SBRT for early lung cancer

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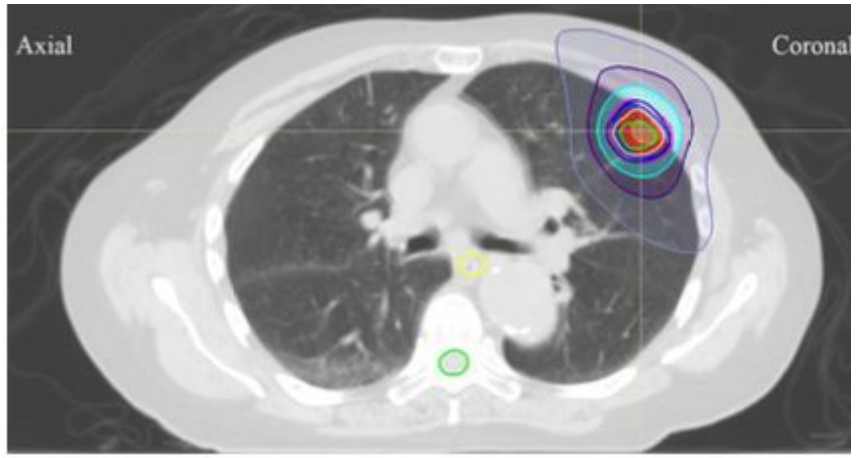
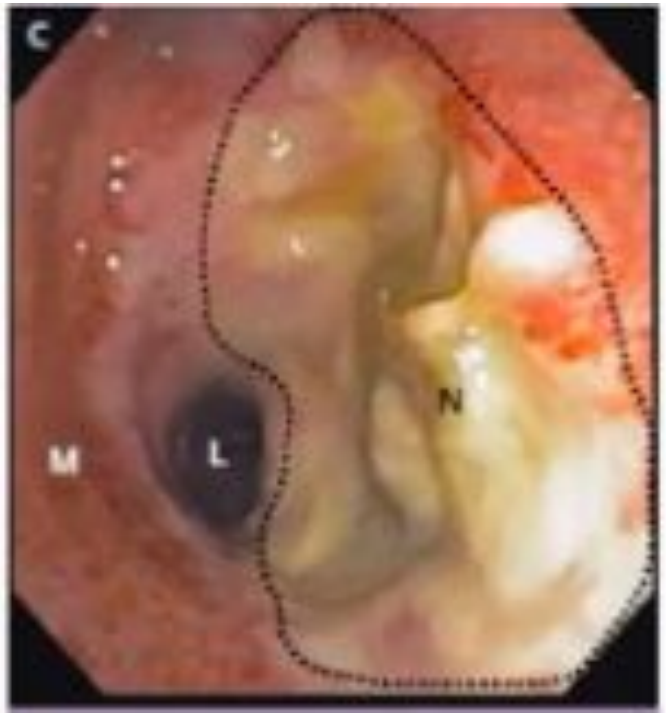




Introduction

- Lung cancer is amongst the MC malignancies and leading cause of cancer related deaths worldwide
- Appox. 15% pts with NSCLC are diagnosed in early stage with T1-2N0
- Traditional T/t for ES NSCLC is lobectomy with systematic hilar and mediastinal LND – yields 5 y survival of 60-90%
- Significant number of patients are however medically inoperable due to their co morbidities or refuse for surgery

SURGERY	SBRT
Tissue available for pathologic and molecular analysis	Non Invasive
Mediastinal LNs adequately sampled	Mediastinal LNs not addressed
15-20% pts may not be fit for anaesthesia/surgery	Majority pts would be suitable except those with ILD or poor PS
Post op Complications- pneumonia, respiratory failure	Complications- Pneumonitis, cardiac arrythmia, esophagitis, rib fracture- majority are <15%
Post op mortality - <2% in expert hands in a medically fit patient	Mortality due to complication <5%- almost nil in peripheral tms

- ES NSCLC can be divided into 3 groups
- Low risk surgical patients (Anticipated surgical morbidity <1.5-2%)- Lobectomy with Mediastinal + hilar LND
- High risk surgical pts- T/t options are sub lobar resection/SBRT- needs discussion in MDT and understand patient preference
- Medically inoperable- SBRT

SBRT Lung is gaining acceptance

- Medically inoperable pts due to excellent LCR
- Alternative to surgery in operable pts due to relative clinical equipoise from randomized data
- Safety of delivery and low toxicities
- Increasing proportion of pts diagnosed with early cancer due to increase in medical imaging and adoption of CT based screening for high risk population

SBRT = SABR

- UK National Radiotherapy Implementation Group –precise irradiation of an image defined extracranial lesion, using a high total radiation dose delivered in a small no. of fractions

- ASTRO – EBRT method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small no. of fractions

Choosing the right patient

MDT Discussion

- T1 -2,N0 NSCLC, medically inoperable
- High surgical risk e.g – age >75 yrs, poor lung function
- Refuse surgery

Contraindication for SBRT

- Large tm >5 cm
- Direct invasion of central airway- carina/main bronchus
- Interstitial Lung Ds (COPD is not a contraindication for SBRT)
- PS 3 or more
- Life expectancy <1 y

Pre SBRT work up

- Pre SBRT work up should include- PFT\Bronchoscopy
- Mediastinal LN evaluation using EBUS
- PET CT
- +/- Brain MRI
- Pre SBRT biopsy is strongly recommended but not a pre requisuite for patients unwilling to undergo invasive biopsy or patients with an excessive high peri procedural risk

UNBIOPSIED NODULES AND EMPIRICAL SBRT

- Many pts treated with SBRT have poor pulmonary reserve and significant co morbidities and are at significant risk of developing complications from biopsy
- SBRT without tissue diagnosis carries risk of over treatment especially in tropical country like ours with high incidence of TB
- SBRT for lung tumour >3 cm – obtain PET CT—if lesion is FDG avid- can proceed for SBRT without tissue sampling
- Pulmonary nodule ≤3 cm-can use pre test probability prediction/Lung-RAD

- Patients who fall into lung RAD category 4A or 4Bcan undergo PET CT

Table 4 Lung-RAD® suspicious categories

Category	Finding
4A	Solid nodule(s): ≥8 to <15 mm at baseline or growing <8 mm or new 6 to <8 mm
	Part solid nodule(s): ≥6 mm with solid component ≥6 mm to <8 mm or with a new or growing <4 mm solid component
	Endobronchial nodule
4B	Solid nodule(s): ≥15 mm or new or growing, and ≥8 mm
	Part solid nodule(s) with: a solid component ≥8 mm or a new or growing ≥4 mm solid component
4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy

UNBIOPSIED NODULES AND EMPIRICAL SBRT

- **Size**
  - <4 mm - < 1%
  - > 8mm - 10%–20%

- **Margins and contour**
  - Benign - well-defined margins, smooth contour
  - Malignant - spiculated margins, lobular or irregular contour

- **Cavitary nodules**
  - benign - smooth, thin walls (wall thickness < 5 mm – 92%)
  - Malignant - thick, irregular walls (wall thickness > 15 mm- 95%)

- **Air bronchogram sign** - more frequently in malignant (29%) than in benign (6%)

- **PET CT Scan- SUV MAX >2.5**

October Special Issue 2014 radiographics.rsna.org

HISTORY IS IMPORTANT

Factors - increased risk for developing lung cancer

- The patient's age
- The presence of symptoms
- A history of smoking
- A history of exposure to asbestos, uranium, or radon
- History of malignancy

Lung tumour classification for SBRT

- SBRT for peripheral lung tumours - safe
- Surgical resection in central lung tms requires a larger resection and has more complications
- Likewise central lung Tm SBRT also remains more challenging

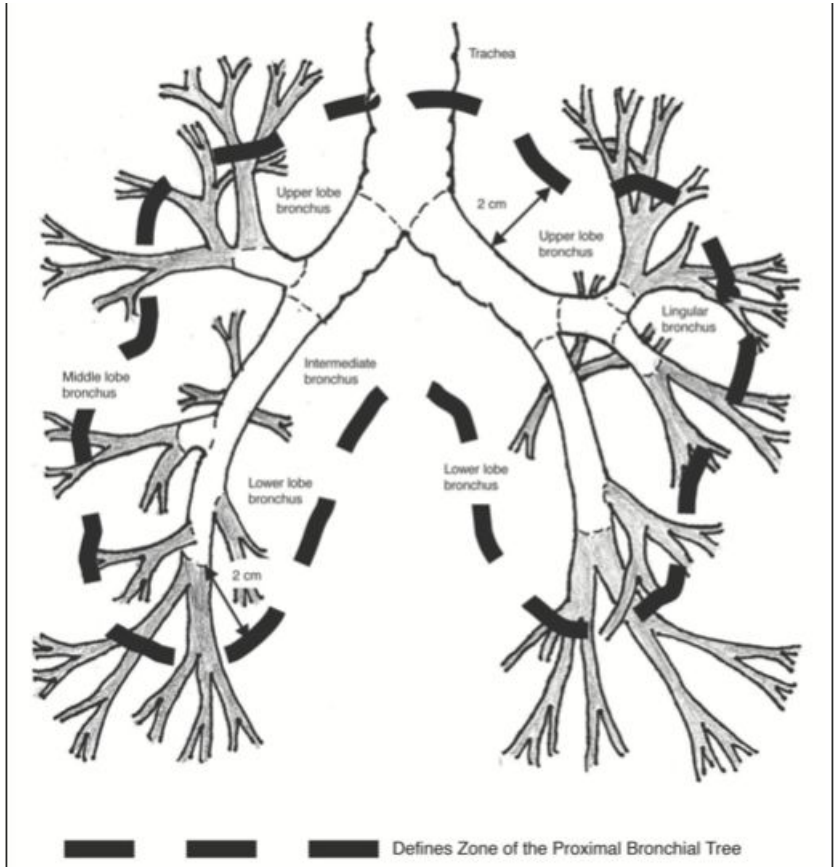
VOLUME 24 · NUMBER 30 · OCTOBER 20 2006
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

PhII study- 60-66Gy/3fr
11 times higher toxicity in CLT then peripheral tms
Location was strong predictor of gr 3-5 AE (p=0.04)

Concept of “No fly zone” within 2 cm of PBT



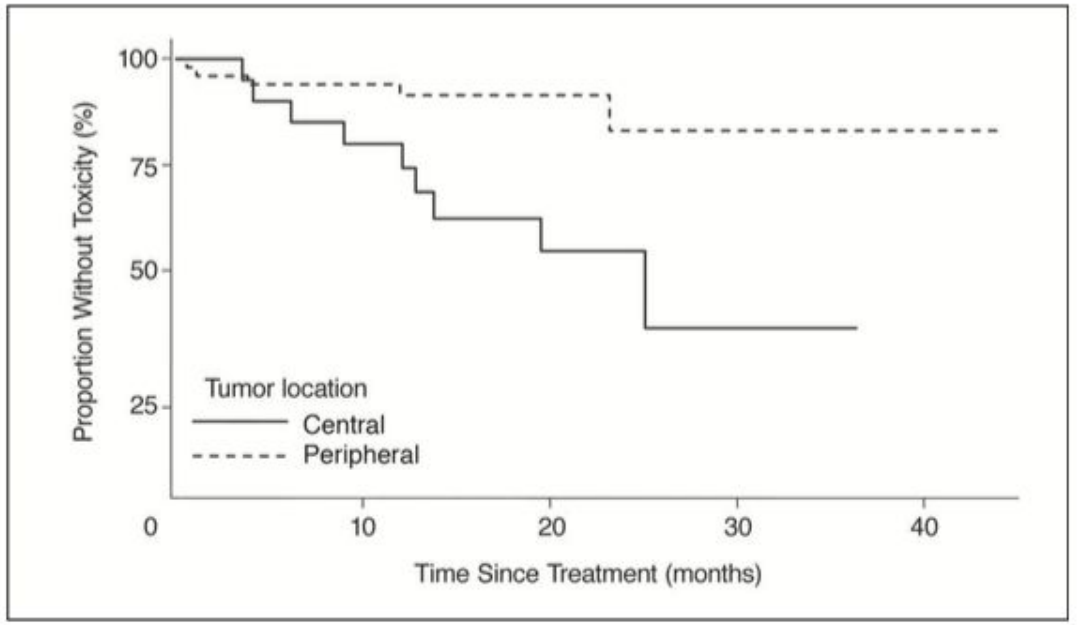


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

Definition of Central Lung Tumour

- ASTRO defn- within “2 cm in all directions around PBT”

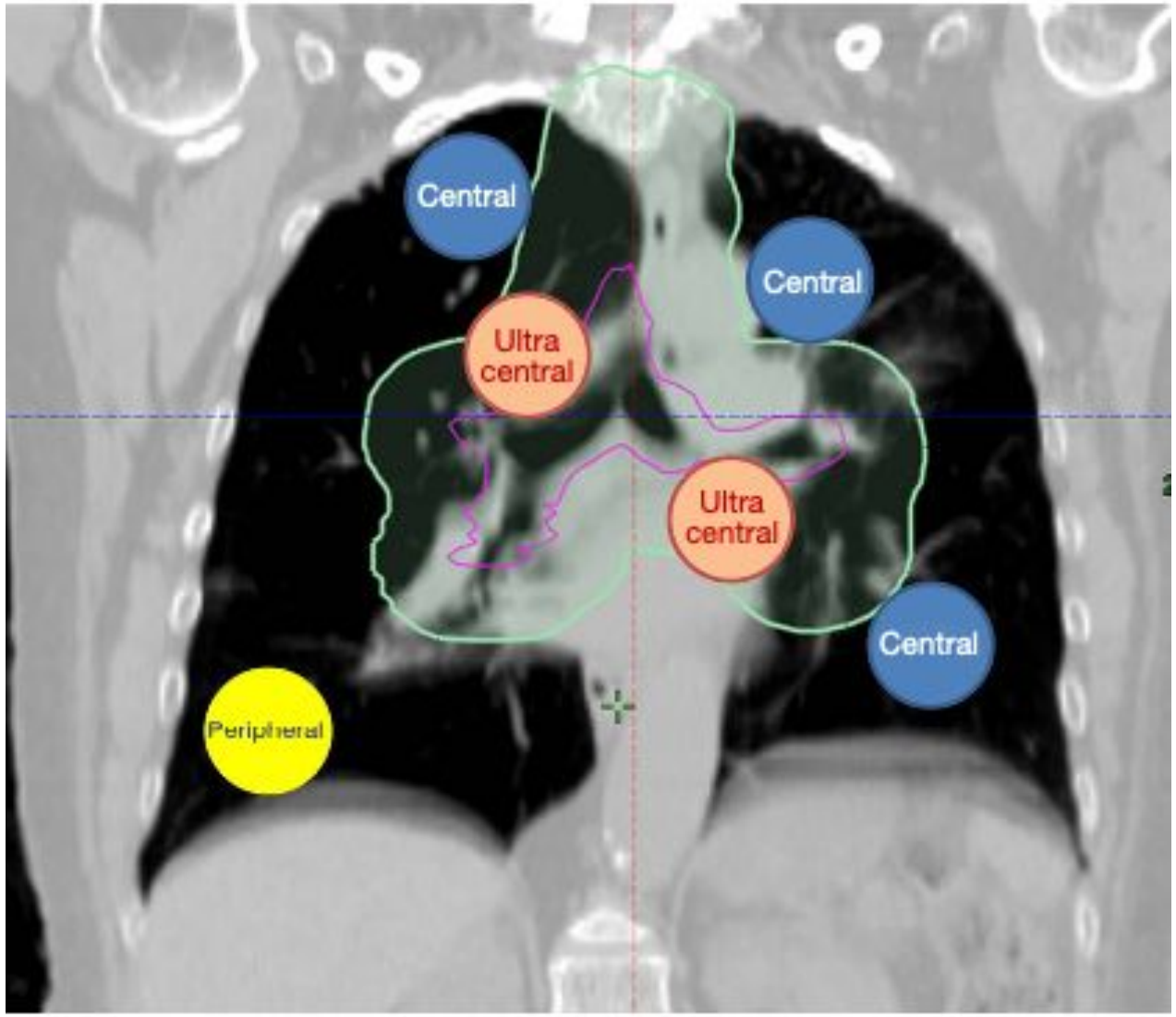
- IASCLC – Tumour within 2cm to any mediastinal structure including bronchial tree, esophagus, heart, major vessels, spinal cord, b plexus, phrenic and recurrent Laryngeal N

- RTOG 0813- Tm within 2 cm of PBT OR touching mediastinal/pericardial pleura
- Nordic Hilus- Tm within 1 cm of PBT

UCT

- First definition of UCT was proposed by Chaudhari AA- GTV abutting central airways including trachea and PBT
- **Various other definitions are-**
- *PTV overlapping trachea /PBT*
- *PTV overlapping or abutting PBT/Esophagus*
- *PTV in contact with PBT/Trachea/Esophagus/Pulm A or V*

Ref Lung Cancer 2015; 89(1):50-6



Central Lung tumours – are no longer considered no fly zones rather one needs adaptation and caution in using SBRT in this zone

Roesch *et al. Radiation Oncology* (2016) 11:157
DOI 10.1186/s13014-016-0732-5

Radiation Oncology

RESEARCH Open Access

SBRT for centrally localized NSCLC – What is too central?

J. Roesch[1*], C. Panje[1], F. Sterzing[2], F. Mantel[3], U. Nestle[4], N. Andratschke[1] and M. Guckenberger[1]

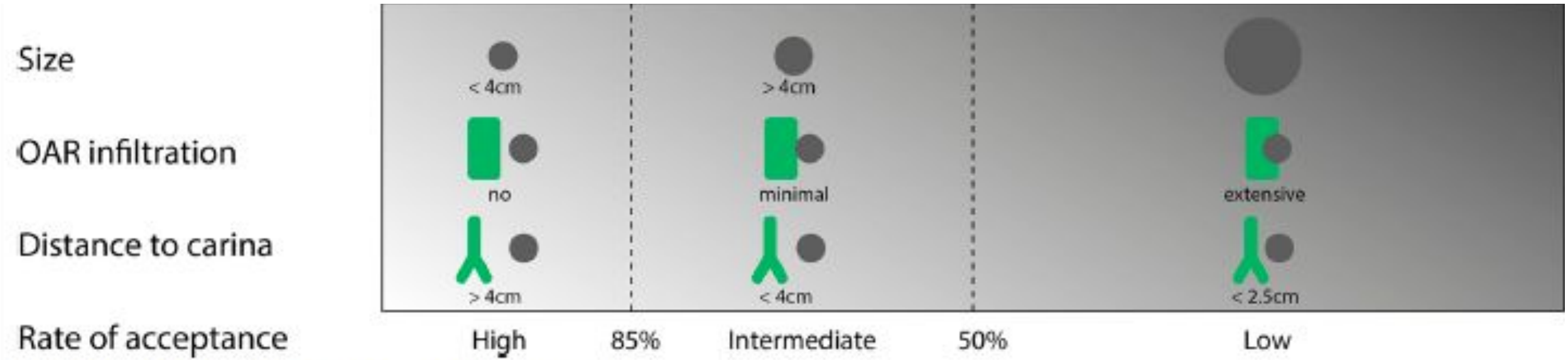


Fig. 1 Criteria influencing the decision for or against SBRT

Risk Adapted approach

		BED 10 (Gy)	BED 3 (Gy)
Peripheral T1 Tumour	18Gy x 3 fr (54 Gy) 15Gy x 3 fractions (45Gy) 12Gy x 4 fr (48Gy) 12Gy x 5 Fr (60Gy)	151 112.5 105.5 132	378 270 240 300
Peripheral T2 or tumour in broad area of contact with chest wall	11Gy x 5 fr (55Gy)	115.5	257
Central	10Gy x 5 fr (50Gy) 9Gy x 5 fr (45Gy) 7.5Gy x 8 fr (60Gy) 12.5Gy x4 fr (50Gy)	100 85.5 105 112.5	217 180 210 258
Ultra central	6Gy x 8 fr (48Gy) 7.5Gy x 8fr (60Gy)	77 105	144 210

SBRT workflow and challenges

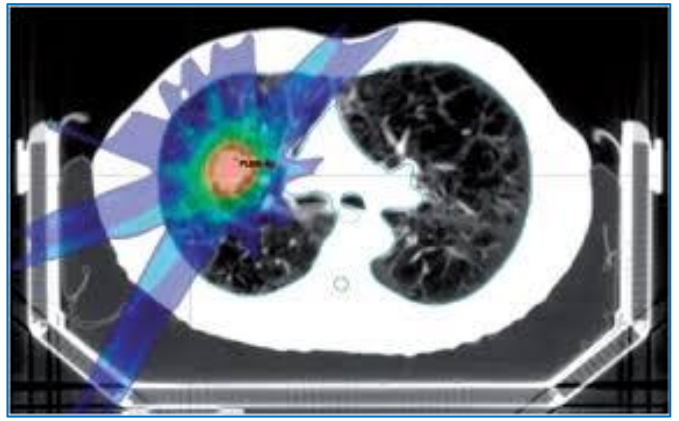
- Goal of SBRT is - accurately target the tumour and deliver sufficient dose to achieve local control with minimum dose to surrounding OARS
- SBRT for ES NSCLC is pioneered based on principles of SRS brain- but has more challenges due to
- 1.Lack of stereotactic frame
- 2. Intrafractional breathing motion

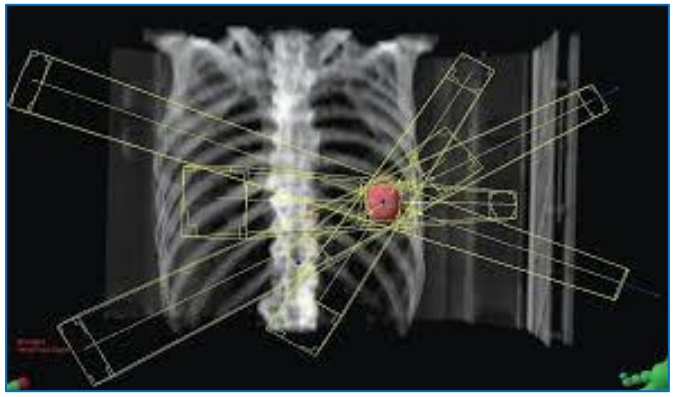
- SBRT lung requires additional attention towards immobilization and motion management

SBRT

Essential technical components for Lung SBRT

- Immobilization
- Motion management
- Target delineation
- Conformal treatment planning -Steep Dose gradient
- Daily image guidance





IMMOBILISATION TECHNIQUES

Helps in reducing inter-fraction motion

Body wrapping techniques such as body fix or any other suitable external immobilization technique

Motion Management

Two parts

- Assessment of motion magnitude
- Motion Mitigation

Several methods are available for both- choice generally depends on

- Available resources/equipment
- Patient Factors- Age, fitness and compliance for breath hold etc.
- Location of organ and tumour

How to assess magnitude of motion?

- X ray Fluoroscopy
- USG
- Slow CT scan
- 4 DCT scan- Respiratory correlated CT Scans
- Breath Hold CT scans
- Cine CT/MRI

Summary of Motion evaluation

- Needs individual approach
- Best method- 4 D CT scan (Best available but not ideal/perfect)
- Tumour motion assessment is more accurate then any surrogate
- If 4 D CT is not available- Slow CT, Breath hold CT, Fluoroscopy
- Fluoroscopy- quick screening tool

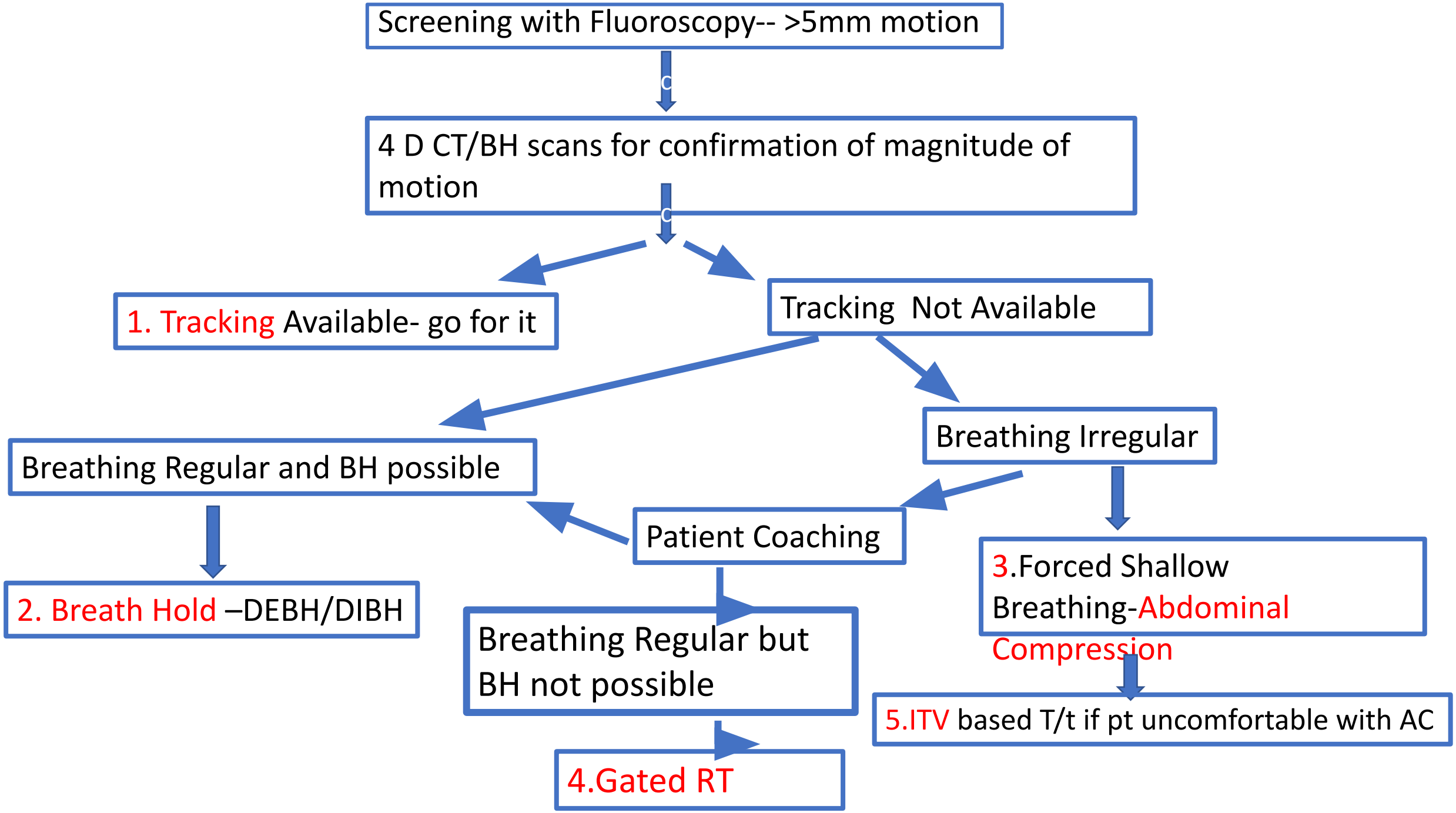
Motion Management Options

Motion Compensating

- ITV based T/T
- Gating
- Tracking

Motion Restricting

- Shallow Breathing
  - Mild Anxiolytic -Lorezapam
  - Abdominal Compression
- Breath Hold-
  - DIBH/DEBH
  - Voluntary/ABC (Active Breathing Control)

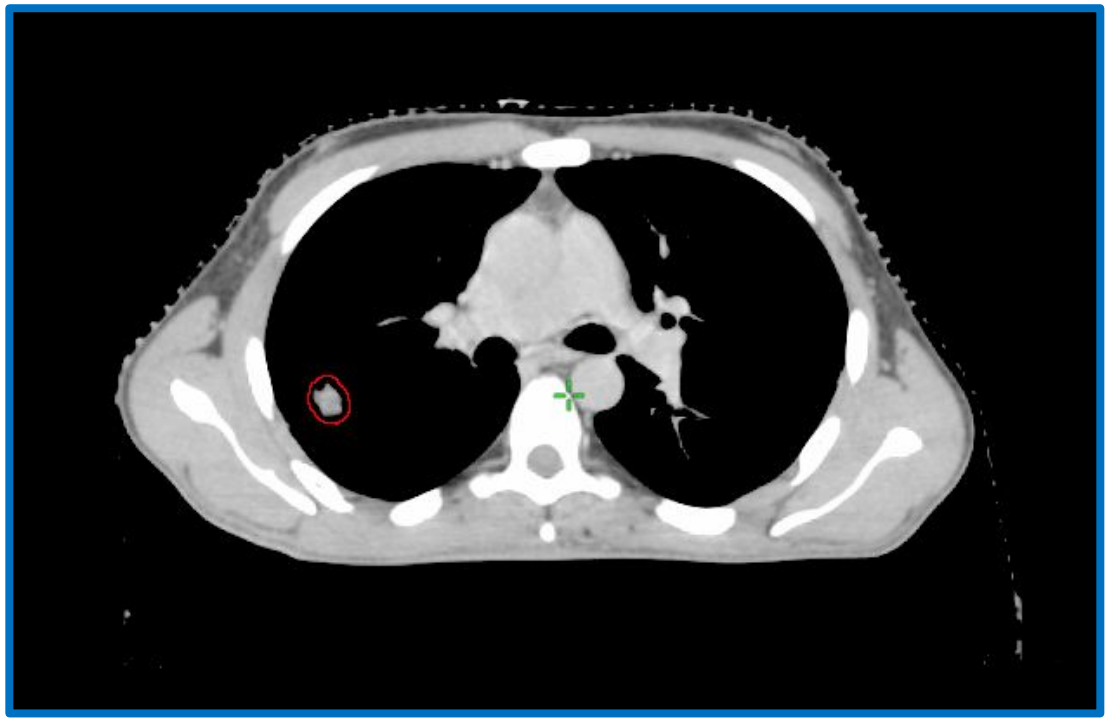

Screening with Fluoroscopy-- >5mm motion
4 D CT/BH scans for confirmation of magnitude of motion
1. Tracking Available- go for it
Tracking Not Available
Breathing Regular and BH possible
2. Breath Hold –DEBH/DIBH
Breathing Irregular
Patient Coaching
Breathing Regular but BH not possible
4.Gated RT
3.Forced Shallow Breathing-Abdominal Compression
5.ITV based T/t if pt uncomfortable with AC

The Management of Respiratory Motion in Radiation Oncology

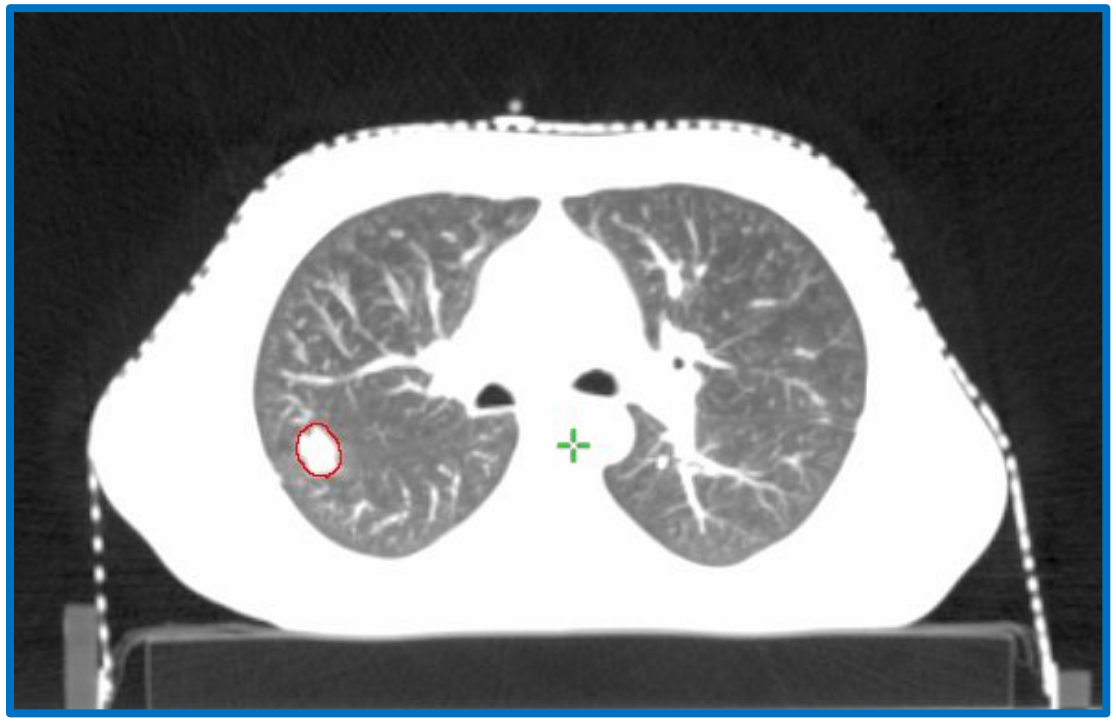
Report of AAPM Task Group 76

CONTOURING

ACQUISITION WINDOW



LUNG WINDOW



Treatment Planning

- Conformal Plan
- 3 DCRT/IMRT/VMAT
- Multiple Coplanar and no coplanar beams (Typically 7-11)
- High dose rate
- FFF

- Pre Treatment QA

TREATMENT SYSTEMS AVAILABLE FOR SBRT

- Conventional Gantry based LINAC
  - Varian
  - Elekta
- Robotic LINAC – Cyberknife
- MRI –LINAC – ViewRay/ELEKTA
- PROTON - IMPT

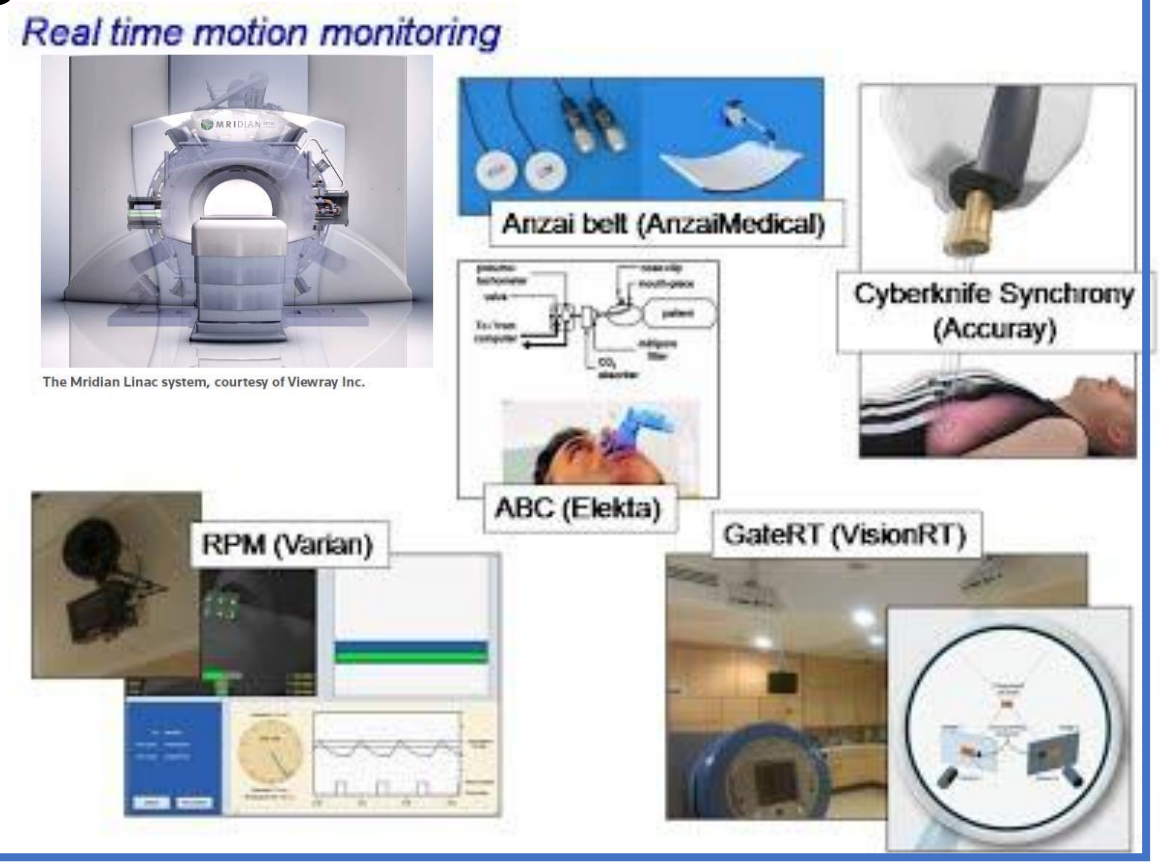


IMAGE GUIDANCE

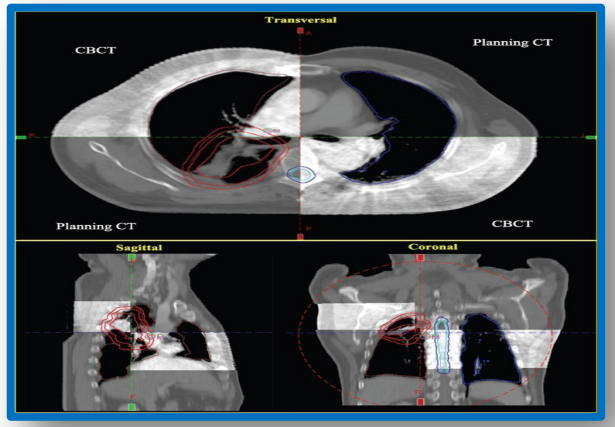


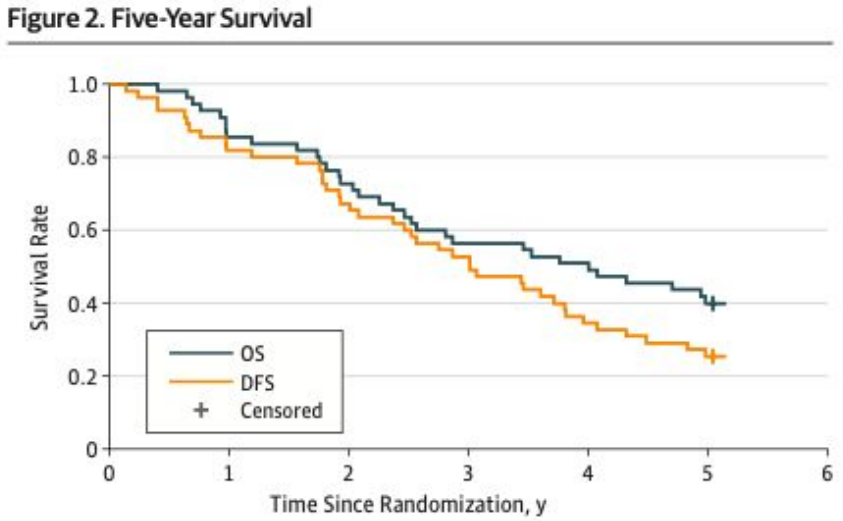
Image guidance allows for reduction in PTV margins

- Goal of IGRT is to improve treatment accuracy by accurately aligning patient and his/tumour prior to treatment delivery
- Can be achieved using KV/MV Xrays or cone beam KV/MV CT scans
- CBCTs provide volumetric imaging and significantly improves target accuracy and reduces set up errors- allows for change in tumour size /position relative to critical OARs
- New advancement is respiratory corelated 4 DCBCT/BH CBCT depending on motion management protocol used for patient's T/t

SBRT in Medically inoperable patients

RTOG 0236

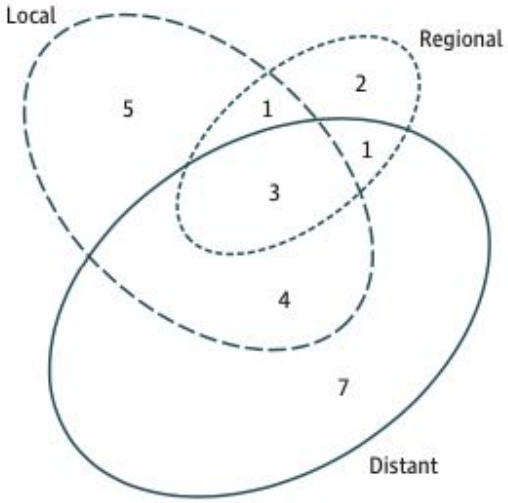
- Single arm phase II study of SBRT for medically inoperable ES NSCLC
- Dose 54Gy/3 fr @18Gy/fr
- N=59 pts (Study period 2004-2006)
- 5Y DFS 25.5% with 5 Y OS 40%
- Median DFS 3Y; Median OS 4 Y
- No Grade 5 toxicities
- Grade 3 and 4 toxicities were 27% and 4%
- Majority AE were pulmonary and musculoskeletal (rib fracture)



RTOG 0236

- 5 Y Recurrence rates
- Primary tm -7.3%
- Primary tm and Involved lobe- 20%
- Regional- 10.9%
- Loco regional 25.5%
- Distant 23.6%

Figure 1. Patterns of Failure Among 23 Patients Experiencing Progression on NRG Oncology RTOG 0236



Surgery Vs SBRT in medically operable pts

- Three randomized trials- ROSEL, STARS and ACOSOG Z4099 were launched to compare SBRT Vs Lobectomy in medically operable pts- All 3 closed prematurely due to poor accrual

Senan S- IJROBP 2008; 70:685-92

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†*

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This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on August 31, 2015

See Comment page 597

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Summary

Background The standard of care for operable, stage I, non-small-cell lung cancer (NSCLC) is lobectomy with mediastinal lymph node dissection or sampling. Stereotactic ablative radiotherapy (SABR) for inoperable stage I NSCLC has shown promising results, but two independent, randomised, phase 3 trials of SABR in patients with operable stage I NSCLC (STARS and ROSEL) closed early due to slow accrual. We aimed to assess overall survival for SABR versus surgery by pooling data from these trials.

Methods Eligible patients in the STARS and ROSEL studies were those with clinical T1–2a (≤4 cm), N0M0, operable NSCLC. Patients were randomly assigned in a 1:1 ratio to SABR or lobectomy with mediastinal lymph node dissection or sampling. We did a pooled analysis in the intention-to-treat population using overall survival as the primary endpoint. Both trials are registered with ClinicalTrials.gov (STARS: NCT00840749; ROSEL: NCT00687986).

Findings 58 patients were enrolled and randomly assigned (31 to SABR and 27 to surgery). Median follow-up was 40·2 months (IQR 23·0–47·3) for the SABR group and 35·4 months (18·9–40·7) for the surgery group. Six patients in the surgery group died compared with one patient in the SABR group. Estimated overall survival at 3 years was 95% (95% CI 85–100) in the SABR group compared with 79% (64–97) in the surgery group (hazard ratio [HR] 0·14 [95% CI 0·017–1·190], log-rank p=0·037). Recurrence-free survival at 3 years was 86% (95% CI 74–100) in the SABR group and 80% (65–97) in the surgery group (HR 0·69 [95% CI 0·21–2·29], log-rank p=0·54). In the surgery group, one patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) patients in the SABR group had grade 3 treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or cough, and one [3%] fatigue and rib fracture). No patients given SABR had grade 4 events or treatment-related death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3–4 treatment-related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [15%] patients), and lung infections (two [7%]).

Interpretation SABR could be an option for treating operable stage I NSCLC. Because of the small patient sample size and short follow-up, additional randomised studies comparing SABR with surgery in operable patients are warranted.

Funding Accuray Inc, Netherlands Organisation for Health Research and Development, NCI Cancer Center Support, NCI Clinical and Translational Science Award.

STARS AND ROSEL - Randomized Trials

Level 1 Evidence

SBRT Vs. Lobectomy			
	SABR	**SURGERY**	
3 Years RFS	86%	80%	HR=0.69
3 Years OS	95%	79%	HR = 0.14 P=0.03

Chang et al. Lancet Oncol 2015; 16: 630–37

Complications – SBRT Vs. Surgery

GRADE – 3 TREATMENT RELATED COMPLICATIONS	
SABR	SURGERY
10%	44%

MORTALITY	
SABR	SURGERY
0%	4%

Chang et al. Lancet Oncol 2015; 16: 630–37

- Pooled analysis of STARS and ROSEL is not very reliable- small sample size
- Retrospective analyses of large studies have shown improved OS in the surgery groups

- This is likely in part due to selection bias - as SBRT arm had inoperable
  - Older pts
  - More co morbidity
  - Inferiorty of clinical staging (vs pathological staging in surgical arm)

ONGOING RANDOMISED PHASE III TRIALS

- UK – SABRTooth Trial- recently opened, randomize "high-risk" operable patients with ES-NSCLC to surgery or SABR, depending on their perioperative risk.
- The "STABLE MATES" trial (Timmerman) –USA – randomising high risk pts to SABR or sublobar resection
- Veterans Affairs VALOR trial

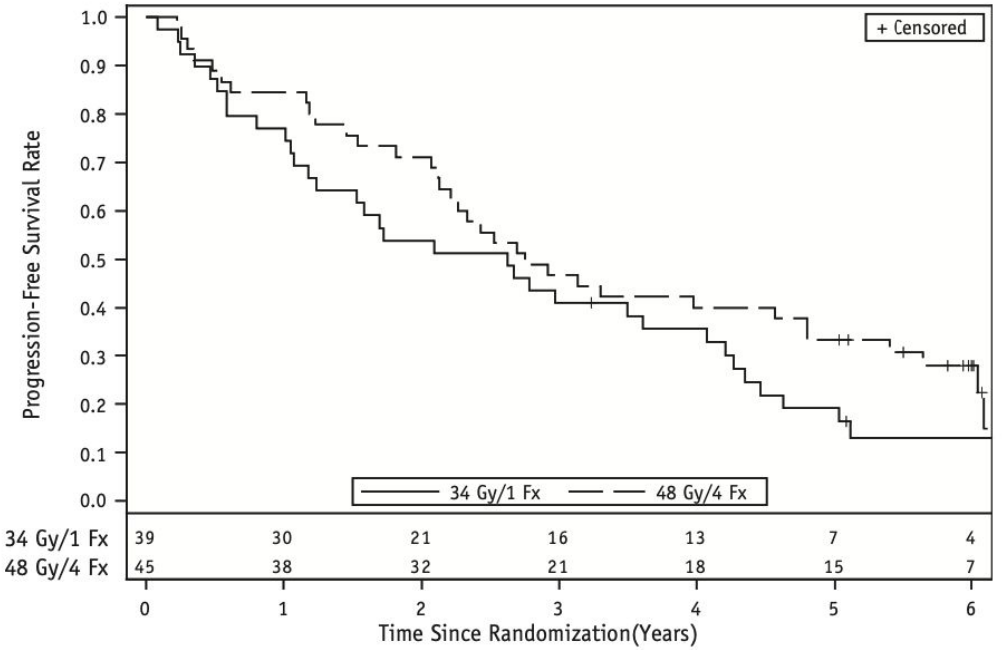
Murray P et al. Br J Radiol 2017; 90: 20160732

SBRT Vs. Sublobar anatomical resection

- In older pts with comorbidities who are not candidate for lobectomy-, both SABR and Sublobar anatomical/wedge resection are an option

RTOG 0915-

- Ph II study comparing two SBRT schedules for medically inoperable stage I NSCLC from 2009-2018
- N=94
- Dose 34 Gy/1 F Vs. 48Gy/4 fractions
- ≥3 grade AE-Arm 1 2.6% and 4.1% in arm 2
- MC PoF- Distant failure- 37.5% in arm 1 and 41.2% in arm 2



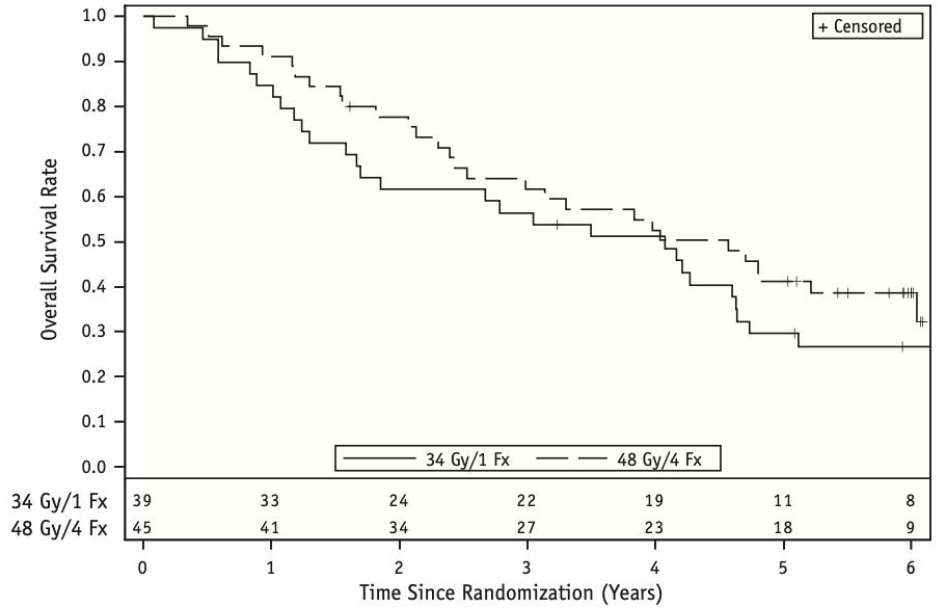


TABLE 1. Prospective Phase 2 Trials of Stereotactic Body Radiation Therapy in Medically Inoperable Patients

Source	Stage	Patients, No.	Dose	Follow-Up, mo	Local Control	Cancer-Specific Survival	Overall Survival	Toxicity
Hoyer 2006[29]	T1-2, < 6 cm	40	15 Gy × 3	29	2 y: 85%	2 y: 62%	2 y: 47%	Grade 2+: 48% Grade 5: None
Fakiris 2009[30]	T1-2, ≤ 7 cm	70	20 Gy × 3 22 Gy × 3	50	3 y: 88%	3 y: 82%	3 y: 43%	Grade 3/4: 10% Grade 5: 7%
Baumann 2009[31]	T1-2	57	15 Gy × 3	35	3 y: 92%	3 y: 88%	3 y: 60%	Grade 3/4: 30% Grade 5: None
Timmerman 2010[32]	T1-2, < 5 cm	55	20 Gy × 3	34	3 y: 91%	NR	3 y: 56%	Grade 3/4: 16% Grade 5: None
Ricardi 2010[33]	T1-2, < 5 cm	62	15 Gy × 3	28	3 y: 88%	3 y: 73%	3 y: 57%	Grade 3/4: 10% Grade 5: None
Bral 2011[34]	T1-3, ≤ 6 cm	40	20 Gy × 3 15 Gy × 4	16	2 y: 84%	NR	2 y: 52%	Grade 3/4: 17% Grade 5: 3%
Nagata 2015[35]	T1	100	12 Gy × 4	47	3 y: 87%	NR	3 y: 60%	Grade 3/4: 12% Grade 5: None
Sun 2017[36]	T1-2, ≤ 5 cm	65	12.5 Gy × 4	86	7 y: 92%	NR	5 y: 56% 7 y: 48%	Grade 3/4: 5% Grade 5: None

SBRT in medically operable pts

ROG 0618- SBRT for ES NSCLC

- First trial to test SBRT in operable pts
- Single arm ph II study 2007-2010- 26 pts (23 T1 and 3 T2)
- Operable biopsy proven peripheral lung Ca
- SBRT dose 54Gy/3 fractions @18Gy
- Median FU 48 Months/4 Y
- 2 Y primary tm control rate was 96%
- Regional failure – 3 pts
- 4 Y loco regional control rates was 88%
- 4 Y DM – 12%
- No grade 4-5 toxicities; 15% grade 3 toxicities
- Limitations- Small pilot study with no control/randomized arm

Current Challenges

- 1. Centrally/ultracentrally located NSCLC-
- After Publication from Timmerman group, it was realized that probably we need to adapt more fractionated approach rather then 1-3 fractions for central lung SBRT

RTOG 0813- Central Lung SBRT

- Ph I/II trial evaluated fractionation schedule of 5 fractions every 2-3 days up to a total dose of 50-60Gy escalating in 0.5Gy/fractions steps

- With median FU 38 Months- max tolerated dose reported was 5 x12.0 Gy/fx with accompanying 7.2% DLT (grade 5 sinus bradycardia, Hypoxia, Pneumonitis, pleural effusion)
- LCR at 2 Y in 11.5 Gy/fx and 12Gy/fx was 89.4% and 88% respectively
- With OS of 68% and 73%
- 19% pts had grade 3 or higher toxicity and 6 pts had grade 5 toxicity

ORIGINAL ARTICLE

The HILUS-Trial—a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy

- Ph II multicentre trial on SBRT to central tms
- Defn of central tms- - tm located within ≤1 cm from PBT
- Total 74 pts
- 42 pts had tm located close to main bronchus (Arm A)
- 31 pts had tm located close to lobar bronchus (Arm B)
- ≥ Grade 3 toxicity- Arm A- 14.3 % Arm B- 3.2%

- Lindeberg K
- J Thorac Oncol 2017;12:S340
- Acta Oncol 2015; 54:1096-104

Nordic HILUS trial

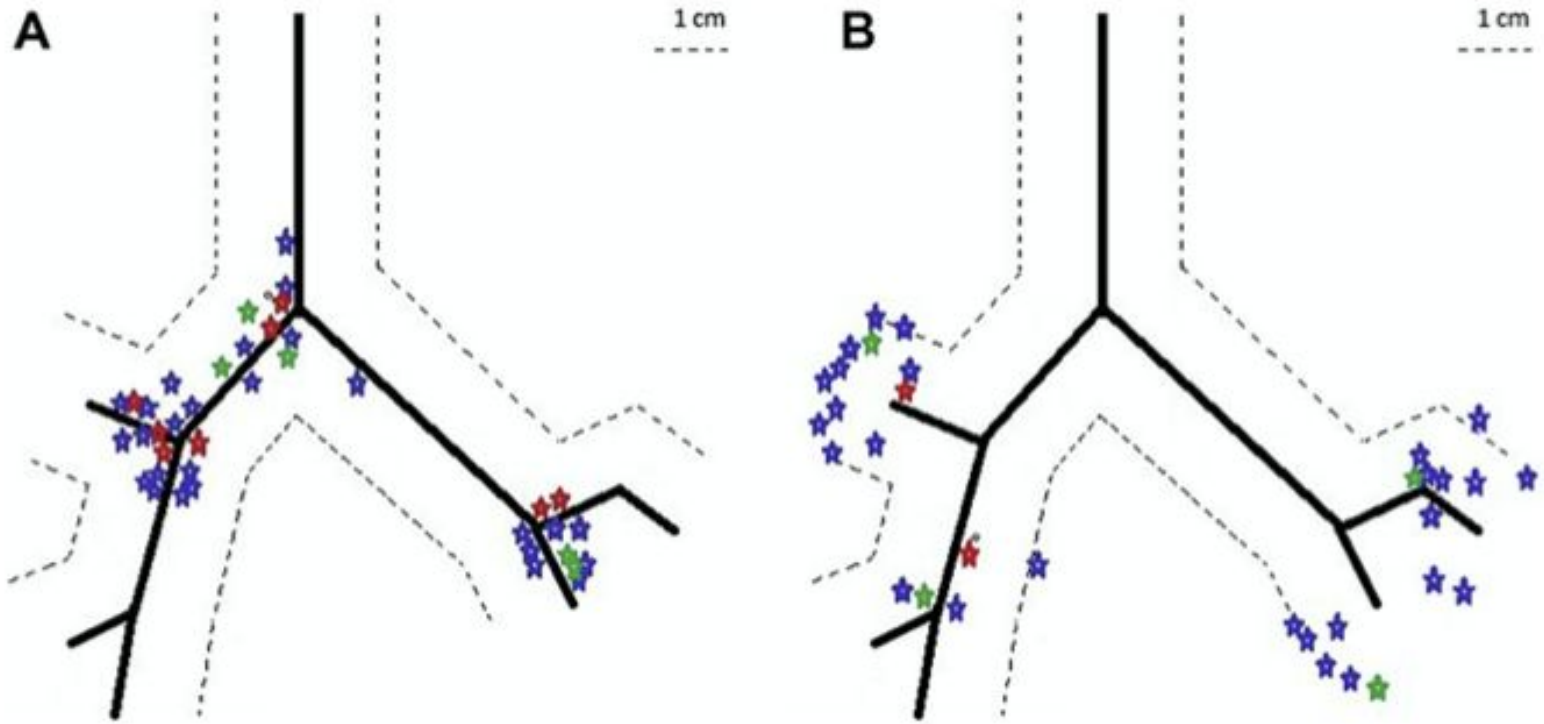
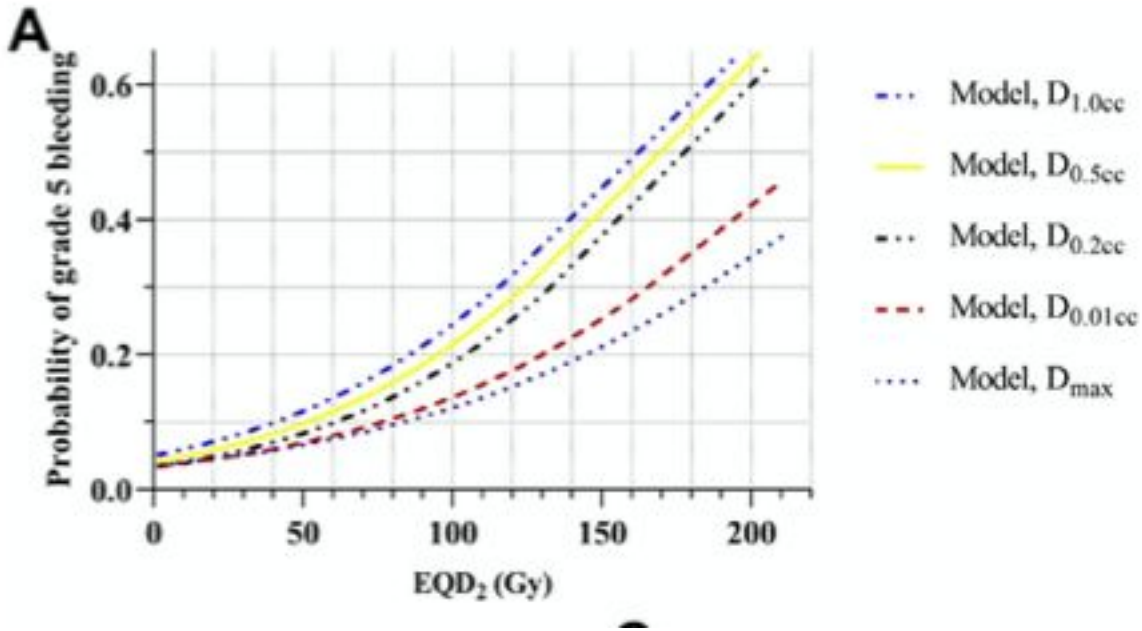


Figure 1. Localization of (*A*) tumors in group A and (*B*) tumors in group B. Red indicates grade 5 toxicity; green, local failure; blue, no grade 5 toxicity + local control.



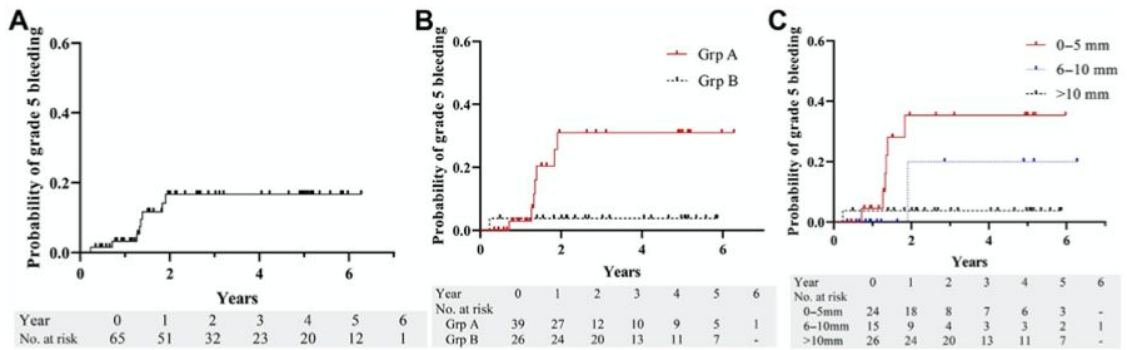


Figure 3. Time to grade 5 bleeding for (*A*) the entire cohort treated per protocol, (*B*) divided in Grps A and B ($p < 0.05$), and (*C*) divided dependent on distance between the tumor and the main bronchus ($p < 0.05$). Grp, group.

Study	Year	# of patients	FUP (years)	Tumor location		Dose	# of Fractions	Local control (%)	Overall survival (%)
Chang *et al.* (60)	2015	27	1.4	Central	≤2 cm from PBT	50 Gy	4	100	–
Haasbeek *et al.* (61)	2011	63	3	Central	≤2 cm from PBT and/or ≤1 cm from heart or mediastinum	60 Gy	8	92.6	64.3
Li *et al.* (62)	2014	82	2	–	Location not amenable to 50 Gy/4 fx according to institutional standards	70 Gy	10	96	66.9
Chaudhuri *et al.* (49)	2015	34	2	Central	≤2 cm around the PBT or adjacent to the mediastinal or pericardial pleura	50 Gy	4-5	90	–
				Ultracentral	tumor abutting central airway			100	
Haseltine *et al.* (63)	2016	10	2	–	≤1 cm from PBT	45 Gy	5	77.4	63.9
		8		–	>1 cm from PBT				
Bezjak *et al.* (RTOG 0813) (46,64)	2016	71	2	Central	≤2 cm from PBT or adjacent to mediastinal or pericardial pleura	57.5/60 Gy	5	89.4/87.7	70.2/72.7
Tekatli *et al.* (50)	2016	47	2.4	Ultracentral	PTV overlapping trachea or central airway	60 Gy	12	100	20.1
Stam *et al.* (65)	2017	104	5	–	≥1 and <2 cm from PBT	54 Gy	3*	–	58
				–	<1 cm from PBT				14
Daly *et al.* (66)	2017	42	1.8	Central	–	50 Gy	5*	–	–
				Ultracentral	–				
Lindberg *et al.* (12)	2017	74	2	Central	≤1 cm from PBT	56 Gy	8	–	–
Roach *et al.* (67)	2018	64	1	Central	>2 cm in all directions from the PBT	45–60 Gy	5	95.4	81.2

*median. PBT, proximal bronchial tree.

Central lung tm SBRT- Conclusions

- Comparable LCR but substantially higher toxicities including fatal toxicities
- International guidelines recommend using- risk adapted fractionation schedule- optimal fractionation is not yet identified

- SUNSET trial- Ongoing – evaluating MTD starting at 60Gy/8 fractions
- (Ref Giuliani M Clin Lung Cancer 2018; 19 e 529-32)

2 Patients with coexisting ILD

- ILD are a heterogenous group of diffuse parenchymal lung disorders with various patterns of inflammation and fibrosis
- IPF- Idiopathic Pulmonary Fibrosis is MC form of ILD and is a chronic and progressive fibrosing condition of lung tissue. It is a/w poor prognosis and MS of 2-3 years
- It is a/w higher treatment related toxicity and is ineligible for T/t

Conventional RT Vs SBRT

- CHISEL
- LUSTRE
- SPACE

SBRT vs Standard Therapy – stage I NSCLC

Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

David Ball, G Tao Mai, Shalini Vinod, Scott Babington, Jeremy Ruben, Tomas Kron, Brent Chesson, Alan Herschtal, Marijana Vanevski, Angela Rezo, Christine Elder, Marketa Skala, Andrew Wirth, Greg Wheeler, Adeline Lim, Mark Shaw, Penelope Schofield, Louis Irving, Benjamin Solomon, on behalf of the TROG 09.02 CHISEL investigators

Summary

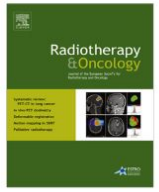
Background Stereotactic ablative body radiotherapy (SABR) is widely used to treat inoperable stage 1 non-small-cell *Lancet Oncol* 2019

Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



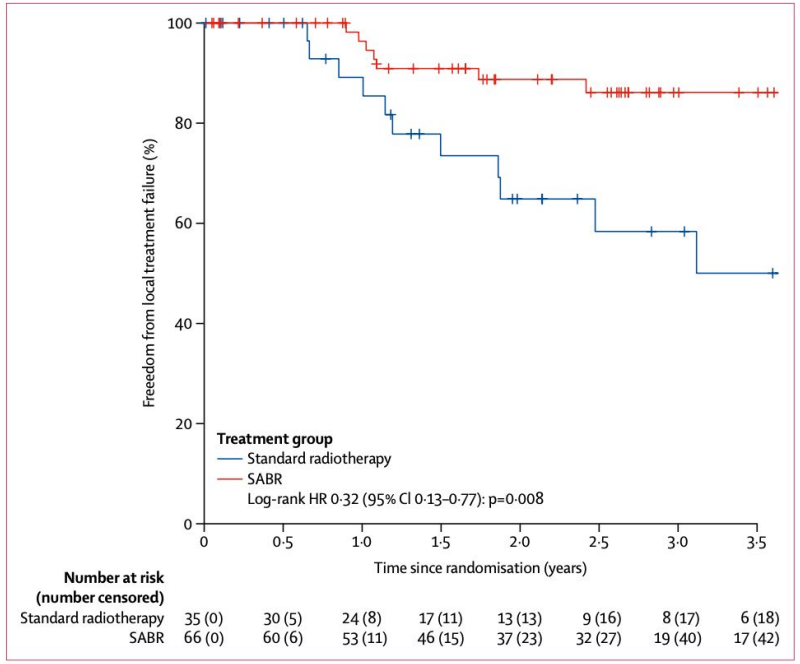
Original article

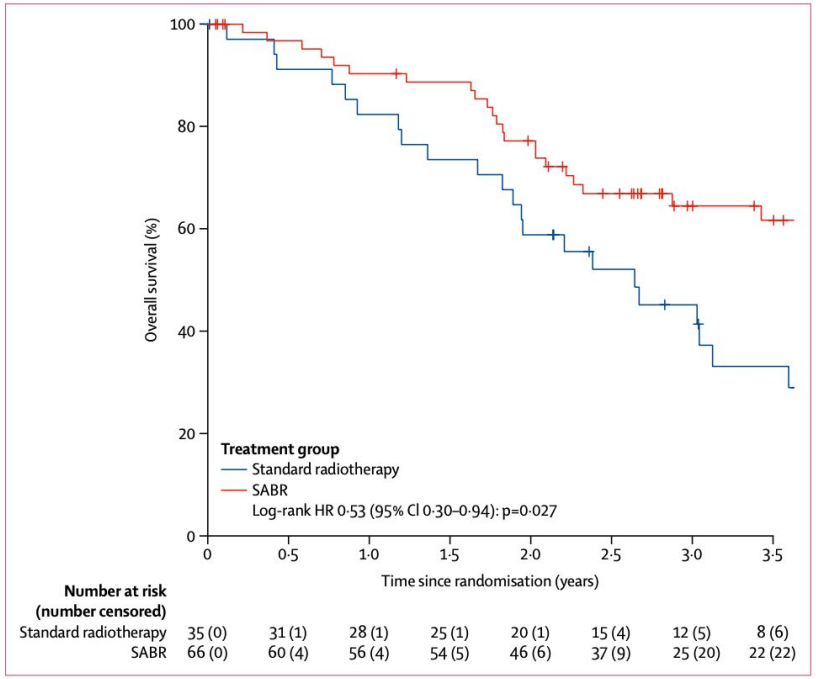
SPACE – A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC

Jan Nyman [a,*], Andreas Hallqvist [a], Jo-Åsmund Lund [b], Odd-Terje Brustugun [c], Bengt Bergman [a], Per Bergström [d], Signe Friesland [e], Rolf Lewensohn [e], Erik Holmberg [a], Ingmar Lax [e]

CHISEL TROG09.02

- Multicentre Ph III RCT (Australia and NZ)
- Biopsy proven stage I (T1-T2aN0M0) diagnosed on FDG PET and medically inoperable/refused surgery, PS1,
- 101 pts with Peripheral tm
- Test arm SABR 54Gy/3 fr @18Gy/r
- Control arm- 66Gy/33 fr or 50Gy/20 fr@2.5Gy/fr
- 2:1 randomization (66 SABR and 35 CFRT)





CHISEL TROG09.02

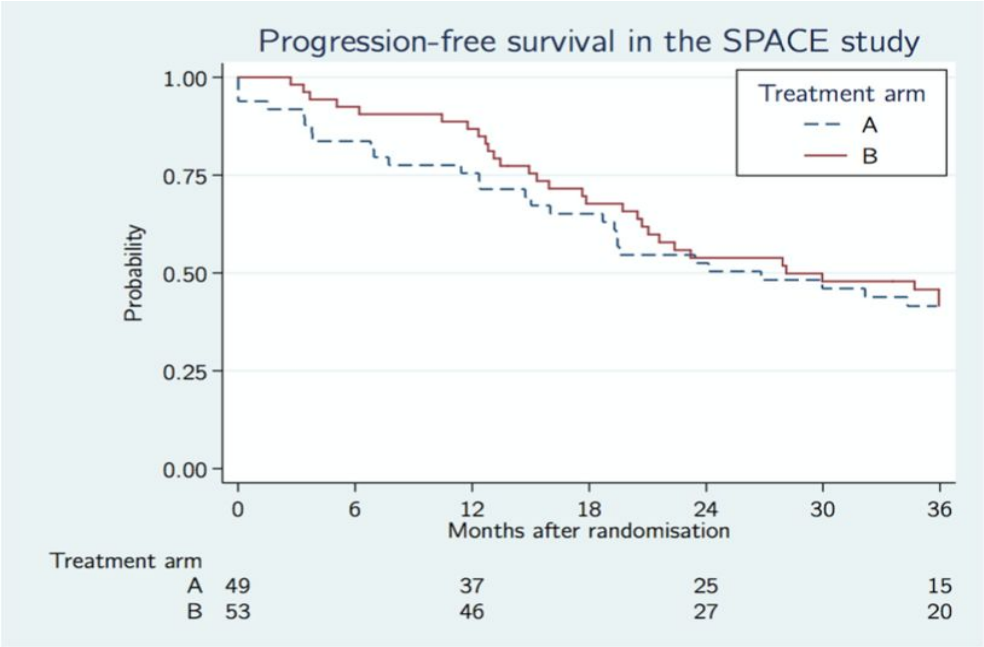
- Local treatment failure – SBRT 10% Vs 26% in CFRT
- 2Y OS in SABR 77% and 59% in CFRT

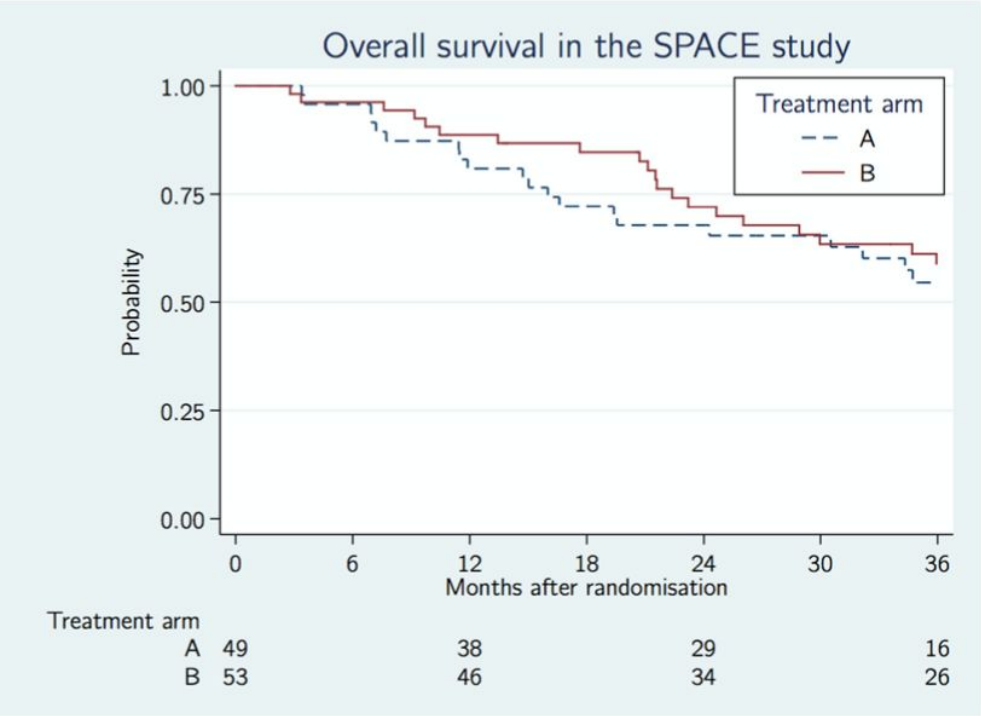
- Toxicity- SABR- Grade 4- 1 pt (Dyspnoea) and grade 3- seven pts
- Standard arm- Grade 3 events- 2 pts (chest pain)

- Criticism -29% pts in control arm received 50Gy/20 fractions which is a suboptimal dose- time corrected BED for 66Gy regimen is 72.4Gy and 50Gy regimen is 62.4Gy- correct dose would have been 55Gy/20fr

SPACE Trial-(Stereotactic Precision And Conventional radiotherapy Evaluation)

- Ph II study of SBRT Vs CFRT- 101 pts- peripheral tms only; refused surgery/medically inoperable
- Biopsy was done when safely feasible
- SBRT 66Gy/3 fractions prescribed at 68% isodose (15Gy at periphery)
- Control arm- 70Gy/35 fractions with 3 DCRT
- Mean age 74 (57-86) and 60% women
- Median FU-37 months





There was no difference in PFS/OS b/w two arms

SABR arm pats had tendency for improved ds control (70% pts in SABR had not progressed as compared to 59% in 3DCRT

Any grade pneumonitis -19% in SABR Vs 34% in control arm

Any grade esophagitis -8% in SABR Vs 30% in control arm

HRQoL evaluated by EORTC QLQ 30 and LC14 module- 3 DCRT pts experienced worse dyspnea/cheat pain and cough

Criticism – Ph II Study

Lung Cancer 118 (2018) 20-26

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

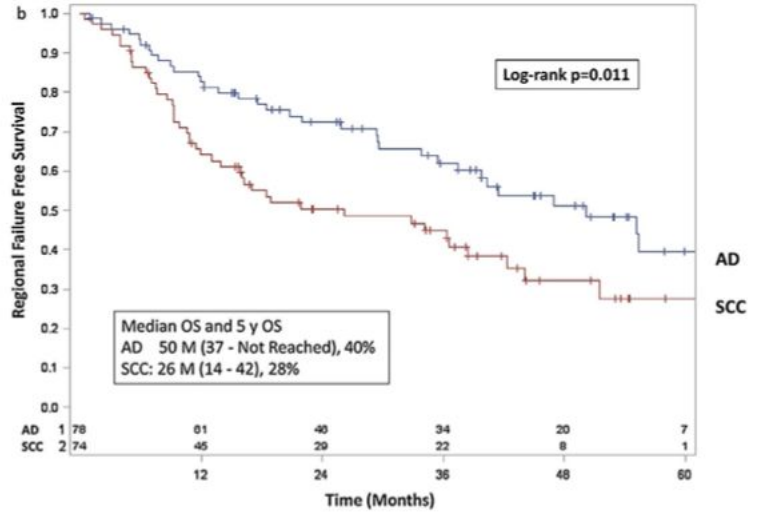
Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer

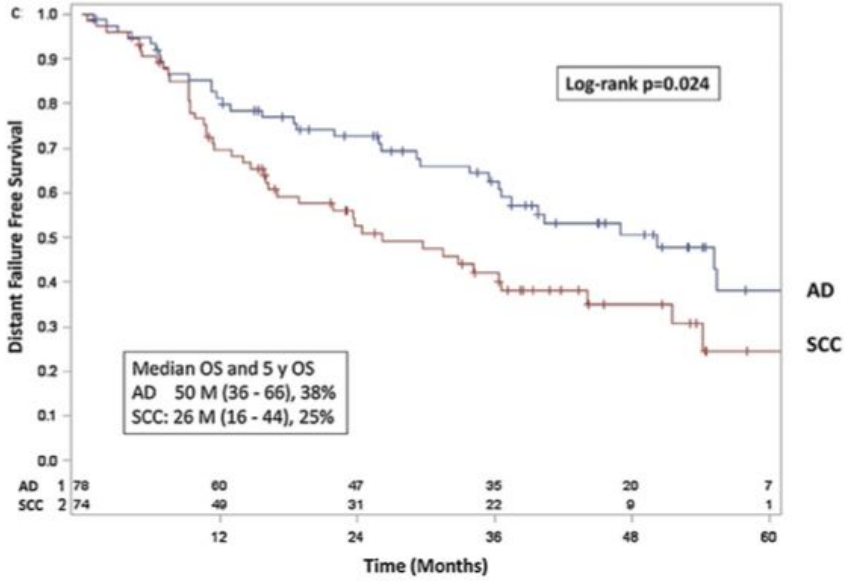
Michael J. Baine[a], Vivek Verma[a], Caitlin A. Schonewolf[b], Chi Lin[a], Charles B. Simone II[c,*]

Prevailing notion is that SBRT is eqi efficacious in both SCC and ADC

Retrospective review of 152 consecutive pts from 2 academic institutions-

SCC has worse outcomes





SBRT

-

	L.C	O.S
> 100 Gy	91.6%	53.9%
< 100 Gy	57.1%	19.7%

Chang et al, Int J Radia Oncol Biol Phys 2008;72:967-71

OUTCOME IN RELATION TO BED

- n - 498 (US -NCDB)
- Underwent SABR for NSCLC - 2003 to 2006

Dose	Fractions	BED (Gy_{10})
60Gy	3#	180
48Gy	4#	105.6
54Gy	3#	151.2
45Gy	3#	112.5
48Gy	3#	124.8Gy

Statistically significant improvement noted in OS in patients with T2 tumours and a calculated BED of > 150Gy.

Koshy et al , Int J Radia Oncol Biol Phys 2015; e27-33

Impact of BED

- BED10 > 100Gy is a significant predictor of LCR
- Oshiro et all BED10-80Gy – LCR-60%
- Bradley- BED10-86Gy-2Y LCR 86%
- Row et all-2YLCR 94% with BED >100Gy and 80% with BED <100Gy

PATTERNS OF FAILURE- SBRT

- Largest series n= 676

	LOCAL	REGIONAL	DISTANT
5-yr	10.5%	12.7%	19.9%

- Nearly half recurrences – isolated distant mets at 8.3 mths after treatment (suggesting existing subclinical disease undisclosed by baseline PET)

Senthi et al, Lancet Oncol 2012;13:802-9

PoF

- Main PoF after lung SBRT is DM- in about 20-30% pts
- Some guidelines recommend evaluation of adjuvant chemotherapy after SBRT in pts with high risk such as – poor tumour differentiation, vascular invasion, pleural involvement and unknown Ln status
- It’s a controversial area

Woode DE NCCN 2015
Guckenberger M J Thor Oncol 2013;8:1050-8

COMPLICATIONS OF SBRT

- Chest wall toxicity - rib fracture, chronic chest wall pain (5% - 25%)
- Pneumonitis - 0% to 29%
- Skin toxicity
- Central airway toxicity- stenosis/stricture, airway necrosis, fistula
- Esophageal toxicity - mild esophagitis to stricture, perforation, TOF
- Vascular injury -hemoptysis secondary to aortic damage, aortic aneurysm,aortic dissection

Kylie et al, Cancers 2015,7, 981-1004

Accepted Manuscript

Sinoatrial Node Toxicity after Stereotactic Ablative Radiotherapy to Lung Tumors

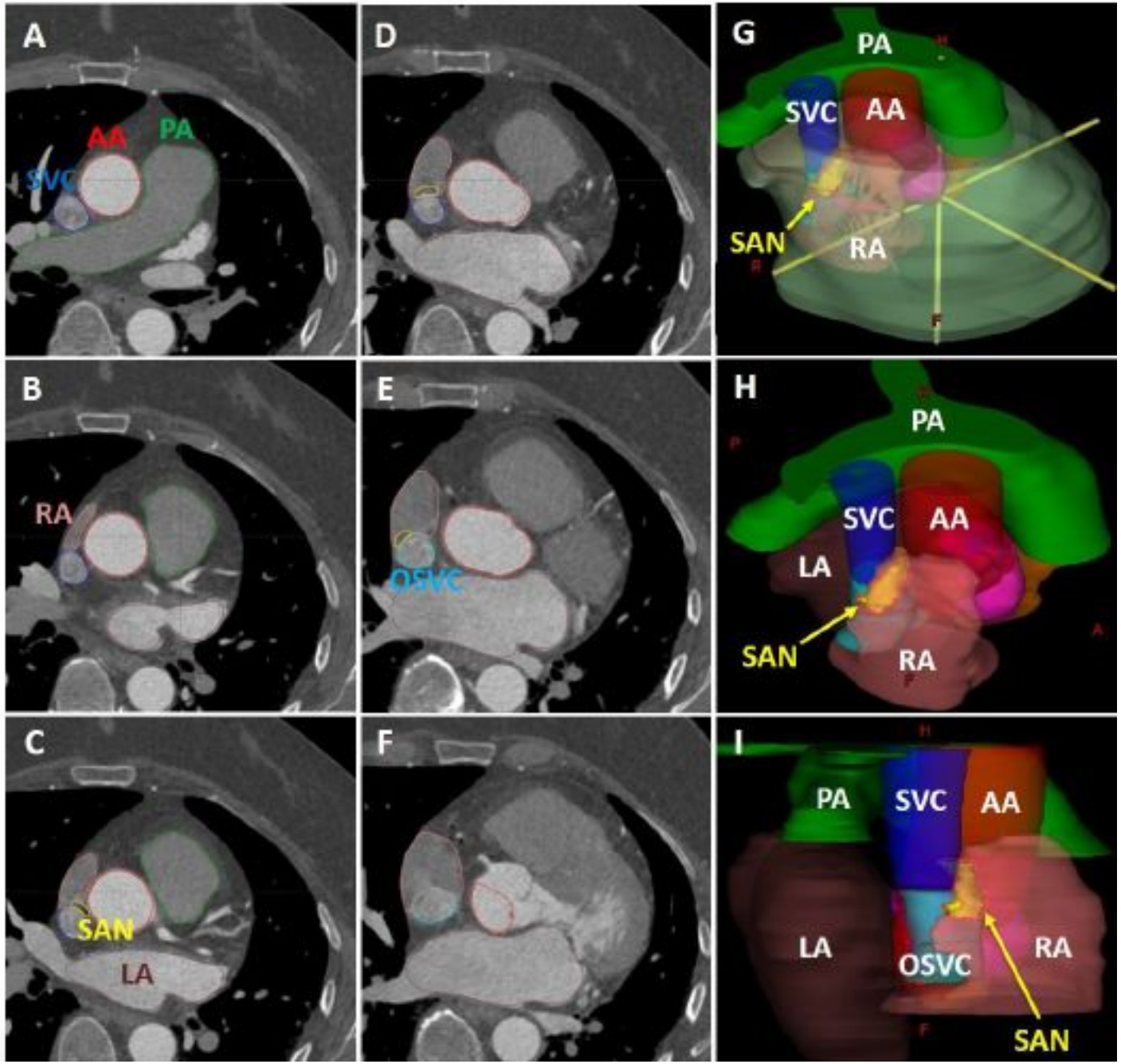
Yushen Qian, Han Zhu, Erqi L. Pollom, Ben Y. Durkee, Aadel A. Chaudhuri, Michael Gensheimer, Maximilian Diehn, David B. Shultz, Billy W. Loo

PII: S1879-8500(17)30111-X
DOI: doi: 10.1016/j.prro.2017.04.005
Reference: PRRO 756

To appear in: *Practical Radiation Oncology*

Received date: 2 February 2017
Revised date: 16 March 2017
Accepted date: 10 April 2017

- Retrospective review of 47 pts with Rt sided lung tm (primary or mets) with central location and treated with SBRT
- One patient developed symptomatic sick sinus syndrome, requiring pacemaker placements 6 months after SBRT- psot pacemaker follow up of 2 years with ds controlled
- Her acute onset and short interval b/w SBRT and onset of symptoms was suggestive of SAN toxicity due to radiation injury
- SA node is a crescent shaped subepithelial structure located at junction b/w SVC and Rt Atrium– In this location it gets subjected to significant incidental dose from SABR treatment to rt sided especially central tms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Follow up

- CT imaging every 3-6 monthly for atleast 2 years
- Distinguishing b/w post RT changes and recurrence is complex
- High risk imaging features-
- Bulging margins
- Increase in craniocaudal extent
- Disappearance of linear margin
- FDG PET is routinely not recommended- should be used where differentiation b/w post SBRT fibrosis and tumor recurrence is otherwise difficult

Peulen H IJROBP 2016; 96:134-141
Huang K Radiother Oncolo 2013; 109:51-7

Growing interest

- Potential abscopal effect of SABR

- The addition of immune - modulating systemic therapies in combination with SABR may help eradicate potential micrometastatic deposits within central draining lymph nodes and beyond.

Murray P et al. Br J Radiol 2017; 90: 20160732

We have a long way to go to improve our understanding……..

Thanks for your attention!!