MIDWEST RADIATION ONCOLOGY SYMPOSIUM

SBRT in Centrally-Located Stage I Lung Cancer: Navigating Treatment Challenges

Qateeb Khan, M.D.

Disclosures

- I have no conflicts of interest to disclose

Goals and Objectives

MIDWEST RADIATION ONCOLOGY SYMPOSIUM

- To understand the unique challenges associated with using SBRT to treat centrally located stage I lung cancer
- To review the current evidence on the efficacy and safety of SBRT for centrally located stage I lung cancer
- To explore emerging strategies and future directions for optimizing SBRT treatment in centrally located stage I lung cancer

Definitions: Stage 1 Lung Cancer

AJCC 9e will likely split N2 into N2a/N2b and M1c into M1c1 and M1c2

- The primary tumor is no larger than 4 cm in size
- There is no nodal or metastatic involvement

TABLE 25.2: AJCC 8th ed. (2017) Staging for Lung Cancer

T/M \ N		cN0	cN1	cN2	cN3
T1	a ≤1 cm[1]	IA1	IIB	IIIA	IIIB
	b 1.1–2 cm	IA2			
	c 2.1–3 cm	IA3			
T2[2]	a 3.1–4 cm	IB			
	b 4.1–5 cm	IIA			
T3	• 5.1–7 cm • Invasion[3] • Same lobe nodules	IIB	IIIA	IIIB	IIIC
T4	• >7 cm • Invasion[4] • Separate lobe nodules				
M1a	• Separate nodules in contralateral lobe • Pleural nodules • Malignant pleural/pericardial effusion	IVA			
M1b	• Single extrathoracic metastasis in single organ • Single non-regional lymph node				
M1c	• Multiple extrathoracic metastasis	IVB			

Essentials of Clinical Radiation Oncology

An Introduction to Central Lung Cancer

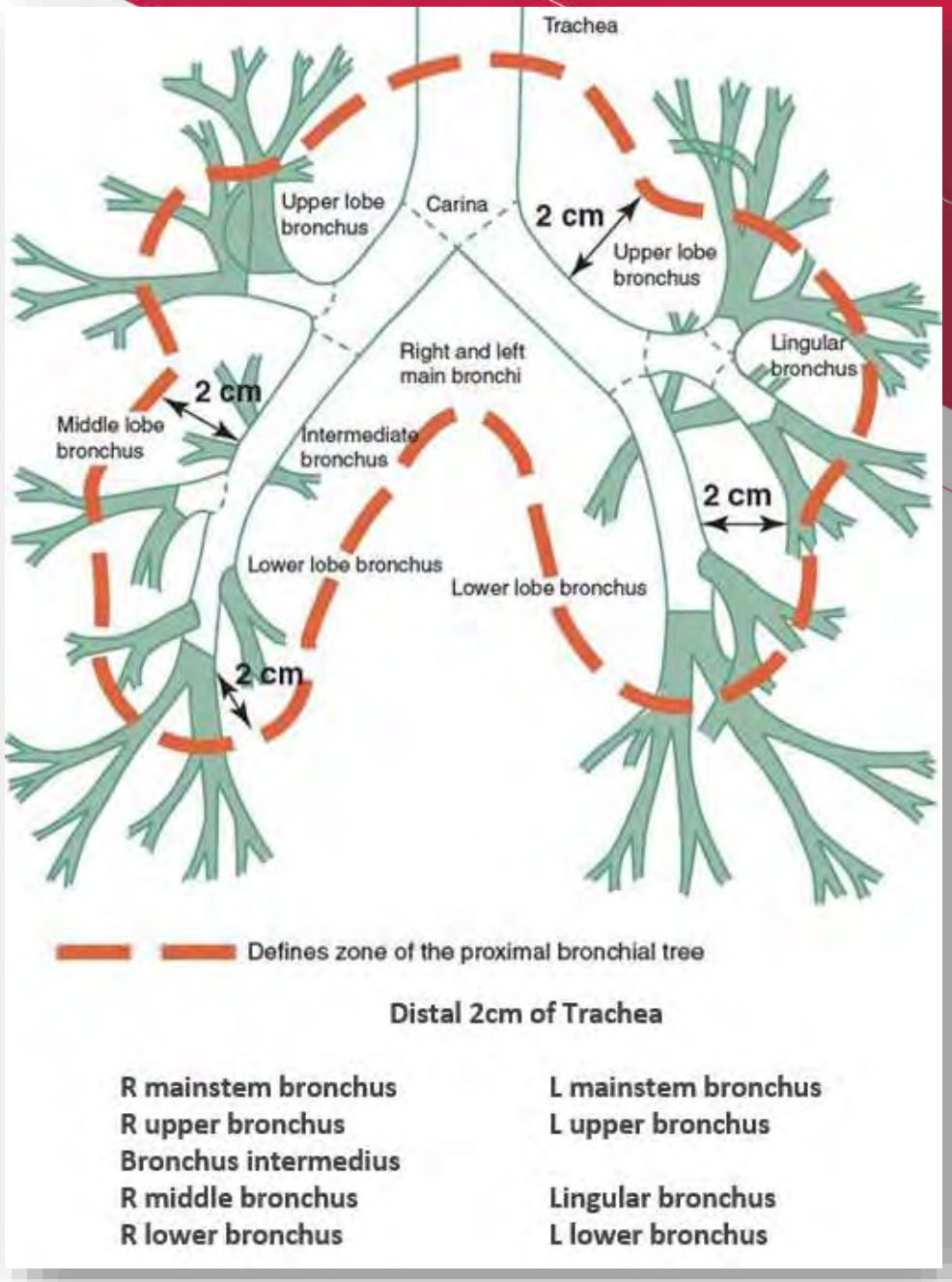
Timmerman included patients with tumors up to 7 cm

- Early work with lung SBRT revealed that centrally located tumors had a greater propensity for treatment related toxicity (relative to peripheral tumors)
  - Timmerman (PMID: 17050868) demonstrated that lung SBRT provided a local control rate of 95% in early-stage lung cancers
    - Patients with peripheral lung tumors had a 2-year freedom from severe toxicity of 83%
    - Patients with central lung tumors had a 2-year freedom from severe toxicity of 54%

- This led to the adoption of a “No Fly Zone”

Definitions: No Fly Zone

- The NFZ is defined as:
  - A 2 cm radius around the proximal bronchial tree (PBT)

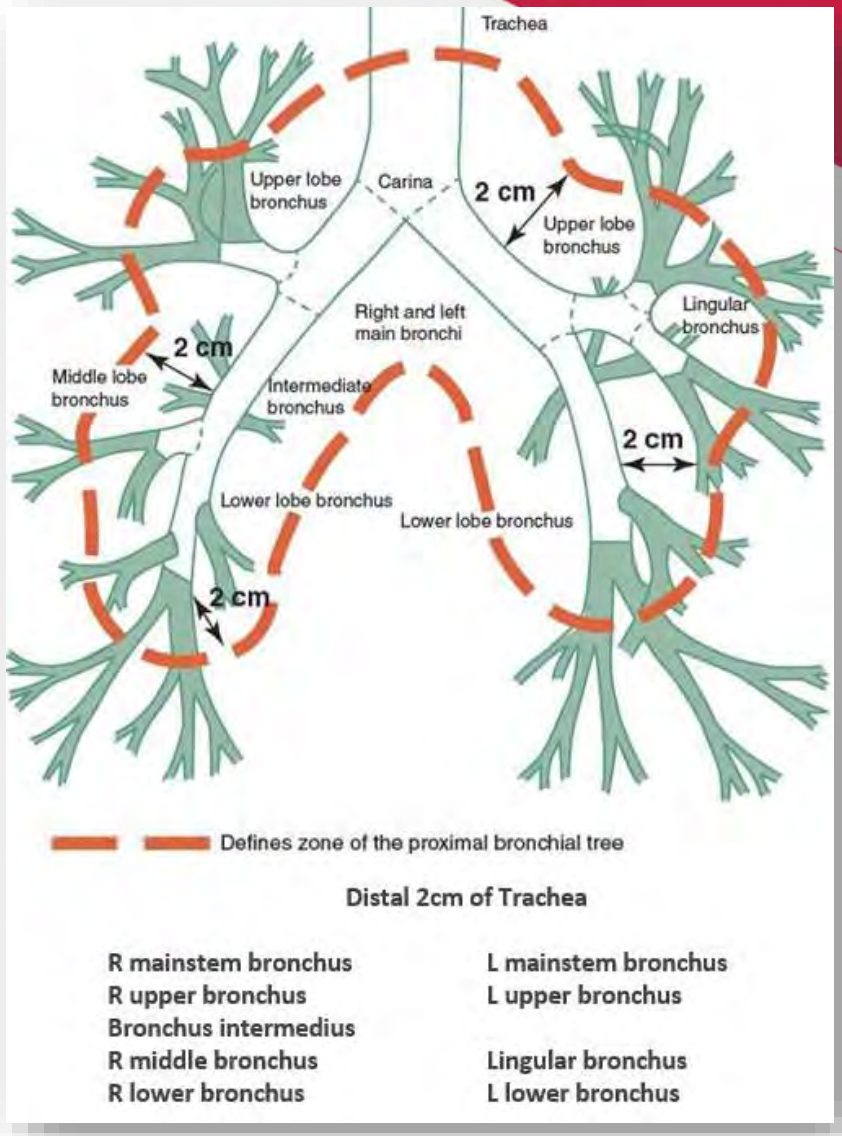


Definitions: Central and Ultracentral

There is no universally accepted definition of a centrally located tumor

- **Central tumors:**
  - **If the PTV touches the "No Fly Zone" (the 2 cm margin) then the tumor is classified as central**

- Ultracentral:
  - If the PTV touches the actual PBT, esophagus, pulmonary artery, or the pulmonary vein then it is often classified as ultracentral



Benefits of Lung SBRT

Overall survival was improved in patients receiving SABR as well

TROG 09.02 CHISEL

- Phase 3 PRT of 101 patients with biopsy proven peripheral stage 1 NSCLC
  - Randomized 2:1 to:
    - SBRT (54 Gy/3 fx or 48 Gy/4 fx)
    - Conventional fractionation (66 Gy/33 fx or 50 Gy/20 fx)
  - With MFU of 2.1 years, freedom from local treatment failure was improved in the SABR group compared with the standard radiotherapy group (SS)
    - 14% (9/66 patients) in the SABR group experienced progression
    - 31% (11/35 patients) in the standard radiotherapy group experienced progression
  - **Conclusion: SABR resulted in superior local control of the primary disease without an increase in major toxicity.**

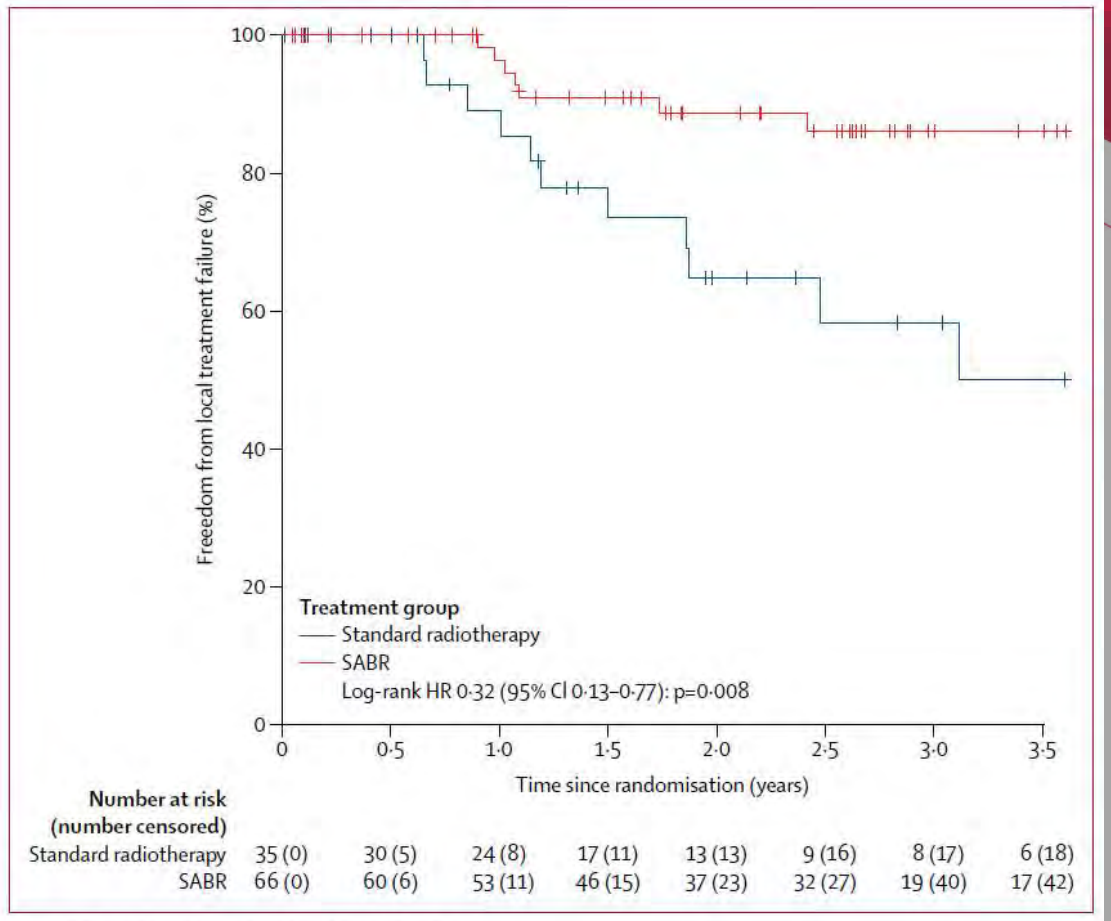


Figure 2: Freedom from local treatment failure
Tick marks represent censored patients (patients were censored for regional failure and distant metastasis, as well as for withdrawal, death, and loss to follow-up). SABR=stereotactic ablative body radiotherapy.

Biologically Effective Dose

BED is a measure of the dose delivered by a particular schema of dose per fraction and total dose to a particular tissue

Dose / Fractionation	α/β = 10	α/β = 3
50 / 5	100	217
56 / 8	95	187
60 / 8	105	210
60 / 15 (Hypofx)	84	140
60 / 30 (Conventional)	72	100

BED and Efficacy of SBRT

BED ≥ 100 was also correlated with improved OS

Onishi (PMID 17603311)

- RR of 257 patients from 14 institutions treated with hypofractionated stereotactic radiotherapy
- Local progression occurred in 14% of the cohort (n=36)
  - The local recurrence rate was 8.4% for a BED of 100 Gy or more
  - The local recurrence rate was 42.9% for a BED less than 100 Gy

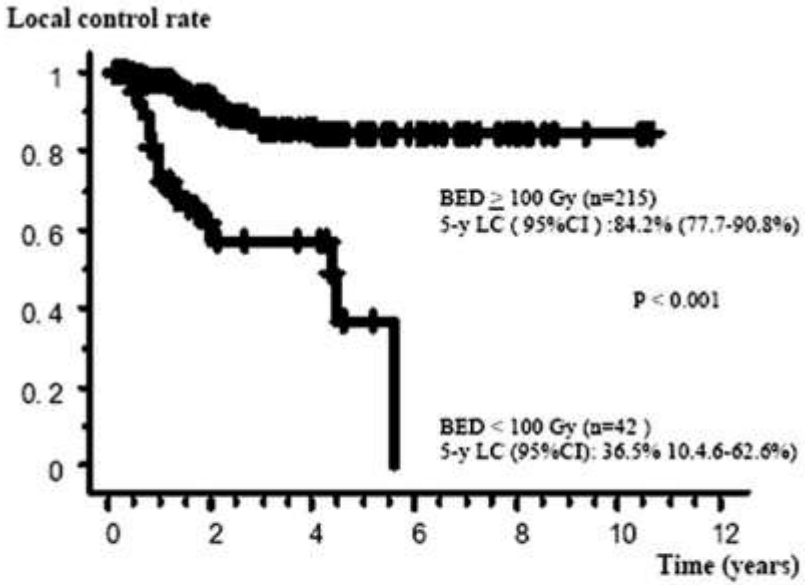


FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

Toxicities of Lung SBRT

Central was defined as PTV within 2 cm of the PBT, or touching the mediastinal/pericardial pleura

RTOG 0813

- Phase I/II study of the maximum tolerated dose (MTD) and efficacy of SBRT for central tumors
  - Dose started at 50 Gy/5 fx, and escalated by 0.5 Gy/fx increments, to a max of 60 Gy/5 fx
  - MTD was defined as a dose limiting toxicity of 20%

- At MFU of 37.9 months, MTD was 60 Gy / 5 fx (with a DLT of 7.2%)

Toxicities of RTOG 0813

- No patients receiving 50 Gy in 5 fx experienced a grade 3+ adverse event

	Grade, No.											
	Level 6: 10.5 Gy/fx (n = 7)			Level 7: 11.0 Gy/fx (n = 14)			Level 8: 11.5 Gy/fx (n = 38)			Level 9: 12.0 Gy/fx (n = 33)		
System Organ Class Term	3	4	5	3	4	5	3	4	5	3	4	5
Worst overall	0	0	1	3	0	1	5	0	3	5	1	1
Cardiac disorders	0	0	0	0	0	0	0	0	0	2	0	0
Heart failure	0	0	0	0	0	0	0	0	0	1	0	0
Restrictive cardiomyopathy	0	0	0	0	0	0	0	0	0	1	0	0
Sinus bradycardia	0	0	0	0	0	1	0	0	0	0	0	0
GI disorders	0	0	0	0	0	0	1	0	0	1	1	0
Dysphagia	0	0	0	0	0	0	1	0	0	0	0	0
Esophageal pain	0	0	0	0	0	0	0	0	0	1	0	0
Esophageal perforation	0	0	0	0	0	0	0	0	0	0	1	0
Esophagitis	0	0	0	0	0	0	1	0	0	1	0	0
General disorders and administration site conditions	0	0	1	0	0	0	0	0	1	0	0	0
Death NOS	0	0	1	0	0	0	0	0	1	0	0	0
Investigations	0	0	0	0	0	0	2	0	0	0	0	0
Platelet count decreased	0	0	0	0	0	0	1	0	0	0	0	0
Weight loss	0	0	0	0	0	0	1	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	1	0	0	0	0	0
Anorexia	0	0	0	0	0	0	1	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	3	0	0	5	0	2	3	0	1
Atelectasis	0	0	0	1	0	0	1	0	0	0	0	0
Bronchopulmonary hemorrhage	0	0	0	0	0	0	0	0	2	0	0	1
Dyspnea	0	0	0	0	0	0	3	0	0	1	0	0
Hypoxia	0	0	0	1	0	0	2	0	0	1	0	0
Pleural effusion	0	0	0	0	0	0	0	0	0	1	0	0
Pneumonitis	0	0	0	1	0	0	0	0	0	1	0	0
Other	0	0	0	0	0	0	0	0	0	2	0	0
Vascular disorders	0	0	0	0	0	0	1	0	0	0	0	0
Hypertension	0	0	0	0	0	0	1	0	0	0	0	0

Toxicities of Lung SBRT

Central was defined as PTV within 2cm of PBT, or touching the mediastinal/pericardial pleura

RTOG 0813

- Given the results of the phase 1 trials, the true conclusion of RTOG 0813 was central lesions can be taken to 60Gy/5fx; however:
  - Given the safety profile of 50Gy/5fx (i.e.: no grade 3+ toxicity), this became the predominant dose for central lung cancers

Central Lung Cancer: Planning Considerations

- 4DCT: accounting for tumor motion
- VMAT: ensuring the most conformal plan is made
- IGRT: allows for precise delivery of RT

Per NCCN

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

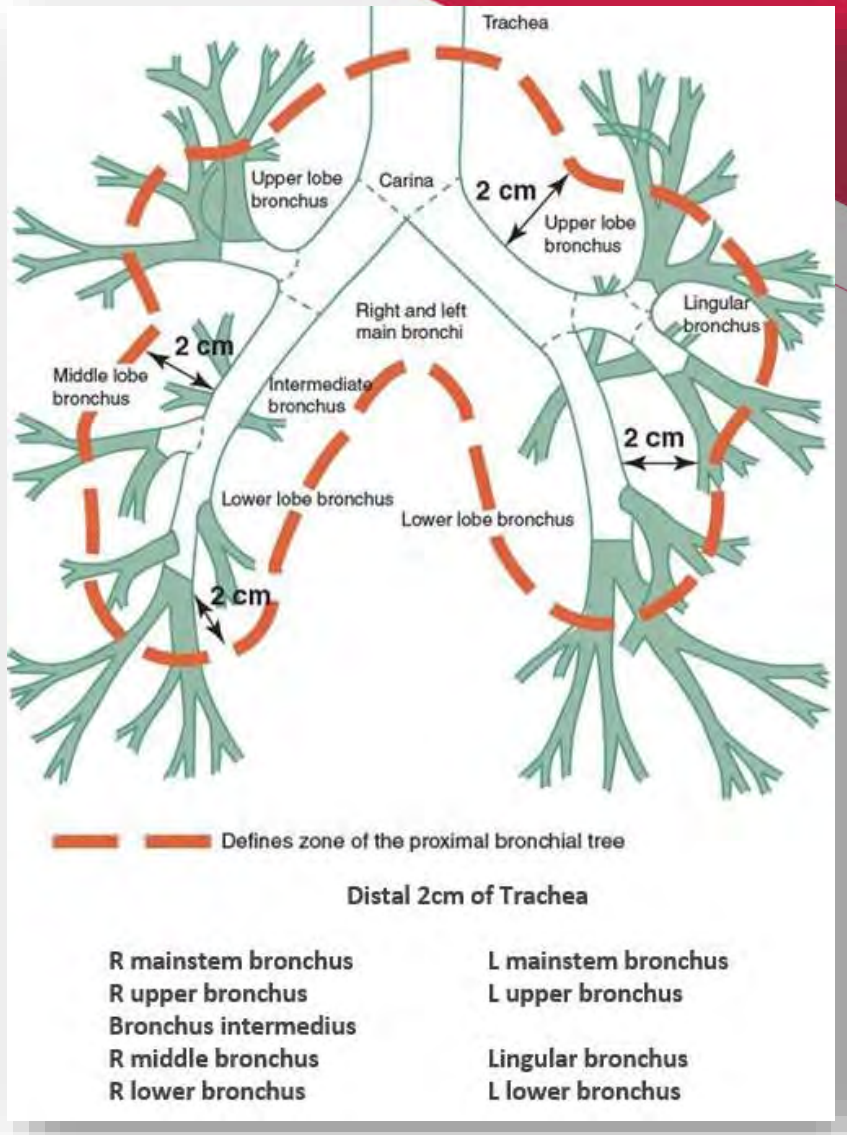
*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^For central tumor location. NS = not specified.

Definitions: Central and Ultracentral

- Central tumors:
  - If the PTV touches the “No Fly Zone” (the 2 cm margin) then the tumor is classified as central

- **Ultracentral:**
  - **If the PTV touches the actual PBT, Esophagus, Pulmonary Artery, or the Pulmonary Vein then it is often classified as ultracentral**

The term ultracentral is more recent and also not uniformly applied



Hypofx in Central Lung Cancers

27% of tumors were centrally located
12% of tumors were ultracentral

LUSTRE

- Phase III RCT with stage I NSCLC
- Randomized 2:1 to receive either:
  - SBRT of 48 Gy/4 fractions (peripheral NSCLC) or 60 Gy/8 fractions (central NSCLC - within 1 cm of mediastinum or 2 cm of the proximal bronchial tree)
  - CRT of 60 Gy/15 fractions
- Trial closed early due to slow accrual
  - 154 patients received SBRT
  - 79 received CRT
- With a MFU of 36 months, 3-year LC rate was 87.6% for SBRT and 81.2% for CRT (NSS)

Long-Term Toxicity in Ultracentral Patients on LUSTRE

UC = PTV directly overlaps with the proximal bronchial tree (PBT)

- Patients with UC tumors on the LUSTRE trial were identified:
  - 21 patients received SBRT (60 Gy in 8 fractions)
  - 8 patients received CRT (60 Gy in 15 fractions)
- With MFU of 2.9 years, the 3-year local control rate of all patients was 88.3%

- All patients who developed any grade 3+ toxicity were treated with SBRT:
  - There were 3 patients with late grade 3 toxicity (bronchial stricture, chest pain, and atelectasis)
  - There was 1 patient with late grade 5 toxicity (bleeding/hemorrhage)

- **Conclusion: 60Gy/8fx provides good local control but carries an approximately 15-20% rate of late grade ≥3 toxicity. 60Gy/15fx provides acceptable LC as well.**

LUSTRE Planning Constraints

It may be more important to minimize volumetric PBT dose rather than maximum point dose to reduce risk of severe late toxicity.

SBRT 48 Gy in 4 Fractions	
Spinal canal	27 (6.75)
Esophagus	30 (7.5)
Brachial plexus	27 (6.75)
Heart	35 (8.75)
Vessels (SVC/IVC/Aorta)	48 (12)
Trachea	40 (10)
Proximal bronchial tree	40 (10)
Skin	36 (9)
Ribs	50 (12.5)
Stomach	28 (7)

SBRT 60 Gy in 8 Fractions	
Spinal canal	32 (4)
Esophagus	40 (5)
Brachial plexus	38 (4.75)
Heart	64 (8)
Vessels (SVC/IVC/aorta)	64 (8)
Trachea	64 (8)
Proximal bronchial tree	64 (8)
Skin	45 (5.6)
Ribs	60 (7.5)
Stomach	40 (5)

CRT 60 Gy in 15 fractions	
Spinal canal	36 (2.27)
Esophagus	48 (3.2)
Brachial plexus	50 (3.33)
Heart	66 (4.4)
Vessels (SVC/IVC/aorta)	66 (4.4)
Trachea	66 (4.4)
Proximal bronchial tree	66 (4.4)
Skin	45 (3)
Ribs	66 (4.4)
Stomach	48 (3.2)

Ultracentral SBRT

Included tumors located less than or equal to 1 cm from the proximal bronchial tree

HILUS Trial

- Phase 2 trial of patients receiving SBRT for tumors located within 1 cm of the proximal bronchial tree
  - 56Gy/8fx prescribed to the 67% IDL
  - Patients were stratified to
    - Group A (tumors ≤ 1 cm from the main bronchi and trachea)
    - Group B (all other tumors)
- 65 patients (39 group A and 26 group B) were evaluated
  - 2-year local control was 83%
  - Grade 3 to 5 toxicity was noted in 34% of patients, with a 15% rate of grade 5 toxicity
    - Bronchopulmonary hemorrhage, n = 8
    - Pneumonitis, n = 1
    - Fistula, n = 1

Ultracentral SBRT

Pooled data from this trial demonstrated maximum doses to the mainstem and intermediate bronchus, along with PBT compression, to be significant risk factors for grade 5 bleeding events

HILUS Trial

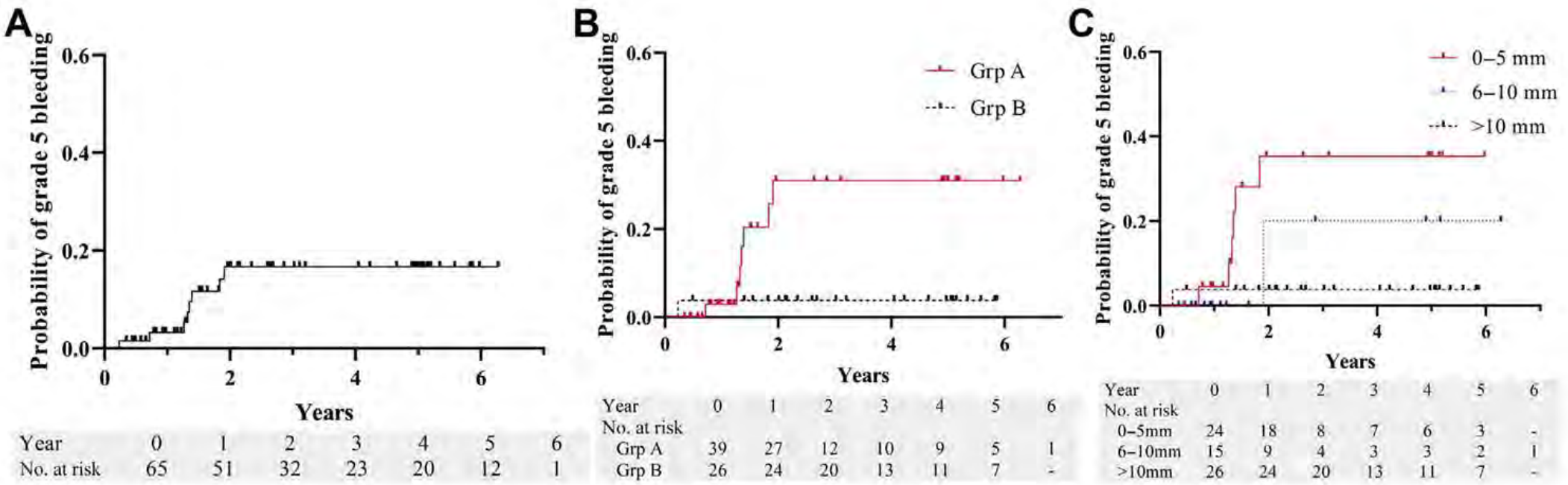
- The rates of toxicities here were notably higher than previously reported meta-analyses
  - 10% risk of grade 3+ toxicity and 5% rate of treatment-related mortality (PMID: 31075543)

- The HILUS trial had significant flaws:
  - There was heterogeneity in treatment set-up and margins (5 – 15 mm margins) which led to critical structures receiving unacceptable dose
  - Contouring critical OARs are not mandated per protocol, and these organs were not optimally planned
  - Treatment plans were prescribed to the 67% isodose line, which to led to 150% hotspots
    - Tumors in group A had a 5 mm median distance to the mainstem bronchus, and 87% (n = 35) had PTV overlap with the proximal bronchial tree

- **Conclusion: Delivering ultracentral SBRT must be done in a more accurate fashion**

Time to Grade 5 Bleed

Per Nordic-HILUS



Year	0	1	2	3	4	5	6
No. at risk	65	51	32	23	20	12	1

Year	0	1	2	3	4	5	6
No. at risk							
Grp A	39	27	12	10	9	5	1
Grp B	26	24	20	13	11	7	-

Year	0	1	2	3	4	5	6
No. at risk							
0–5mm	24	18	8	7	6	3	-
6–10mm	15	9	4	3	3	2	1
>10mm	26	24	20	13	11	7	-

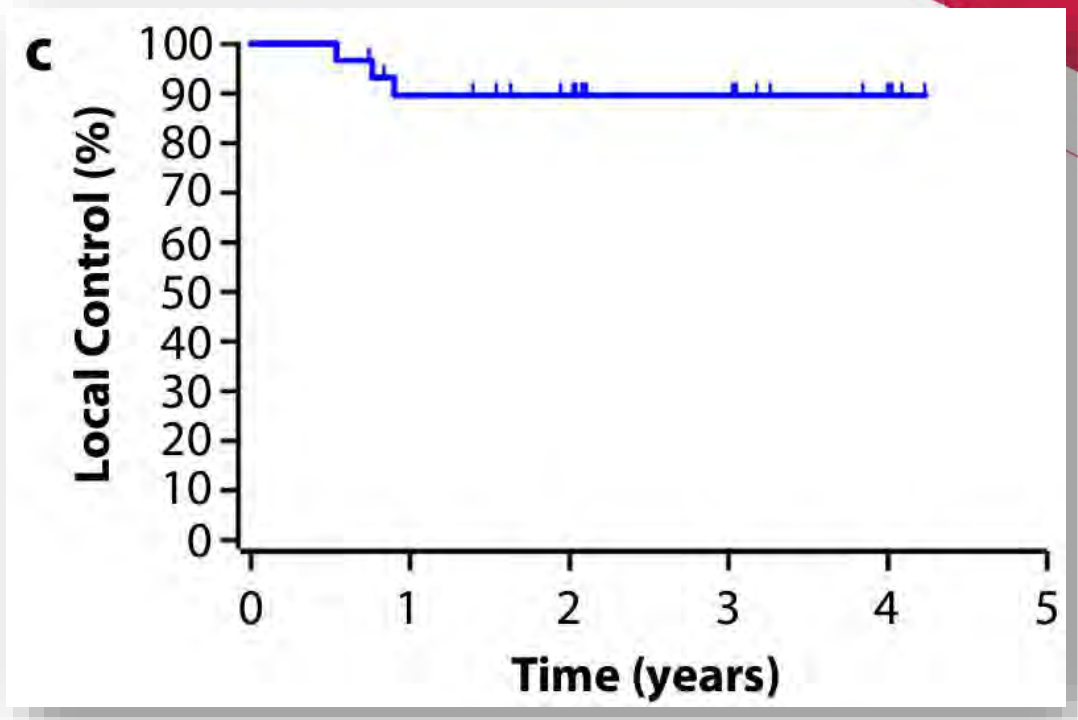
Figure 3. Time to grade 5 bleeding for (*A*) the entire cohort treated per protocol, (*B*) divided in Grps A and B ($p < 0.05$), and (*C*) divided dependent on distance between the tumor and the main bronchus ($p < 0.05$). Grp, group.

Ultracentral SBRT

Hotspot limited to 120%

SUNSET

- This study aimed to determine the MTD tolerated dose of SBRT for ultracentral NSCLC, with a starting dose of 60Gy/8fx
  - MTD was defined as the dose of radiation therapy associated with a ≤30% rate of grade 3+ toxicity
- 30 patients received 60 Gy in 8 fractions
- With a MFU of 37 months,
  - Two patients (6.7%) experienced G3-5 adverse events related to treatment
    - 1 patient with G3 dyspnea and 1 G5 pneumonia
  - Three-year local control was 89.6% (OS was 72.5%)
- **Conclusion: 60Gy/8fx, planned properly, has a favorable adverse event rate and results in excellent control for ultracentral tumors.**



SUNSET Dose Constraints

Table 2 Recommended Dose Constraints

Organ	Metric	Fraction		
		5/6	8/10	15
Spinal canal	Max	30 Gy	32 Gy	39.5 Gy
Spinal canal PRV (3 mm)	Max	32 Gy	34 Gy	42 Gy
Esophagus	Max	40 Gy	45 Gy	50.5 Gy
	5 cc	35 Gy	40 Gy	48 Gy
Brachial plexus	Max	32 Gy	39 Gy	50 Gy
Heart	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Trachea	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Proximal bronchus	Max	62 Gy	64 Gy	66 Gy
	10 cc	50 Gy	60 Gy	62 Gy
Non-GTV lung	Mean	< 12 Gy	< 12 Gy	< 14 Gy
Aorta and major vessels	Max	62 Gy	64 Gy	64 Gy
	10 cc	50 Gy	60 Gy	60 Gy
Stomach and intestines	Max	40 Gy	45 Gy	50 Gy
	10 cc	35 Gy	40 Gy	48 Gy

Abbreviations: GTV = gross tumor volume; PRV = planning organ-at-risk volume.

Treatment Summary

Stage 1 Lung Cancer

Central → **50 Gy in 5 fx**

Ultra Central → **60 Gy in 8 fx (with consideration of 60 Gy in 15 fx)**

Dose / Fractionation	α/β = 10	α/β = 3
50 / 5	100	217
56 / 8	95	187
60 / 8	105	210
60 / 15 (Hypofx)	84	140
60 / 30 (Conventional)	72	100


Thank you