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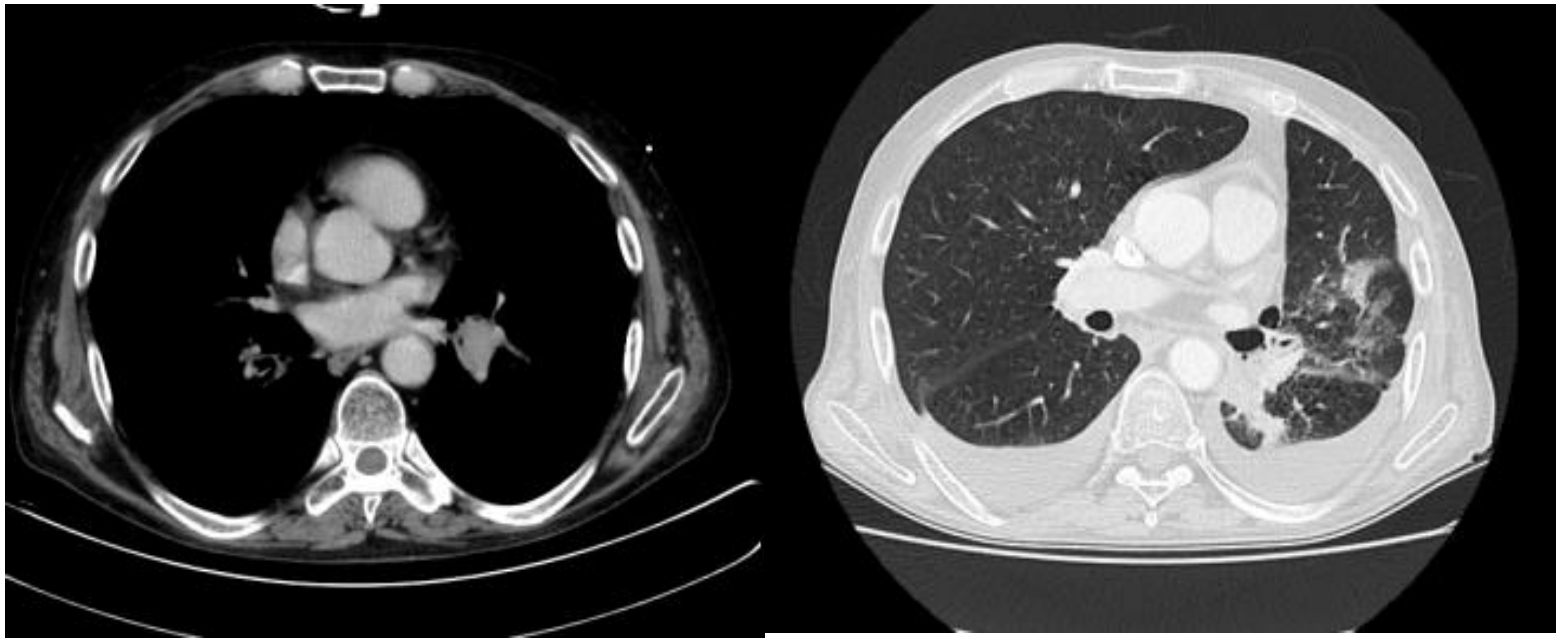


Peripheral, central or too central:
Tumor location and practice of SBRT for early stage NSCLC

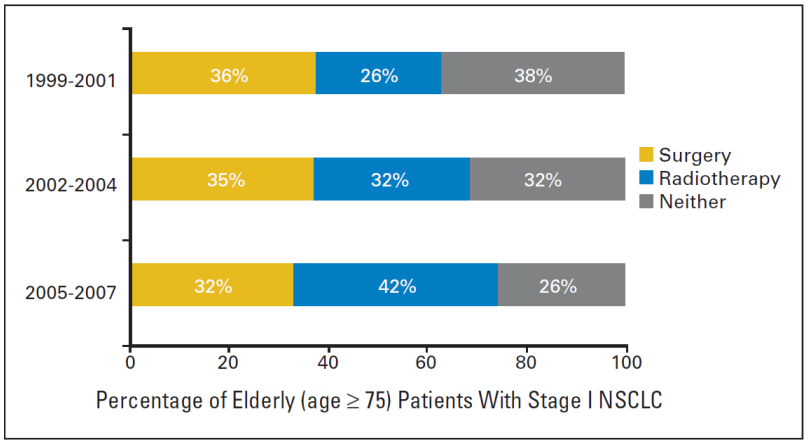
Ursula Nestle

ELCC Geneva, 14.4.2016

SBRT: success story …

Palma D, 2010

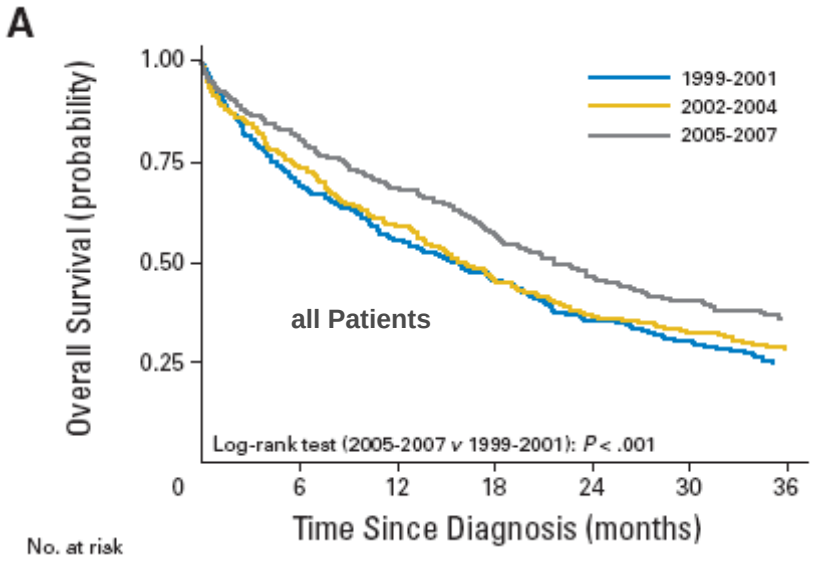
Population registry –North Holland

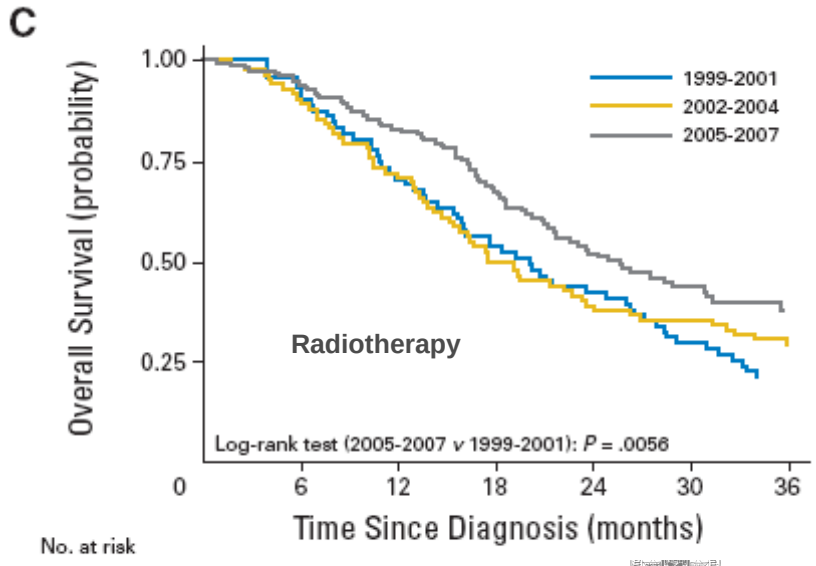


N = 843 stage I patients ≥75 years

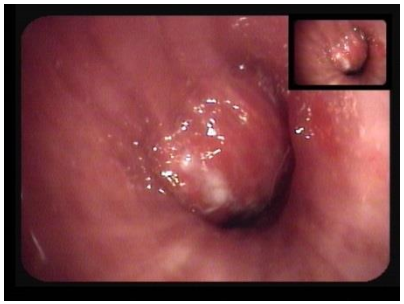
SBRT introduction associated with

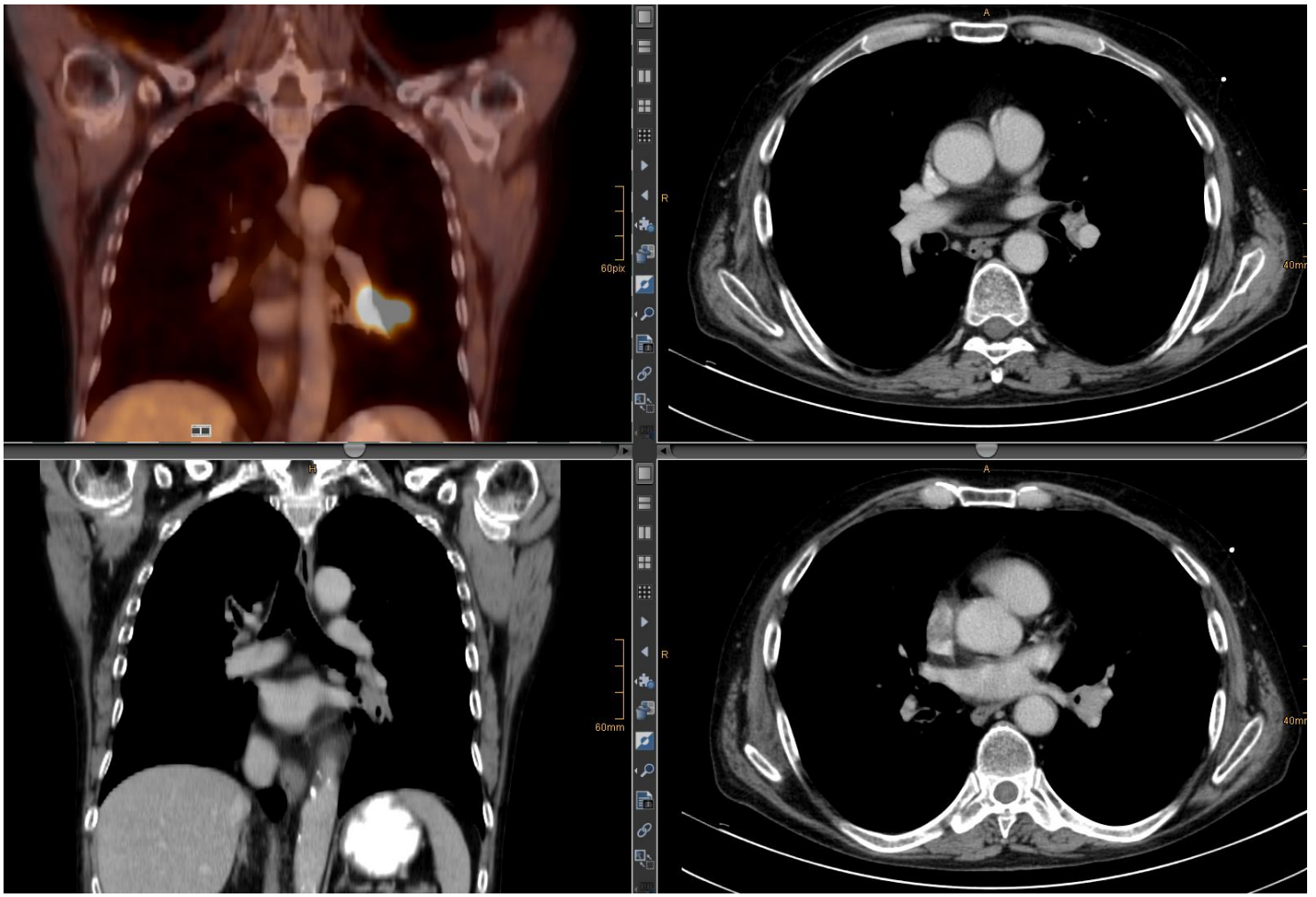
- 16% increase in RT utilization
- improved survival for whole cohort
- improved survival for RT patients





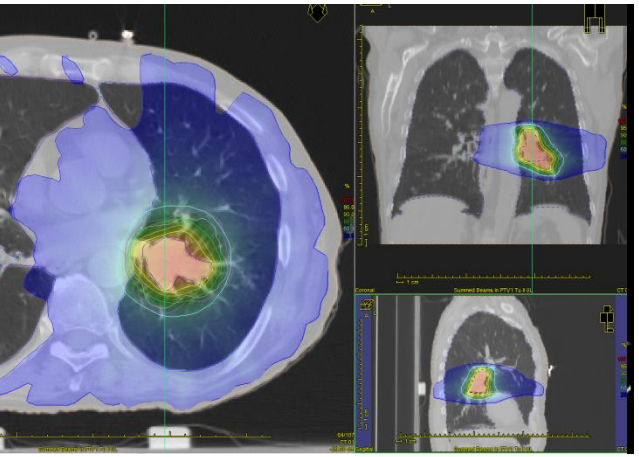
Pat. S.D.



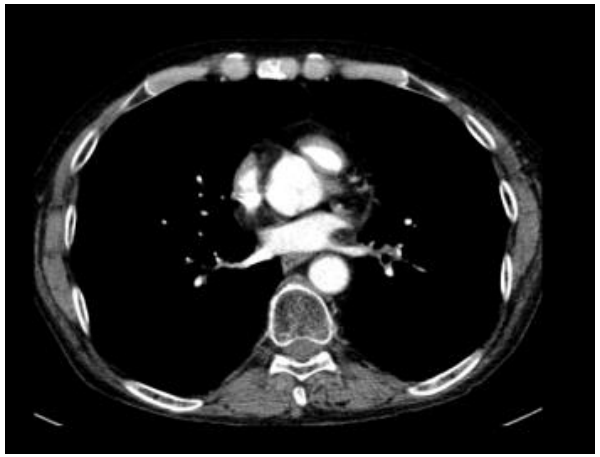


Mr. S.D., *1943
1/2010: diagnosis of a squamous cell carcinoma (G2) of the left lower lobe
bronchoscopy: submucous tumor in the lower lobe bronchus
Staging: T2 N0 M0
heavy smoker, arteriosclerosis, COPD GOLD III, high-risk resection candidate
severe claustrophobia

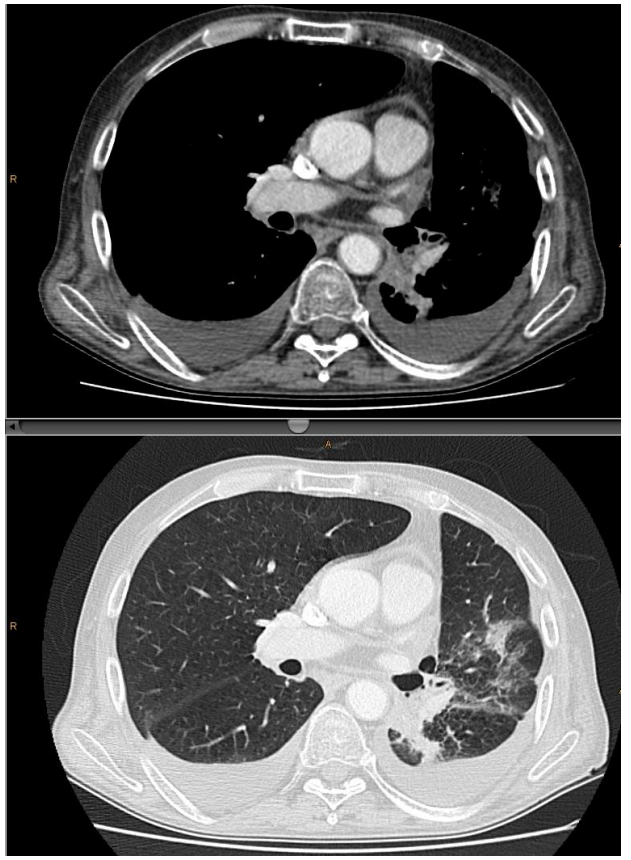
Pat. S.D. *1943, SCC



1/2010



3/2011



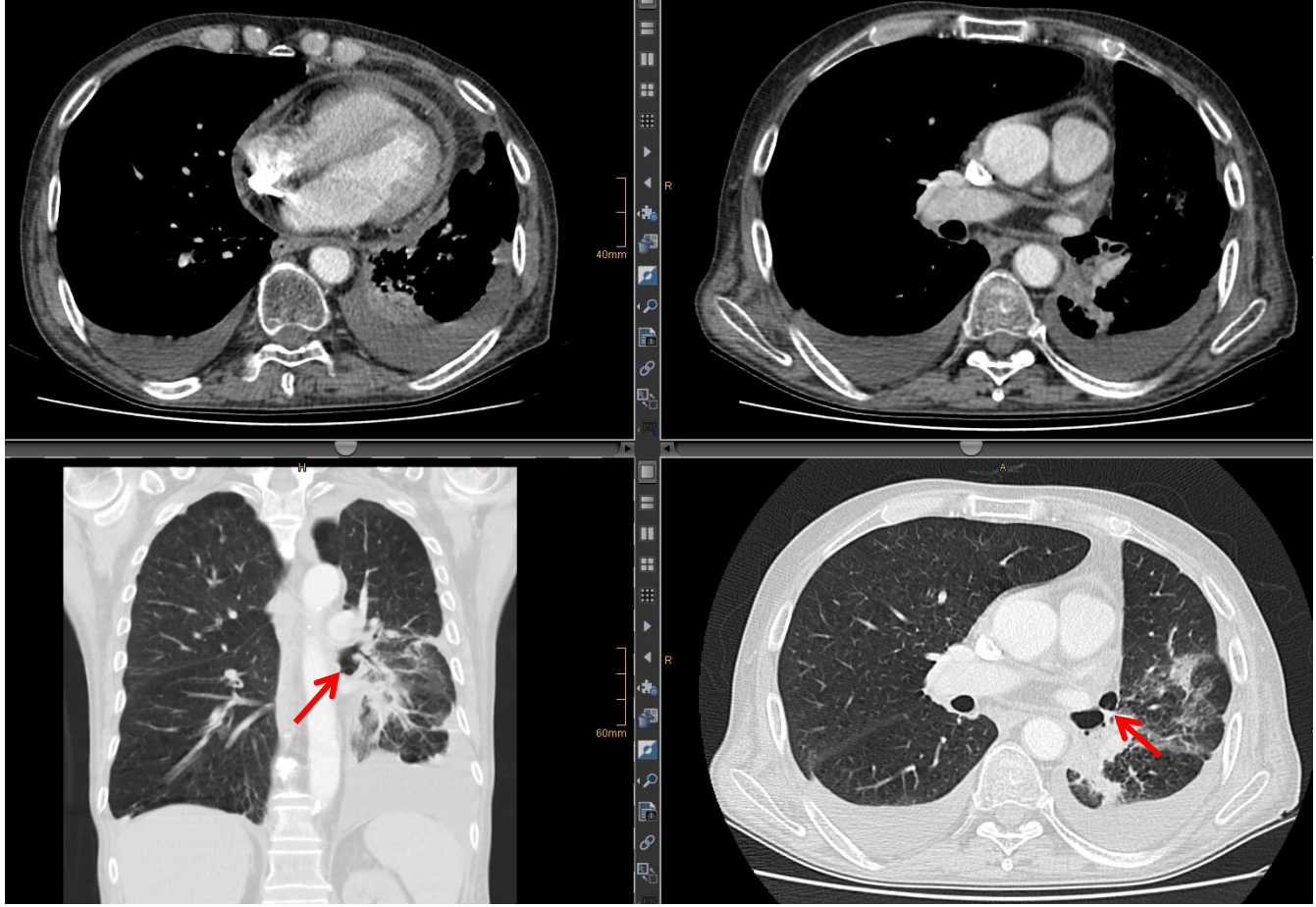
7/2011

Mr. S.D., *1943
1/2010: pat. refuses surgery due to high risk and claustrophobia
treatment: SBRT (5x7 Gy on 60% isodose due to central location)
setup under sedation by Propofol due to claustrophobia

Chest-CT follow up until 3/2011: complete tumor remission

7/2011: repeated signs of infection, fever, dyspnea

Pat. S.D.
*1943,
SCC



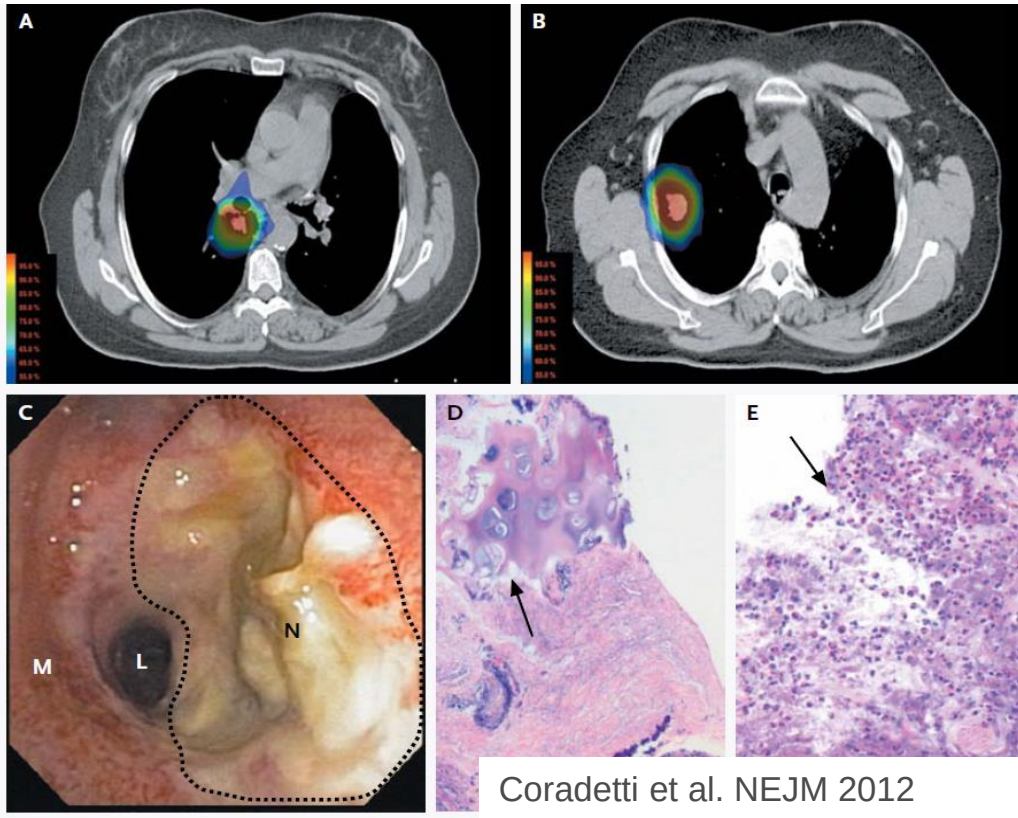
7/2011:
bronchoscopy: necrotic cavity left lower lobe bronchus,
fistula into mediastinum and pericardium,
fibrotic changes of B6 bronchus

histology: granulocytary necrosis, isolated tumour suspicious cells

Another fatal necrosis after central SBRT…

Case report: Central Airway Necrosis after SBRT

- SBRT to two NSCLC,
  one of them centrally located
- 8 months later:
  mediastinal LN recurrence,
  extensive changes within
  irradiated bronchus
  (**biopsy**: fibrosis)
- **Chemo** / hemoptysis / intubation
- Died 11 months after SBRT



Coradetti et al. NEJM 2012

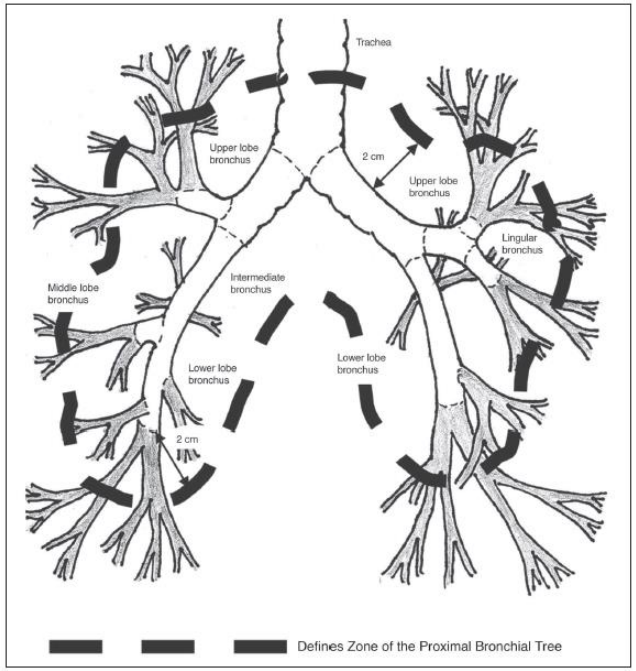
Proximal bronchial tree

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

70 pts.,
T1/T2 NSCLC
3x20Gy; 3x22 Gy
prescription to 80%
Type A
no density corrections



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

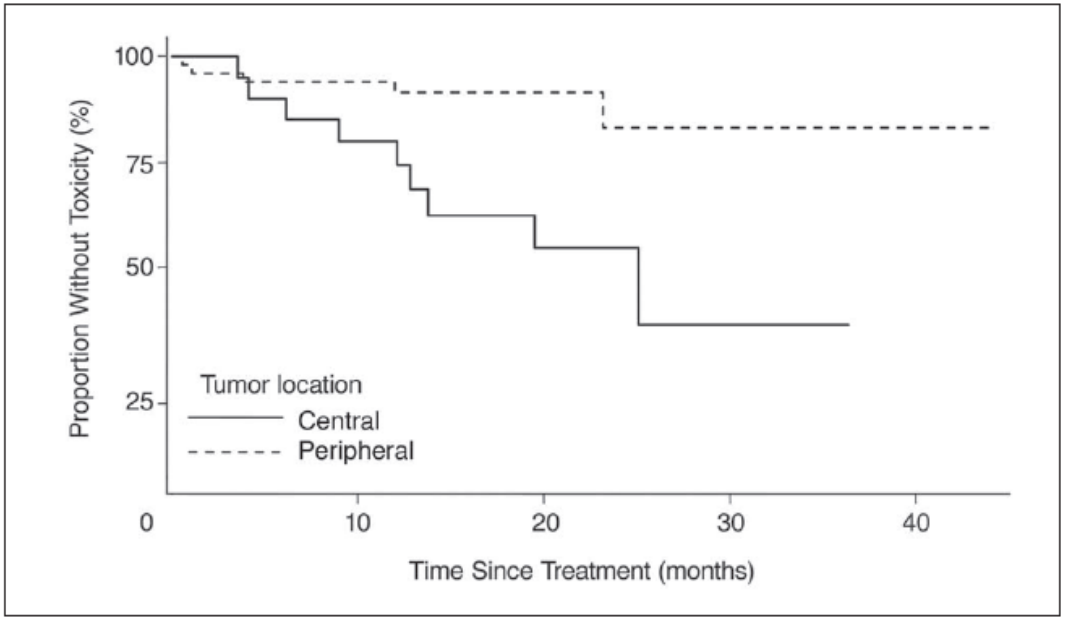


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

Reviewed: Toxicities after central SBRT

Table 3
Treatment-related mortality and severe toxicity.

4 prospective, 16 retrospective studies

223 cases RTOG-„central“, 340 not

Grade III/IV toxicity: 8.6%

Treatment related mortality: 2.7%

TRM with BED_3 < 210 Gy:

frequently missing information:
- prescription dose vs. dose to OARs
- dose inhomogeneities

- # cases at risk for respective OARs
- OAR volumes exposed …

						Grade 3–4 toxicity (clinical details if provided)	Grading system
[34] (2011)						None	–
Haasbeek [32] (2011)	35	63	63[c]	No[f]		None	–
Bral [23] (2011)	16	17	17	Yes		*	–
Olsen [38] (2011)	11	15	15[c]	No[f]		2 × Bronchial stricture (Max dose 40/4 both, BED_3 173 Gy)	CTC (v2)
Stauder [39] (2011)	16	47[a,b]	Not specified	Yes		1 × Pneumonia, 1 × pericarditis	CTC (v3)
Rowe [37] (2012)	11	51[a,c]	30	No[f]		1 × Apnoea, 1 × pneumonia, 2 × pleural effusion, 1 × anxiety (At median 7.6 months, 2 in central tumours)	CTC (v2)
Nuyttens [30] (2012)	23	58[a]	39	No[f]		*	–
Taremi [25] (2012)	19	20	20	Unclear		1 × pneumonit…	CTC (v3)
Janssen [31] (2012)	14	29[b]	Not specified	Unclear		…1 × dyspnoea	CTC (v3)
							–
							–
							–
						…1 × rib …ents)	CTC (v3)
						…a. Late …tients)	CTC (v3)
							–
							CTC (v3)
							CTC (v4)
						…onitis. Late 6 × pneumonitis. (3 were …SBRT-related, 7 were more likely felt to be COPD exacerbation).	CTC (v3)
						*	–
						None	–

Central tumors: outcome from expert treatment

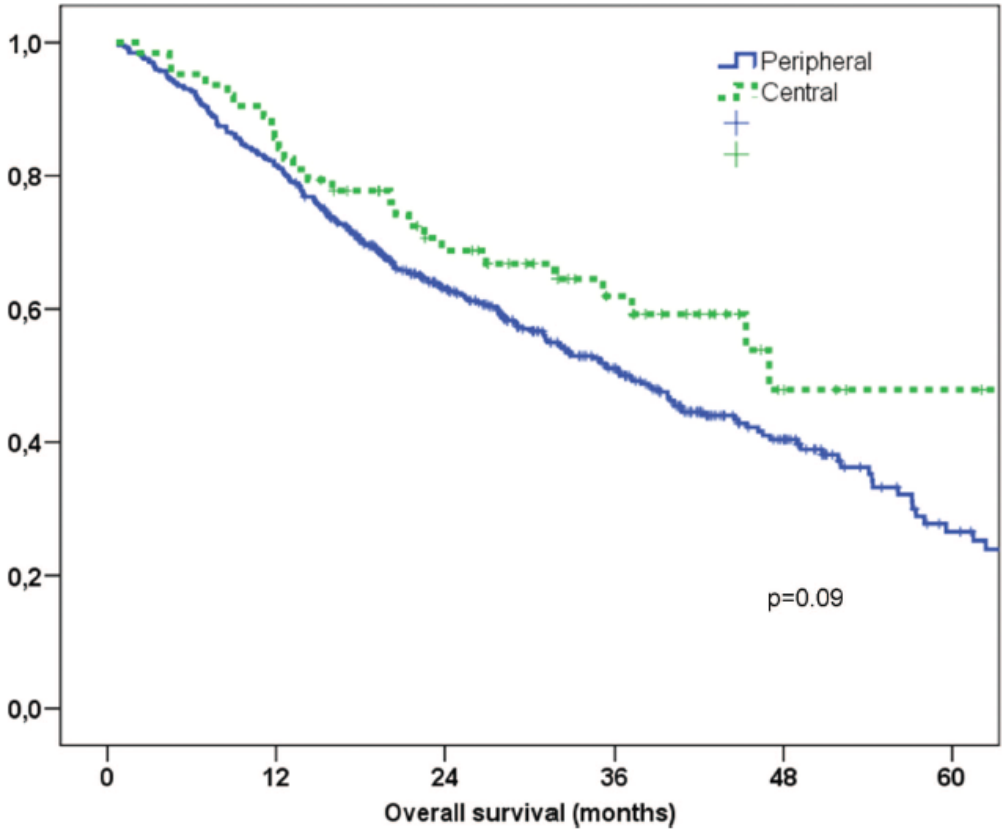
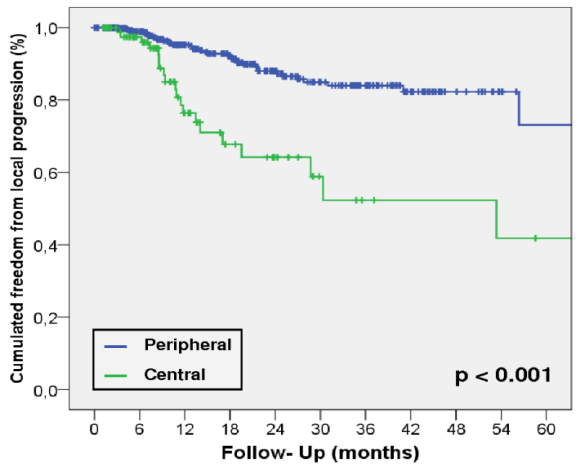


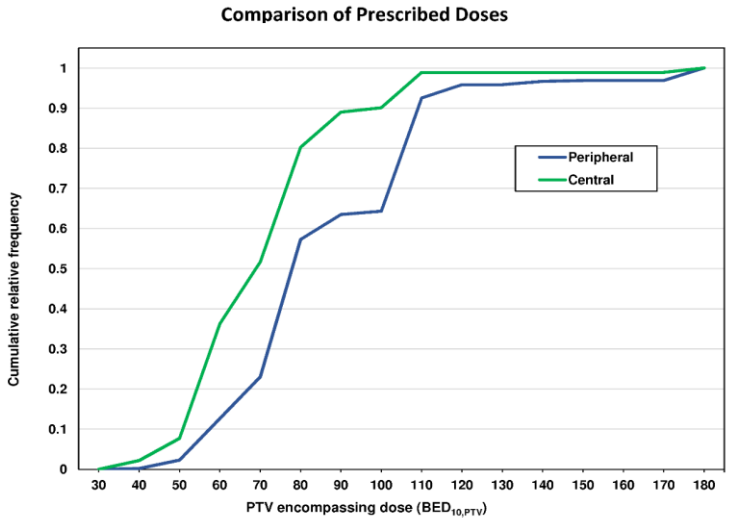
FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

Haasbeek JTO 2011, BED_{10}=105 Gy

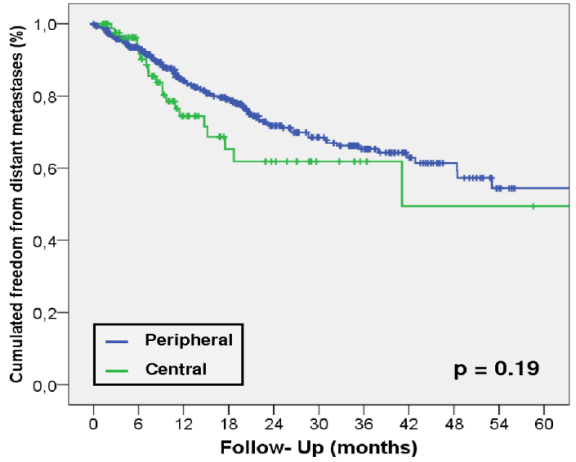
Central tumors: outcome in nonprospective multicenter setting

A

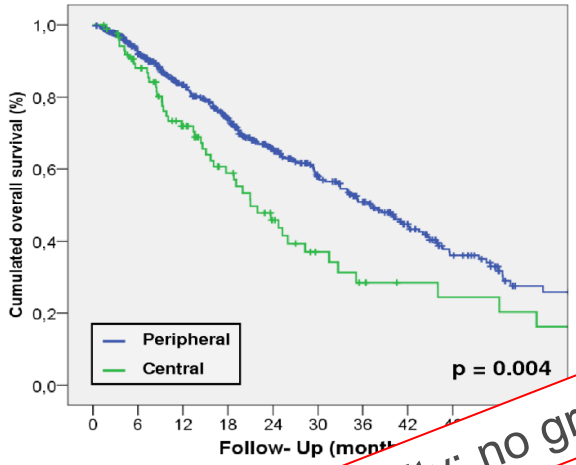




C

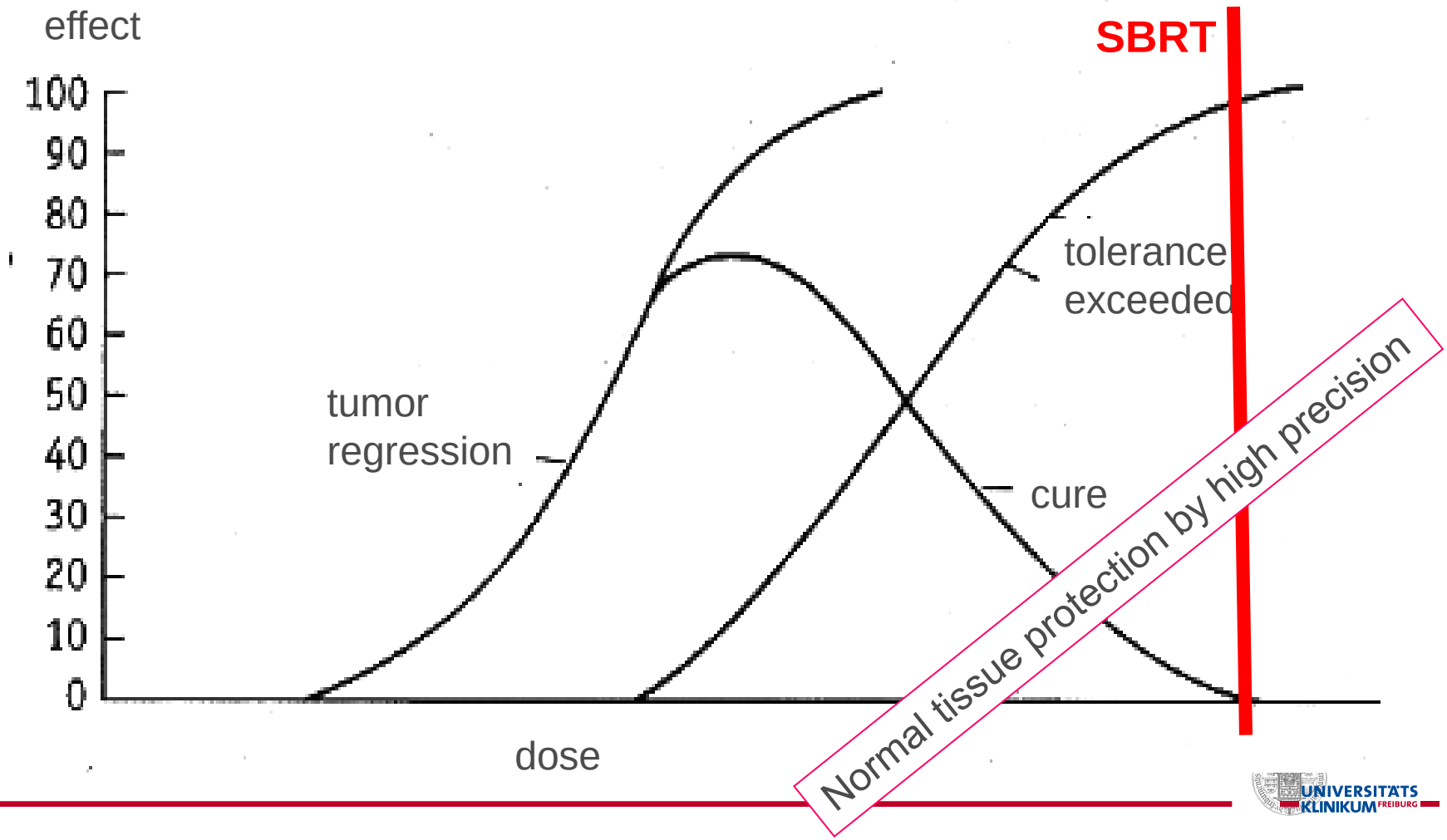


D

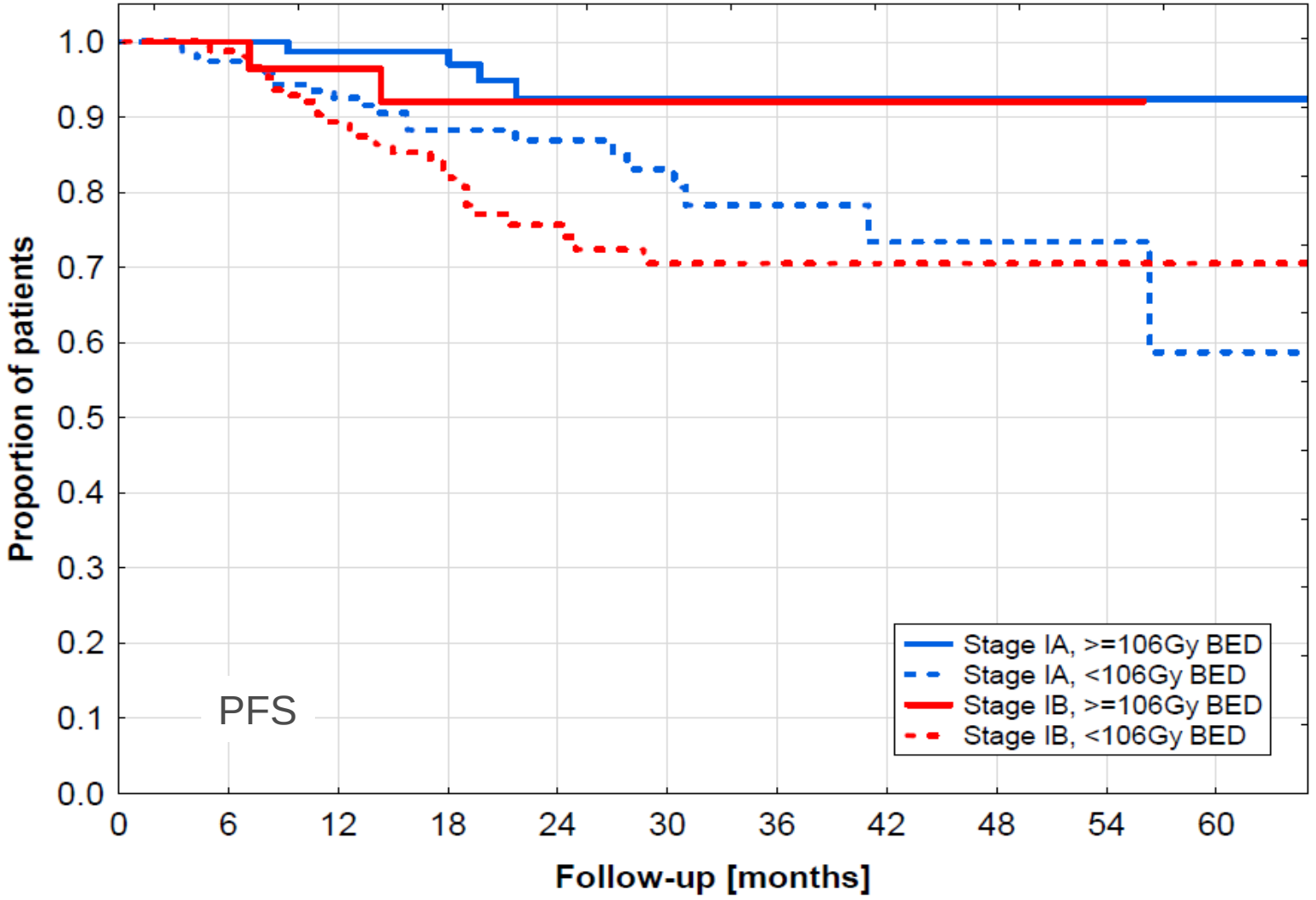


Toxicity: no grade III/IV, 1 grade V

SBRT of central tumors: reason to be scared …



SBRT: „magic BED_{10}“ of 100 Gy



M. Guckenberger et al. JTO 2013

SBRT: a knife without suture

Differences in physiological NT-reaction to high dose RT:

Fibrosis (lung, liver), necrosis (brain, bone), strictures (esophagus, bronchi)

Difference in clinical consequences:

Parallel vs. serial organs

Parallel (lung, liver):

small volume of damage no problem (fibrosis)

Serial (esophagus, vessel):

small volume of damage

may cause life threatening effects

Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

Donald M. Cannon, Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon

J Clin Oncol 31:4343-4348.

Conclusion

Although this dose-escalation model limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols, especially when using hypofractionation.

57 Gy – 85.5 Gy in 25 fractions
EQD2 predicting 5% complication rate @2y:
75-83 Gy

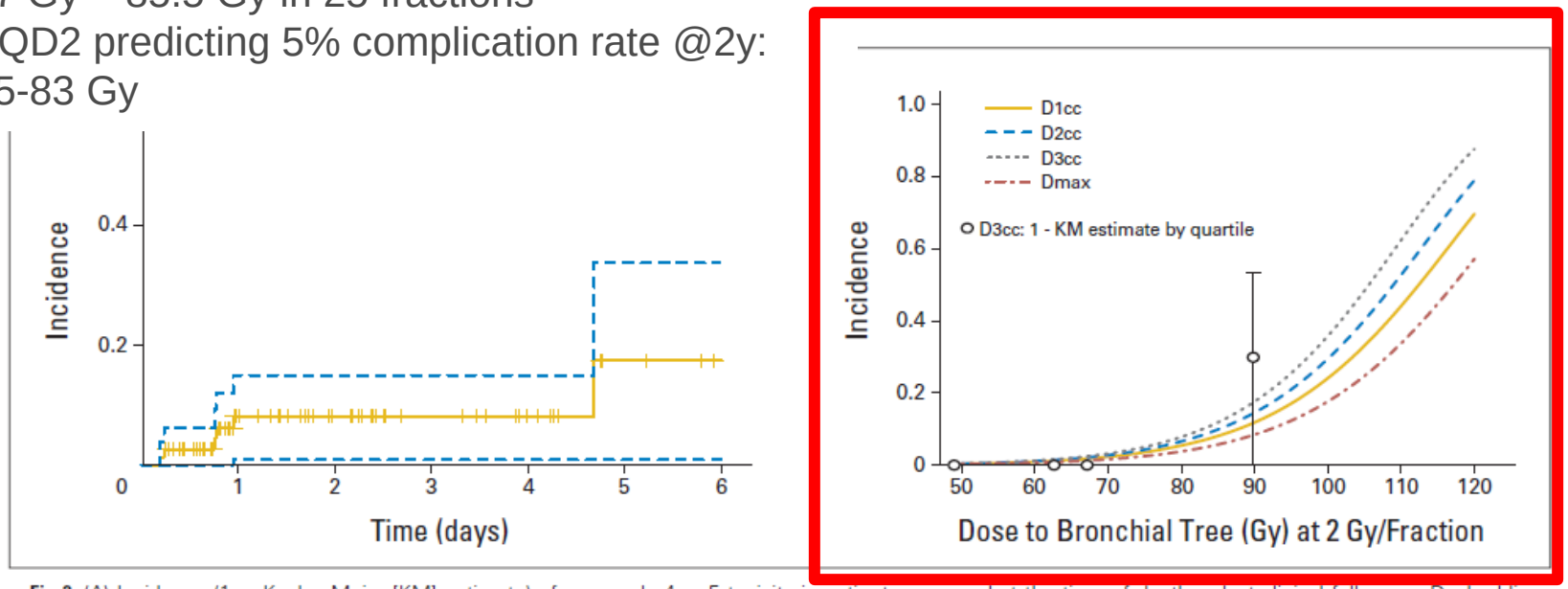
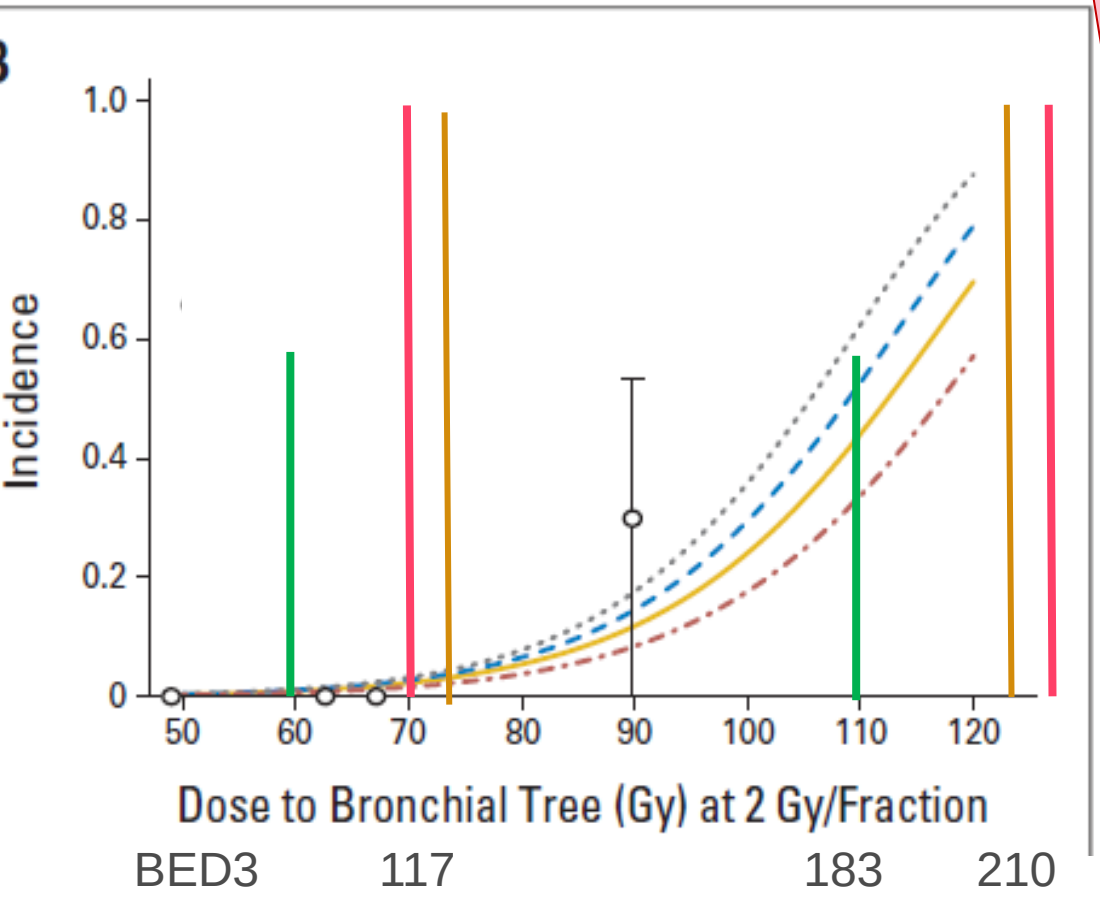


Fig 2. (A) Incidence (1 − Kaplan-Meier [KM] estimate) of any grade 4 or 5 toxicity in patients censored at the time of death or last clinical follow-up. Dashed lines represent the 95% CI. (B) Two-year probabilities of late grade 4 or 5 toxicity according to dose-per-fraction normalized dose (EQD2) to the proximal bronchial tree and estimated using a Cox proportional hazards model. Open circles represent the 1 − KM estimate (± 95% CI) for quartiles of EQD2 D3cc (centered at the quartile mean). DXcc, maximum dose D such that X cm^3 of the structure received a dose ≥ D; Dmax, maximum dose to any voxel within structure.

What is the dangerous SBRT dose to the central mediastinum?

MTD of 83 Gy/ 2Gy
= „magic“ BED_{10} of 100 Gy,
Narrow therapeutic corridor



prescribed by	physical dose Gy	EQD2 Gy (αβ=3)
Cannon min.	25x2.28	60
max.	25x3.42	110
Timmerman	3x18	226
VU prescription	8x7.5	126
VU restriction	8x5.5	74.8
Coradetti patient	5x10	130
Freiburg patient encompassing	5x7	70
maximum	5x11.6	130

Need for a more detailed view on doses and volumes..

Results – Highest toxicity grade

SBRT Dose	# pts	Grade 2	Grade 3	Grade 4	Grade 5
10X5	8	5	0	0	0
10.5X5	7	1	0	0	1
11X5	14	4	1	0	0
11.5X5	38	11	4	0	2
12X5	33	4	5	1	1

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A. Bezjak, RTOG 0813 early results; World Lung 2015

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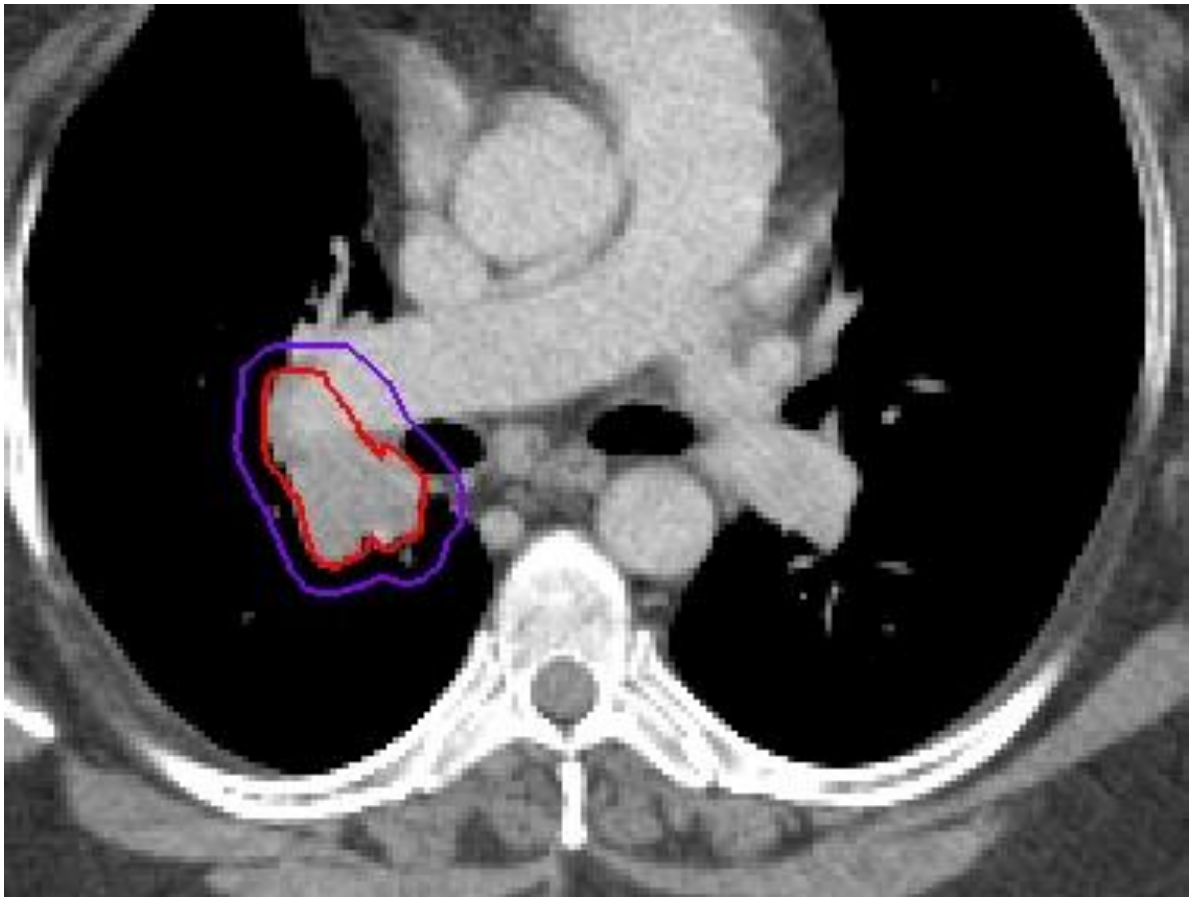
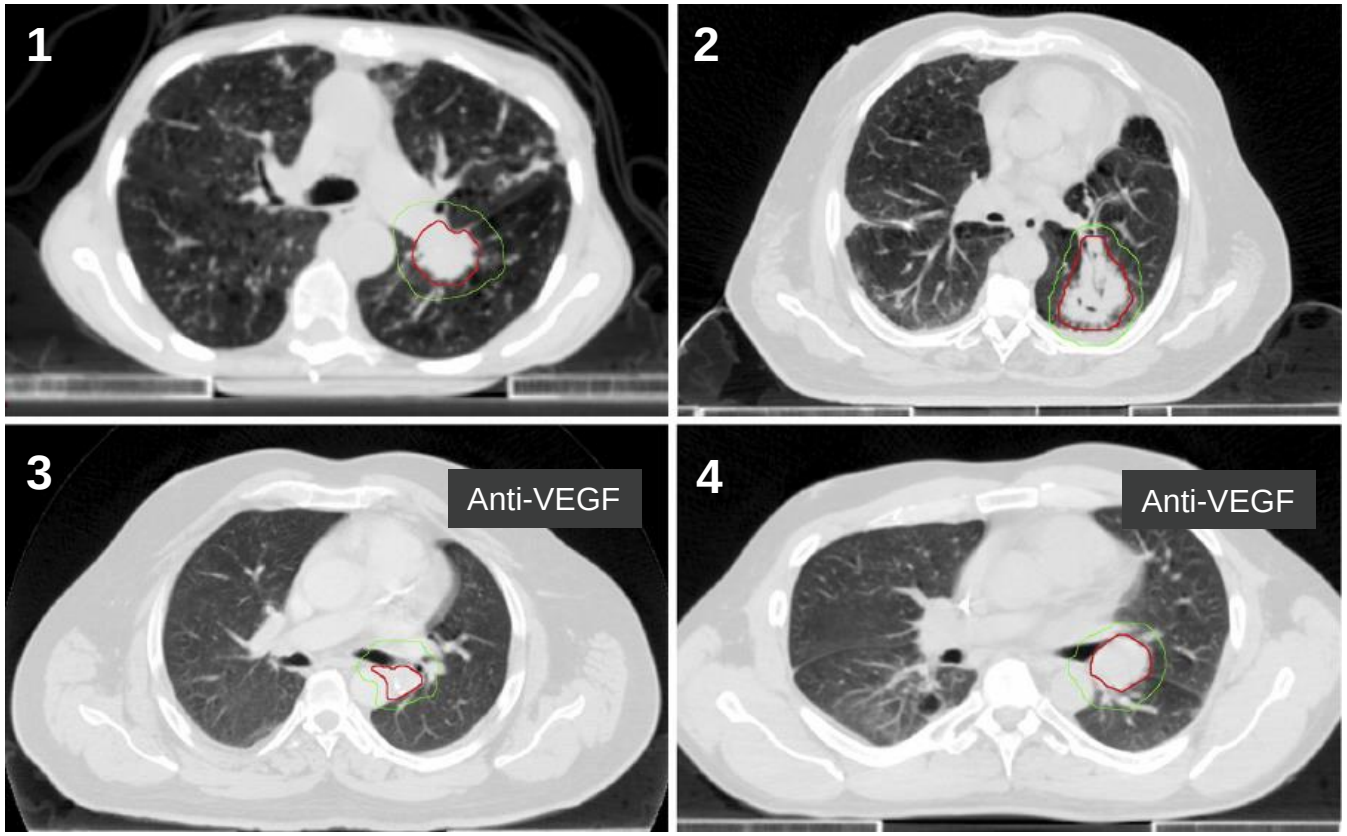
Is it only toxicity?
Tumor bridging bronchus and vessel



SBRT related deaths: tumors abutting PBT



Haseltine et al PRO, 2015:

N=108, 18 abutting PBT
4 SBRT related deaths,
All in abutting tumors

- Pat 1: 5X9Gy (aß3, EqD2 108Gy), Dmax pBT/NFZ: 44.8/47.8Gy (**EqD2 107.2/120.1**)
- Pat 2: 5X9Gy (aß3, EqD2 108Gy), Dmax pBT/NFZ: 45.0/45.3Gy (**EqD2 108.0/109.3**)
- Pat 3: 5X9Gy (aß3, EqD2 108Gy), Dmax pBT/NFZ: 47.2/49.4Gy (**EqD2 116.0/127.3**)
- Pat 4: 5X10Gy(aß3, EqD2 130Gy), Dmax pBT/NFZ: 51.4/54.6Gy (**EqD2 137.0/151.5**)

Lung Cancer 89 (2015) 50–56

Contents lists available at ScienceDirect

Lung Cancer

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

Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors

Aadel A. Chaudhuri[a], Chad Tang[a], Michael S. Binkley[a], Michelle Jin[a], Jacob F. Wynne[a], Rie von Eyben[a], Wendy Y. Hara[a,b], Nicholas Trakul[a], Billy W. Loo Jr.[a,b,**], Maximilian Diehn[a,b,c,*]

[a] Department of Radiation Oncology, Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA 94305, USA
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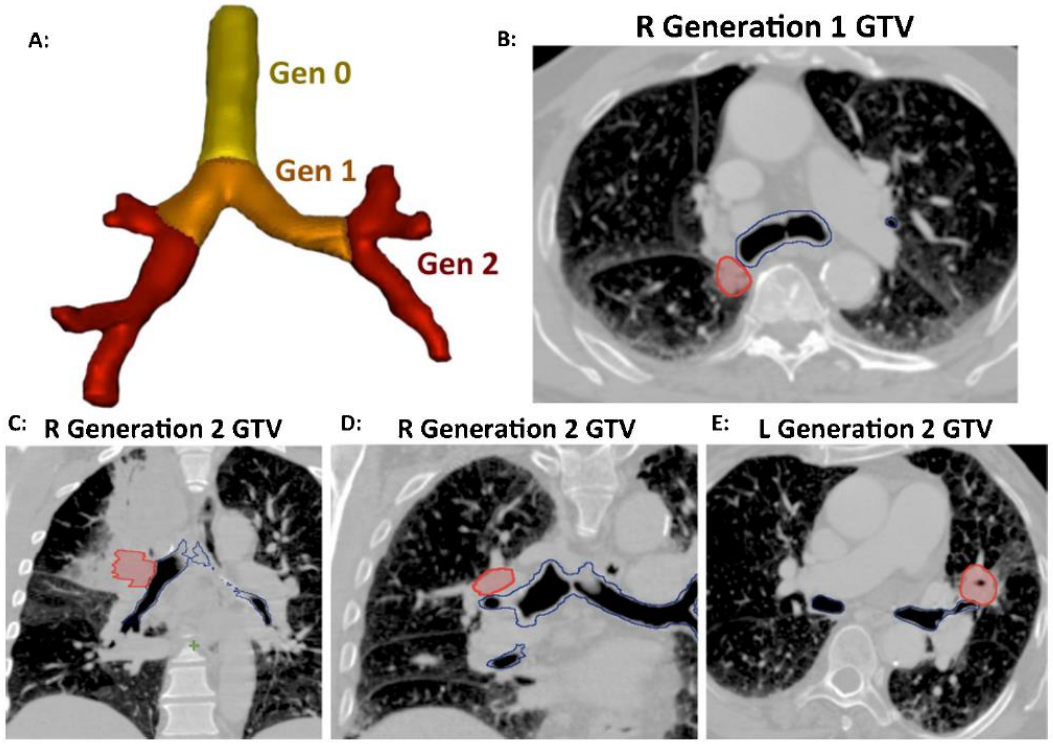


N=68,
34 peripheral
34 central
7 ultra-central
50 Gy/4-5 fr

no severe toxicity
No difference in outcome

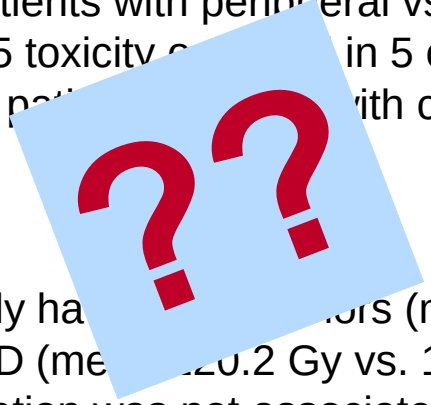
CENTRAL SBRT: DISCORADANT LITERATURE REPORTS

- ***Timmerman, J Clin Oncol. 2006***:

  Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors.

- ***Fakiris, Int. J. Radiation Oncology Biol. Phys., 2009***:

  - no significant survival difference between patients with peripheral vs. central tumors (MS 33.2 vs. 24.4 months, p = 0.697). Grade 3 to 5 toxicity o[illegible] in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 pa[illegible]ith central tumors (Fisher's exact test, p = 0.088).



- ***Park, JTO, published ahead of print 2015:***

  Patients with central tumors were… more likely ha[illegible]ors (mean 2.5 cm vs. 1.9 cm, p<0.001), and be treated with a lower BED (me[illegible]20.2 Gy vs. 143.5 Gy, p<0.001). Multivariable analysis revealed that tumor location was not associated with worse overall survival, local control, or toxicity. Patients with central tumors were less likely to have acute grade ≥3 toxicity than those with peripheral tumors (odds ratio 0.24, p=0.02).

- ***Mangona, Int. J. Radiation Oncology Biol. Phys., 2015:***

  With 79 central and 79 peripheral tumors matched, no differences in AEs were observed after 17 months median follow-up. Moderate-dose SBRT yields a similarly safe toxicity profile for both central and peripheral lung tumors

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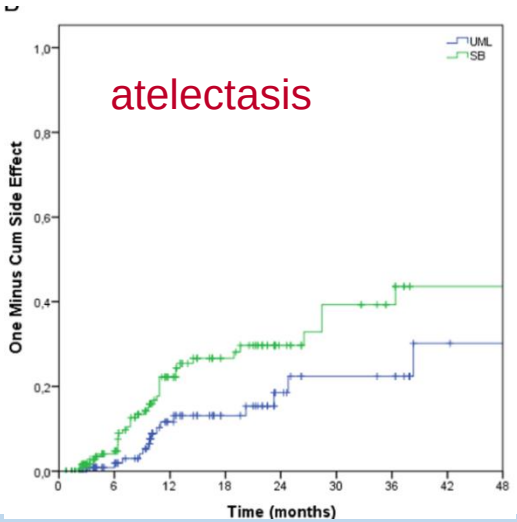
Seminars in
RADIATION
ONCOLOGY

Dose and Volume of the Irradiated Main Bronchi and Related Side Effects in the Treatment of Central Lung Tumors With Stereotactic Radiotherapy

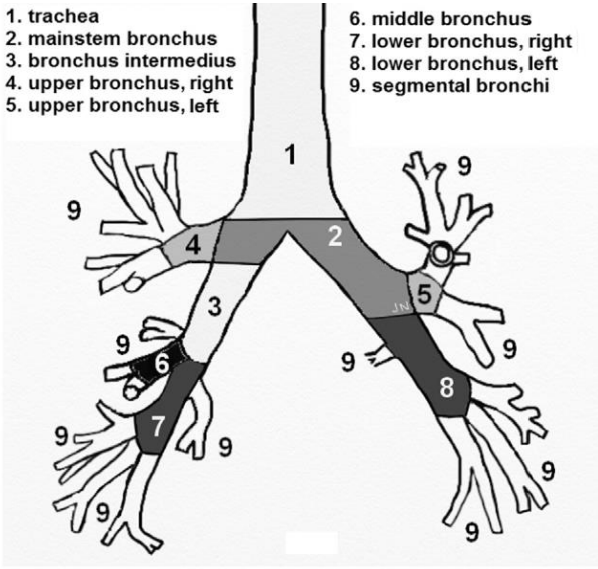
Marloes Duijm,* W. Schillemans,* Joachim G. Aerts, MD, PhD,† B. Heijmen,* and Joost J. Nuyttens*

Semin Radiat Oncol 26:140-148

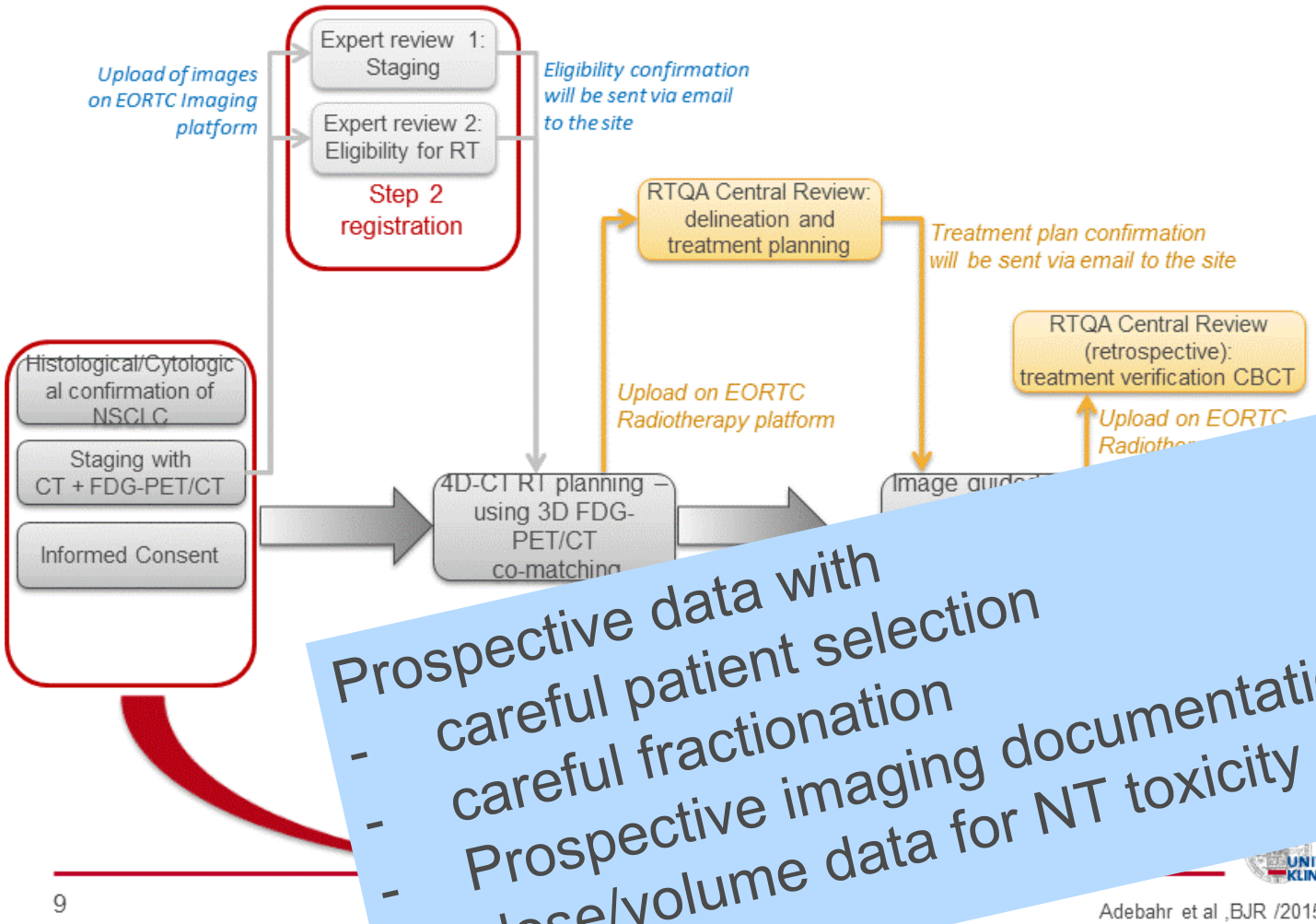


N=134 central SBRT, 5fr
NTCP (CT assessed)
Vs. local dose

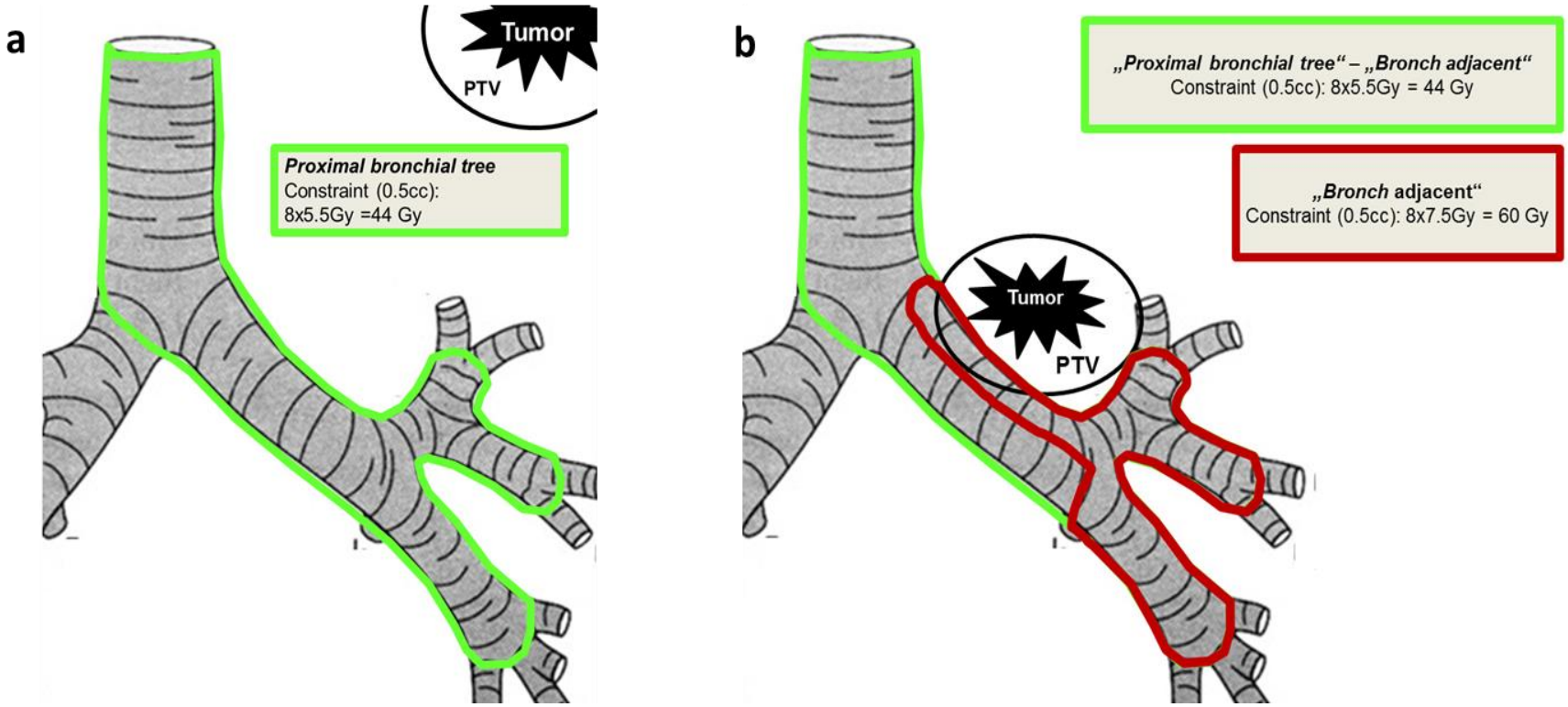
50% risk level Dmax:
55 Gy for mid-bronchi
65 Gy for mainstem bronchi



22113 – 08113 Trial design



Loosening the dose constraints for the EORTC LungTech trial



Dose constraints for the proximal bronchial tree

a) The general dose constraint for the whole structure **“proxBT” (green) is 44Gy (0.5cc) in 8 fractions**.
b) For PTVs near or abutting the main bronchus a subvolume **“Bronch adjacent**” has to be generated (red). The dose constraint for this volume is **60Gy/8 fractions (0.5cc),** while the constraint for the rest of the **“proxBT**” (green) **remains 44Gy/8 fractions (0.5cc).**

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Summary: SBRT for central NSCLC

Toxicity is threat for central SBRT, concerning the proximal bronchial tree, but also esophagus, large vessels and heart

More protracted fractionation may be one key to lower patient's risk and high dose inhomogeneities may be a problem

Local dose/volume assessment in bronchial substructures is necessary and prospective data needed to predict and model

In any case, careful patient selection, and care about the high risk of toxicity for tumors abutting proximal bronchi is necessary

SBRT to central tumors in any combination with anti VEGF should be avioded