The Role of Stereotactic Body Radiation Therapy (SBRT) in Lung Cancer: Where we are now and where we are going

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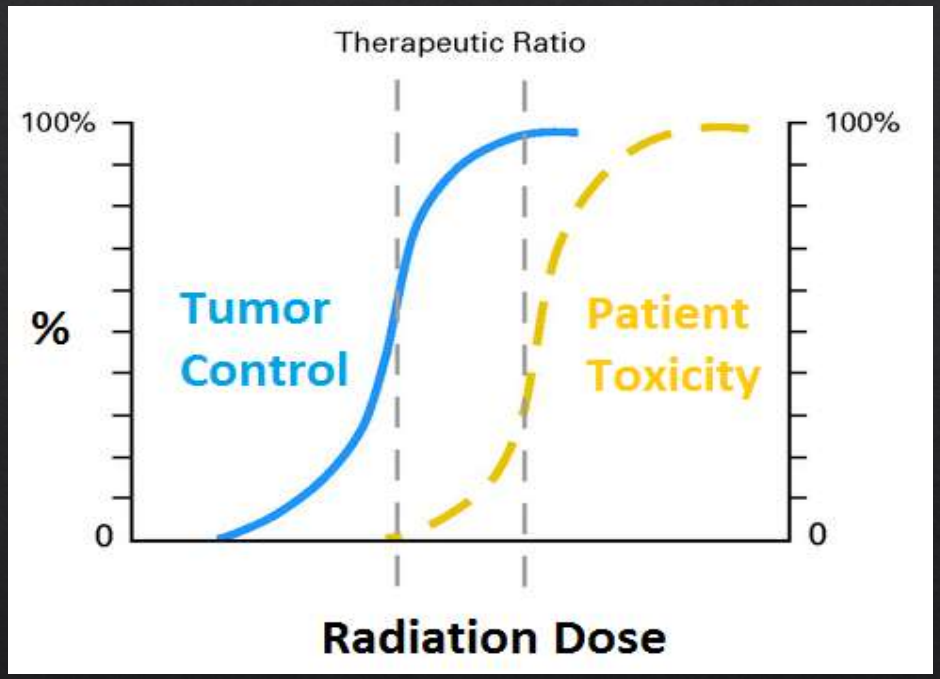
Outline

- Background – what is stereotactic body radiation therapy?
- Role of SBRT in early stage NSCLC
- Role of SBRT in oligometastatic NSCLC

Radiation Therapy (RT) Background

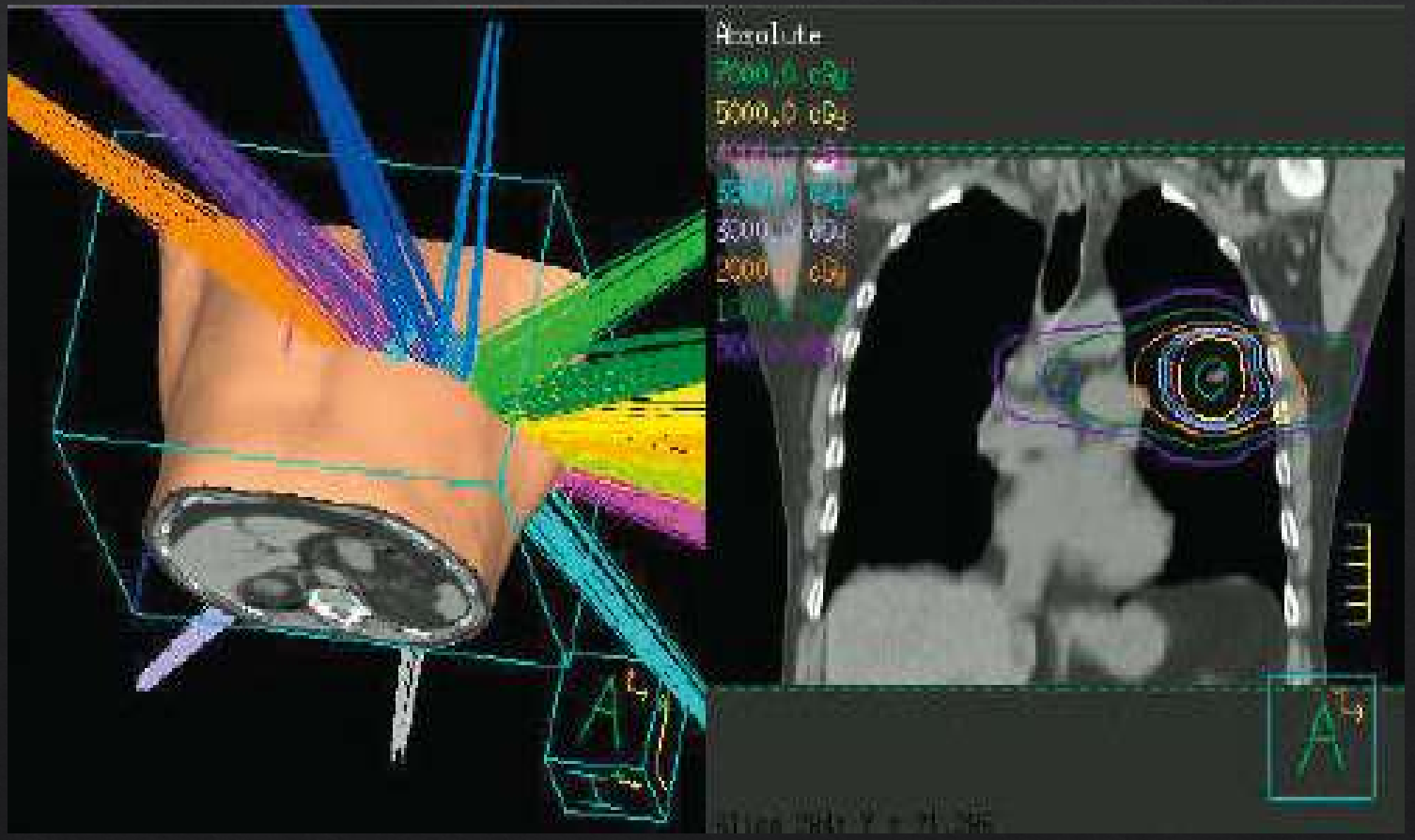
- The goal of radiation (like chemotherapy and oncologic surgery) is to offer:
  - Maximal Tumor Control
    - Accomplished by ↑dose of RT to the tumor
  - Minimal Treatment-Related Side effects
    - Accomplished by ↓dose and volume of RT to normal tissue



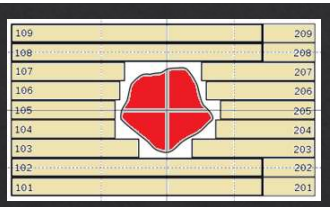
Additive Beams = ↑Tumor Dose, ↓Normal Tissue Dose

"Flashlights on the Floor"

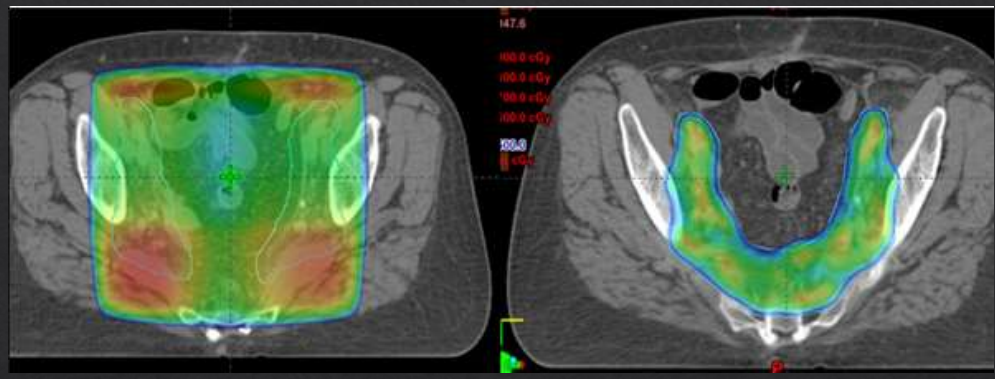
Analogy



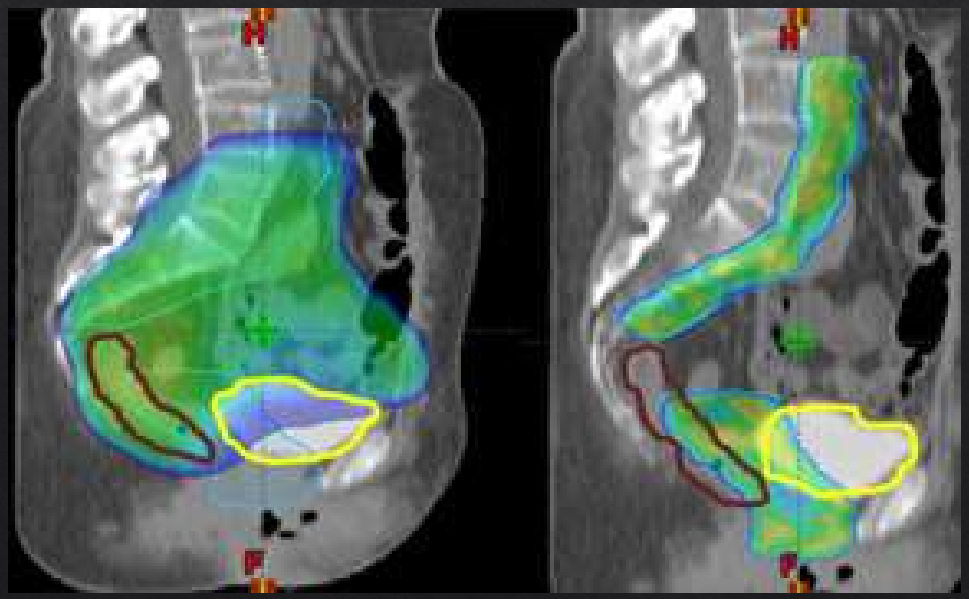
IMRT



- Intensity Modulated Radiation (IMRT)
  - "Inverse" planning
  - Dynamic multi-leaf collimators can modulate beam intensity during treatment
  - Can conform dose to incredibly complicated shapes
  - Allows "dose-painting" (aka integrated boosts) to high-risk areas
    - Used for <u>almost all</u> head and neck plans
  - IMRT requires more time-intensive planning for dosimetrist, physicist, and physician. Usually takes 1-2 weeks from simulation to treatment start.



3D Conformal **IMRT**

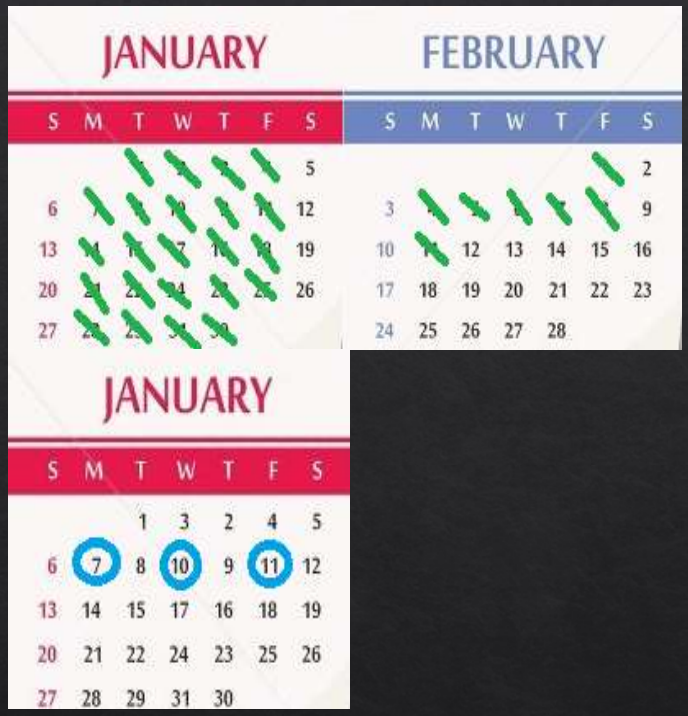


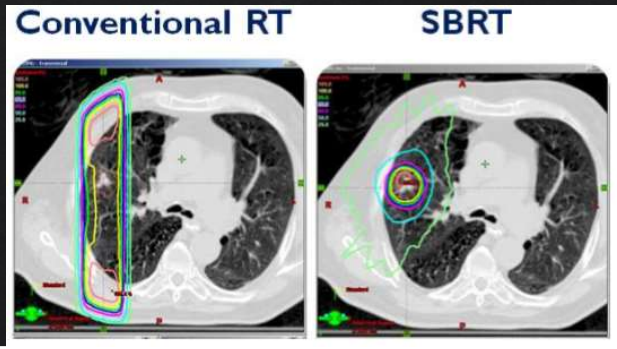
Comparing Conventional Radiation and SBRT

- **Conventional Radiation Therapy**
  - Small Dose Doses of radiation delivered 5 days per week (Monday – Friday)
  - Typically ~ 25-35 treatments over 5-7 weeks
  - Low doses ~ 2 Gy per treatment
  - Often delivered with **concurrent chemotherapy**

- **Stereotactic Body Radiation (SBRT)**
  - Typically 1-5 total high-dose treatments, may be completed in 1-2 weeks
  - Typical doses are much larger, ~ 8-20 Gy per treatment
  - Typically delivered <u>without</u> concurrent chemotherapy

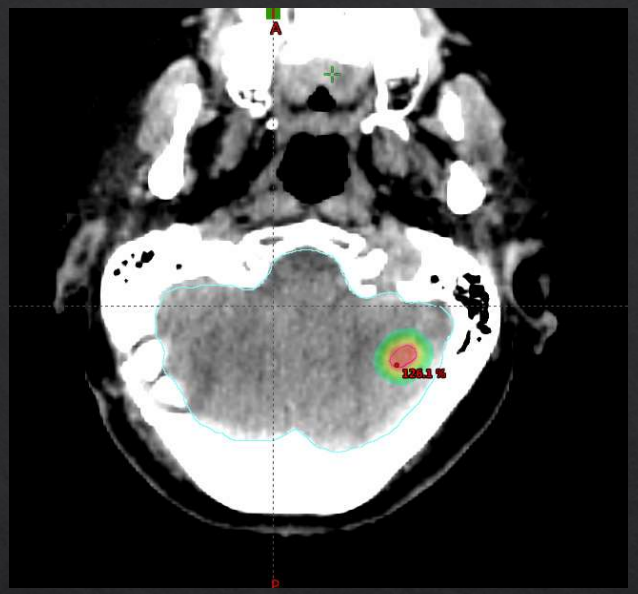
  - Nomenclature typically includes "**Stereotactic**" in the name
    - **Stereotactic Body Radiation Therapy (SBRT)**
    - **Stereotactic Ablative Radiation Therapy (SABR)**
    - **Stereotactic Radiosurgery (SRS)**

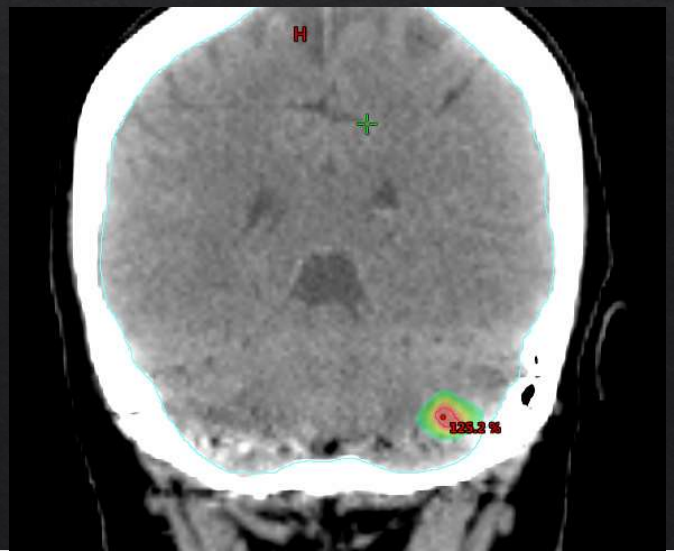




SBRT/SRS is "Ablative"

- Complete ablation of tumor is the goal AND
- Significant loss of normal tissue function in the target area should be assumed
- Conceptually similar to other ablative treatments (e.g. surgical resection, RFA)
- Great for well-localized targets, without lymph node involvement
- Thus, paradoxically applied to tumors on opposite ends of the oncologic spectrum:
  - Early stage lung cancers
  - Well-defined metastatic deposits
- Not good for:
  - Large, poorly-defined targets
  - Lymph node regions

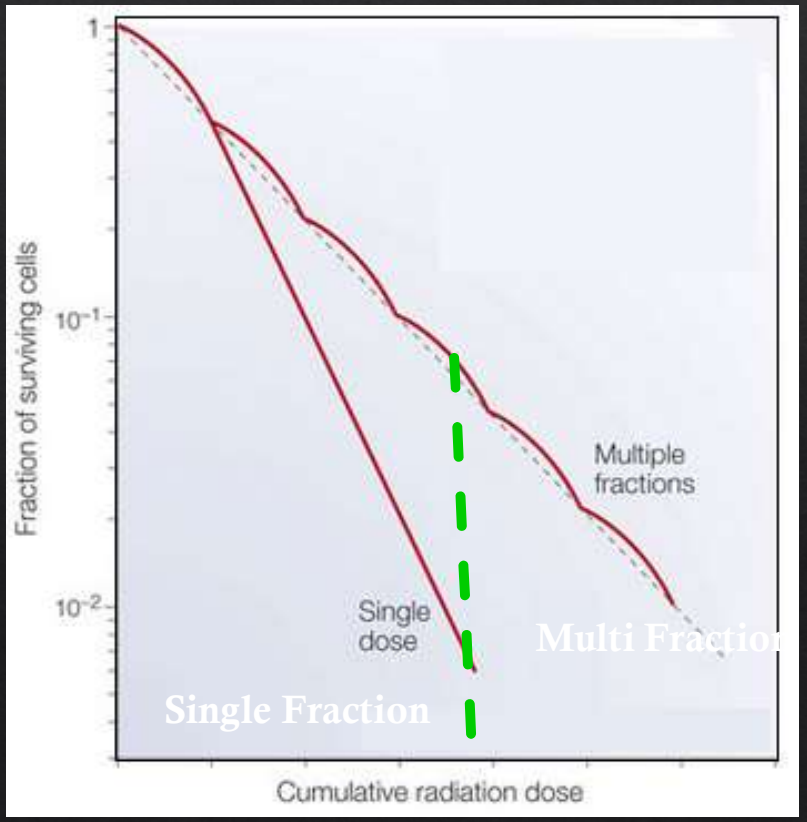




Why not use high doses (SBRT) for Everything?

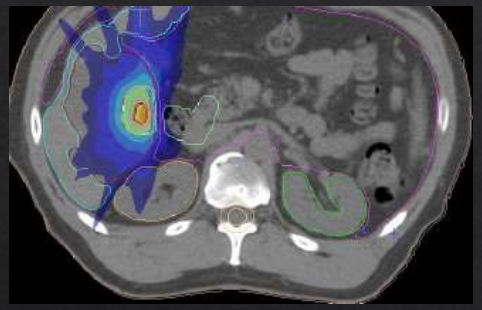
- ↑Dose-per-fraction causes ↑↑ In Tumor Cell Kill
- ↑Dose-per-fraction is ALSO the primary driver of ↑↑ late fibrosis and irreversible normal tissue toxicity (worry about this in the pediatric population)
- . . . So with SBRT, you can't treat very large fields and you need to be very confident about what you're targeting.

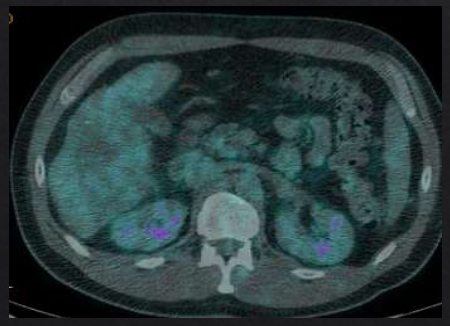
Normal Tissue Survival



Liver

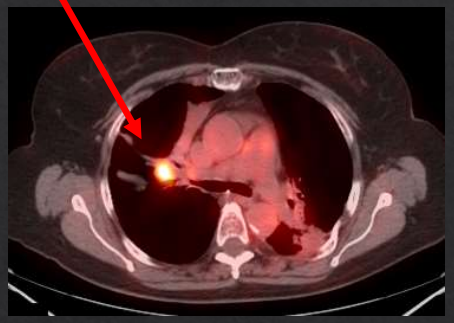
Pre-Treatment



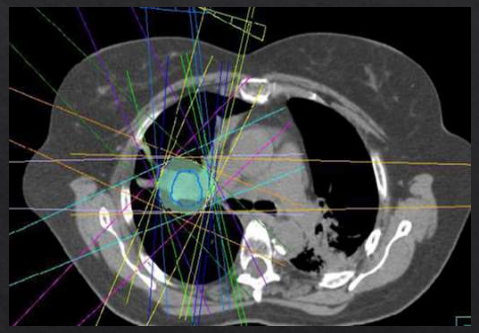


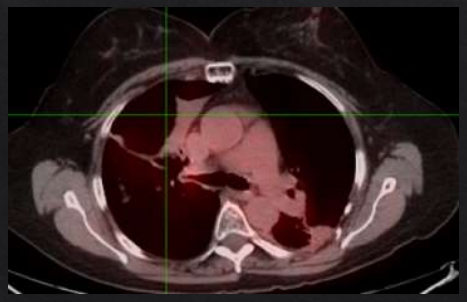
3 Month Post-SBRT

Lung/Hilar Lymph Node



Pre-Treatment

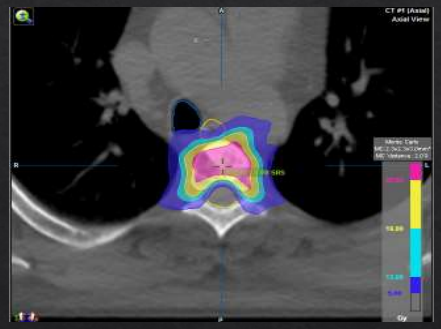




3 Months Post-SBRT

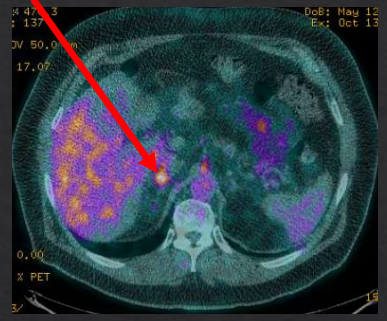
Spine

Pre-Treatment

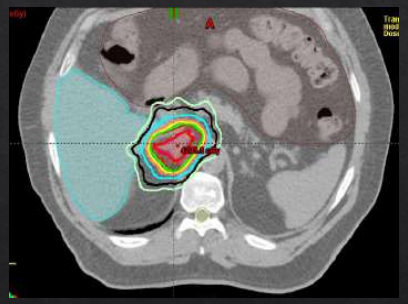


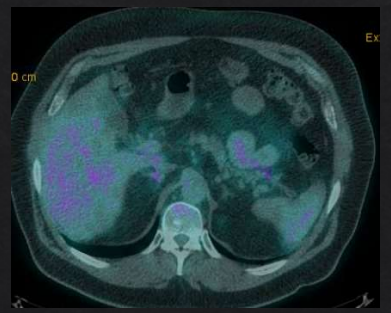
3 Months Post-SBRT

Adrenal



Pre-Treatment



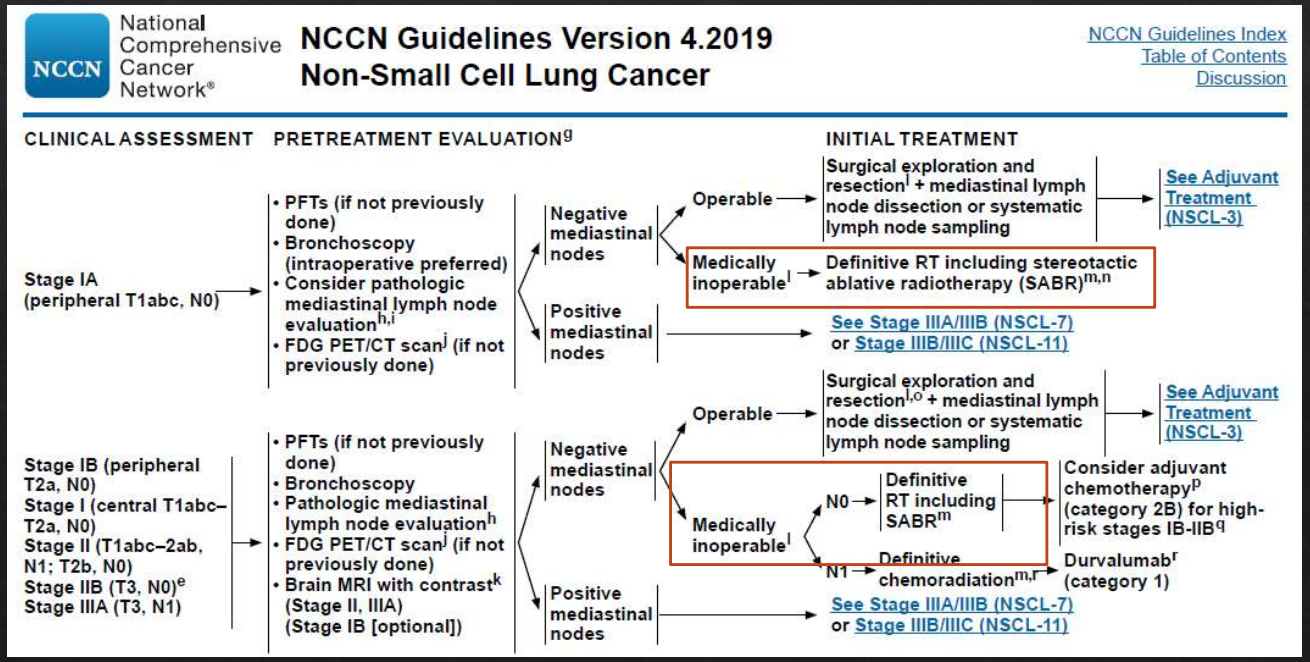


4 Months Post-SBRT

Switching Gears

SBRT for Older Patients with Early Stage NSCLC

- Good for older patients with poor pulmonary or cardiac reserves
  - FEV1 ≤ 50% or <1-1.2 L; DLCO ≤ 50%
- Patients who refuse surgery



Utilizing PET for Mediastinal Staging

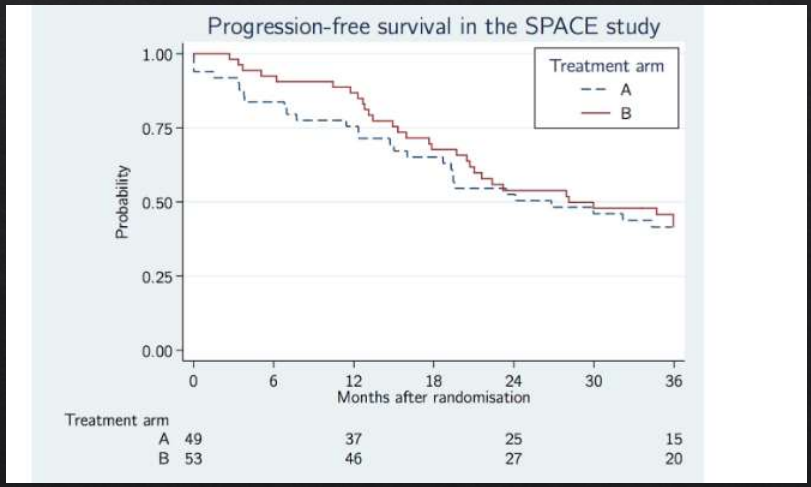
- Only for those who cannot tolerate EBUS/mediastinoscopy
- Overall accuracy ~80%
- Good option in frail elderly
- Centrally located more likely to have occult mediastinal involvement despite PET negativity

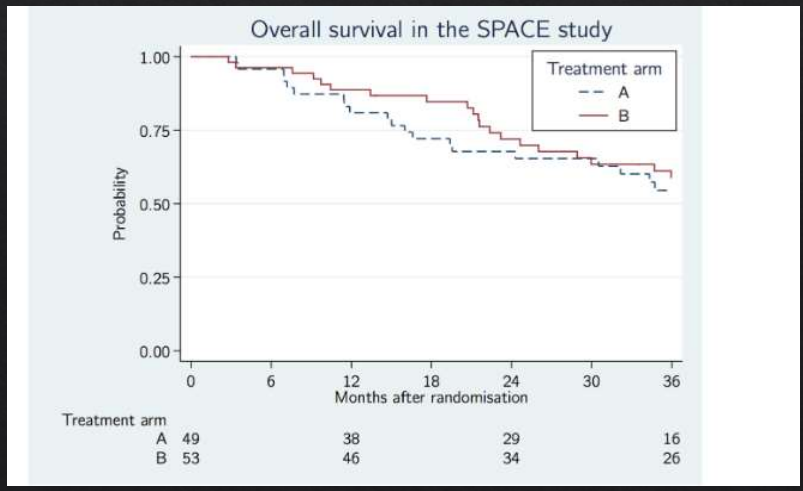
Table 3 Individual study results

Modality	Lead author	Year	*N*	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
FDG-PET/CT fusion	Magnani [40]	1999	28	78	95	90	88	89
	Antoch [67]	2003	26	89	94	94	89	93
	Cerfolio [41]	2004	129	64	94	99	49	96
	Shim [68]	2005	106	85	84			84
	Halpern [22]	2005	36	60	85	85	60	78
	Tourney [42]	2007	105	84	84	85		
	Lee [43]	2007	336	86	81	95	56	82

Conventional RT Versus SBRT: SPACE Trial

- SBRT (66 Gy in 3 fractions) vs 3DCRT (70 Gy in 35 fractions)
- Stage I peripheral
- 3-yr PFS 62% SBRT vs 58% 3DCRT
- Local control > SBRT (72% vs 59%)
- Toxicity better with SBRT (decreased pneumonitis and esophagitis)





Conventional RT Versus SBRT: TROG 09.02 CHISEL

- Phase 3 trial
- Inoperable T1-T2a
- SBRT (48-54 Gy in 3-4 fx) vs (66 Gy in 33 fx or 50 Gy in 20 fx)
- Local failure 14% (SBRT) vs 31% (conventional)

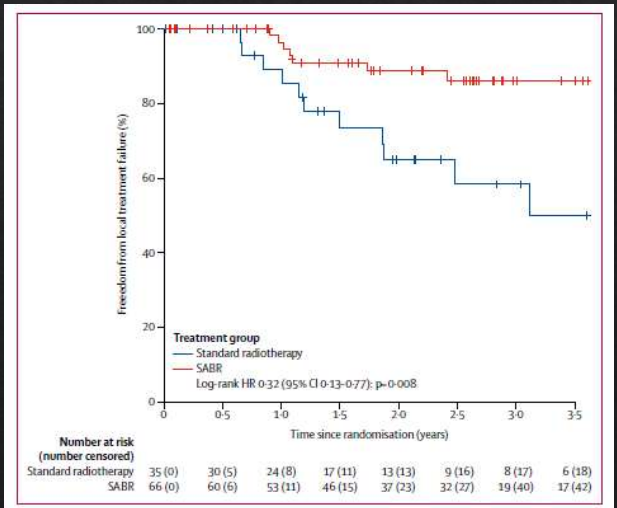


Figure 2: **Freedom from local treatment failure**
Tick marks represent censored patients (patients were censored for regional failure and distant metastasis, as well as for withdrawal, death, and loss to follow-up). SABR=stereotactic ablative body radiotherapy.

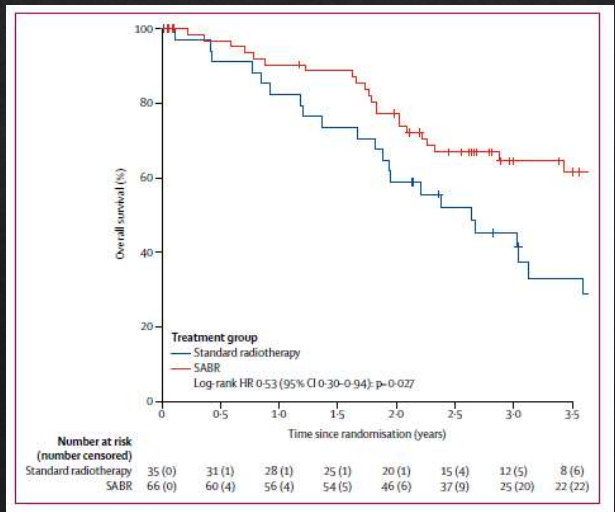


Figure 3: **Overall survival**
Tick marks represent censored patients (patient withdrawal and loss to follow-up were the only censoring events). SABR=stereotactic ablative body radiotherapy.

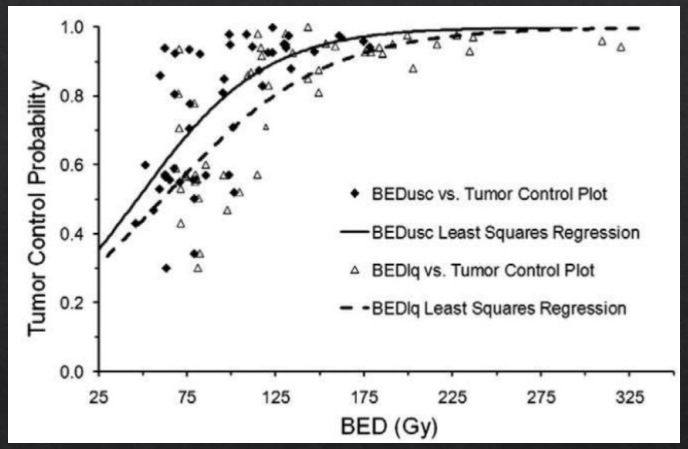
SBRT Dose and Local Control

- Dose escalation leads to control rates ~90%

Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control

Niraj Mehta MD, Christopher R. King MD, PhD, Nzhde Agazaryan PhD, Michael Steinberg MD, Amanda Hua BA, Percy Lee MD*

Department of Radiation Oncology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California



Hypofractionated Stereotactic Radiotherapy (HypoFXSRT) for Stage I Non-small Cell Lung Cancer: Updated Results of 257 Patients in a Japanese Multi-institutional Study

Hiroshi Onishi, MD, Hiroki Shirato, MD,† Yasushi Nagata, MD,† Masahiro Hiraoka, MD,‡ Masaharu Fujino, MD,† Kotaro Gomi, MD,§ Yuzuru Niibe, MD,|| Katsuyuki Karasawa, MD,|| Kazushige Hayakawa, MD,¶ Yoshihiro Takai, MD,# Tomoki Kimura, MD,** Atsuya Takeda, MD,†† Atsushi Ouchi, MD,‡‡ Masato Hareyama, MD,‡‡ Masaki Kokubo, MD,§§ Ryusuke Hara, MD,|||| Jun Itami, MD,|||| Kazunari Yamada, MD,¶¶ and Tsutomu Araki, MD**

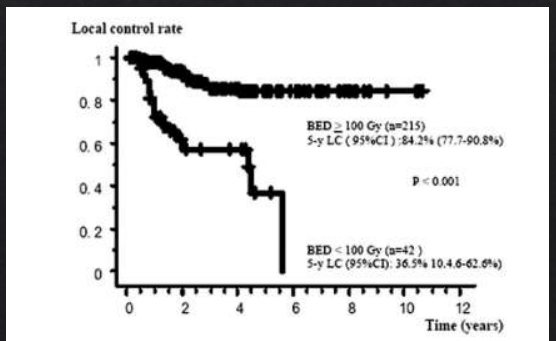


FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

Surgery vs SBRT

Table 1
Studies evaluating surgical outcomes in early-stage non-small cell lung cancer.

Study	Patients	Age (years)	Clinical stage	Pathologic stage	Surgery	Postoperative mortality	Major (G≥2) complications	OS
Morandi et al [10]	85	≥70	NR	57% I 14% II	75% (Bi-)Lobectomy 13% Pneumonectomy	1.1%	18.8%	3-yr 47%
Birim et al [11]	126	≥70	NR	76% I	76% (Bi-)Lobectomy 18% Pneumonectomy	3.2%	13% CCI 3≥: 35%	5-yr 37%
Brock et al [12]	68	≥80	I	60.3% I 20.6% II	73% (Bi-)Lobectomy 23.5% Limited Resection	8.8%	44%	3-yr 51%
Dominguez-Ventura et al [13]	294	≥80	NR	67% I 14% II	66.7% (Bi-)Lobectomy 7.1% Pneumonectomy	6.3%	48%	5-yr 35%
Beshay et al [14]	53	≥75	NR	3% I 86% II	60% Lobectomy 30% Pneumonectomy	1.9%	60%	3-yr 65%
Brokx et al [15]	124	≥80	93% I	64% I 22% II	73% (Bi-)Lobectomy 12% Pneumonectomy	4.0%	NR	2-yr 55% 5-yr 24%
Cattaneo et al [16]	164	≥70	I	85% I	Lobectomy	3.6%	13.4%	NR
Mun et al [17]	55	≥80	I	80% I	69% (Bi-)Lobectomy 31% Limited Resection	3.6%	25.6%	3-yr 76.4%
Voltolini et al [18]	96	≥80	NR	63.5% I 17.7% II	75% (Bi-)Lobectomy 9.4% Pneumonectomy	9.4%	17.70%	3-yr 51%
Berry et al [19]	338	≥70	NR	72% I	Lobectomy	3.8%	47%	2-yr 69%
Okami et al [20]	367	≥80	I	82% I	67% Lobectomy 33% Limited Resection	1.4%	8.4%	3-yr 70.6%
Port et al [21]	121	≥80	NR	65% I 25% II	Lobectomy	1.7%	28.9%	5-yr 56.6%
Zhang et al [22]	52	≥80	NR	75% I	65.4% Lobectomy 38.5% Limited Resection	3.8%	44.2%	3-yr 59.8%
Endoh et al [23]	295	≥75	NR	68% I 13.9% II	80% Lobectomy 3.4% Pneumonectomy	2.4%	18.6%	5-yr 59%
Pei et al [24]	476	≥70	NR	44.1% I 26.7% II	82.3% (Bi-)Lobectomy 7.4% Pneumonectomy	2.3%	13.4% CCI 3≥: 30x more likely	NR
Miura et al [25]	49	≥80	NR	65.3% I 18.4% II	61.2% (Bi-)Lobectomy 36.7% Limited Resection	4.1%	40.8%	3-yr 79.6%
Hino et al [26]	94	≥80	91% I	70.5% I 14% II	73% Lobectomy 27% Limited Resection	1.1%	27.7%	5-yr 57.5%

G = grade; OS = overall survival; NR = not reported; CCI = Charlson comorbidity index.

Surgery vs SBRT

- Overall matched pair studies show similar outcomes; a few showing surgery is better

Table 2
Stereotactic body radiation therapy (SBRT) studies in early-stage nonsmall cell lung cancer.

Study	Patients	Age (years)	Median RT dose (Gy/fractions)	Median f/u (months)	LC	RF	DM	PFS	OS	Toxicities
Haasbeek et al [32]	193	≥75	60/5 (peripheral) 60/8 (central)	12.6	3-yr 89.3%	3-yr 8.4%	3-yr 20.7%	NR	3-yr 45.1%	Pneumonitis G≥3: 2.1% Chest wall G≥1: 4.7%
Van der Voort van Zyp et al [8]	38	≥80	60/3 (peripheral) 60/8 central	23	2-yr 100%	NR	NR	NR	2-yr 44%	Pneumonitis G≥3: 2.6% Chest wall G≥2: 2.6%
Palma et al [33]	60	≥75	60 in 3, 5, or 8Fx	43	NR	NR	NR	NR	3-yr 42%	NR
Chan et al [34]	16	≥70	54-60/3 (peripheral) 50/5 (central)	22	2-yr 91%	NR	NR	2-yr 71%	2-yr 87%	Pneumonitis/Chest wall G≥2: 0%
Takeda et al [7]	109	≥80	50/5 (peripheral) 40/5 (central)	24.2	3-yr 83.6%	3-yr 9.9%	3-yr 23.2	3-yr 65.9%	3-yr 53.7%	Pneumonitis G≥3: 4.6% Chest wall G2: 8.3%
Samuels et al [35]	46	≥75	48/4 and 54-60/3	12.4	98%	9%	6%	84.8%	80.4%	Pneumonitis G≥3: 0% (5/11 missing grade) Chest wall G≥1: 20%
Karam et al [36]	31	≥65 (Median 73)	48/4 (peripheral) 50/10 (central)	13	1-yr 80%	1-yr 20%	NR	1-yr 68%	1-yr 70%	Global G≥2: 0%
Sandhu et al [9]	24	≥80	48/4 (peripheral)	27.6	2-yr 100%	2-yr 9%	2-yr 17%	2-yr 77%	2-yr 74%	Pneumonitis G≥3: 0% Chest wall G≥3: 0%
Hayashi et al [37]	20	≥85	48/4 (peripheral) 60/10 (central)	29	3-year 91.8%	NR	NR	3-yr 44.7%	3-yr 40.7%	Pneumonitis G≥3: 10% Rib fracture: 25%
Nakagawa et al [38]	35	≥75	50/4-5	45	40% LRC		NR	NR	3-yr 73.7%	Pneumonitis G5: 2.8%
Mancini et al [39]	126	≥75	54/3 (peripheral) NR (central)	35.5	3-yr 84.2%	NR	3-yr 11%	NR	3-yr 47.5%	Pneumonitis G≥3: 9% Chest wall G≥3: 0%
Wang et al [40]	74	≥70 (Mean 82)	60/5	61.9	68.8% 3-yr LRC		NR	3-yr 43.7%	3-yr 54.9%	NR
Brooks et al [41]	330	≥75	50/4 (peripheral) 70/10 (central)	55.2	93%	10.3%	16.7%	NR	3-yr 57.5%	Pneumonitis G≥3: 0.6% Chest wall G≥2: 5.4%
Kreinbrink et al [42]	31	≥80	54/3 (peripheral) 60/8 (central)	15.8	100%	3-yr LRC	2-yr 19.9%	NR	2-yr 59.2%	Global G≥2: 0%
Cassidy et al [43]	58	≥80	50/5	19.9	90%	21%	10.4%	NR	3-yr 56.4%	Pneumonitis G≥3: 3.5% Chest wall G≥2: 5.2%
Videtic et al [44]	19	≥90	50/5	17.3	94.4%	15.9%	10.6%	2-yr 48.6%	2-yr 47.8%	Pneumonitis G≥ 1: 0% Chest wall G≥1: 5.2%
Maebayashi et al [45]	43	≥65	48/4	46	93%	4.70%	16.30%		2-yr 71.5%	Pneumonitis G≥2: 13.9% Rib fracture: 20.9%

LC = local control; RF = regional failure; DM = distant metastasis; PFS = progression free survival; OS = overall survival; NR = not reported; G = grade; LRC = locoregional control; f/u = follow up.

Surgery vs SBRT: The Phase III Study

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†*

- STARS/ROSEL trial
  - N=58
  - STARS (28 sites in USA, China, France)
  - ROSEL (10 centers in Netherlands)
  - 3-yr OS: 95% (SABR) vs 79% (surgery); p-0.037
  - 3-yr RFS: 86% (SABR) vs 80% (surgery); p=0.5379

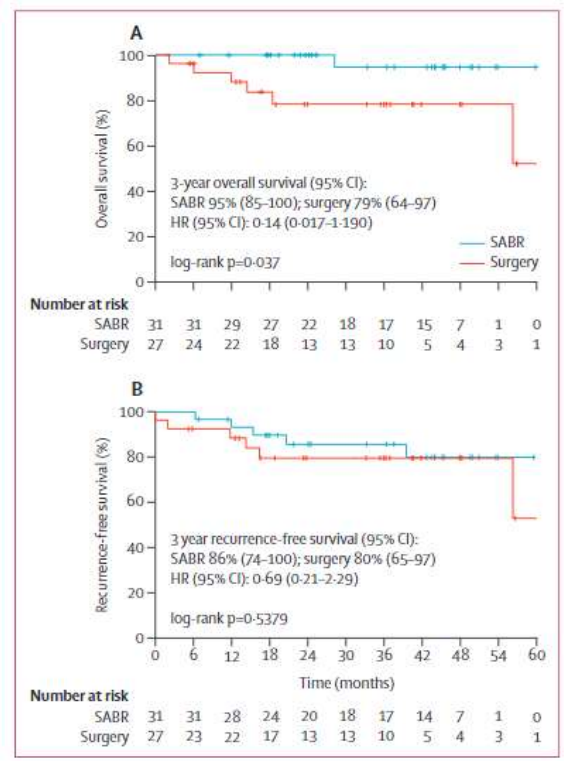
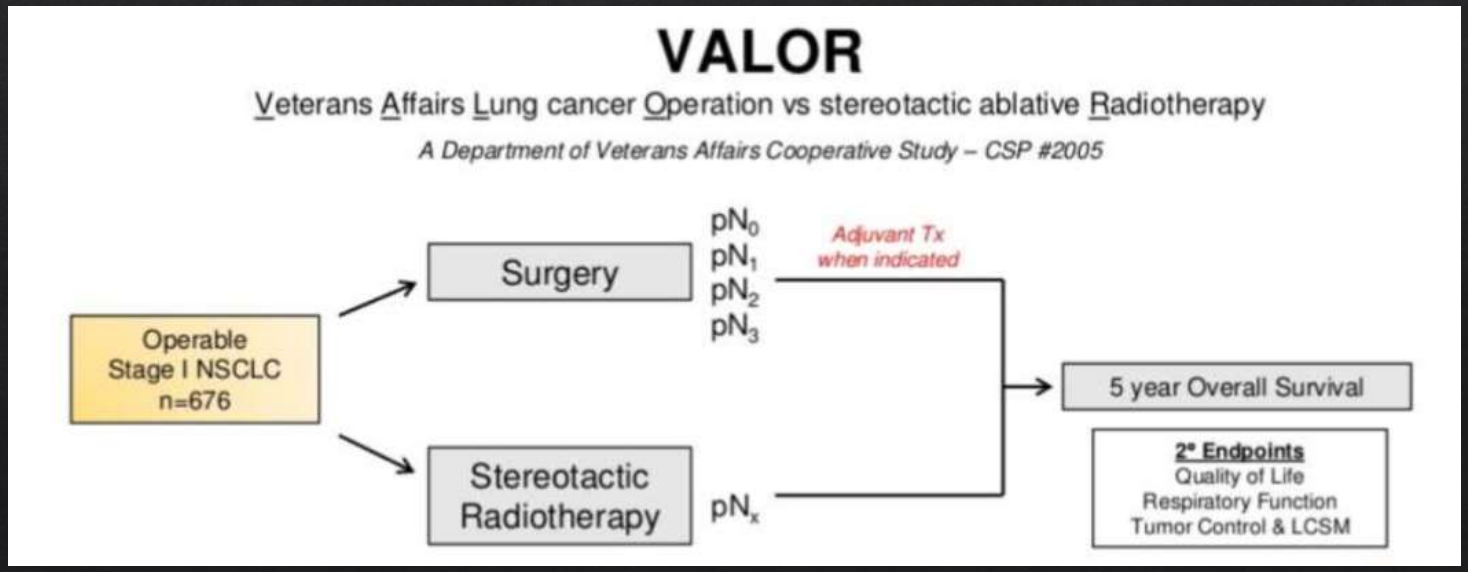


Figure 2: **Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Ongoing Studies

- VALOR: Veterans Affairs Lung Cancer Operation vs Stereotactic ablative Radiotherapy
  - Operable stage I NSCLC randomized to surgery or SABR
  - Primary outcome 5-year OS



Future Directions

- Combining SBRT with immunotherapy in early-stage NSCLC
  - SBRT has a high rate of local control but primary failure is regional and/or distant
  - 5-year regional recurrences ~30-40% (RTOG 0236)
  - 5-year distant recurrences ~31%
- Applying SBRT to more advanced lung cancer (stage II and above) in combination with molecular agents and immunotherapies

SBRT in Oligometastatic NSCLC

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**

- In subsequent follow up presented in 2018, there was a benefit in OS

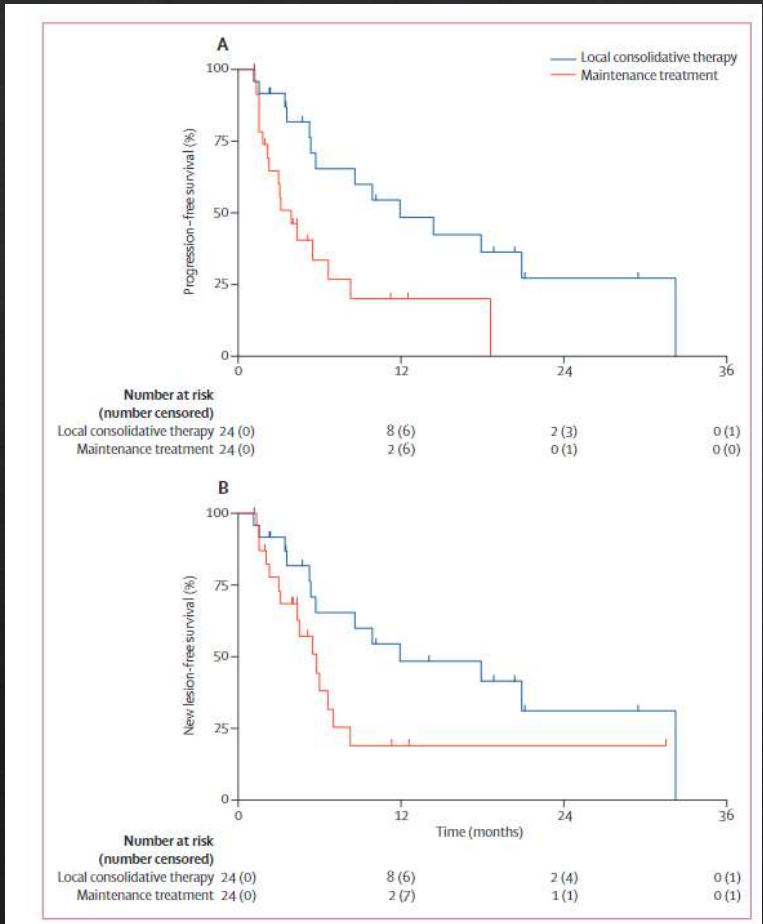


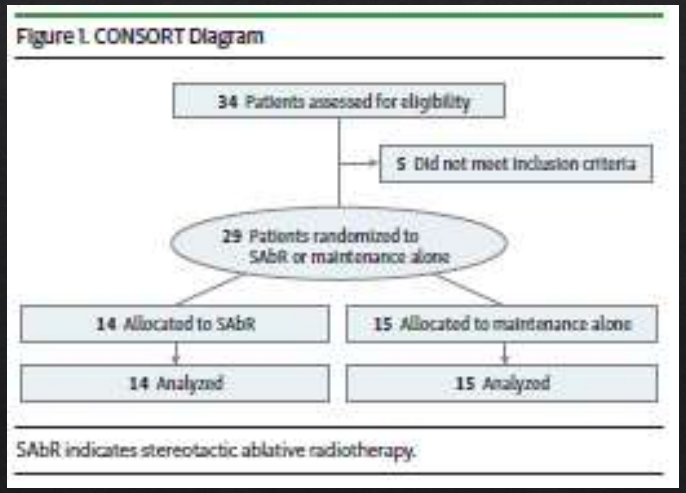
Figure 2: Progression-free survival (A) and time to appearance of disease at a new site (B)

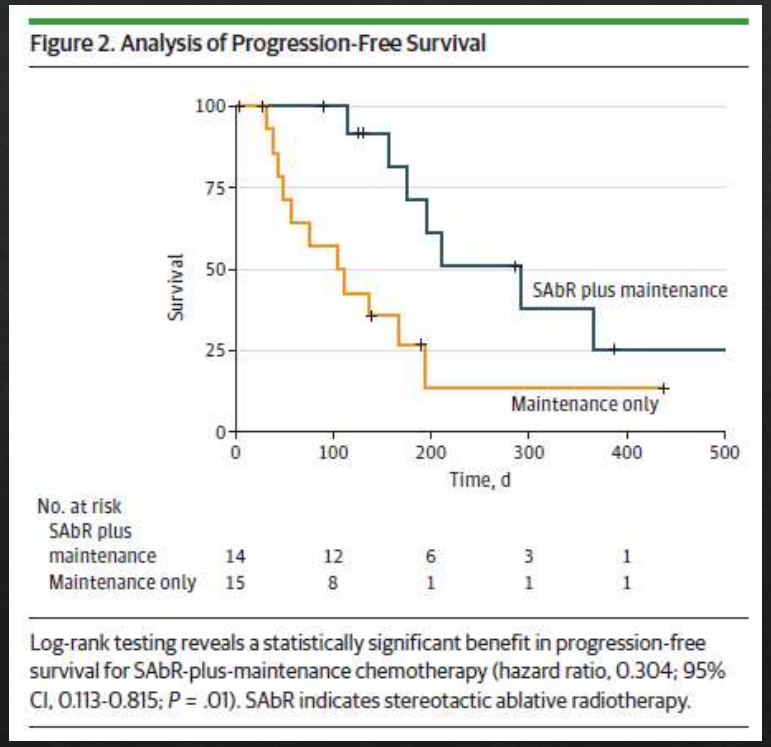
SBRT in Oligometastatic NSCLC

JAMA Oncology | Original Investigation

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer
A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD





SABR-COMET

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

- 99 patients included
- 5 or less metastatic sites
- 18% were lung

Median OS was 28 mo (control) vs 41 mo (SABR)

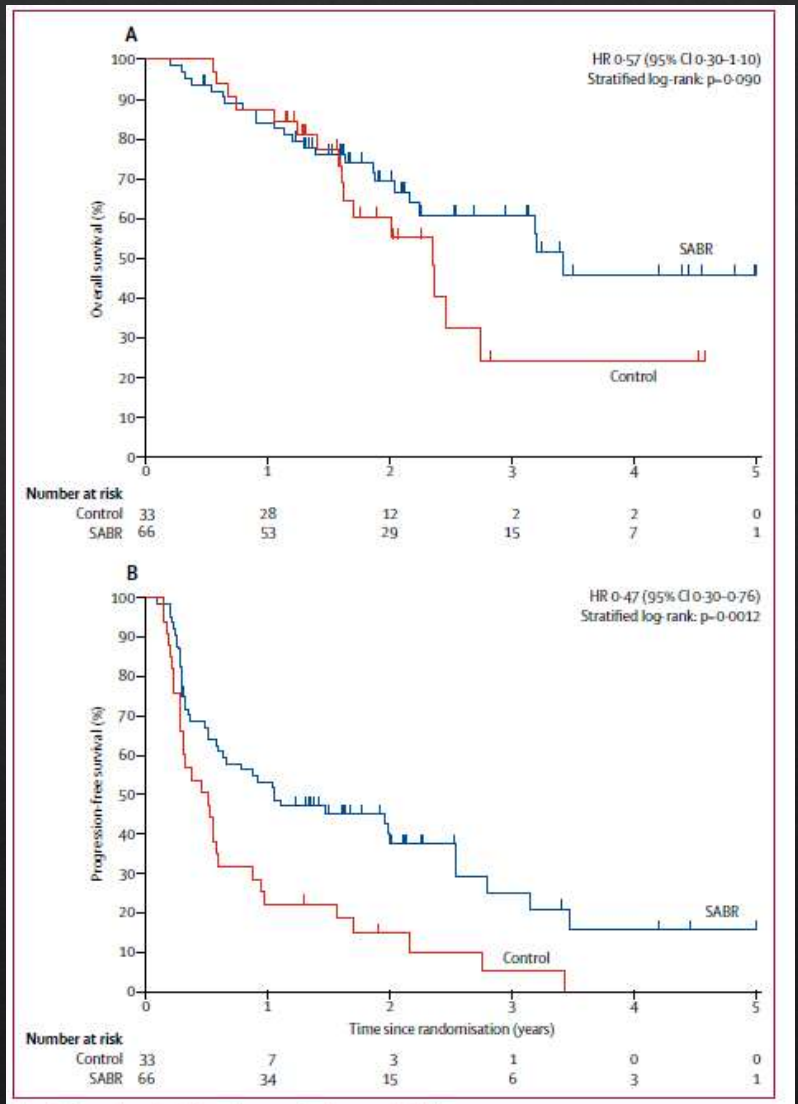


Figure 2: **Overall survival (A) and progression-free survival (B)**
SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Future Directions in Oligometastatic Lung

- Combination with other modalities (surgery, ablation)
- Evaluating with immunotherapy, targeted therapies, etc
- Changing the definition of oligometastatic?
- Timing of SBRT?
- Using radiation to prime the immune system
- SBRT/SRS and immunotherapy/targeted therapy combinations for brain metastases

Thank You

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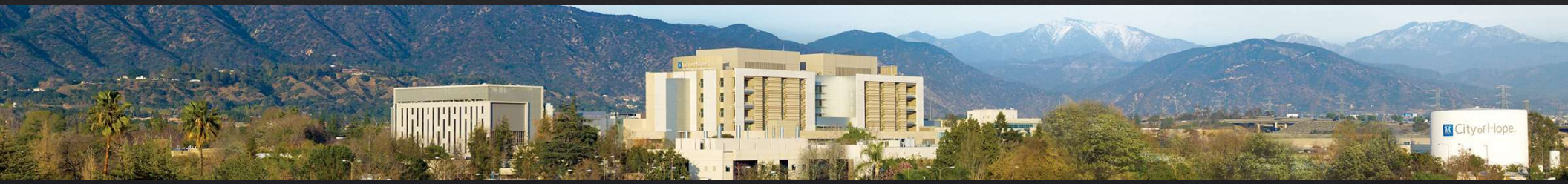

Question

In the only randomized trial comparing surgery to SBRT in operable, early stage NSCLC, what were the outcomes?

A) SBRT and surgery had equivalent local control outcomes

B) Surgery had improved survival outcomes

C) Overall survival was the same between surgery and SBRT

D) Local control rates were better with surgery