EUROPEAN LUNG CANCER CONFERENCE 2016

Stereotactic ablative radiotherapy (SABR,SBRT) for stage I NSCLC

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Disclosures

- Speakers honoraria: Varian Medical Systems, Lilly Oncology

- Research agreement between the Department of Radiation Oncology at VUMC and Varian Medical Systems

- Patent for image feature analysis for response assessment after SABR (non-commercialized)

Overview

- **Peripheral early-stage NSCLC**
  - Treatment indications
    - Outcomes in operable cases
    - Outcomes in elderly patients
    - British Thoracic Society Guidelines, Asian recommendations
    - Cautionary data - interstitial lung disease
  - Follow-up
    - Approach to suspicious lesions on imaging
    - Importance of pathology and consider SCLC
    - Smoking cessation
- **Moderately central early-stage NSCLC**

SABR Guidelines

- **ESMO Guidelines** [Vansteenkiste J, 2014]
- SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

- ESMO Guidelines 2013: BED_{10} ≥100 Gy recommended; tumors of up to 5 cm

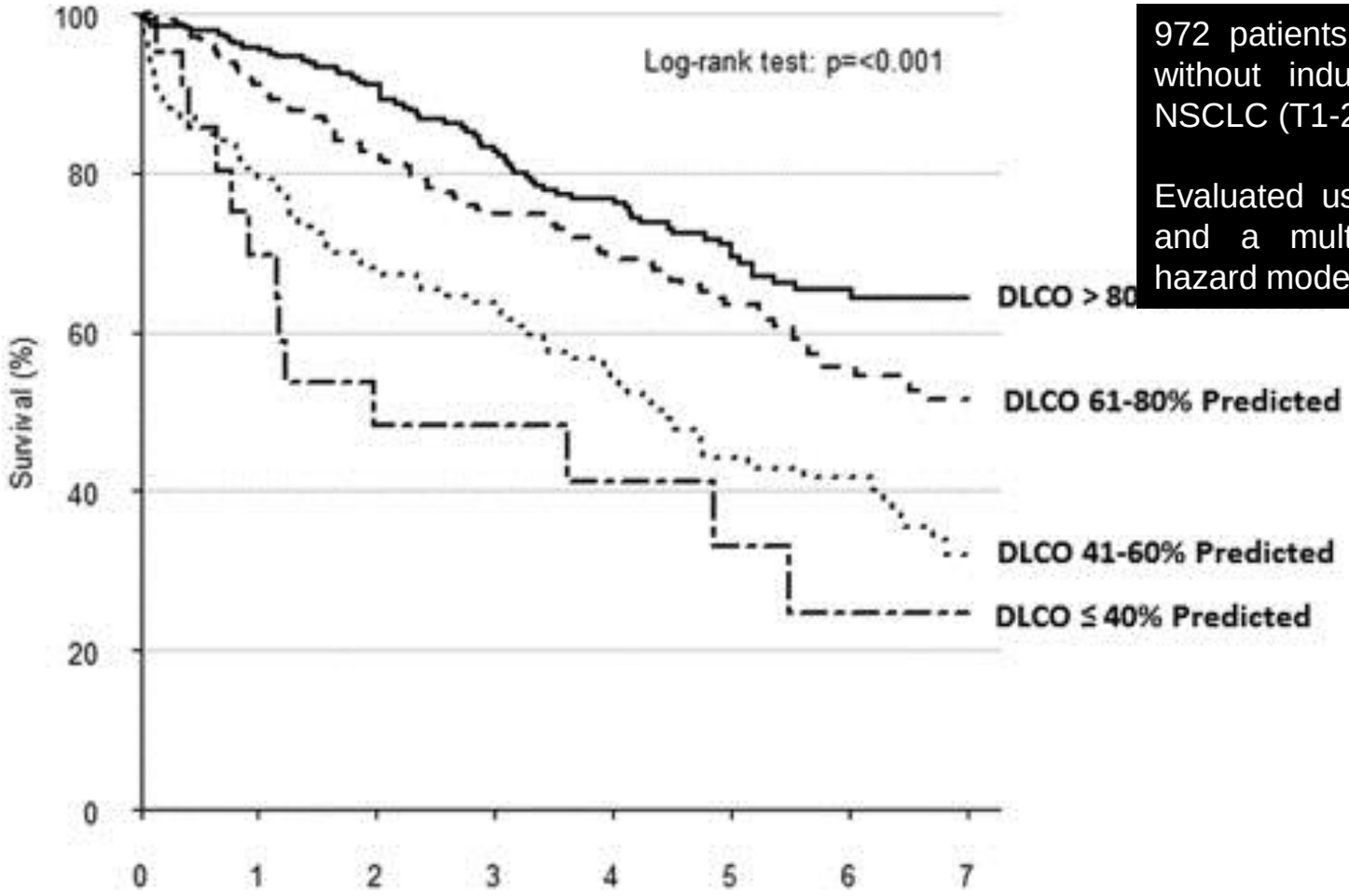
- **NCCN Guidelines** [version 7.2015]
- SABR is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation.

SABR outcomes in operable lung cancer

SABR data		Stage	3-year survival
SABR - Japan	Onishi H, 2011	T1-2N0	83%
SABR - Dutch	Lagerwaard F, 2012	T1-2N0	85%
SABR – US (RTOG 0618)	Timmerman R, 2013	T1-2N0	77%
SABR - Dutch	Verstegen N, 2013	T1-2N0	80%
SABR - Japan (JCOG 0403)	Nagata Y, 2015	T1N0	76%
Surgical data		**Stage**	**3-year survival**
Sublobar resection (ACOSOG)	Fernando HC, 2014	T1N0	71%

Lagerwaard F, IJROBP 2012; Nagata Y, IJROBP 2015; Onishi H, IJROBP 2011; Verstegen NE, Ann Oncol 2013; Timmerman JCO 2013; Fernando HC, JCO 2014

Overall survival stratified by redicted DLCO



972 patients who underwent lobectomy without induction therapy for stage I NSCLC (T1-2N0M0) from 1996 to 2012

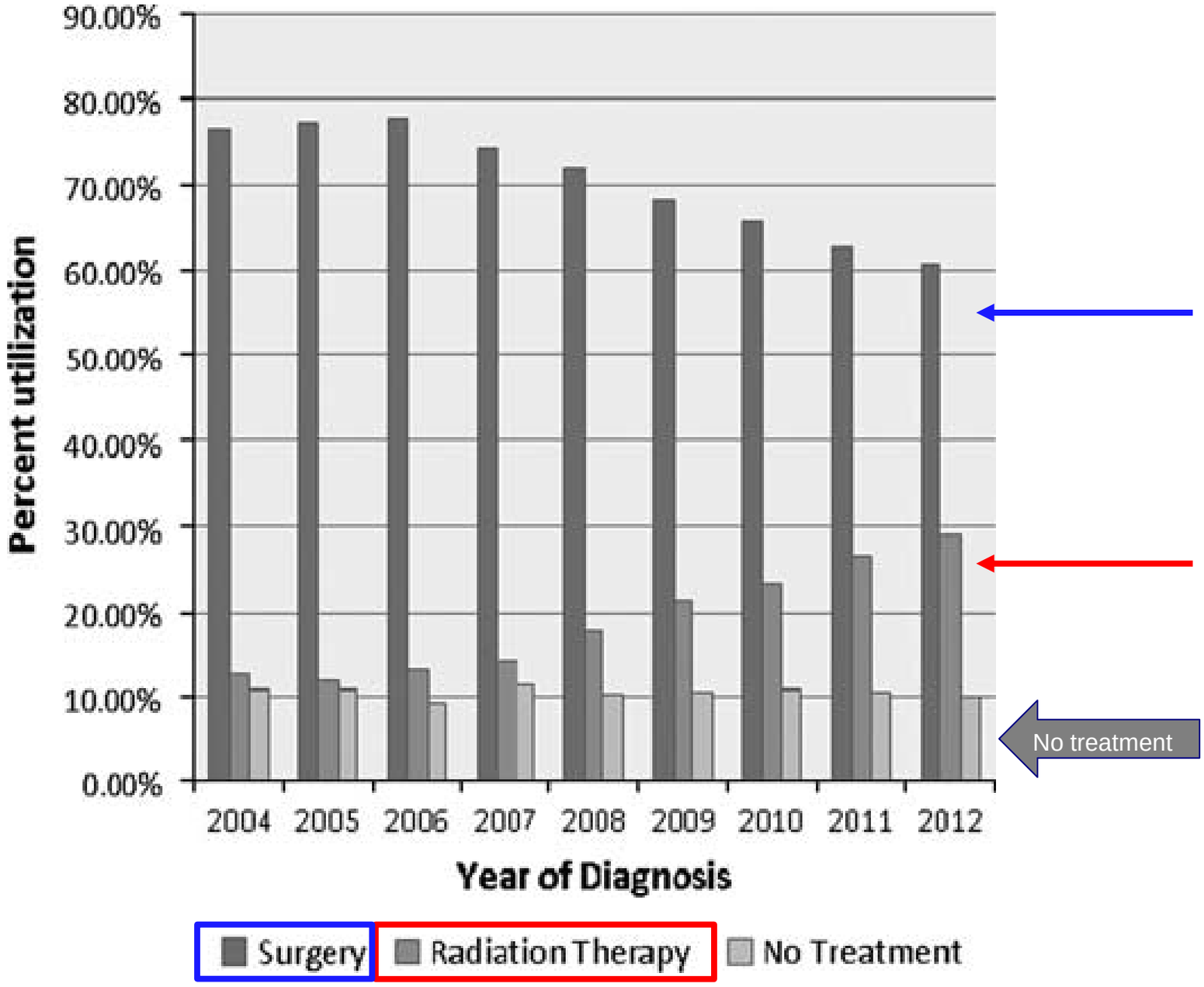
Evaluated using Kaplan-Meier approach and a multivariable Cox proportional hazard model

Confounding by indication [Walker AM, Epidemiology 1996}

Physicians choose the treatment that they think best for their patients. …….The distortions arise from an imbalance in prognostic factors between compared treatment groups.

Berry MF, ATS 2015

Stage IA NSCLC (SEER 2004-2012)



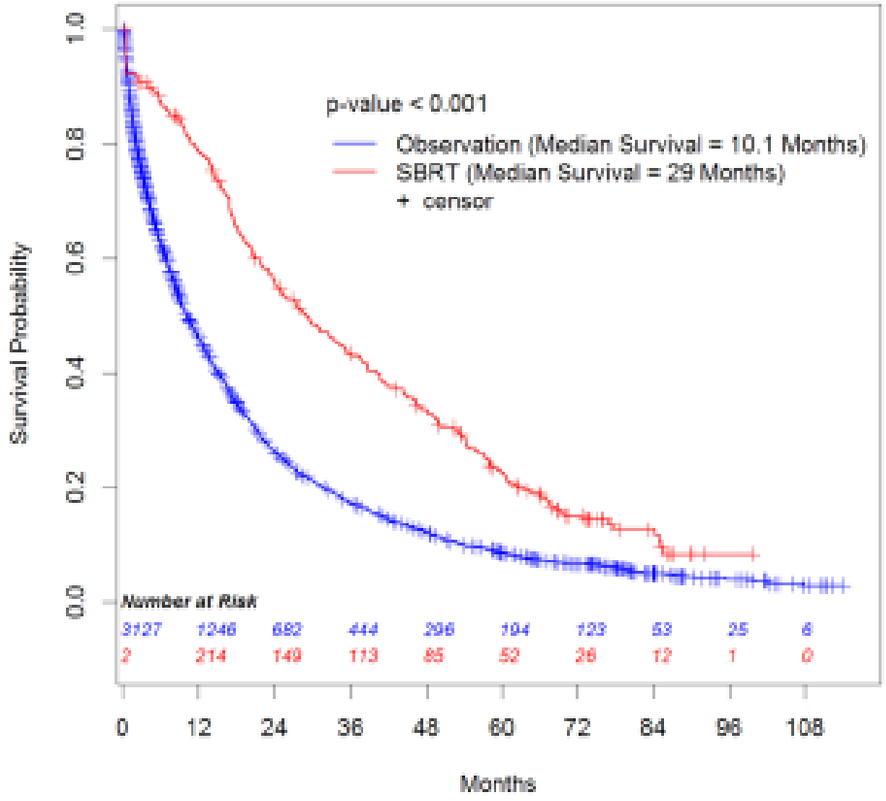
Haque W, AJCO 2016

SBRT vs no treatment (US data, NCDB)

3147 pathology proven patients >70 years (2003-2006)

No treatment = 2889 (91.8%); SBRT = **258** patients (8.2%)

No significant differences in Charlson/Deyo comorbidity index scores



Median survival:

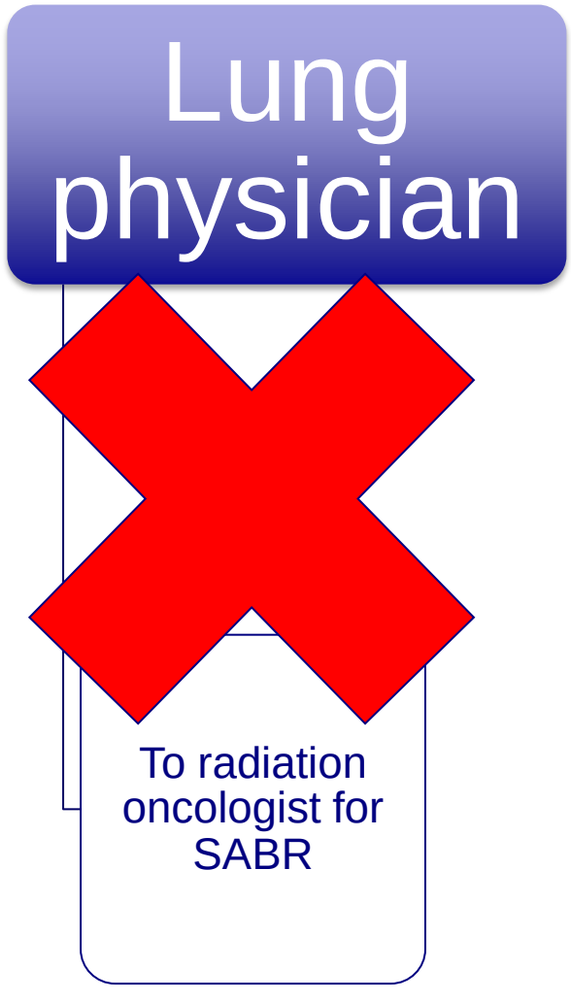
Observation: 10.1 months
SABR: 29 months

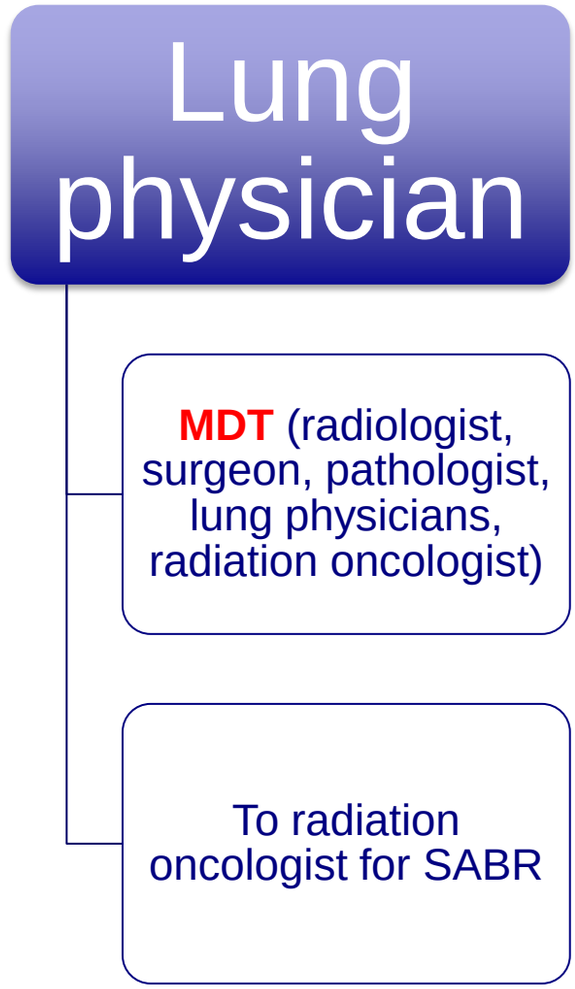
Multivariable analysis: improved overall survival with SBRT compared with observation for the entire cohort (hazard ratio, 0.64; P < .001).

Nanda RH, Cancer 2015

Treatment without pathology?

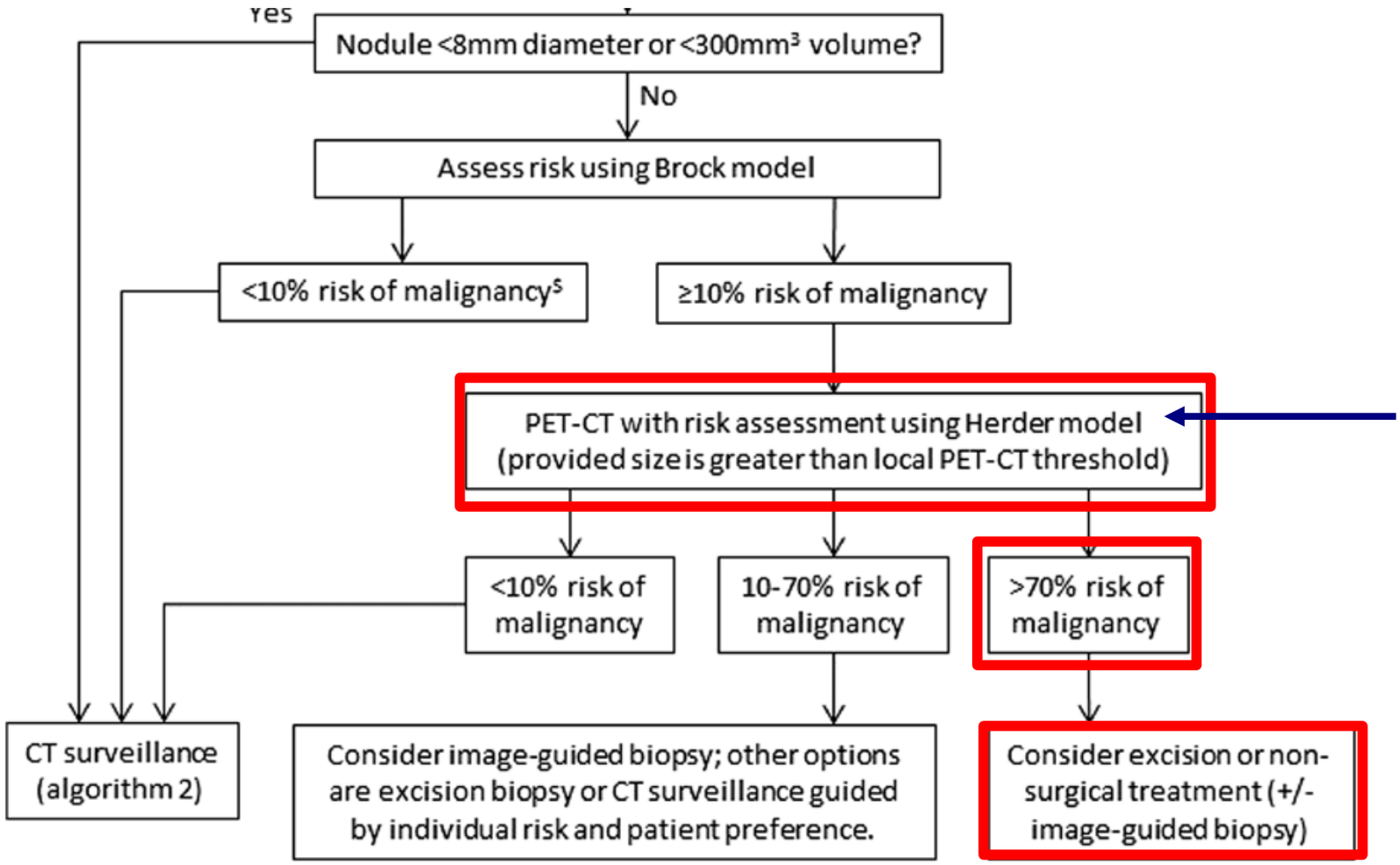
ESMO guidelines [Vansteenkiste J, Ann Oncol 2014]





MDT: thoracic multi-disciplinary team

British Thoracic Society guidelines 2015



In an UK population, use of a 70% threshold led to a “small increase” in risk of benign disease, but reduced chance of treatment delay.

Callister MEJ, Thorax 2015

Asian clinical practice consensus

VUmc

Accepted Manuscript

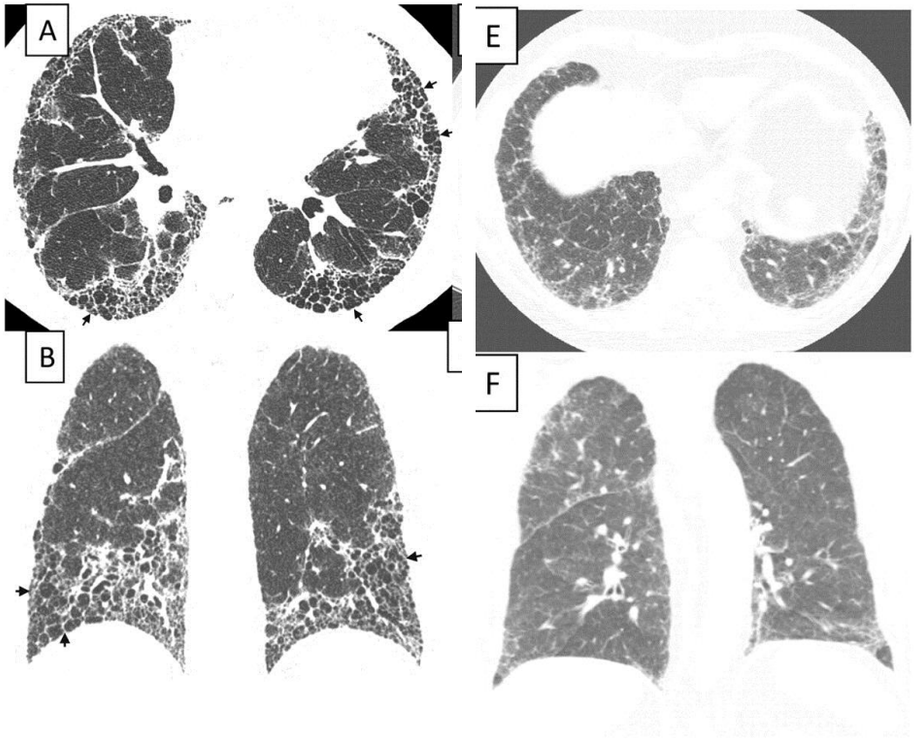
Evaluation of pulmonary nodules: clinical practice consensus guidelines for Asia

Chunxue Bai, MD & PHD, FCCP, Chang-Min Choi, MD & PHD, Chung Ming Chu, MD, FCCP, Devanand Anantham, MBBS, James Chung-man Ho, MD, FCCP, Ali Zamir Khan, MD & PHD, Jang-Ming Lee, MD & PHD, Shi Yue Li, MD & PHD, Sawang Saenghirunvattana, MD & PHD, Anthony Yim, MD & PHD

- High prevalence of granulomatous disease and other infectious causes of pulmonary nodules must be considered.
- Diagnosis risk calculators developed in non-Asian patients may not be applicable
- Tuberculosis in Asia favors **lesser reliance on PET scanning**, and **greater use of non-surgical biopsy** over surgical diagnosis or surveillance

SABR & pulmonary interstitial fibrosis

Raghu G, AJRCCM 2011



IPF is a chronic, progressive fibrotic interstitial lung disease of unknown origin

JCOG0403 (2004-2008), Nagata Y, IJROBP 2015

Exclusion criteria: ”Apparent interstitial pneumonitis or pulmonary fibrosis on chest film”

SABR and Interstitial Lung Disease

Treatment-related toxicity after SABR in early-stage NSCLC with ILD: A systematic review [Chen H., Louie AV et al. *unpublished*]

- Treatment-related mortality was 16%
- ILD-specific toxicity was 26%

Work on **standardize scoring** and **risk assessment**

Ozawa Y, PLOS One 2015

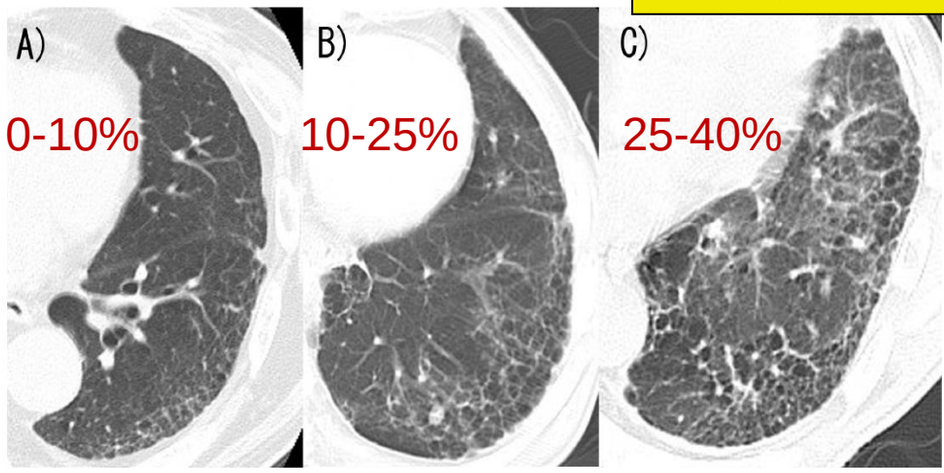


Fig 1. Representative chest computed tomography image of the area used for assessing the presence of preexisting interstitial lung disease. A), B), and C) were scored as 0–10, 10–25, and 25–40%, respectively.

doi:10.1371/journal.pone.0140437.g001

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Fibrosis vs. recurrence after SABR

Systematic review of literature

High-risk features (HRF):

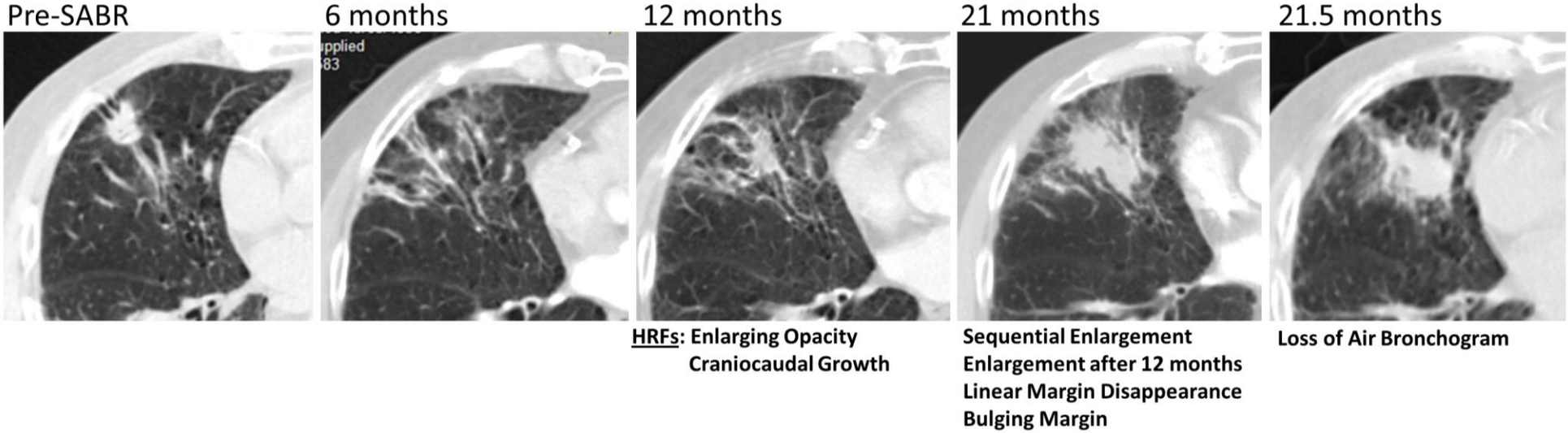
- enlargement of mass
- sequential enlargement on CT
- growing mass after 12 months
- cranio-caudal growth

- bulging margin
- linear margin disappears
- air bronchograms disappear

Huang K, Radioth Oncol 2012, 2013

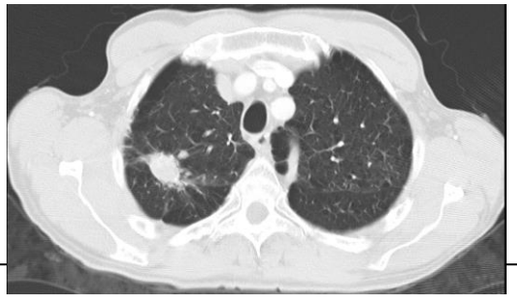
Fibrosis vs. recurrence after SABR

B. Recurrence



- Early prediction of tumor recurrence based on CT texture changes after stereotactic ablative radiotherapy for lung cancer. Mattonen SA, *Med Phys.* 2014
- Imaging texture analysis for automated prediction of lung cancer recurrence after stereotactic radiotherapy. Mattonen SA, *J Medical Imaging* 2015
- Detection of Local Cancer Recurrence After Stereotactic Ablative Radiation Therapy for Lung Cancer: Physician Performance Versus Radiomic Assessment. Mattonen SA, *IJROBP* 2016

SABR for re-irradiation: Risks



Clinical outcomes reported by selected studies.

Author publication year [references]	Follow-up (after salvage treatment, months)	Local control	Overall survival	Severe acute and late toxicity rates
Coon et al. (2008) [23]	12	1-Year: 92%	1-Year: 81%	NA
Kelly et al. (2010) [24]	15	2-Years: 92%	2-Years: 59%	G3 pneumonitis: 28% G3 Esophagitis: 4% Chest wall pain: 31%:
Seung et al. (2011) [25]	18	At 18 months: 86%	At 18 months: 87.5%	None
Peulen et al. (2011) [26]	12	1-Year: 52% 2-Years: 43%	1-Year: 59%	G3 pneumonitis: 30% G4–5: 13% (central lesion)
Trakul et al. (2012) [27]	15	1-Year: 65%	1-Year: 80%	None
Liu et al. (2012) [28]	16	1-Year: 95%	2-Years: 74%	G3 pneumonitis: 19% 1 pt: G5 pneumonitis
Valakh et al. (2013) [29]	22	2-Years: 75%	2-Years: 69%	Late G3 pneumonitis: 22% Late G3 chest wall pain: 11%
Meijneke et al. (2013) [30]	12	1-Years: 75% 2-Years: 50%	1-Years: 67% 2-Years: 33%	None
Reyngold et al. (2013) [31]	12	1-Year: 77% 2-Years: 64%	22 months (median)	G3 pneumonitis: 5% G4 skin:25%
Trovò et al. (2014) [32]	18	1-Year: 86%	1-Year: 59% 2-Years: 29%	G3 pneumonitis: 17% −1 pt: G5 pneumonitis −1 pt: G5 bleeding
Hearn et al. (2014) [33]	14	Not specified*	Four patients presented a local failure at a median of 9.9 months.	No G3–5 toxicity
Kilburn et al. (2014) [34]	11	2-Years: 67%	21 months (median)	Late G3 pneumonitis: 3% 1 pt: G5 aorto-esophageal fistula

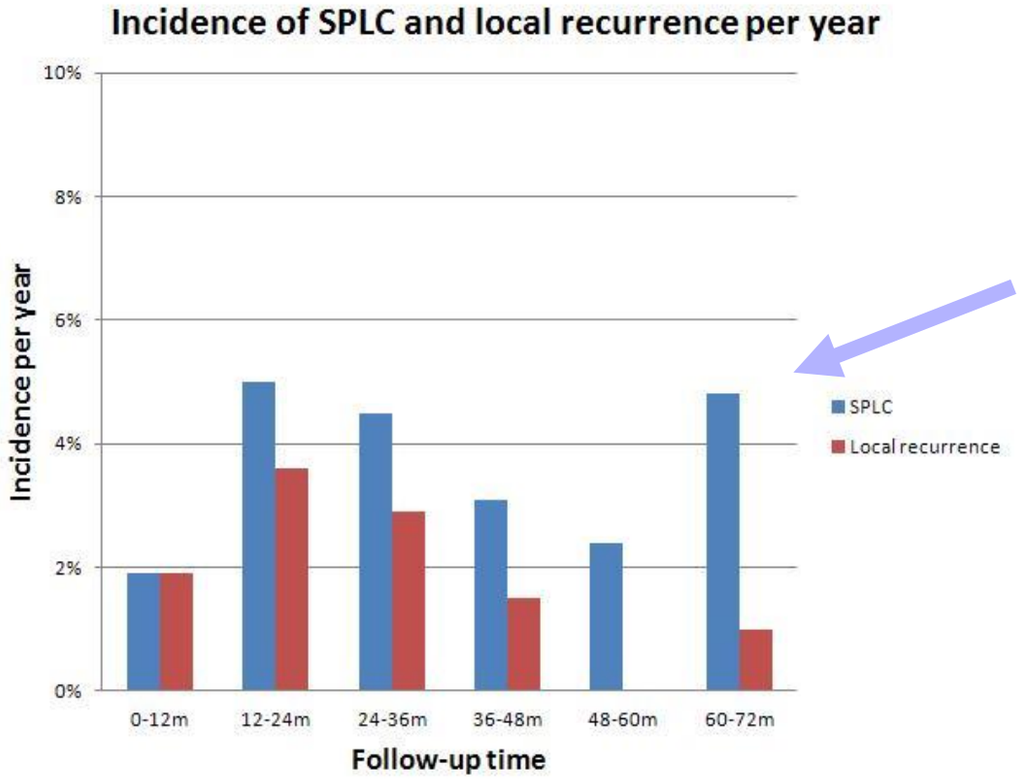
Abbreviations: fx = fractions; NA = Not Available.

* In this study, authors report a description of the outcomes of the patients. Since salvage SBRT, 3 patients are alive and without evidence of disease, with follow-up of 11.7, 13.0, and 43.5 months. A fourth patient had no evidence of disease and died of medical comorbidities 13.0 months after salvage SBRT. Two patients developed distant disease despite local control at 5.1 and 15.6 months.

De Bari B, Cancer Trt Rev 2015

Post-SABR recurrences: **855** patients

- Median follow-up: 52 months



SPLC diagnosed at a median time 34 months post-SABR (range 3-105). Actuarial cumulative incidences of SPLC at 1-, 3-, and 5 years were 1.9%, 11.7%, and 16.7%, respectively.

Verstegen NE, JTO 2015

CT screening: small cell lung cancer

VUmc

Table 2. Incidence of SCLC and Proportion of SCLC with Respect to All Lung Cancers, Median Tobacco Consumption, and Patient Age[a]

Lung Cancer Screening Trial	SCLC (n in 100,000 Person-Years)	SCLC as Percentage of Lung Cancer Cases (%)	Cumulative Tobacco Consumption (Median Pack-Years)	Age (y)
NY-ELCAP[18]	69	10	40	66
DANTE[19]	97	8	47	64
DLST[20,21]	51	11	NA	NA
NLST[16,17]	83	13	56	61
ITALUNG[22]	56	9	42	61
COSMOS[23]	81	10	NA	58
NELSON[7]	26	7	38	58
LUSI[24]	65	13	NA	NA
Current study	22	6	39	57

[a]Data are reported for major lung cancer screening trials worldwide, along with median tobacco consumption and age.
SCLC, small cell lung cancer; NY-ELAP, New York-Early Lung Cancer Action Project; DANTE, Dante Trial. A Randomized Study on Lung Cancer Screening with Low-Dose Spiral Computed Tomography; DLST, Danish Lung Screening Trial; NA, not applicable; NLST, National Lung Screening Trial; ITALUNG, Italian Lung Trial; COSMOS, Continuous Observation of Smoking Subjects; NELSON, Dutch-Belgian Lung Cancer Screening Trial; LUS1, Lung Screening and Intervention trial.

Silva M, JTO 2016

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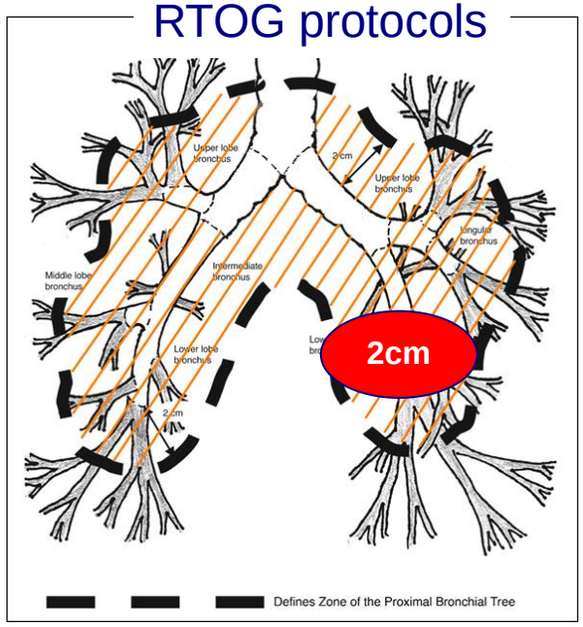
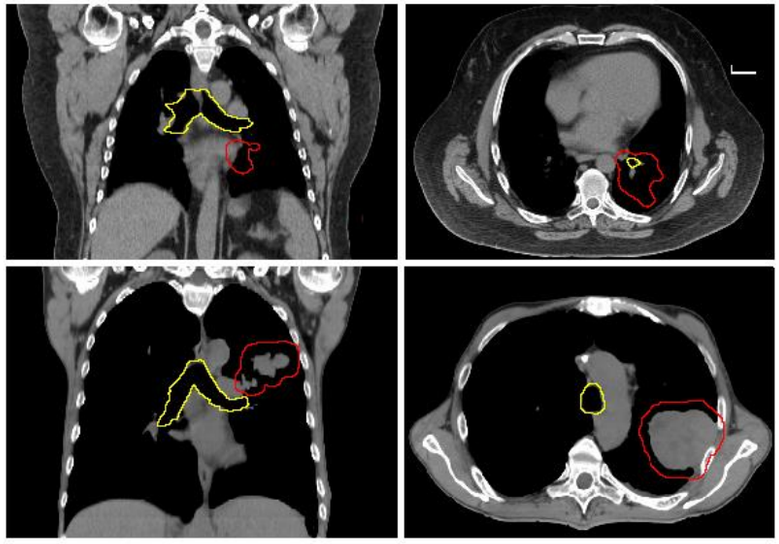
Moderately central vs ‘ultracentral’

RTOG protocols





Tekatli, H. Radioth Oncol 2015

Central tumors and hemorrhage

Grade 5 hemoptysis in 14%

Grade 5 hemoptysis in 13%

fatal hemorrhage in 12%

5 cases of Grade 5 toxicity (including 3 hemoptysis)

Central tumors and hemorrhage

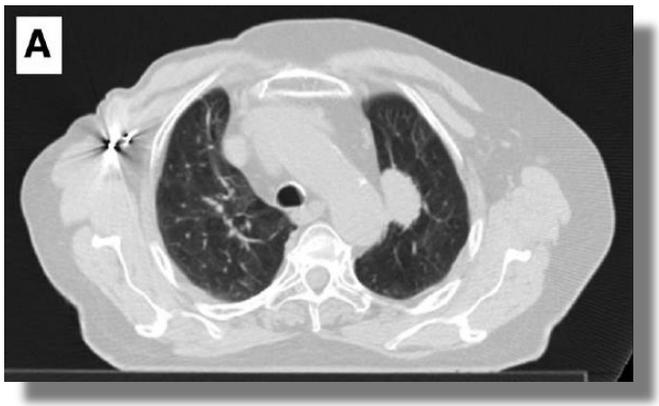
Huber RM, IJROBP 1997: Randomized trial in patients with endobronchial tumor in the trachea, mainstem or lobar bronchus reported Grade 5 hemoptysis in 14% of patients in the conventional radiotherapy arm (max dose 60 Gy)

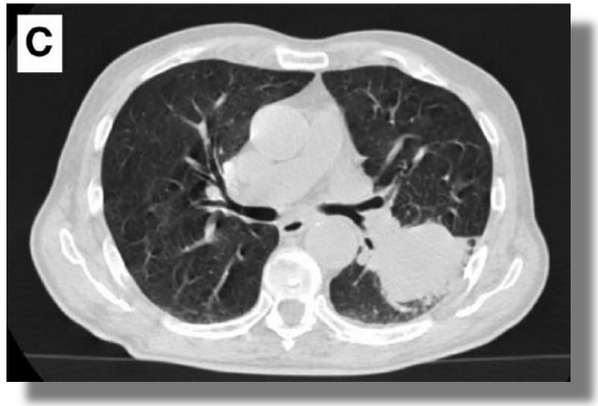
Langendijk JA, Radioth Oncology 1998: Retrospective study reported Grade 5 hemoptysis in 13% of patients with endobronchial tumor ('brachytherapy-eligible') after conventional radiotherapy

Nichols L, Arch Pathol Lab Med. 2012: Post-mortem analysis of 100 lung cancer deaths found fatal hemorrhage in 12% (7 patients had vascular invasion, 1 infected abscess invading artery)

Cannon DM, JCO 2013: Phase I trial in 79 patients treated in 25 fractions (max 85Gy). 5 cases of Grade 5 toxicity (including 3 hemoptysis) in tumors encasing/abutting main or proximal lobar bronchus

SABR outcomes for central tumors





Systematic review
Senthi S, Radioth Oncol 2013

20 papers: 563 central tumors
(315 were early-stage NSCLC)

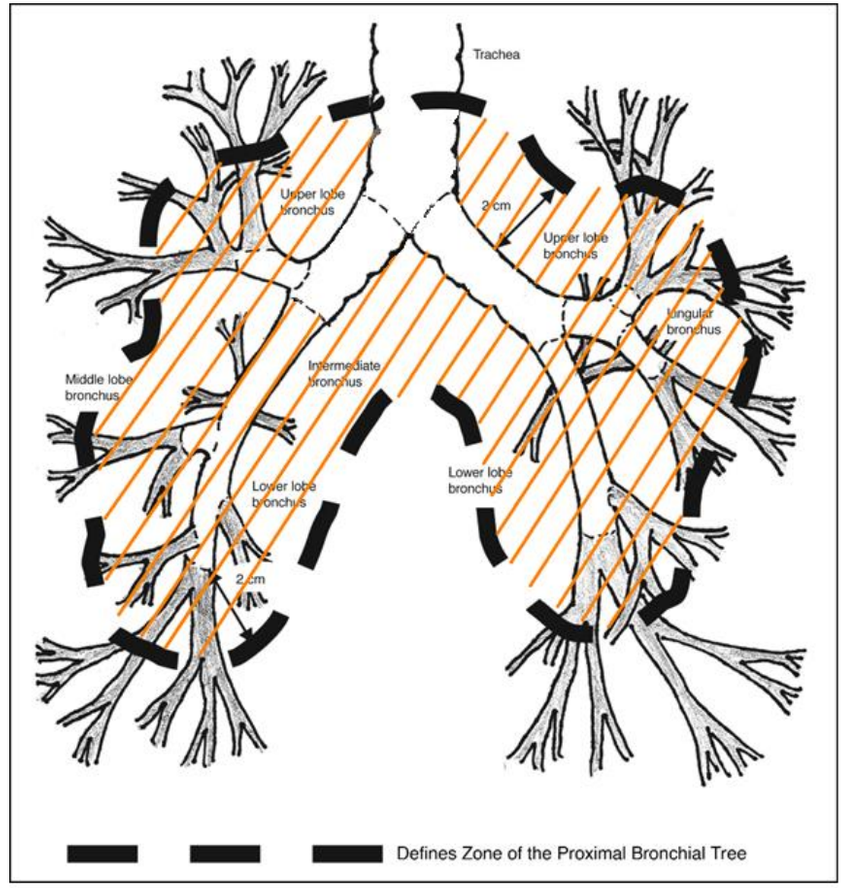
Local control **≥85%** when dose (BED_{10}) was **≥100 Gy**

Treatment-related mortality **2.7%** overall, versus **1.0%** when normal tissue dose (BED_3) was ≤210 Gy

Gr 3-4 toxicities in less <**9%** of patients

Moderately central tumors (Vumc)

- Retrospective cohort analysis
  - 80 patients (2008-2013)
  - 8x7.5Gy using RapidArc
  - No prior lung surgery
  - No prior/simultaneous thoracic, mediastinal/neck radiotherapy



Tekatli, H. Radioth Oncol 2015

Moderately central tumors (VUMC)

Baseline characteristics of patients with a central tumor ($n = 80$).

Characteristics	Number of patients (%) or median (range)
Median age at start index SABR, years	73 (45–94)
Male gender	53 (66%)
WHO performance status	
0–1	57 (71%)
2–3	23 (29%)
History of COPD	50 (62.5%)
GOLD I	8 (10%)
GOLD II	23 (29%)
GOLD III	10 (12.5%)
GOLD IV	9 (11%)
Smoking history	
Yes	74 (92.5%)
No or unknown	6 (7.5%)
Prior treatment for index lesion	
Chemotherapy	2 (2.5%)
Lasertherapy	1 (1.3%)
Pathology proven	41 (51%)
NSCLC TNM stage (7th edition)	
IA	28 (35%)
IB	32 (40%)
IIA	14 (17.5%)
IIB	4 (5%)
IV	2 (2.5%)
Median ITV volume, cm^3	28 (2–165)
Median PTV volume, cm^3	66 (9–286)
Tumor side right lung	27 (34%)

Tekatli, H. Radioth Oncol 2015

Severe toxicity and mortality

Details available on causes of death	38 of 42 deceased (90%)
Grade 5 toxicity	**6 (7.5%)**
Likely treatment-related death	3 (4%)
Possible treatment-related death	3 (4%)
Fatal lung hemorrhage	**4 (5%)**

Patients with interstitial lung disease	4 of total cohort (4%)
≥G2 Radiation Pneumonitis	3

Tekatli, H. Radioth Oncol 2015

Protocol compliance:VUmc & trials

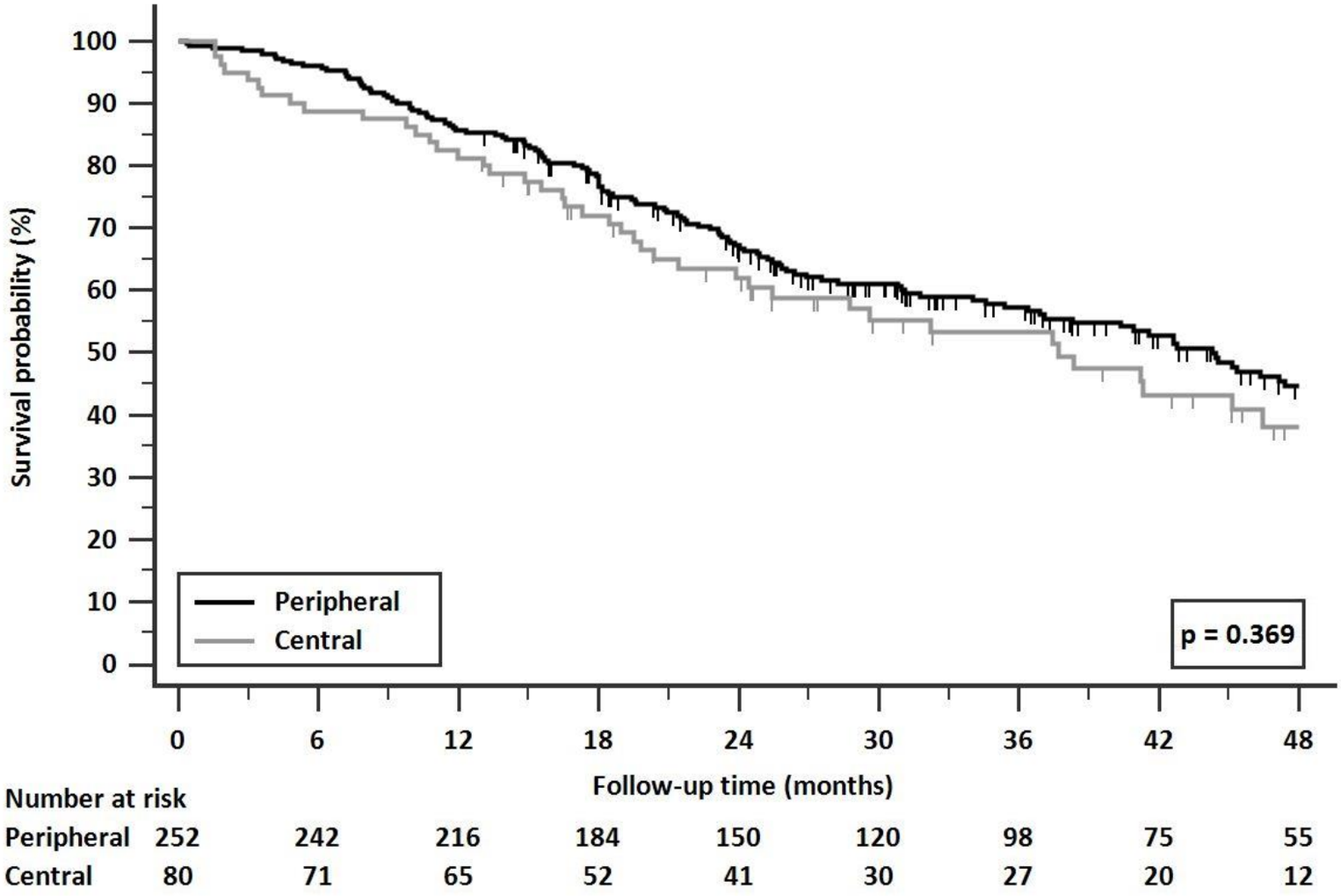
Number of patients who met institutional guidelines, RTOG0813 and LungTech criteria

Organ	Institutional point dose limits (Dmax)	RTOG0813 point dose limits (Dmax)	RTOG0813 volume-dose limits	LungTech point dose limits (Dmax)
PBT	No dose limits	53 (66%)	D4cc: 50 (62.5%)	36 (45%)
Trachea	No dose limits	80 (100%)	D4cc: unknown*	75 (93.8%)
Esophagus	78 (97.5%)	80 (100%)	D5cc: 80 (100%)	78 (97.5%)
Heart	No dose limits	40 (50%)	D15cc: 67 (84%)	No dose limits
Aorta	No dose limits	61 (76%)	D10cc: 80 (100%)	No dose limits
Spinal canal	79 (99%)	80 (100%)	D0.25cc: 80 (100%) D0.5cc: unknown*	80 (100%)

Abbreviations: PBT = Proximal Bronchial Tree. *The dose limit for this volume was <24Gy. As we only evaluated parts of the OARs irradiated with ≥24Gy we did not have this information.

Tekatli, H. Radiother Oncol 2015

Overall survival: central vs peripheral



	Central tumors	Peripheral tumors
Median FU	45 months (95% CI: 40-51)	47 months (95% CI: 43-52)
Median OS	38 months (95% CI 26-50)	44 months (95% CI: 38-51)

Tekatli, H. Radioth Oncol 2015

SABR in moderately central tumors

- SABR (≥100 Gy) appears feasible in moderately patients with a moderately central NSCLC
- More reliable organ at risk **tolerance doses** needed

PRESS RELEASE

First MRIdian System Installed in Europe at VU University Medical Center of Amsterdam

Published: Mar 24, 2016 8:00 a.m. ET

Aa

Patient Treatments with MRI-Guided Radiation Therapy to Begin This Spring

ViewRay (MRIdian)

- Continuous MRI visualization
- Daily plan adaption
- Reconstruction of cumulative doses

Conclusions

- **Peripheral early-stage NSCLC**
  - SABR well established (new data in fit patients, elderly)
  - Caution with interstitial lung disease (ILD)
  - Multi-disciplinary follow-up assessment after SABR
- **Moderately central early-stage NSCLC**
  - More safety data for SABR available
  - Current dose constraints are arbitrary
  - Data from prospective studies awaited