RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA BODY: ESPERIENZE CLINICHE E INTEGRAZIONI CON TERAPIE SISTEMICHE

Moderatori: P. Franzone *(Alessandria)*, M. Orsatti *(Imperia)*

Polmone: letteratura ed esperienza clinica

S. Badellino *(Torino)*

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RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA: NON SOLO TECNICA

Ospedali Galliera – Salone Congressi
Genova, 25 marzo 2017

La sottoscritta BADELLINO SERENA in qualità di relatore, ai sensi dell’art. 3.3 sul Conflitto di Interessi, pag. 18,19 del Reg. Applicativo dell’Accordo Stato-Regione del 12 aprile 2012, dichiara che negli ultimi due anni

non ha avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

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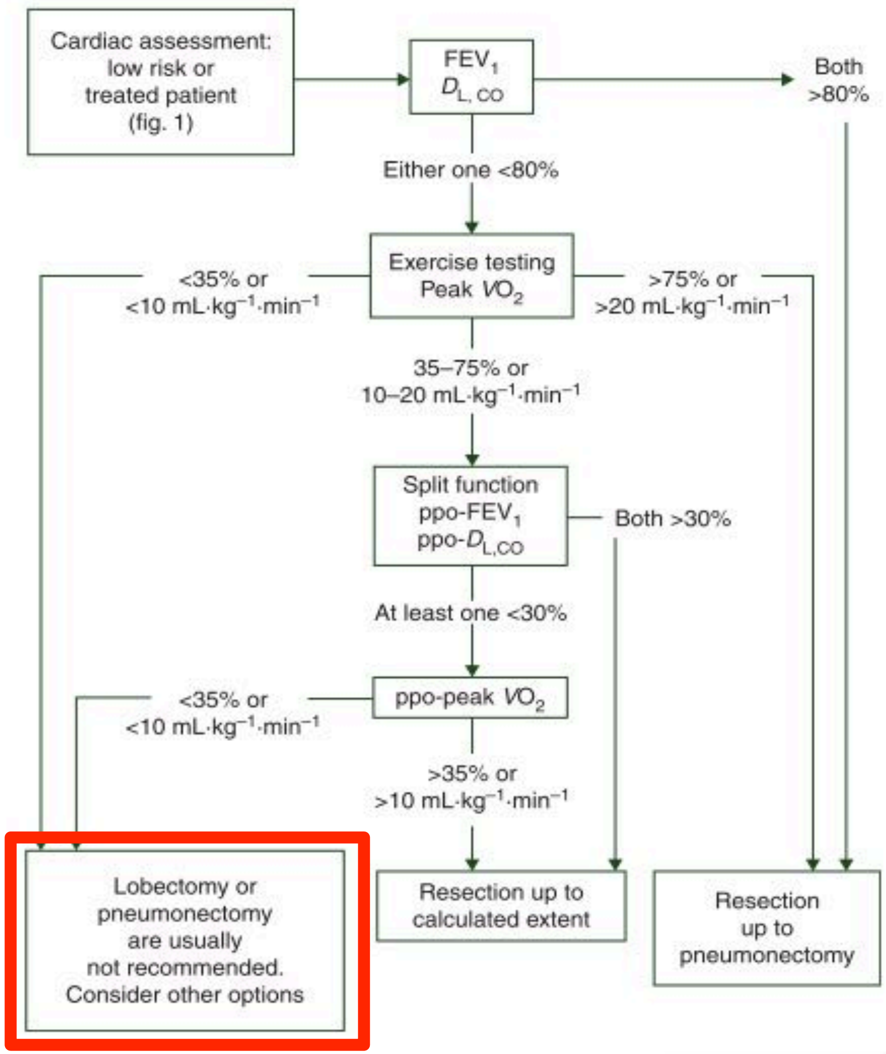
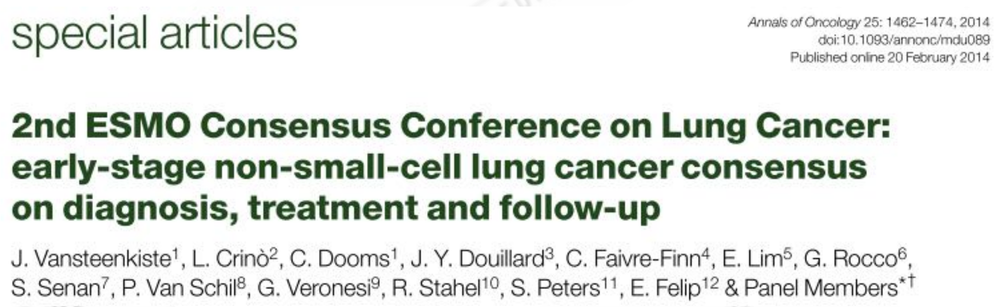
SABR as a standard of care for early stage, medically inoperable: ESMO




special articles

Annals of Oncology 25: 1462–1474, 2014
doi:10.1093/annonc/mdu089
Published online 20 February 2014

2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up

J. Vansteenkiste[1], L. Crinò[2], C. Dooms[1], J. Y. Douillard[3], C. Faivre-Finn[4], E. Lim[5], G. Rocco[6], S. Senan[7], P. Van Schil[8], G. Veronesi[9], R. Stahel[10], S. Peters[11], E. Felip[12] & Panel Members*†

Vansteenkiste, J. et al. 2014. – 2nd ESMO Consensus Conference on Lung Cancer - *Annals of Oncology*

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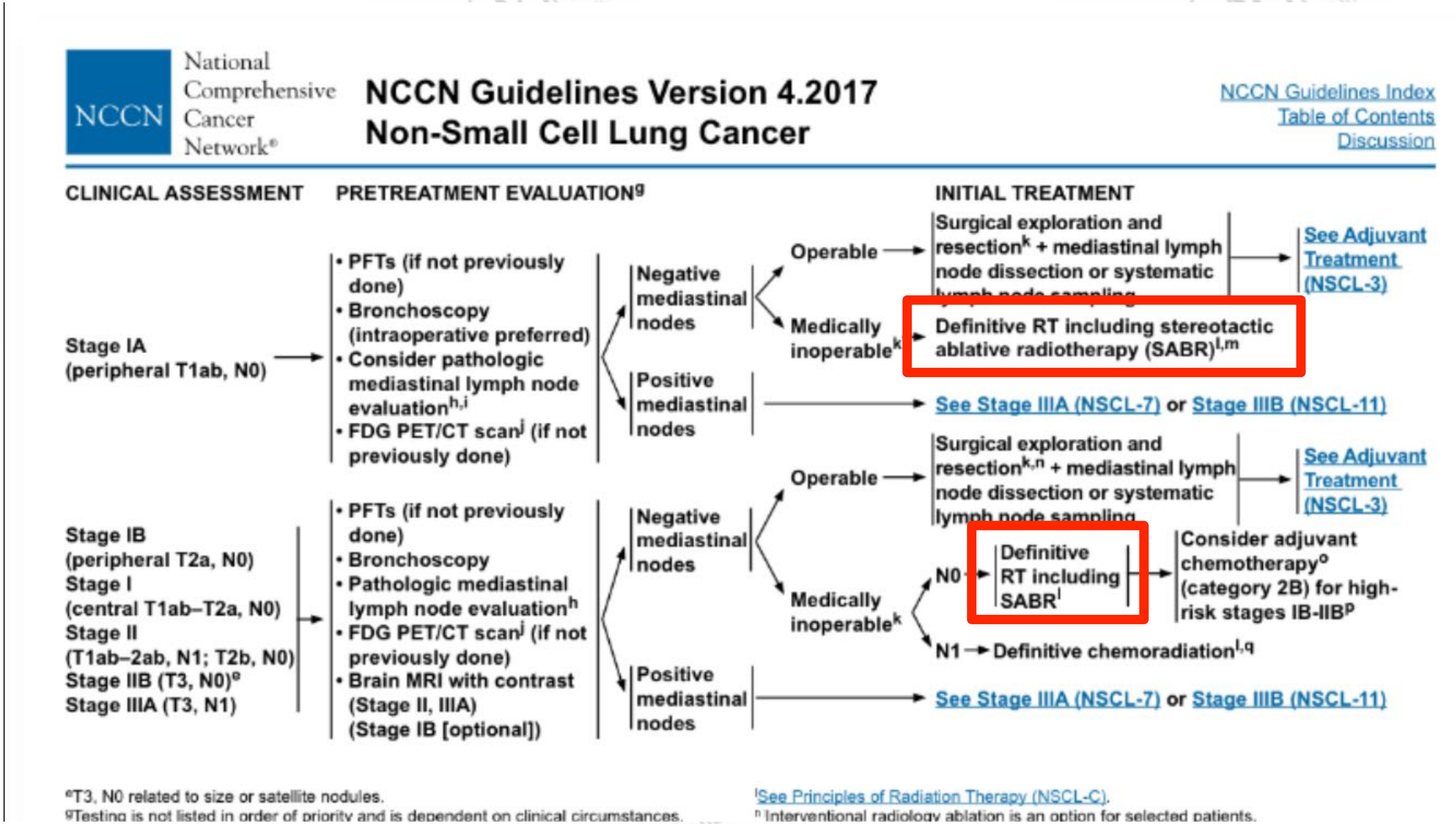
SABR as a standard of care for early stage, medically inoperable: NCCN



NCCN Guidelines Version 4.2017

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SABR in 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]

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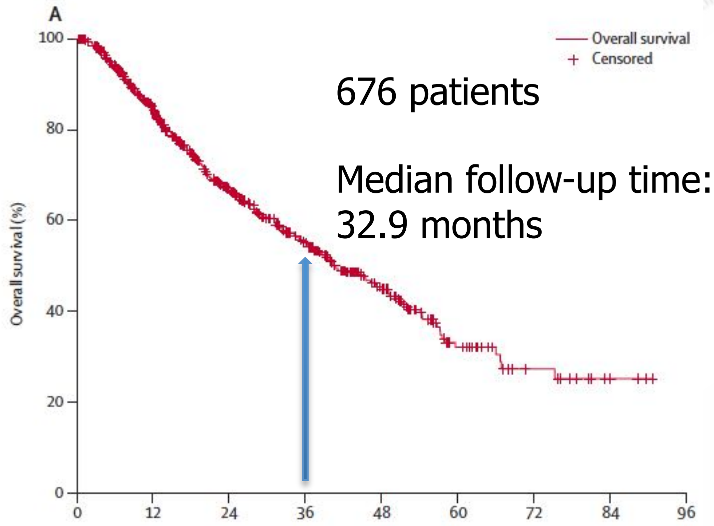
Mono-institutional largest study, with/without histological diagnosis

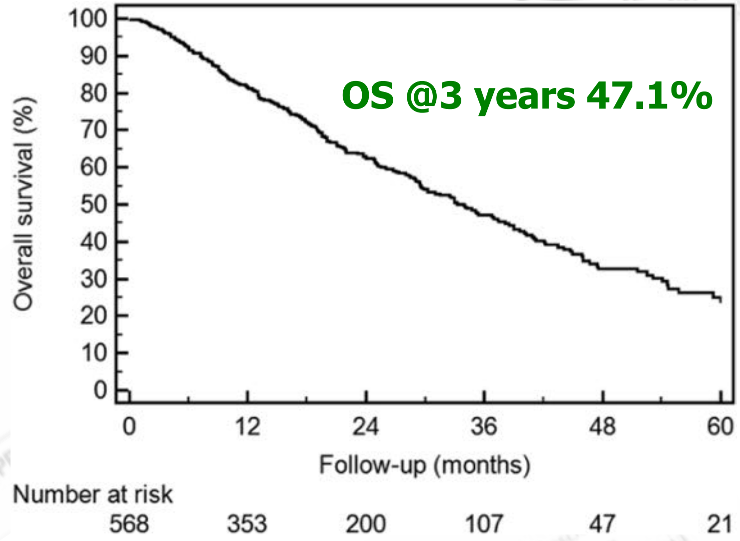


676 patients

Median follow-up time: 32.9 months

[Senthi et al, Lancet Oncol 2012]

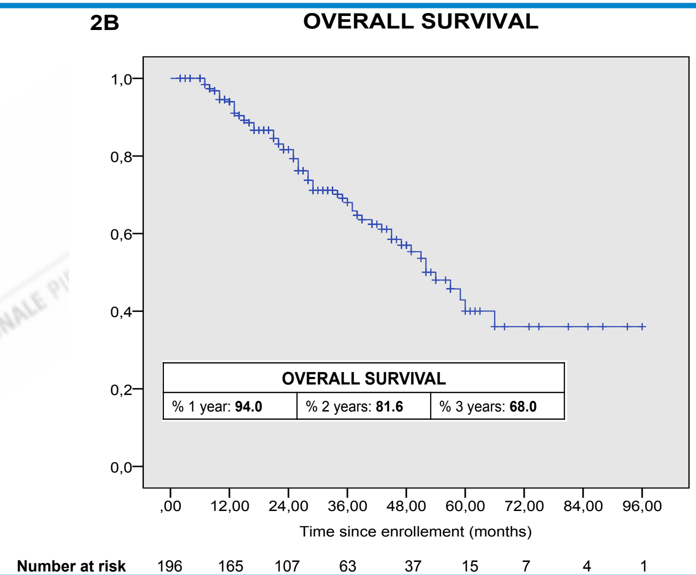
German Society for Radiation Oncology (DEGRO) Observational Multicentric Study



[Guckenberger et al, JTO 2013]

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

[Ricardi et al, Lung Cancer 2014]



Studies demonstrating the variable rates of pathologic confirmation worldwide prior to SABR

Reference	Study type	N° of patients	Region	% biopsy	Overall Survival
Haasbeek	Population registry	1570	Netherlands	72	50% (2 yrs)
Ricardi	Retrospective	196	Italy	100	68% (3 yrs)
Guckenberger	Retrospective	591	Central Europe	85	47% (3 yrs)
Grills	Retrospective	505	United States Canada Netherlands Germany	87-95 72 41 70	48% (3 yrs)
Onishi	Retrospective	2278	Japan	73	91% (2 yrs)
Senthi	Retrospective	676	Amsterdam	35	41 mo (md)
Baumann	Prospective	57	Sweden Denmark Norway	67	60% (3 yrs)
Timmerman	Prospective	55	North America	100	56% (3 yrs)

[Louie et al, R&O 2015]

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Pattern of failure following SBRT

	Local	Regional	Distant
Actuarial 2-year rates	4.9%	7.8%	14.7%
Actuarial 5-year rates	10.5%	12.7%	19.9%

	Median time to event
Local recurrence	14.9 months (95% CI 11.4-18.4)
Regional recurrence	13.1 months (95% CI 7.9-18.3)
Distant recurrence	9.6 months (95% CI 6.8-12.4)
2nd primary tumors	18 months (95% CI 12.5-23.5)

- Stage I-II NSCLC (2003-2011); median follow-up 32.9 months (IQR 14.9 - 50.9);
- 66% of recurrences were distant (DR); isolated DR made up 46% of recurrences

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SABR outcomes in central tumors

Timmerman R, JCO 2006

Used SABR dose of 60/66 Gy in three fractions

"Scheme should not be used for tumors near the central airways due to excessive toxicity"

Systematic review of SABR in central tumors

20 publications: 563 patients (315 early stage NSCLC)

Local control rates $\geq$ 85% when prescription dose (BED_{10}) $\geq$ 100 Gy

Treatment related mortality 2.7% overall vs 1% when normal tissue dose (BED_3) $\leq$ 210 Gy

Grade 3-4 toxicities appear commoner following SABR in central tumors, but occurred in less than 9% of patients

[Senthi et al, R&O 2013]

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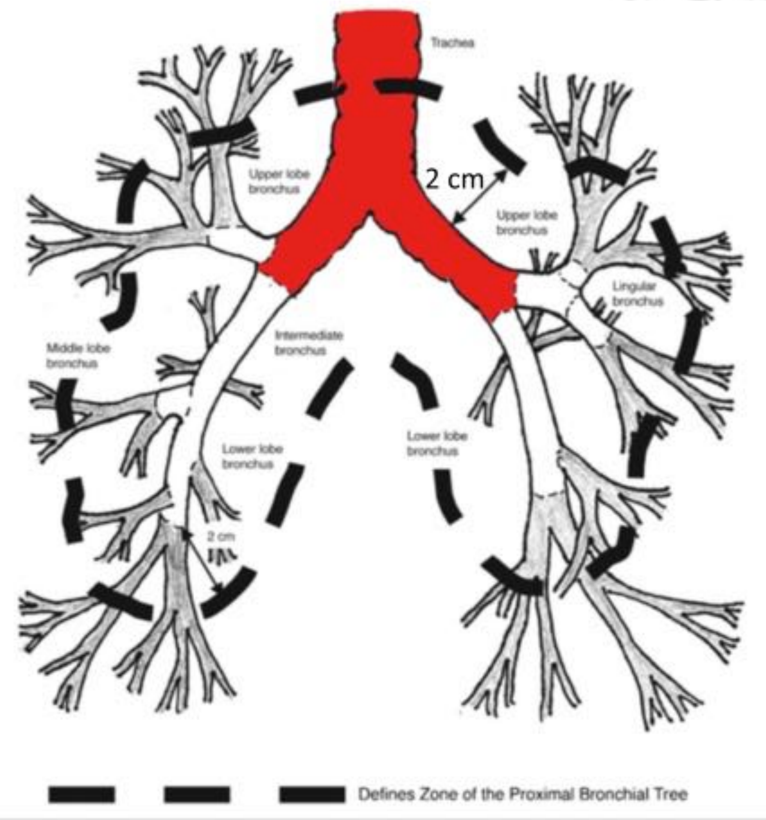
Central and Ultra-central lesions



- Central Lesions
- Ultra-Central Lesions

ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: REVIEW ARTICLE

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

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

RTOG 0813 trial → to establish the safest dose that can be delivered in 5 fractions for central lesions

→ Preliminary data reported that patients treated with the highest dose level (60 Gy in 5 fractions) had a 23 % rate of grade 3–5 toxicity

[Bezjak et al, IJROBP 2016]

SABR in operable patients

CLINICAL INVESTIGATION — **Lung**

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

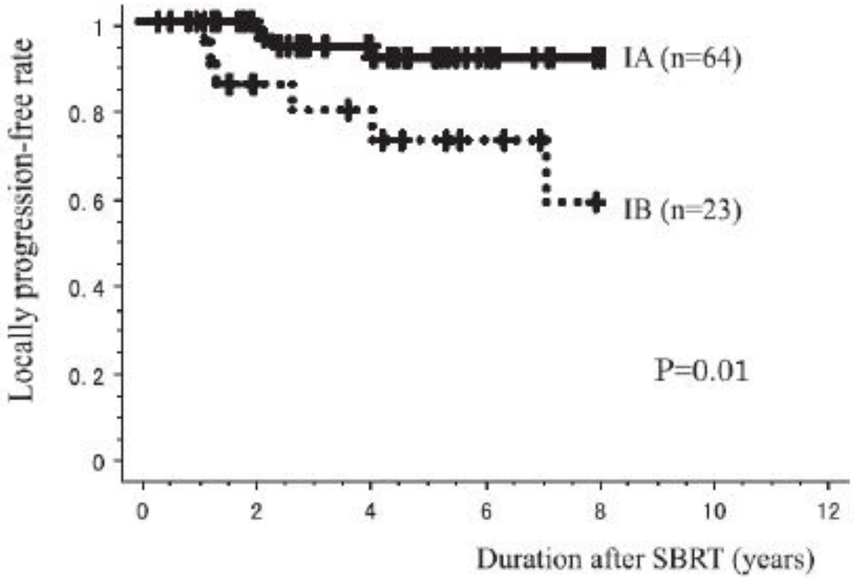


Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy. Values are percentages.

[Onishi et al, IJROBP 2011]

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SABR VS Surgery in Early Stage NSCLC: RCTs

~~ROSEL~~

Collaborators: *The Netherlands Organisation for Health Research end Development*; 9 dutch centers (2008); **terminated in 2010: recruited 22/960 patients**

~~STARS~~

Collaborators: *Accuray©*; 15 centers (2009); **terminated in 2013: recruited 36/1030 patients**

~~ACOSOG~~

Collaborators: *American College of Surgeons*; 53 centers (2011); **terminated in 2013: recruited 10/420 patients**

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CER studies comparing surgery versus SABR in stage I NSCLC

Study	Study design	N° of patients	Surgical procedure	Overall Survival: Surgery	Overall Survival: SABR	Conclusions/ comments
Crabtree	Propensity-score matching	Unmatched: surgey=458 SABR= 151 matched: 112/group	(Bi)lobectomy, 78% sublobar, 19% pneumonectomy, 4%	78% 3 yrs 68% 3 yrs	47% 3 yrs 52% 3 yrs	Althoug surgical resesction seems to result in better OS versus SABR, matching these patients remains challenging
Matsuo	Propensity-score matching	Unmatched: surgey=65 SABR= 115 matched: 53/ group	Sublobar resection	56% 5 yrs	40% 5 yrs	SABR is an alternative to sublobar resection in high-risk patients who cannot tolerate lobectomy due to comorbidities
Shirvani	SEER population, propensity-score matching	Unmatched: surgey= 8711 SABR= 382 matched: 251/group	Lobectomy 83% Sublobar 17%	Lobectomy vs SABR, HR 1.01 (SA: 1.16-1.28)		Lobectomy is preferred for older adults fit for surgery. SABR is promising as it offers a lower risk of periprocedural death
Solda	Systematic review	Weighted average of surgical patients from IASLC database vs reviewed SABR studies		68% 2 yrs	72% 2 yrs	Results favor direct comparison of surgery and SABR for operable localized NSCLC
Varlotto	Match-pair and propensity scoring	Unmatched: surgey=180 SABR= 137 matched: 89/ group	Lobectomy 73% Wedge 27%	69% 3 yrs 86% 3 yrs	41% 3 yrs 42% 3 yrs	On usual matching, wedge and lobectomy had significantly improved OS over SABR, differences disappeared when adjusting for propensity score

CER studies comparing surgery versus SABR in stage I NSCLC

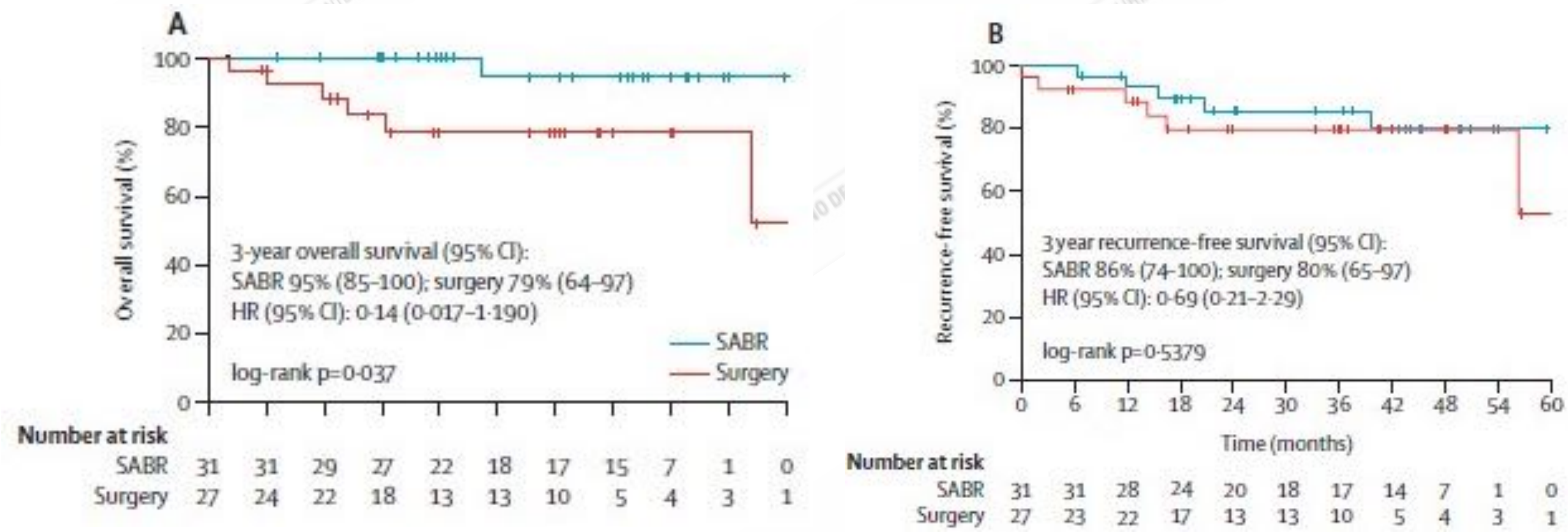
Study	Study design	N° of patients	Surgical procedure	Overall Survival: Surgery	Overall Survival: SABR	Conclusions/ comments
Verstegen	Propensity-score matching	Unmatched: surgey=86 SABR=527 matched: 64/group	VATS lobectomy	77% 3 yrs	80% 3 yrs	No significant difference in OS supports the need to compare the two treatments in a randomized control trial
Grills	Retrospective	Surgery = 69 SABR = 55	Wedge resection	87% 30 mo	72% 30 mo	OS was improved after surgery. SABR patients tended to be older with more comorbidities
Louie	Markov model	Lobectomy and SABR outcomes modeled from various sources		At 5 yrs, surgery 2-3% benefit in OS		Large patient numbers wuold be required to detect small differences in OS
Shah	Markov model	Lobectomy, wedge resection and SABR outcomes modeled from various sources		Not reported, model validated based on recurrence pattern		SABR is the dominant strategy compared to wedge resection. In patinets eligible for lobectomy, surgery is most cost-effective
Zheng	Meta-anakysis	Forty SABR studies (n = 4850) and 23 surgery studies (n = 7071)		~ 80% 3 yrs	57% 3 yrs	When adjusting for potential operability in SABR patients, no difference found in OS

[Louie et al, R&O 2015]

SABR VS Surgery in Early Stage NSCLC: CER

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†*



- **SABR could be an option** for treating **operable stage I NSCLC**
- **Small patient sample size** and **short follow-up: additional randomised studies in operable patients** are warranted

Chang et al., Lancet Oncology 2015

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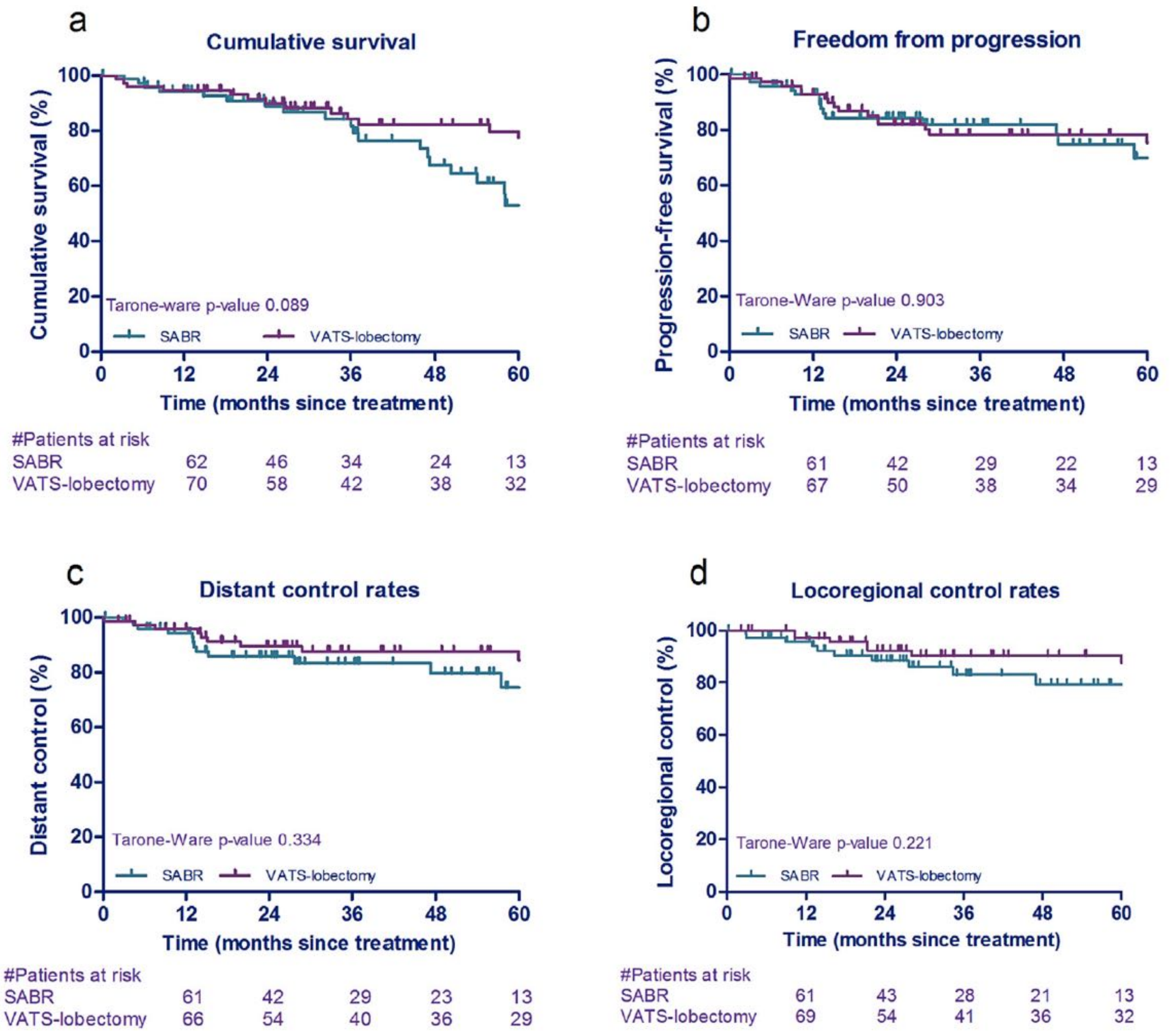

[Mokhles et al, Lung Cancer 2015]

Better outcome for surgery after 3 years:

- optimal lymph node staging: adjuvant therapy
- still some differences between the two groups: matching was done with only a limited number of variables (i.e., staging procedure not included as covariate)
- respiratory failure over time (RILI)
- unable to provide CSS rates

SABR VS Surgery in Early Stage NSCLC: ongoing RCTs

NCT 02629458
Recruiting
A Study to Determine the Feasibility and Acceptability of Conducting a Phase III Randomised Controlled Trial Comparing Stereotactic Ablative Radiotherapy With Surgery in paTients With Peripheral Stage I nOn-small Cell Lung Cancer cOnsidered Higher Risk of Complications From Surgical Resection
Condition: Oncology
Interventions: Procedure: Treatment by Surgical resection; Procedure: Stereotactic Ablative Radiotherapy (SABR)

SABRtooth
Recruiting
A Study to Determine the Feasibility and Acceptability of Conducting a Phase III Randomised Controlled Trial Comparing Stereotactic Ablative Radiotherapy With Surgery in paTients With Peripheral Stage I nOn-small Cell Lung Cancer cOnsidered Higher Risk of Complications From Surgical Resection
Condition: Oncology
Interventions: Procedure: Treatment by Surgical resection; Procedure: Stereotactic Ablative Radiotherapy (SABR)

NCT 02468024
Recruiting
JoLT-Ca Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SAbR) for Lung Cancer
Condition: Non-Small Cell Lung Cancer
Interventions: Procedure: Lung Surgery; Radiation: Radiation therapy

NCT 01753414
Recruiting
Radical Resection Vs. Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC
Condition: Non-small Cell Lung Cancer
Interventions: Radiation: Stereotactic Body Radiation Therapy (SBRT); Procedure: Surgery

VALOR trial
Veteran Affairs Lung cancer surgery OR stereotactic Radiotherapy

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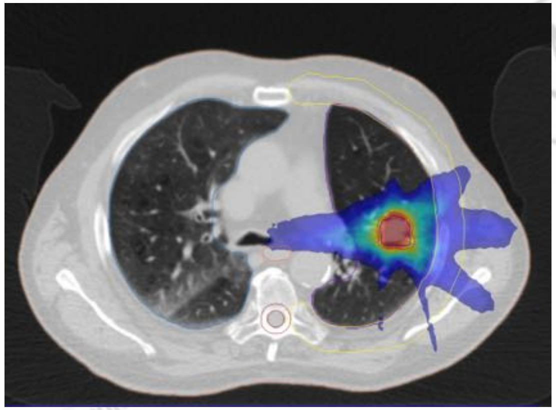
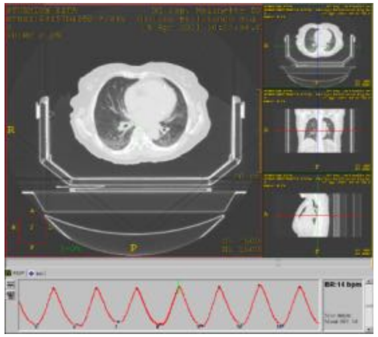
Stereotactic Ablative Radiation Therapy (SABR)

Patient Fixation



Treatment Planning



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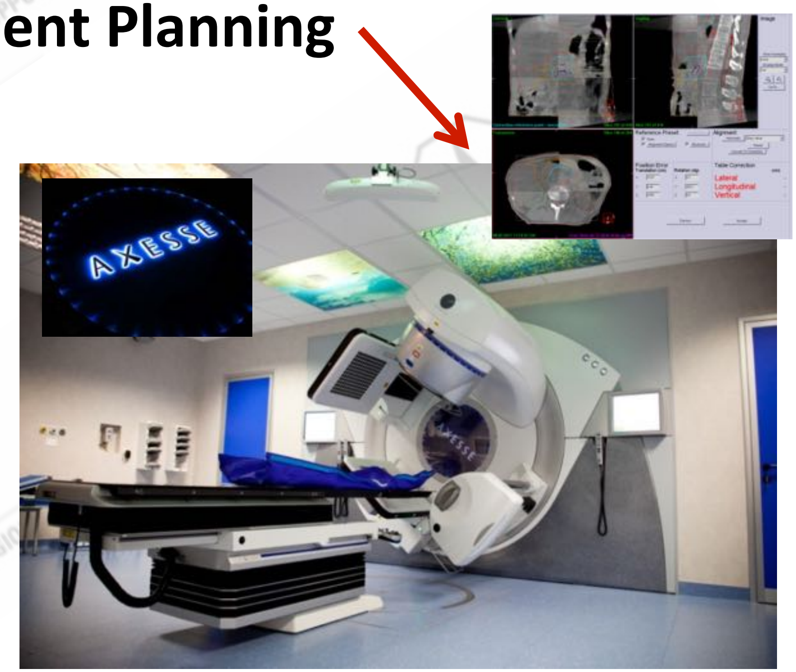
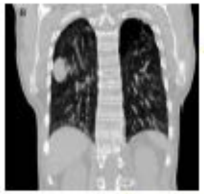
Imaging

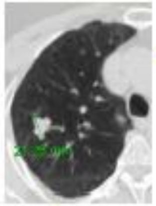


Treatment Delivery

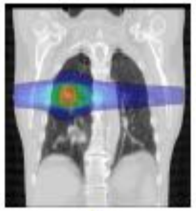
Features of Lung SABR



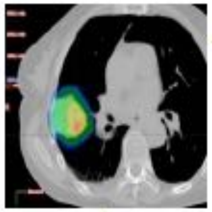
Accounting for Motion
- 4D Planning



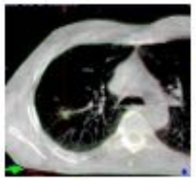
Small tumour volumes
- Small margins



Many Beam Directions
- 7-11 Beams / Arc Therapy



Steep dose gradients
- Inhomogeneous target dose



Accurate Targeting
- CBCT pre-RT

High dose per fraction
- Short total treatment duration

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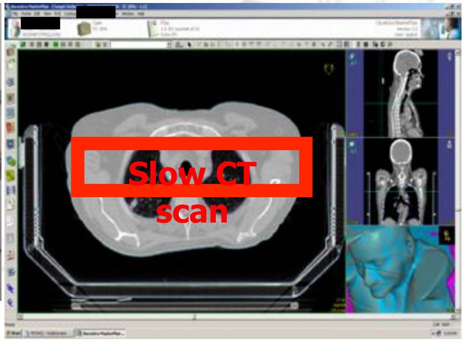
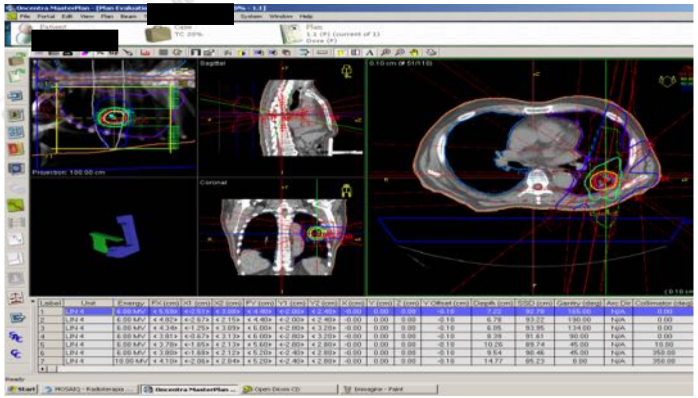
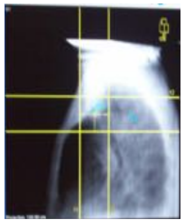
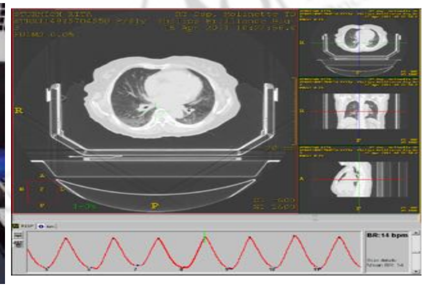
2003

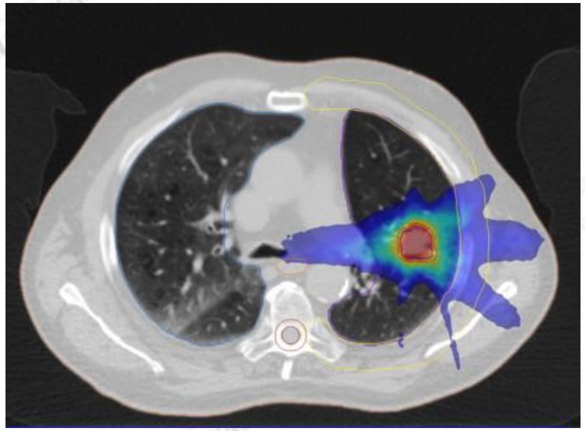


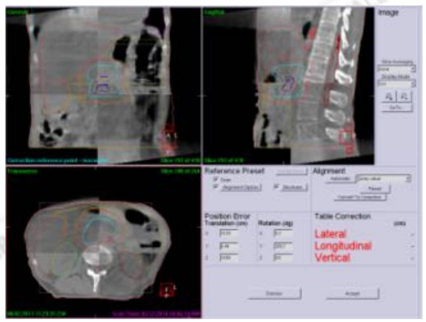




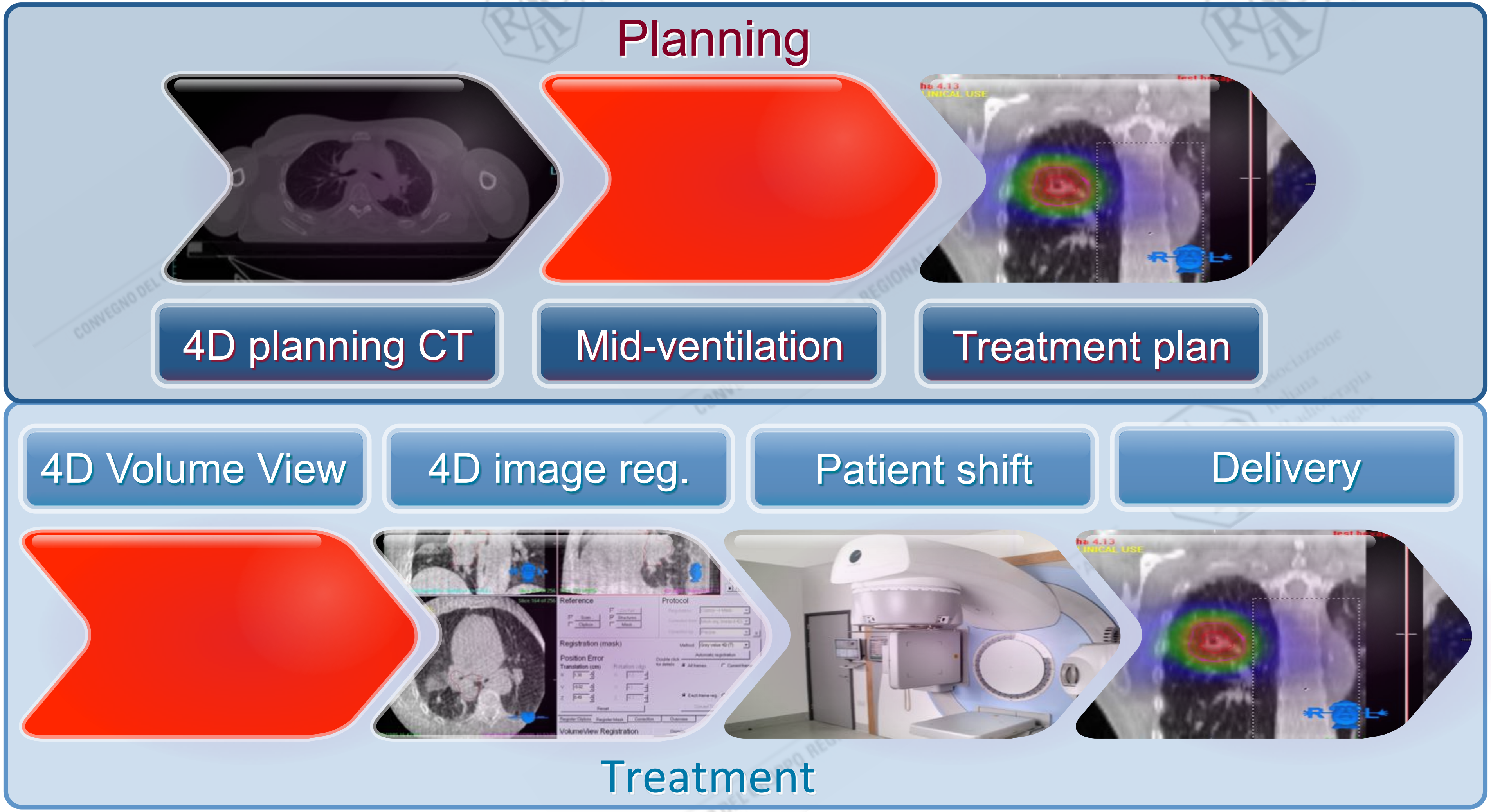
2010







Technical Advances may have an impact on efficacy and toxicity



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SABR Guidelines

AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

LOUIS POTTERS, M.D.,[*] BRIAN KAVANAGH, M.D.,[†] JAMES M. GALVIN, D.SC.,[‡] JAMES M. HEVEZI, PH.D.,[§] NORA A. JANJAN, M.D.,[¶] DAVID A. LARSON, M.D., PH.D.,[**] MINESH P. MEHTA, M.D.,[††] SAMUEL RYU, M.D.,[‡‡] MICHAEL STEINBERG, M.D.,[§§] ROBERT TIMMERMAN, M.D.,[¶¶] JAMES S. WELSH, M.D.,[***] AND SETH A. ROSENTHAL, M.D.[†††]

European Organisation for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Dirk De Ruysscher, Corinne Faivre-Finn, Ursula Nestle, Coen W. Hurkmans, Cécile Le Péchoux, Allan Price, and Suresh Senan

Stereotactic body radiation therapy: The report of AAPM Task Group 101

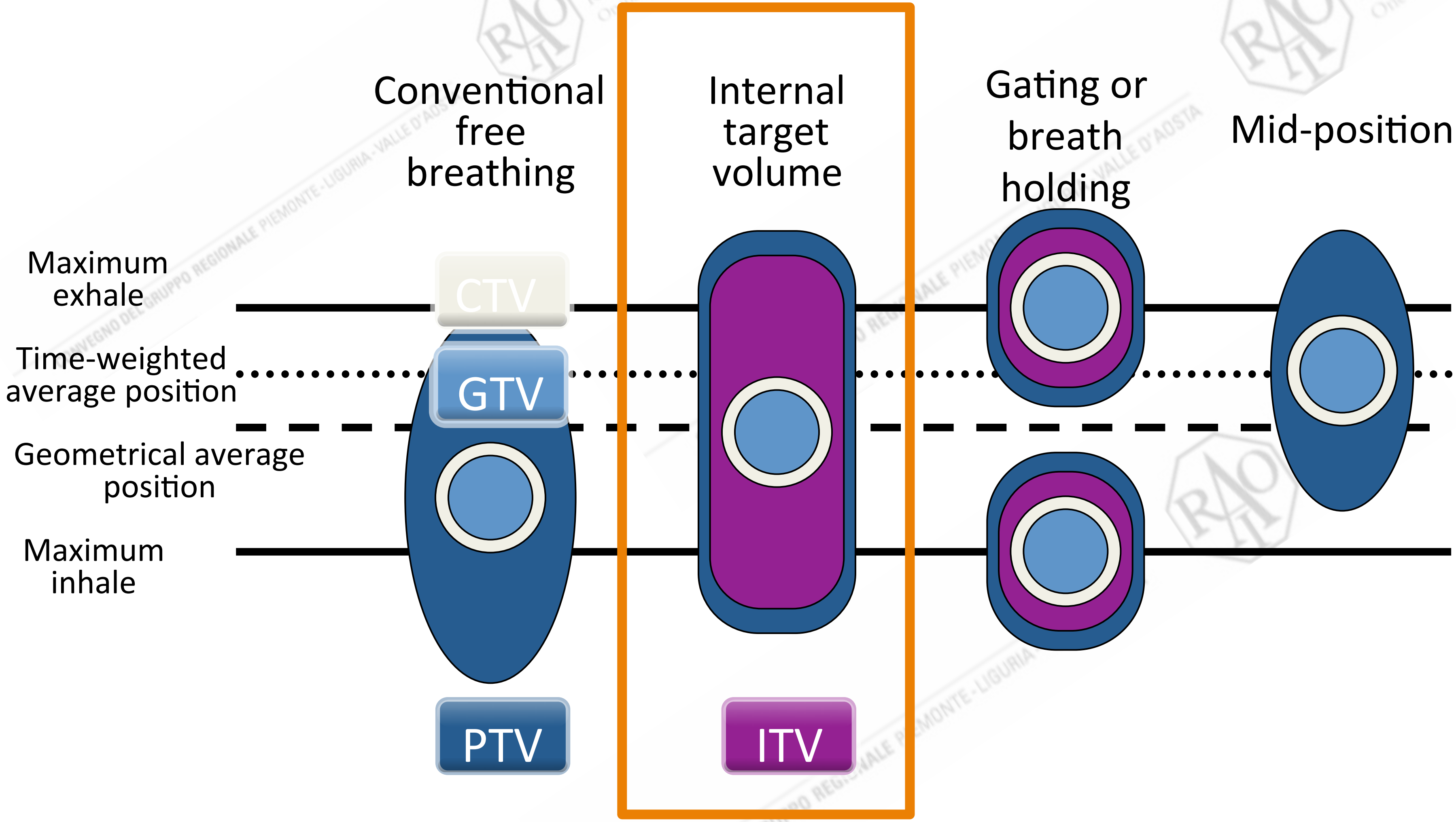
Stanley H. Benedict, Kamil M. Yenice, David Followill, James M. Galvin, William Hinson, Brian Kavanagh, Paul Keall, Michael Lovelock, Sanford Meeks, Lech Papiez, Thomas Purdie, Ramaswamy Sadagopan, Michael C. Schell, Bill Salter, David J. Schlesinger, Almon S. Shiu, Timothy Solberg, Danny Y. Song, Volker Stieber, Robert Timmerman, Wolfgang A. Tomé, Dirk Verellen, Lu Wang, and Fang-Fang Yin

Stereotactic Ablative Radiation Therapy for the Treatment of Early-stage Non–Small-Cell Lung Cancer

CEPO Review and Recommendations

Gino Boily, PhD,[*] Édith Filion, MD,[†] George Rakovich, MD,[‡] Neil Kopek, MD,[§] Lise Tremblay, MD,[‖] Benoit Samson, MD,[¶] Stéphanie Goulet, PhD,[*] Isabelle Roy, MD,[#] and the Comité de l'évolution des pratiques en oncologie[**]

Planning Concepts For Breathing



[Wolthaus et al., IJROBP 2008]

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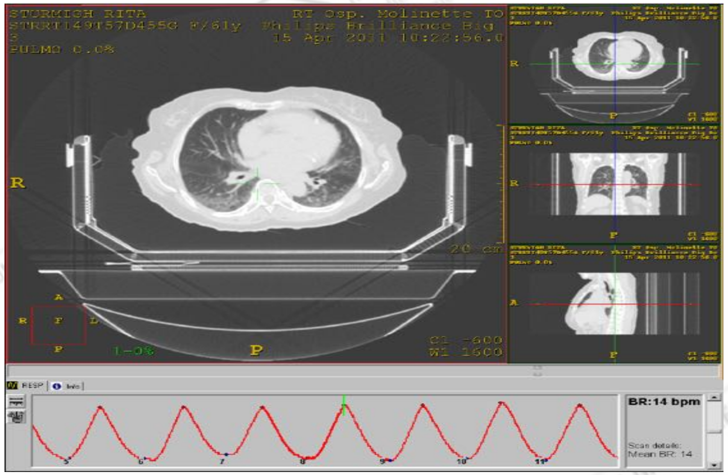
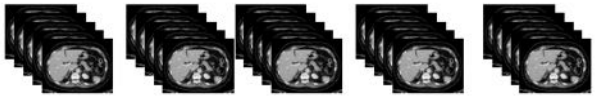
Virtual simulation





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4DCT → accurately compensate for target motion and define patient's specific internal margins

respiratory surrogate: abdominal pressure piezo-electric belt

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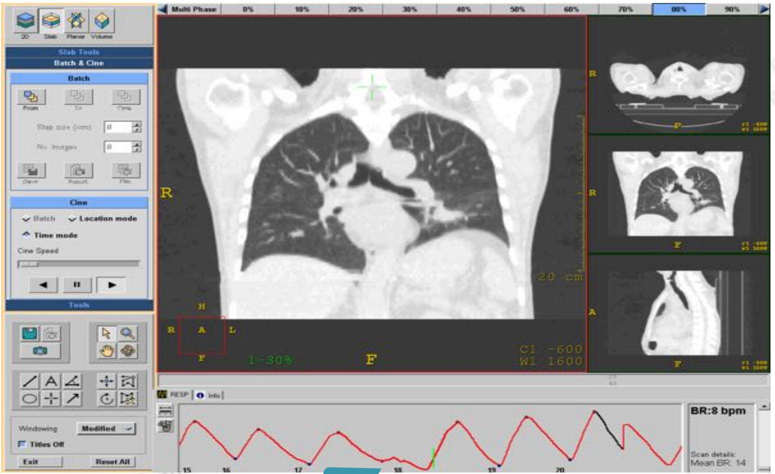
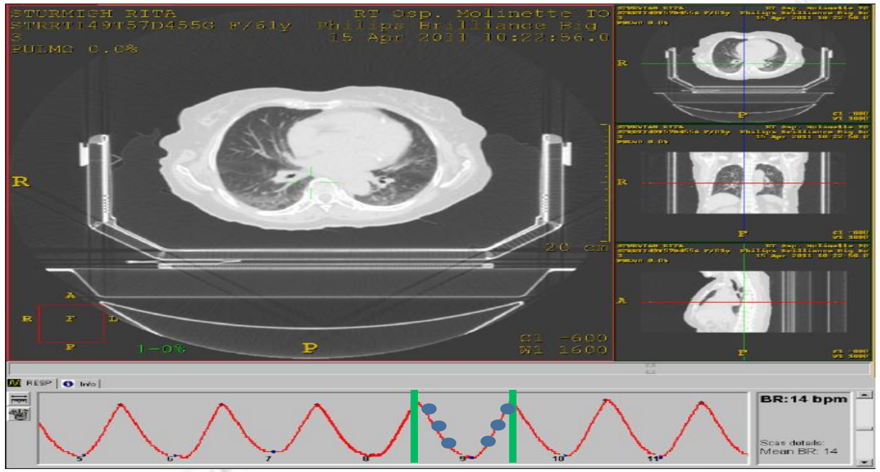
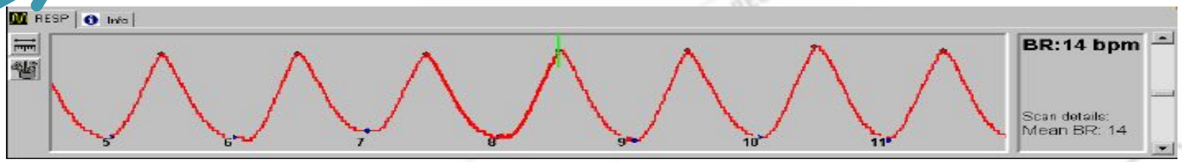
Irregular breath cycle → inaccurate image reconstruction







Scan lenght: 20	Average full exhalation phase: 58%
Numero di cicli catturati: 21	Average full inhalation phase: 99%
Mean BRT: 23 bpm	Amplitude range: 0.89-1.12
Breath rate range: 22-27 bpm	Amplitude standard deviation: 0.05

ASD < 0.2

Mean BRT > 25

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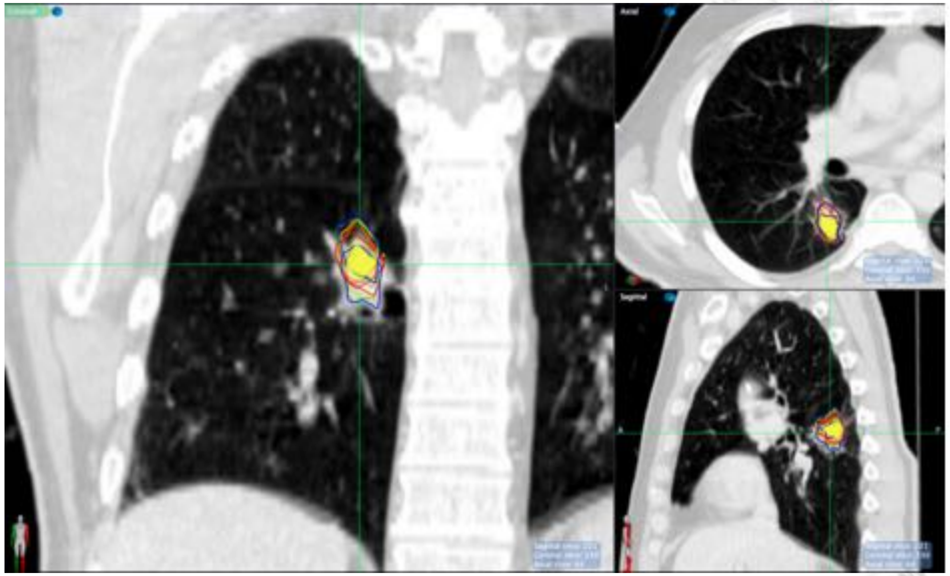
Velocity



Create contours on one phase of respiratory cycle → propagate on all 10 phases (DIR, deformable image registration) → ITV

MIP

20%....

AVERAGE CT

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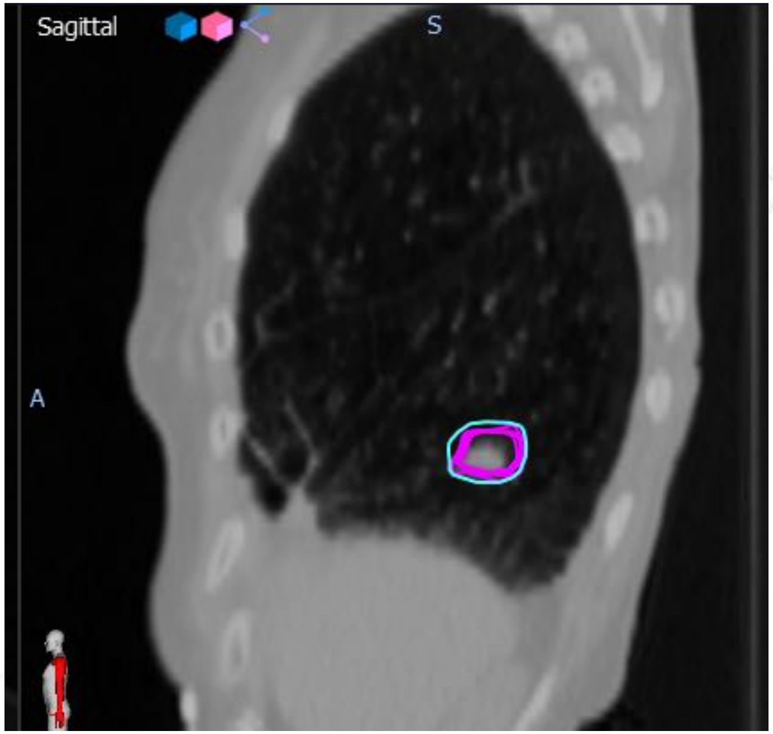
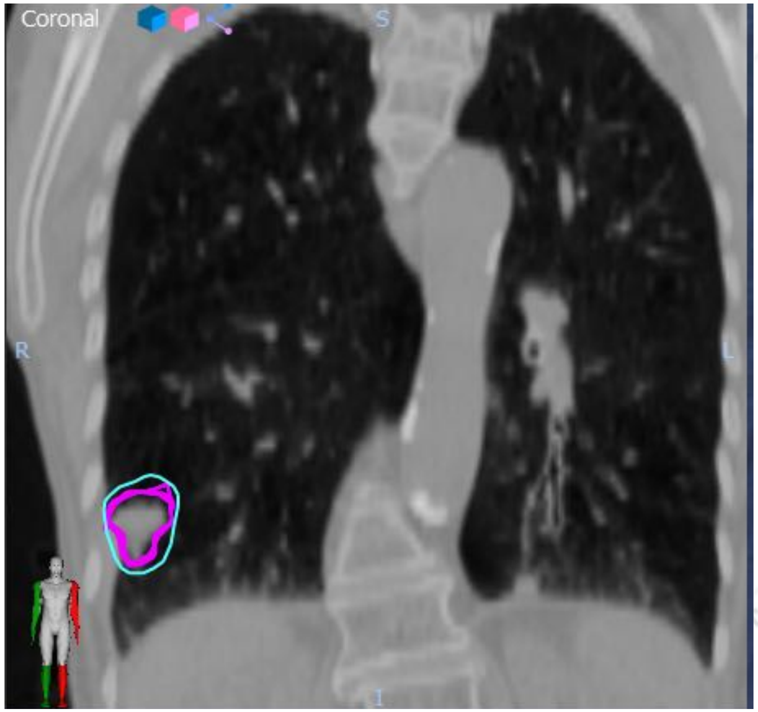
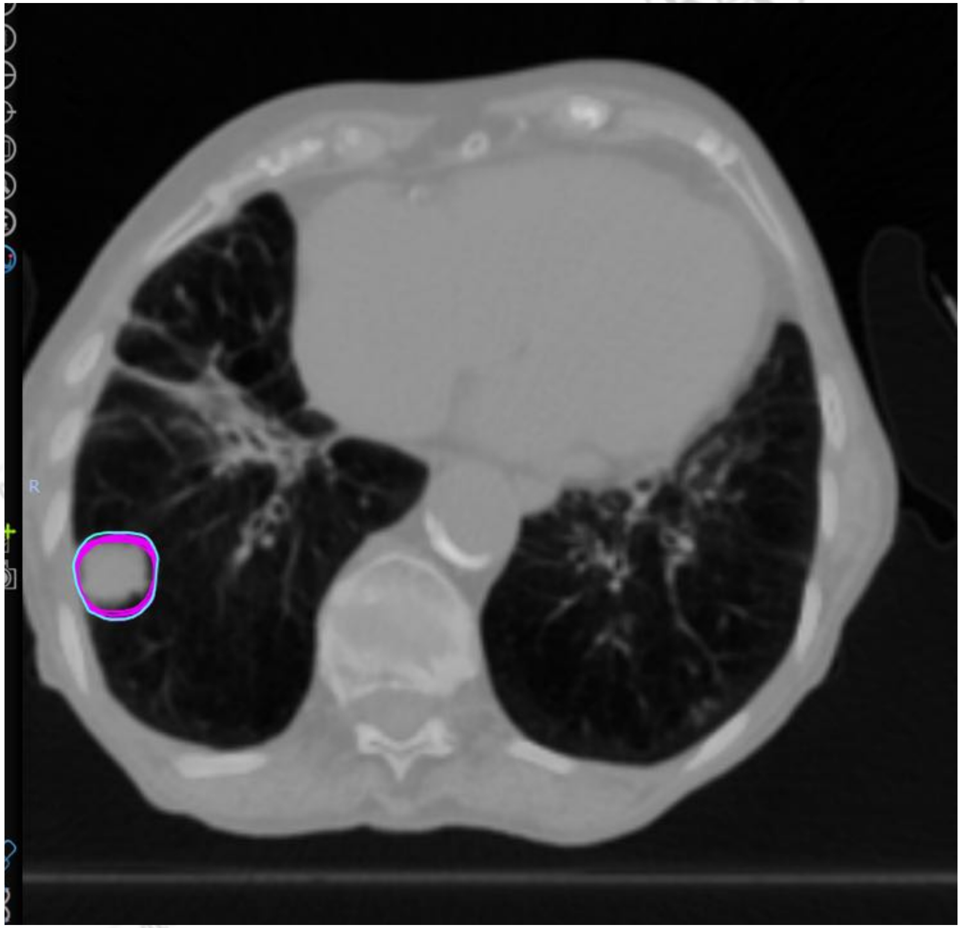
ITV







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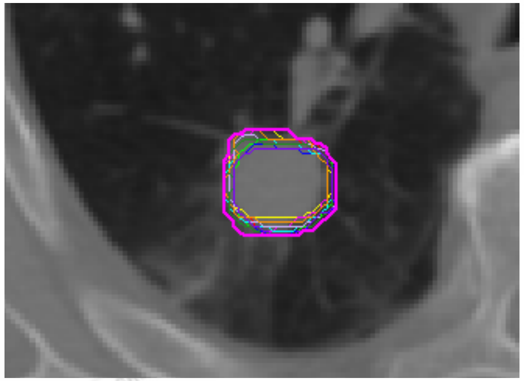
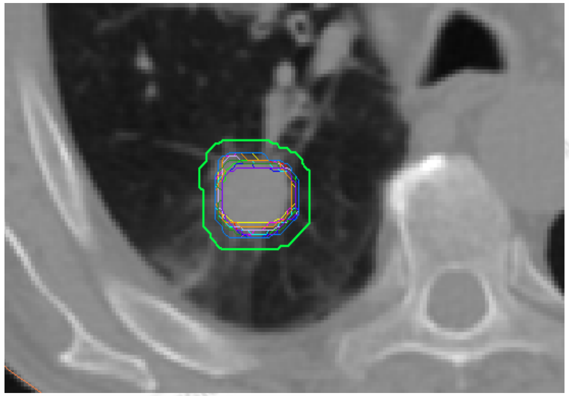
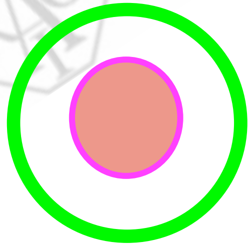
Higher accuracy should translate in less toxicity and better PTV coverage





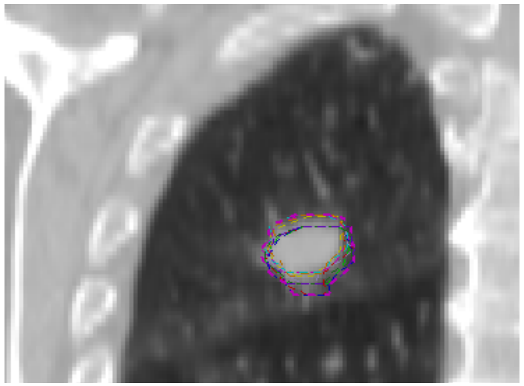


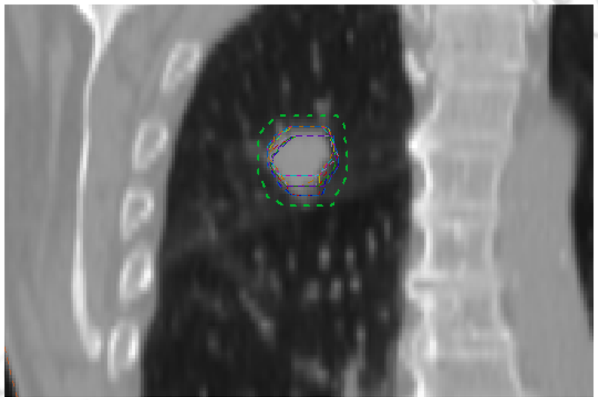
3 mm

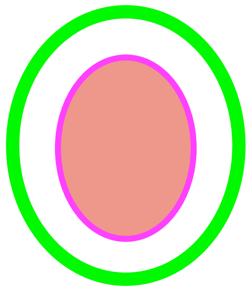
CTV = GTV

ITV_{10} average CT

PTV = ITV + 3 mm isotropic

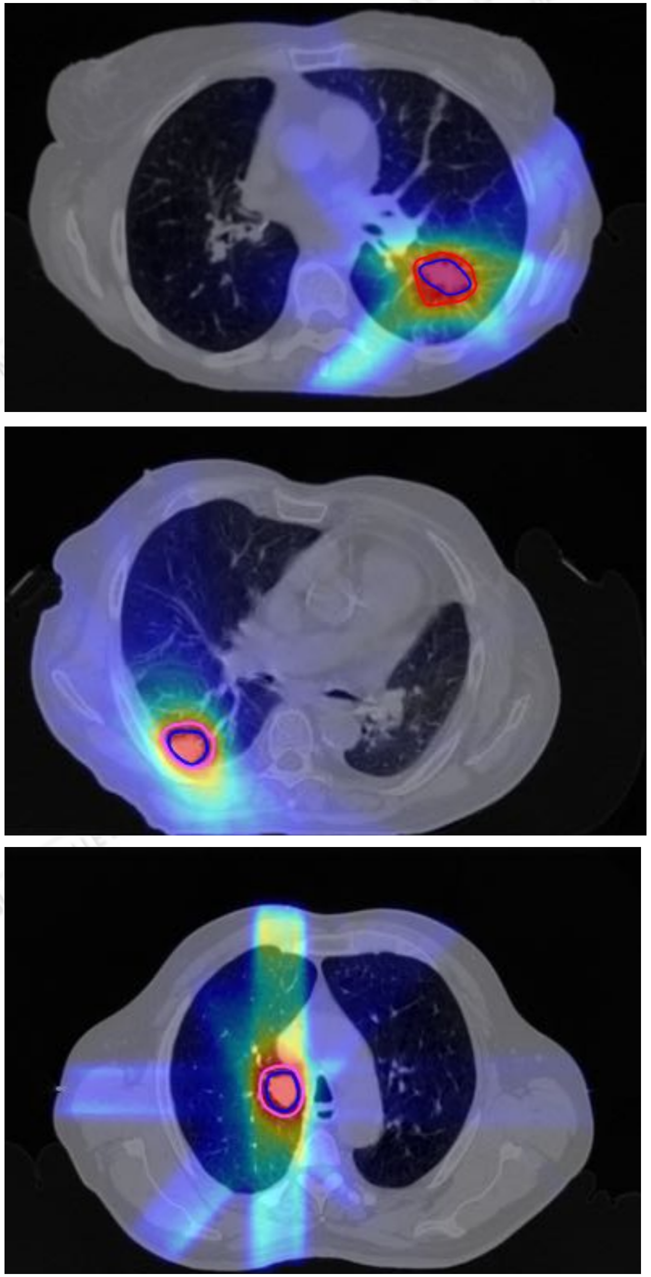






3 mm

Use of "risk-adapted" SBRT protocol



• **Peripheral lesions (T1a-T1b):**

- 54 Gy/ 3 fractions (isodose 80%)
- 45 Gy/ 3 fractions (isodose 80%)

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

- 55 Gy/ 5 fractions (isodose 80%)
- 50 Gy/ 5 fractions (isodose 80%)

• **Central lesions:**

- 60 Gy/ 8 fractions (isodose 80%)

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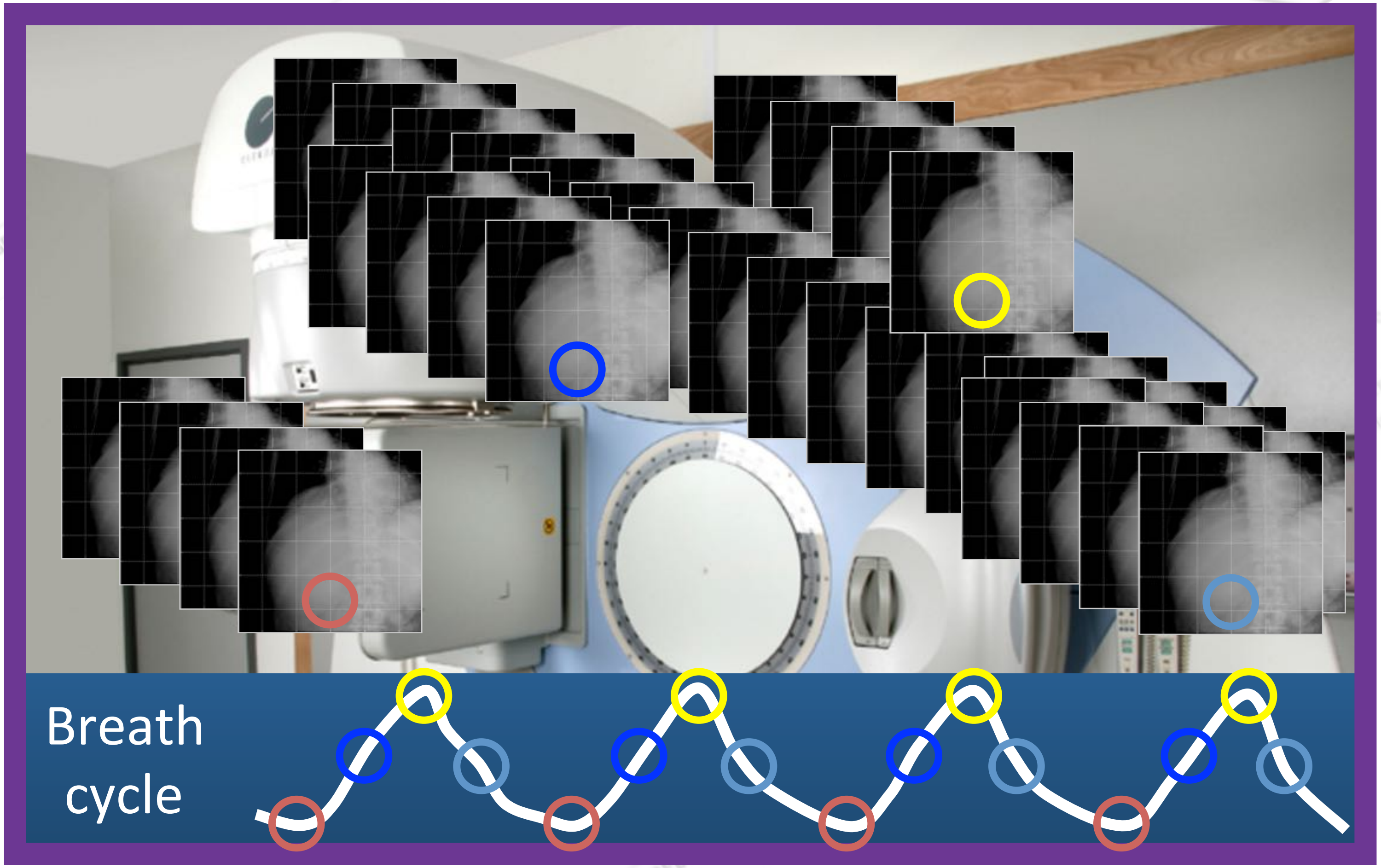
2013→ Advanced IGRT
4D-CBCT



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SABR is well tolerated: toxicity is uncommon

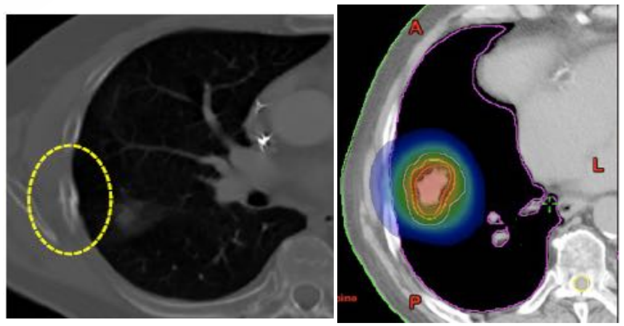
- 505 lung tumors in 483 patients
- Median time to pneumonitis: 0.4 years

Pneumonitis grade	incidence
Grade 2 or higher	7%
Grade 3 or higher	2%
Grade 5	0.2%

Grills IS, JTO 2012

- 500 pts with T1-2N0 tumors (2003-2009)
- Median follow-up 33 months (13-86 months)
- Severe chest wall toxicity uncommon
  - severe pain in 2.2%,
  - rib fractures in 2.7%

Bongers E, 2011



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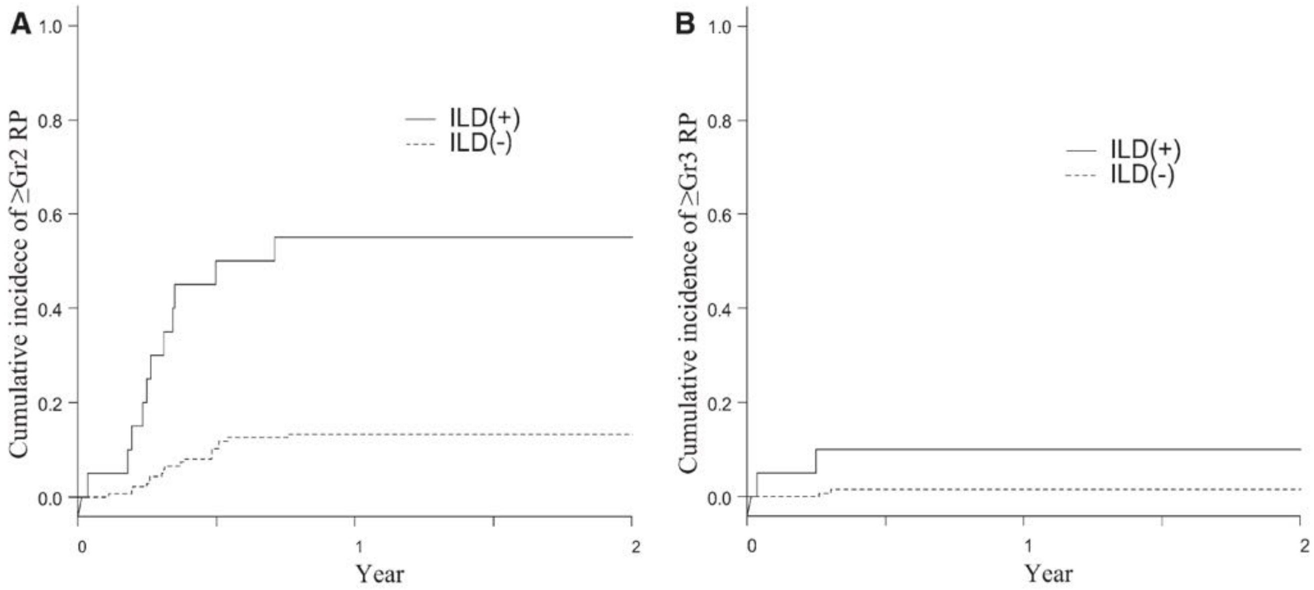
Impact of Pretreatment Interstitial Lung Disease on Radiation Pneumonitis and Survival after Stereotactic Body Radiation Therapy for Lung Cancer

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

(*J Thorac Oncol.* 2015;10: 116–125)



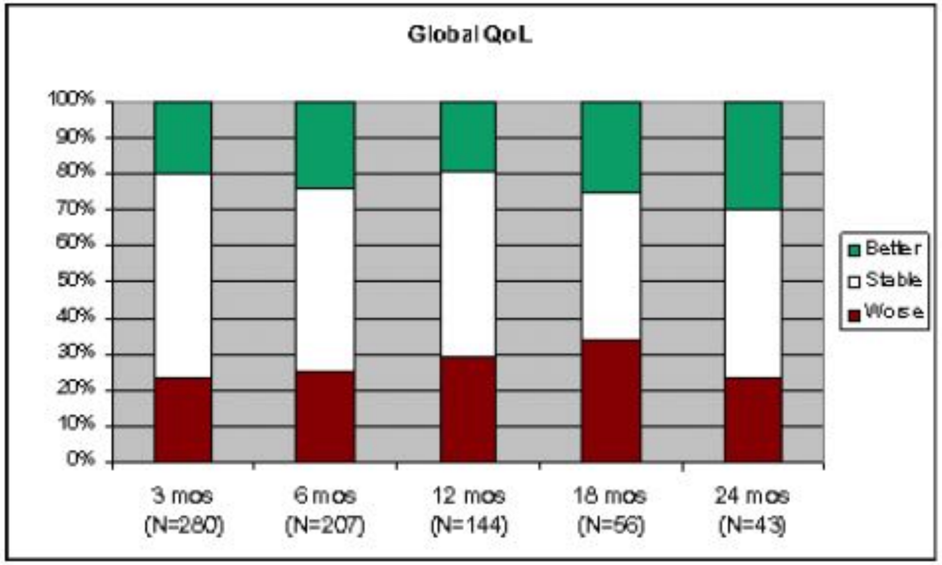
Toxicity and QOL

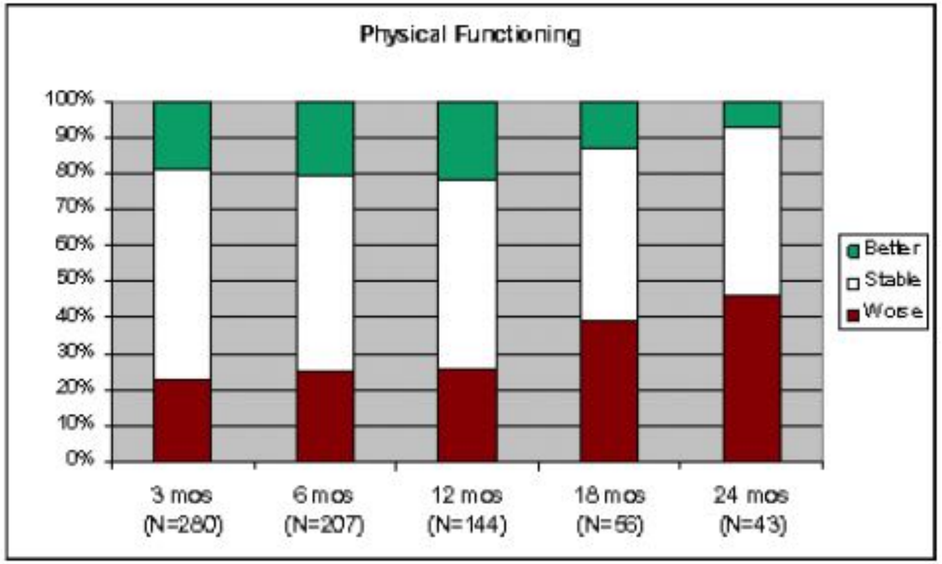
No Clinically Significant Changes in Pulmonary Function Following Stereotactic Body Radiation Therapy for Early-Stage Peripheral Non-Small Cell Lung Cancer: An Analysis of RTOG 0236

- 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]

Quality of Life – self assessed





[Lagerwaard et al, JTO 2012]

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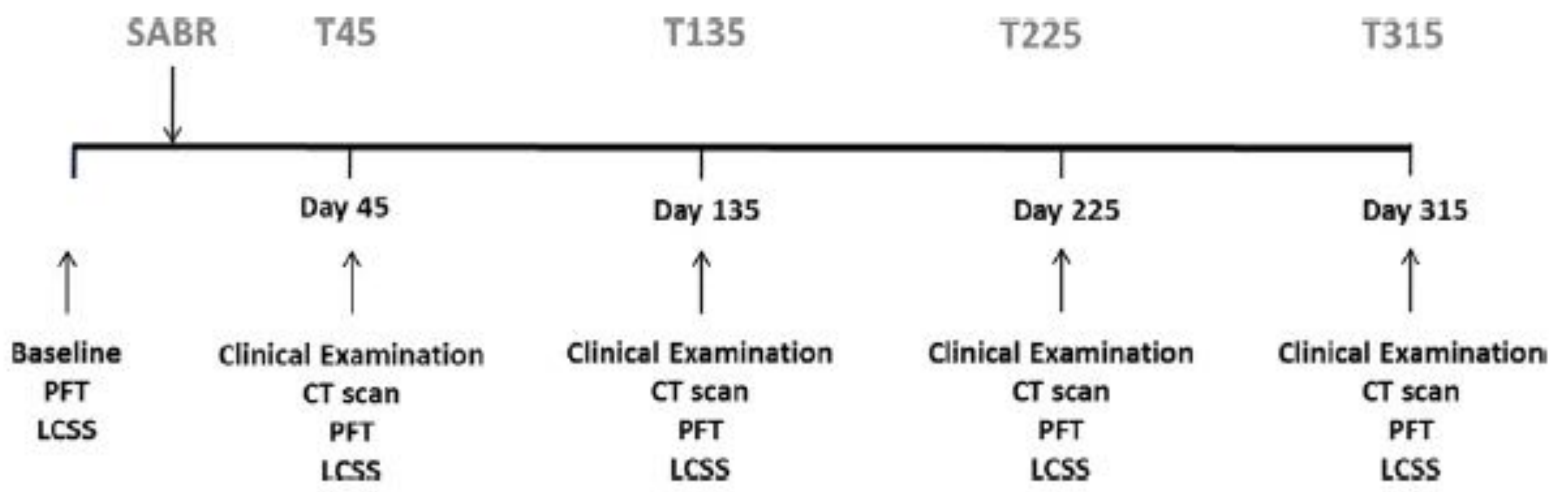
Pulmonary function and quality of life: outline of a prospective study



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Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: a prospective study

Cinzia Ferrero[a,1], Serena Badellino[b,1], Andrea Riccardo Filippi[b,*], Luana Focaraccio[b], Matteo Giaj Levra[b], Mario Levis[b], Francesco Moretto[b], Roberto Torchio[a], Umberto Ricardi[b], Silvia Novello[b]

[a] Respiratory Function and Sleep Laboratory, S. Luigi Hospital, Orbassano, Italy
[b] Department of Oncology, University of Torino, Torino, Italy

Age (mean, range)	77 (61–84)
Male	23 (76.7%)
Female	7 (23.3%)
Former smokers	19 (63.3%)
Active smokers	8 (26.7%)
Never smokers	3 (10%)
Performance status (ECOG)	
0	23 (76.7%)
1	6 (20%)
2	1 (3.4%)
AA Charlson CI (mean, range)	6.9 (3–14)
<7	16 (53.3%)
≥7	14 (46.7%)
Stage	
IA	17 (56.7%)
IB	13 (43.3%)
Tumor max diameter, mm (mean, range)	25.5 (12–55)
Histology	
Adenocarcinoma	9 (30%)
Squamous cell carcinoma	8 (26.7%)
NSCLC NOS	4 (13.3%)
Unknown	9 (30%)
Treatment schedules	
45–54 Gy/3 fr	9 (30%)
55 Gy/5 fr	11 (37%)
60 Gy/8 fr	10 (33%)

[Ferrero, Badellino et al, Lung Cancer 2015]

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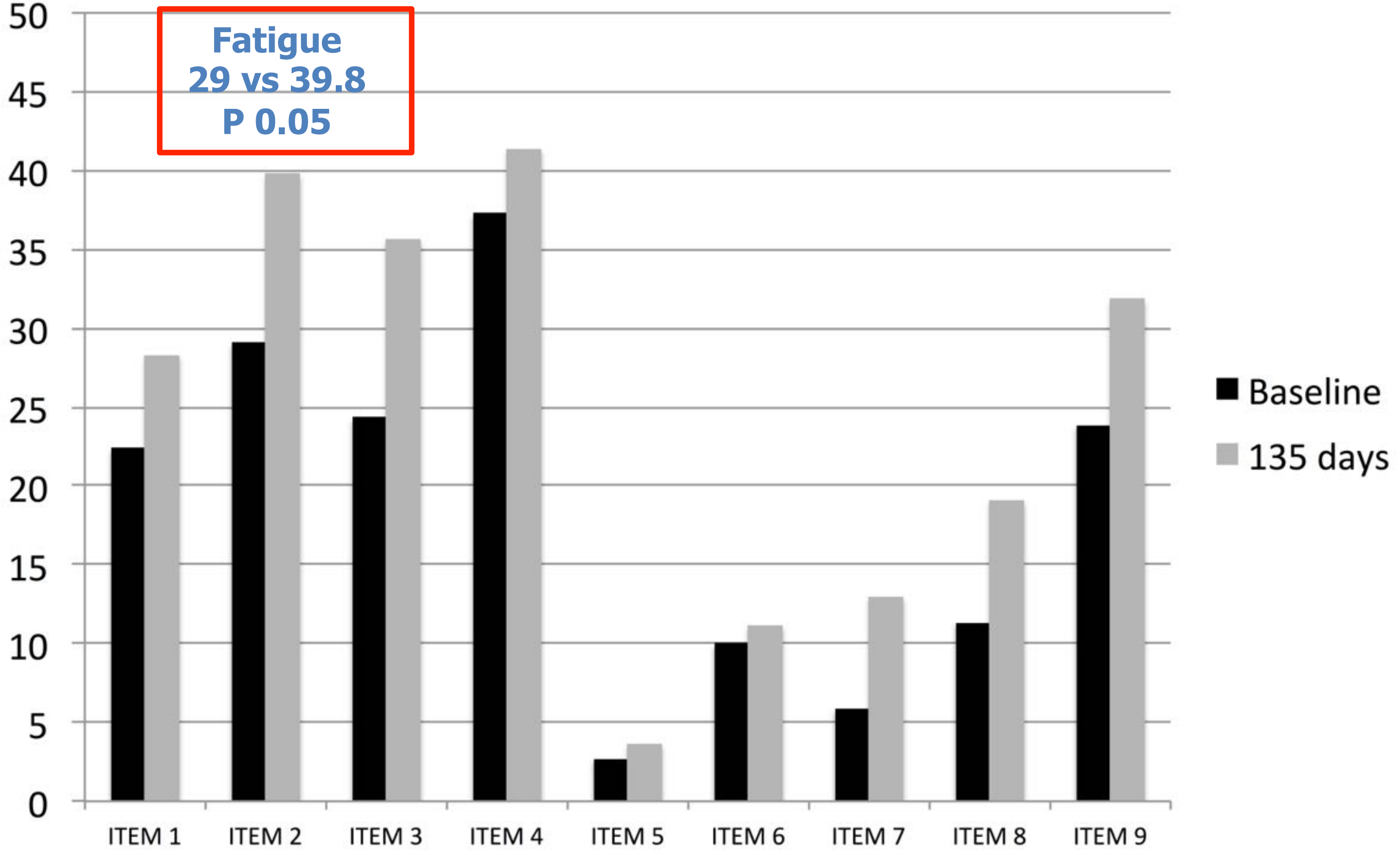
Logistic regression analysis

Logistic regression model analysis of baseline pulmonary function tests and toxicity.

Pulmonary function test	Any pulmonary toxicity			Grade 2+ pulmonary toxicity			Any late radiological toxicity (Koenig)		
	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value
FEV_1 (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	16 (0.1–200)	0.26
FEV_1 (%predicted)	16/30	1.5 (0.1–22)	0.75	11/30	3.1 (0.4–21.4)	0.26	7/24	NA-unstable	–
FEV_1/SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
FEV_1/SVC (%predicted)	16/30	0.02 (0–7.7)	0.2	11/30	0.02 (0–7)	0.18	7/24	NA-unstable	–
SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.1 (0.003–7.8)	0.34
SVC (%predicted)	16/30	0.1 (0–5)	0.22	11/30	0.1 (0–6.7)	0.21	7/24	NA-unstable	–
RV (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
RV (%predicted)	16/30	5.04 (0.4–75.2)	0.24	11/30	8.6 (0.5–150.3)	0.14	7/24	NA-unstable	–
TLC (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.7 (0.1–3.6)	0.68
TLC (%predicted)	16/30	0.03 (0–5.5)	0.19	11/30	0.008 (0–2.8)	0.11	7/24	NA-unstable	–
D_LCO (ml/min/mmHg)	16/30	NA-unstable	–	11/30	0.001 (0–6.5)	0.12	7/24	0.9 (0.6–1.2)	0.39
D_LCO (%predicted)	16/30	8.8 (0.6–136)	0.12	11/30	8.8 (0.7–105.4)	0.09	7/24	NA-unstable	–
D_LCO/VA (ml/min/mmHg)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
D_LCO/VA (%predicted)	16/30	3.9 (0.3–55)	0.31	11/30	3.7 (0.2–75.2)	0.4	7/24	NA-unstable	–
PaO_2 (mmHg)	16/30	1.0 (0.8–1.3)	0.94	11/30	0.9 (0.5–1.6)	0.72	7/24	1.1 (0.9–1.3)	0.41
$PaCo_2$ (mmHg)	16/30	0.8 (0.1–4.3)	0.75	11/30	0.3 (0.1–1.3)	0.12	7/24	NA-unstable	–

Normal lungs dose-volume distributions by development of any grade clinical lung toxicity.

Parameter	All patients (*n* = 30)	Pneumonitis (*n* = 14)	No pneumonitis (*n* = 16)	OR (95% CI)	*P* value
Ipsilateral lung V_{20Gy} (%)	15.6 ± 5.5	15.1 ± 5.8	16.1 ± 5.4	1.03 (0.91–1.18)	0.61
Ipisilateral lung V_{10Gy} (%)	24.5 ± 6.8	22.9 ± 6.9	26.1 ± 6.5	1.07 (0.96–1.21)	0.22
Ipsilateral lung V_{5Gy} (%)	34.9 ± 8.6	31.7 ± 8.2	38.1 ± 8.0	1.11 (0.99–1.24)	0.058
Ipsilateral mean lung dose (EQD_{2Gy})	11.9 ± 3.5	11.7 ± 3.9	12.1 ± 3.1	1.03 (0.83–1.27)	0.82
Bilateral lung V_{20Gy} (%)	7.8 ± 2.6	7.8 ± 2.8	7.8 ± 2.6	0.99 (0.75–1.32)	0.97
Bilateral lung V_{10Gy} (%)	14.4 ± 5.1	14.6 ± 6.1	14.2 ± 3.9	0.98 (0.85–1.14)	0.84
Bilateral lung V_{5Gy} (%)	24.8 ± 7.4	24.7 ± 8.9	24.8 ± 6.0	1.0 (0.90–1.10)	0.97
Bilateral mean lung dose (EQD_{2Gy})	6.9 ± 1.9	7.0 ± 2.2	6.9 ± 1.6	0.98 (0.66–1.44)	0.91
Absolute lung volume spared from a 5 Gy dose (VS5, in cc)	3088.9 ± 790.3	3157.4 ± 699	3020.4 ± 893.5	1.02 (0.78–1.17)	0.65



- Lung Cancer Symptom Scale (LCSS)
- Worsening of the item 2 "Fatigue" (mean basal value =29, mean value at T_{135} = 39.8, p = 0.05)

[Ferrero C, Badellino S et al, Lung Cancer 2015]

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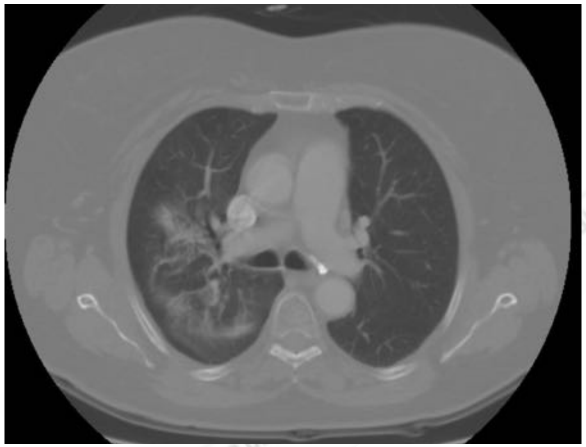
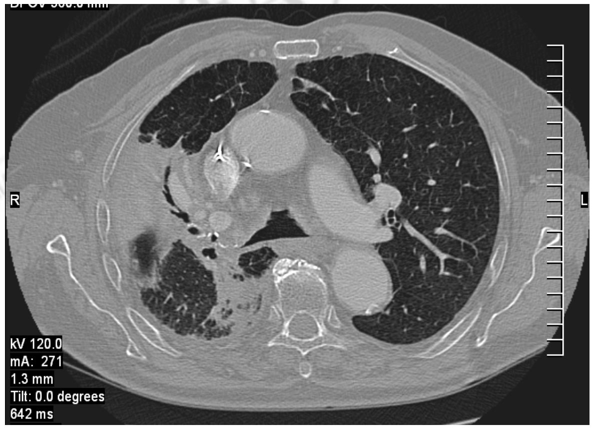
Acute radiological changes after SBRT

- 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%





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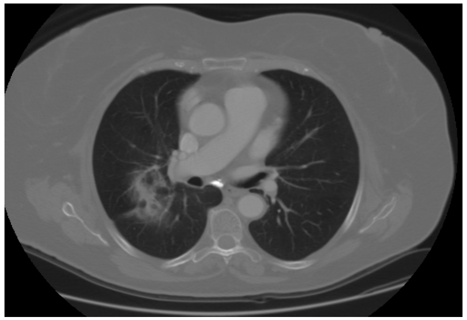
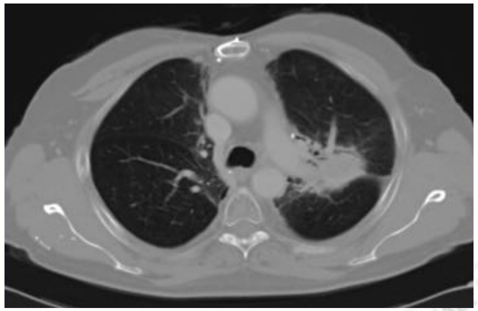
Late radiological changes after SBRT

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

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


Modified conventional pattern


Mass-like pattern


Scar-like pattern

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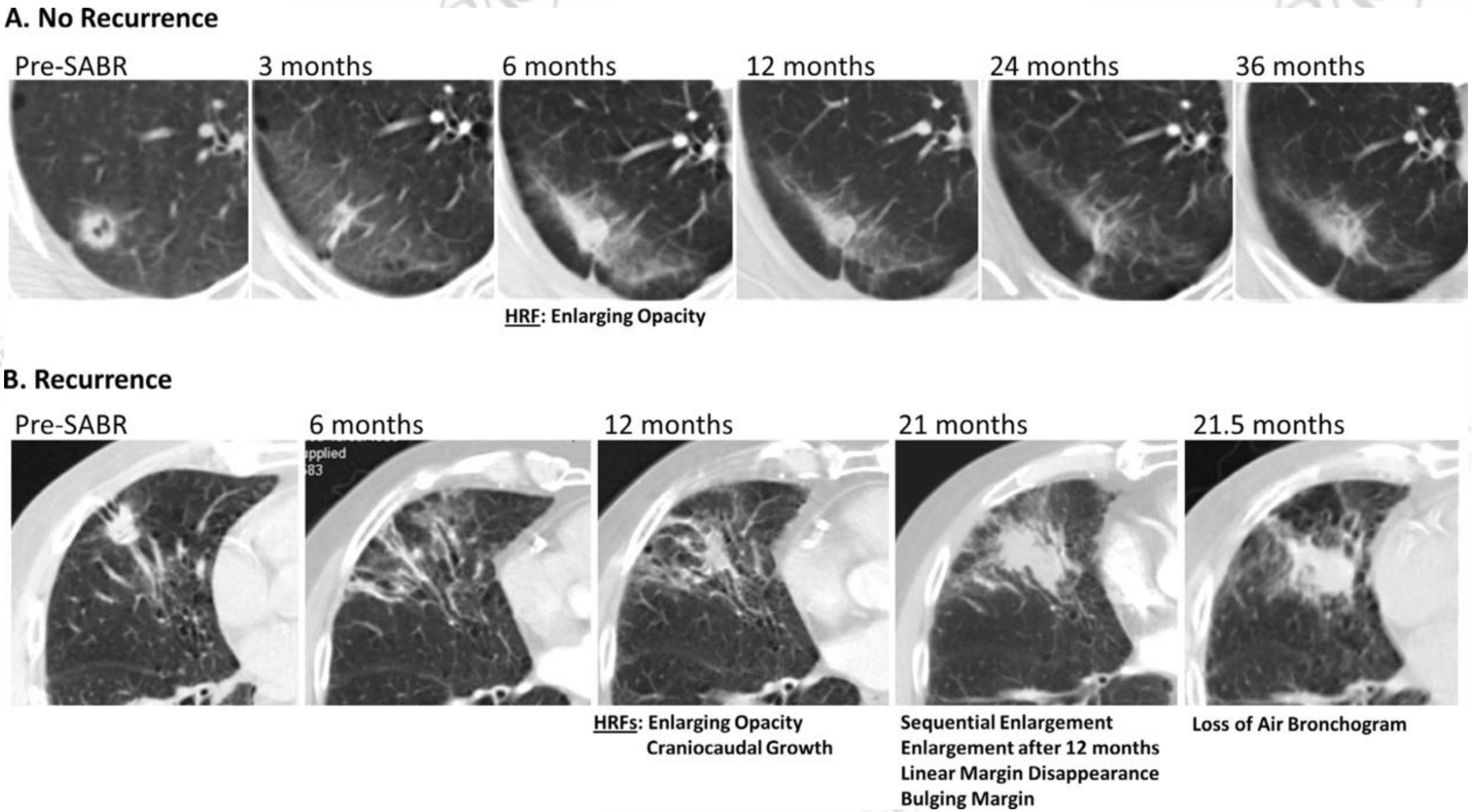
Fibrosis or recurrence after SABR?



[Huang K et al, 2013]

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Fibrosis or recurrence after SABR?

HRF: High Risk Factor

High-risk feature	Sensitivity (%)	Specificity (%)
Enlarging opacity	92	67
Sequential enlargement	67	100
Enlargement after 12 months	100	83
Bulging margin	83	83
Linear margin disappearance	42	100
Loss air bronchogram	67	96
Cranio-caudal growth of ≥5 mm and ≥20%	92	83

[Mattonen et al, 2014]

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Imaging Features Associated With Disease Progression After Stereotactic Ablative Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer: A Multi-Institutional Pooled Analysis

E. Anderson,[1] A.R. Filippi,[2] S. Badellino,[2] U. Ricardi,[2] R. von Eyben,[3] M.F. Gensheimer,[3] M. Diehn,[4] B.W. Loo, Jr,[4] and D.B. Shultz[5]; [1]*Stanford University, Stanford, CA,* [2]*University of Torino, Torino, Italy,* [3]*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA,* [4]*Stanford University Department of Radiation Oncology, Stanford, CA,* [5]*Princess Margaret Cancer Centre, Toronto, ON, Canada*

Conclusion: Imaging biomarkers, particularly maximum SUV, mediastinal pleural contact, and arch ratio are predictive of outcomes in patients treated with SBRT for early stage NSCLC. Further studies may reinforce the value of imaging-based biomarkers for predicting outcomes in early stage lung cancer and potentially guide patient selection for treatment approach and radiation dosing.

Poster ASTRO 2016

Difficult SABR scenarios

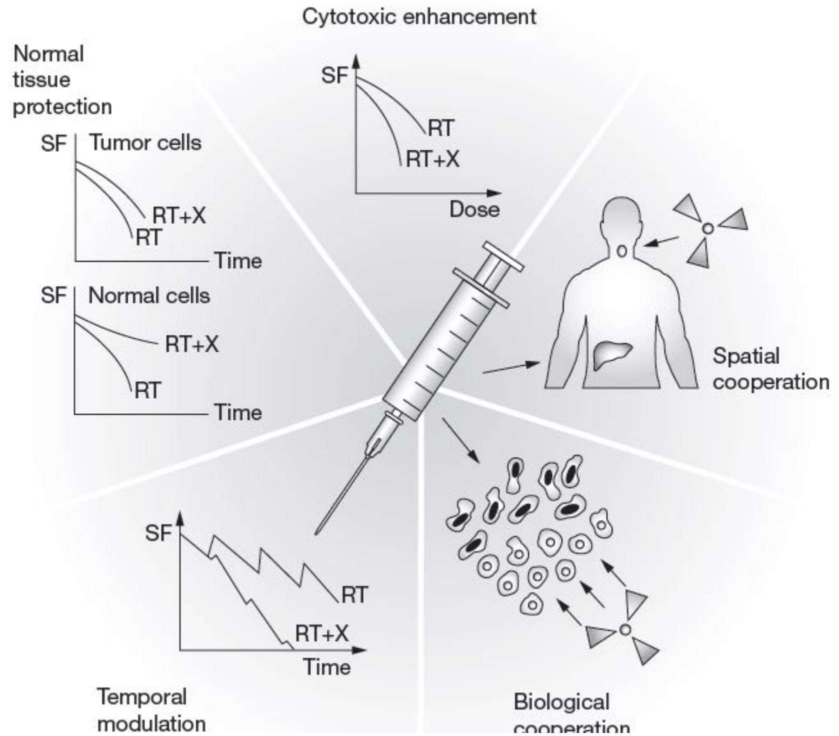
Clinical scenario		Challenges	Potential solutions being explored
Pre Treatment	Incorporating patient preferences for treatment	Choice of SABR in operable NSCLC	• Shared decision-making [19, 20] • Comparative effectiveness research (including patient-reported outcomes, QOL and cost-effectiveness analyses) with "big data" strategies to facilitate data mining • RCTs underway (NCT02629458, NCT01753414, NCT02468024, VALOR study)
	Obtaining a diagnosis	Risks of treating benign disease Risks of biopsy in frail patients	•Use validated models for cancer risk determination in a given population [9] • Explore blood biomarkers [123]
Treatment	Central tumors Multiple primary lung cancers	Proximity to OARs Uncertainty in OAR location Uncertainly in OAR dose constraints	• "Big data" strategies to establish more reliable OAR dose constraints • MRI-guided adaptive RT [44] • Protons [41]
	Oligometastases	Higher pneumonitis risk Identify molecular and clinical characteristics of patients likely to benefit from ablative local therapies Optimize sequencing of RT and new systemic treatments	• Phase I-II trials, as well as randomized trials
Follow-up	Detection of recurrences	Distinguishing post-RT fibrosis vs recurrent disease	• Radiomic approaches [24]
	Survivorship issues	Loco-regional recurrences and second lung tumors Smoking cessation	• Survivorship clinics [124] • Patient-reported outcomes, including financial impact of treatments

Abbreviations *QOL* quality of life, *RT* radiotherapy, *SABR* stereotactic ablative radiotherapy, *NSCLC* non-small cell lung cancer, *OAR* organ at risk, *PTV* planning target volume

[Baker et al., Radiation Oncology 2016]

Systemic Therapy

- Which patients are candidate?
- Classical adjuvant?
- Biomarkers driven/targeted agents?



STEREOtactic Radiation and Chemotherapy in Lung Cancer (STEREO) (STEREO)

This study has been terminated.

(insufficient enrollment)

Sponsor:
James Graham Brown Cancer Center

Information provided by (Responsible Party):
James Graham Brown Cancer Center

ClinicalTrials.gov Identifier:
NCT01300299

First received: February 17, 2011
Last updated: February 29, 2016
Last verified: January 2016
History of Changes

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SABR with Complete mediastinal staging

STAGE study: STereotactic Ablative radiotherapy for lung cancer after staGing with Endosonography

(suspected) NSCLC and possible **SABR candidate**

↓

One of the following features based on CT-PET imaging:
Centrally located clinical T1-T2
Peripheral located T2
Suspicion of N1 or N2 disease
Non-FDG avid primary lung tumor and lymph nodes

↓

Determine loco-regional nodal status (N0-N3) based on CT-PET imaging

↓

INTERVENTION:
Single scope complete mediastinal and hilar staging procedure:
EBUS followed by EUS-B
Optional:
Sputum collection and bronchoscopy with minimal lavage

↓

Determine change of loco-regional nodal status (N0-N3) based on endosonographic staging

Prof Dr J.T.Annema,
email: j.t.annema@amc.uva.nl

Prof Dr S. Senan,

Conclusions

- SABR is currently widely accepted as the best alternative to surgery for inoperable early stage lung cancer
- SABR might be offered also to operable patients
- IGRT-motion management are essential for prescribing high BED: IMRT is an option
- Mature data with long-term follow up are needed to better understand the pattern of relapse across time
- Predictive and prognostic factors are needed to possibly offer to higher risk patients adjuvant therapies

Teamwork is essential!

TEAM

T Together
E Everyone
A Achieves
M More

Credits:

Prof U Ricardi
Dott A Filippi
Dott J Di Muzio
Dott ssa A Guarneri
Dott ssa C Mantovani
Dott M Levis

Grazie per l'attenzione

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