pattern of progression	N
Local recurrence at SABR site	4
New pulmonary metastases	10
Liver metastases	4
Primary tumor uncontrolled	2
Multiple sites	9

Treatment at Relapse

Surgery	4 patients (2 liver, 1 lung, 1 colon)
SABR	3 patients (lung)
RFA	2 patients (liver)
Chemotherapy	7 patients

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SABR as first local therapy for CRC lung mets

Overall Survival rates

Surgery: 64-88% at 2 years and 29-71.2% at 5 years
RFA: 64-73% at 2 years and 34.9-45% at 5 years
SABR: around 50% at 2 years (mixed histologies)

Present study: 73% at 2 years

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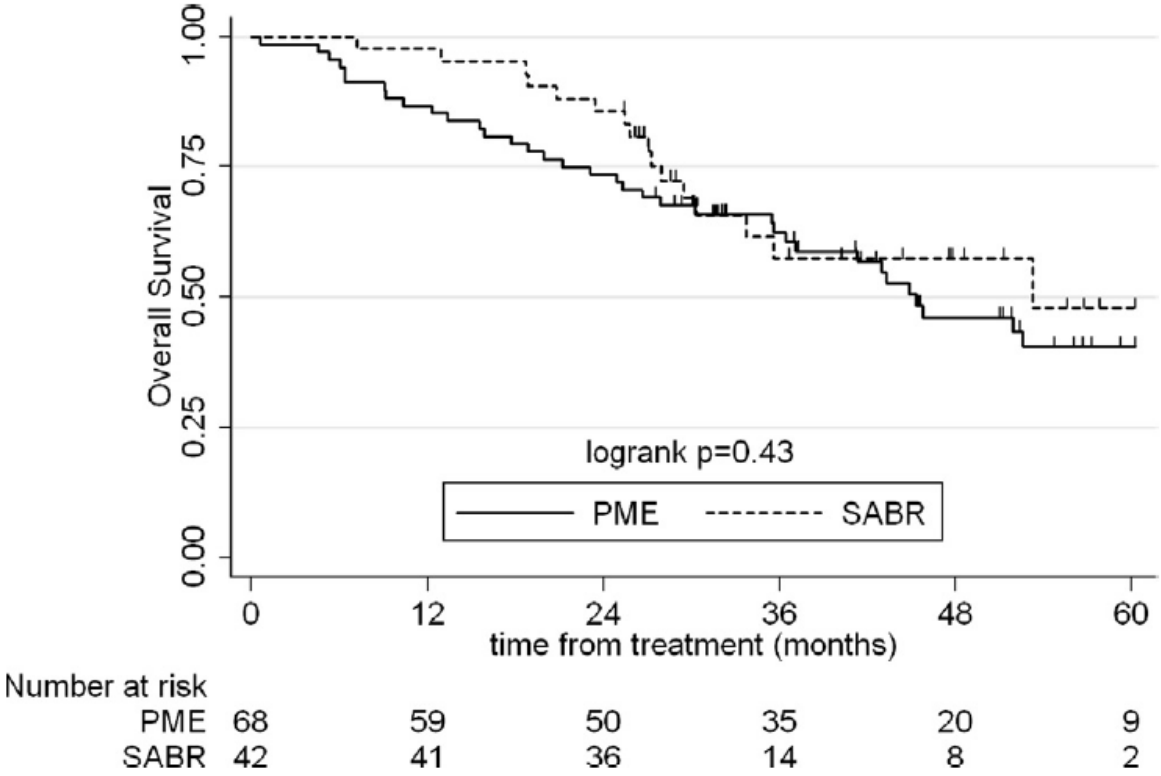
Pulmonary oligometastases: Metastasectomy or stereotactic ablative radiotherapy? ☆

Consecutive patients treated between 2007 and 2010 (68 PME and 42 SABR)



PME: first choice
SABR: second best alternative

3-ys OS years after SABR: 60%
3-ys OS after PME: 62%

Widder et al, R&O, 2013

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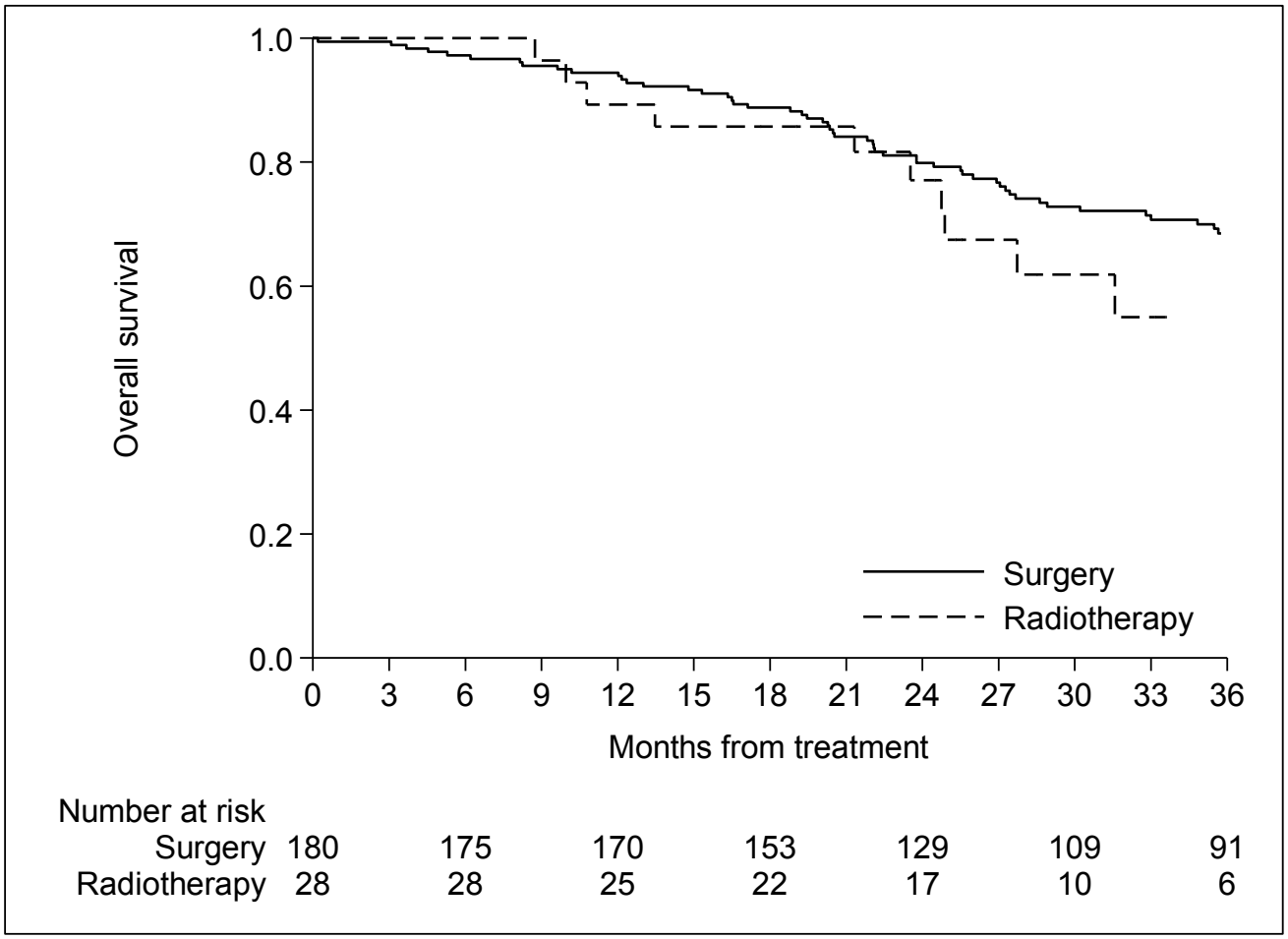
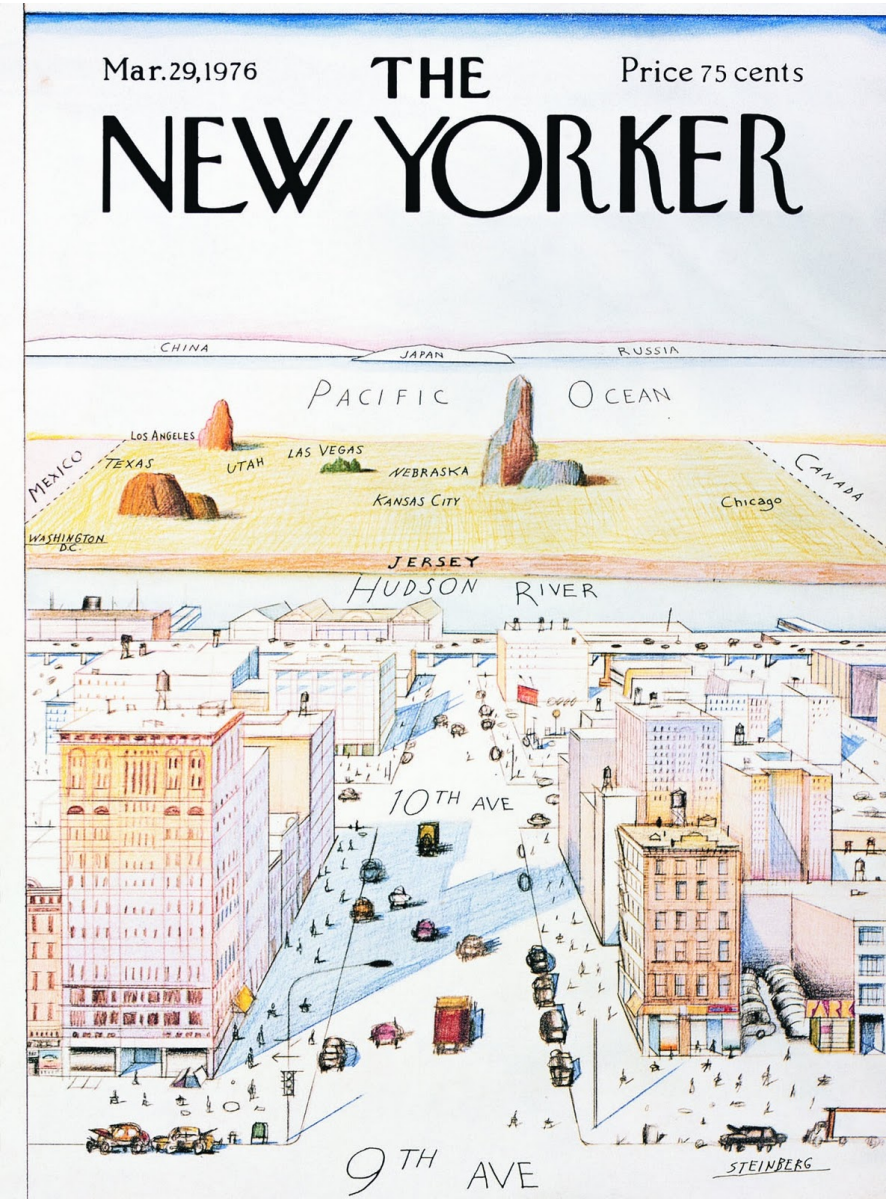
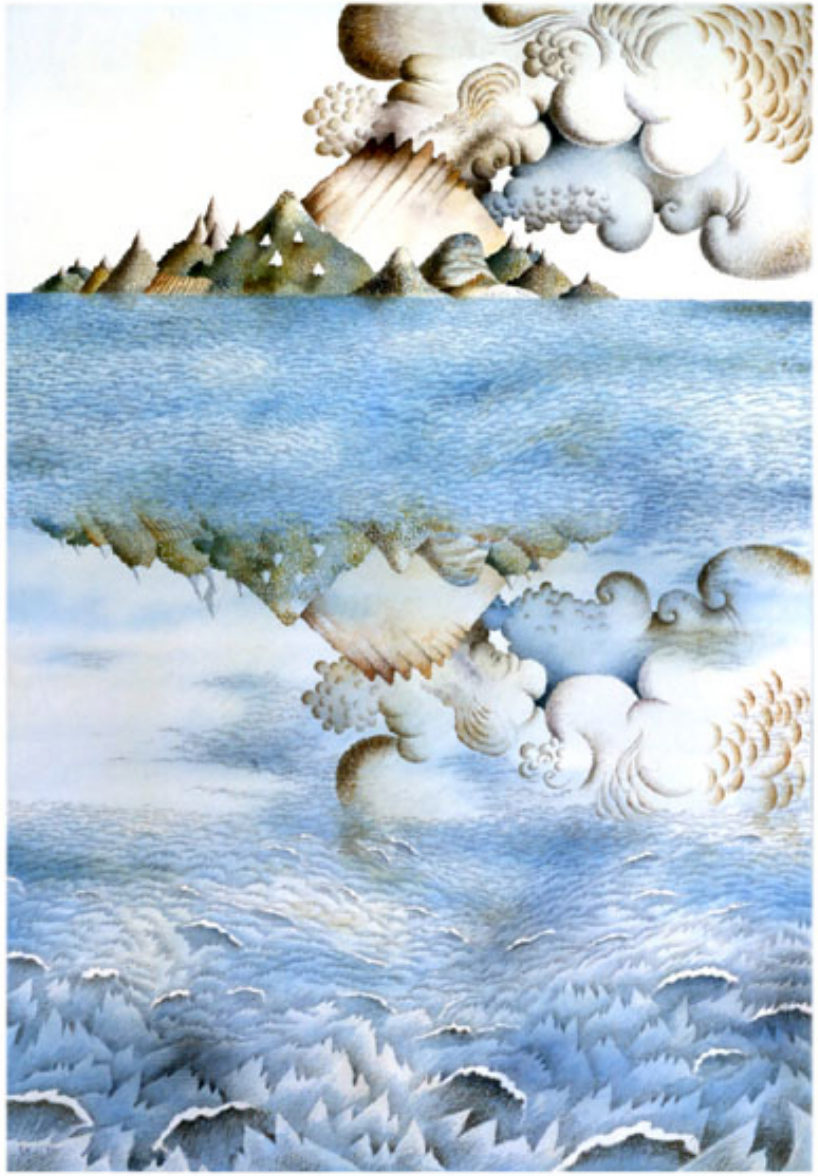
SABR vs Surgery for CRC lung oligometastases : a matched-pair propensity score analysis on 2 years OS



Filippi at al, ESTRO 2015



Steinberg 1976



Pericoli 1984

Towards advances, through different ways, patients need experimental controlled data

Aknowledgements

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