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Stereotactic ablative radiotherapy (SABR) in early-stage I NSCLC

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SABR in early stage NSCLC

Objectives

- Review the different techniques of stereotactic radiotherapy for peripheral and central lung tumours
- Pro and cons of SABR versus standard radiotherapy in patients with poor lung function
- Pro and cons of SABR versus sublobar resection in patients with borderline lung function

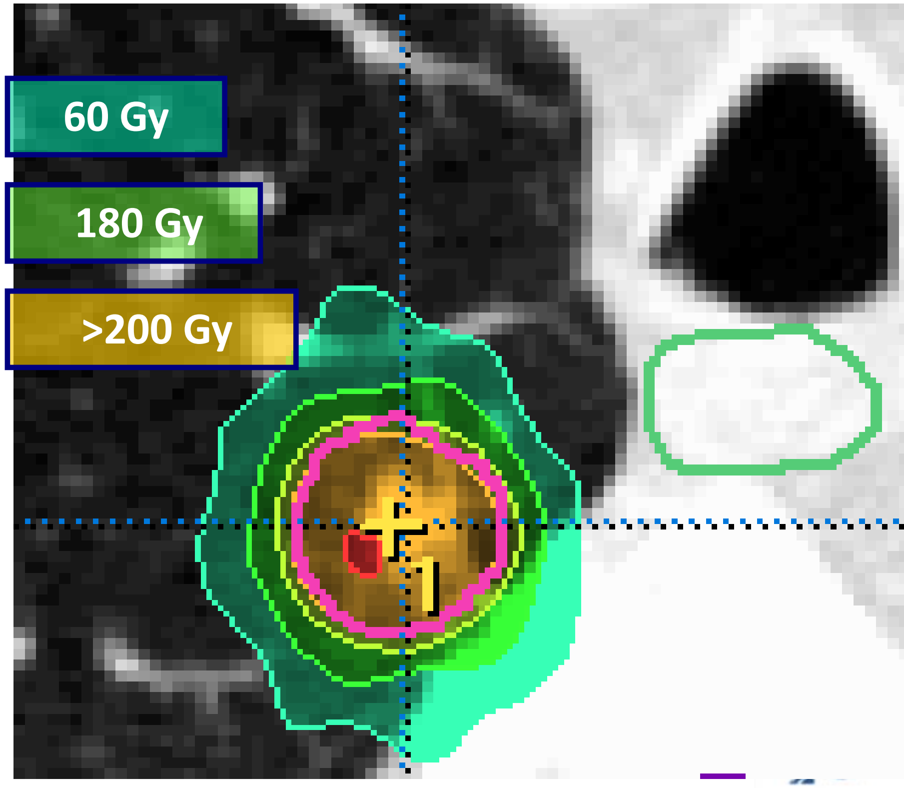
Definition SABR (or SBRT)

A technique for delivering external beam radiotherapy to an extra-cranial target
(i) with a high degree of accuracy,
(ii) using high doses of irradiation,
(iii) delivered in 1-8 treatment fractions.

Senan, Guckenberger, Ricardi, 2014

Key feature of SABR delivery

- Steep dose-gradients



Treatment guidelines in stage I NSCLC

- Surgery is preferred if patients accept procedure-related risks
- In patients who are unfit, stereotactic ablative radiotherapy (SABR) is the preferred treatment because of low toxicity and low failure rates

Clinical Practice Guidelines of the European Society for Medical Oncology, endorsed by the Japanese Society of Medical Oncology [Vansteenkiste J, Ann Oncol 2013]

SABR for stage I NSCLC

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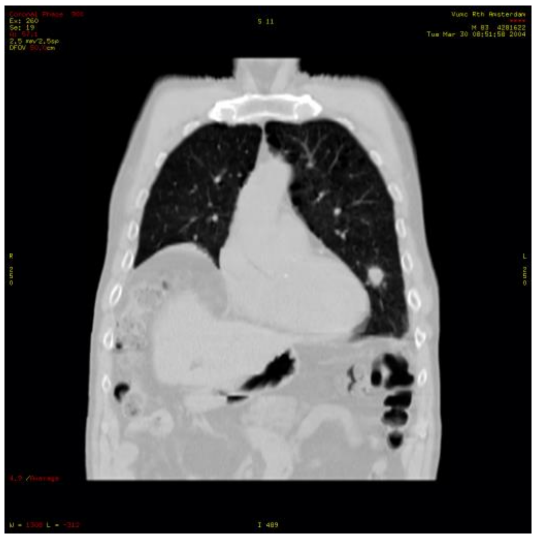
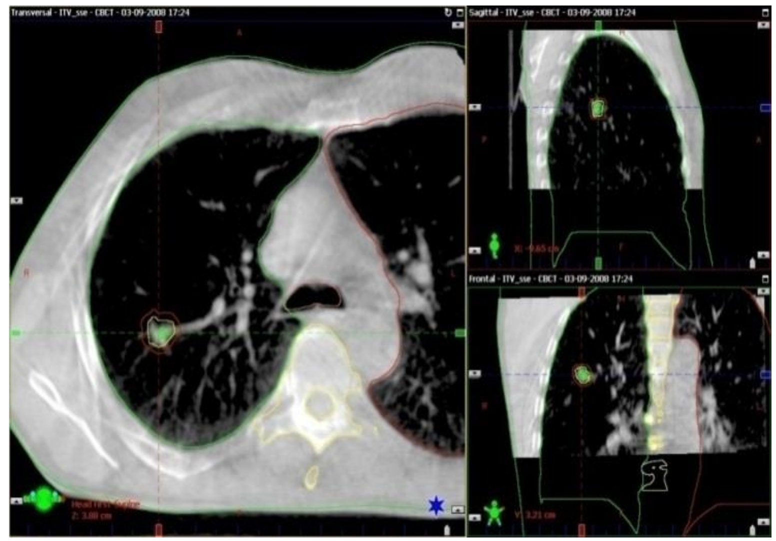
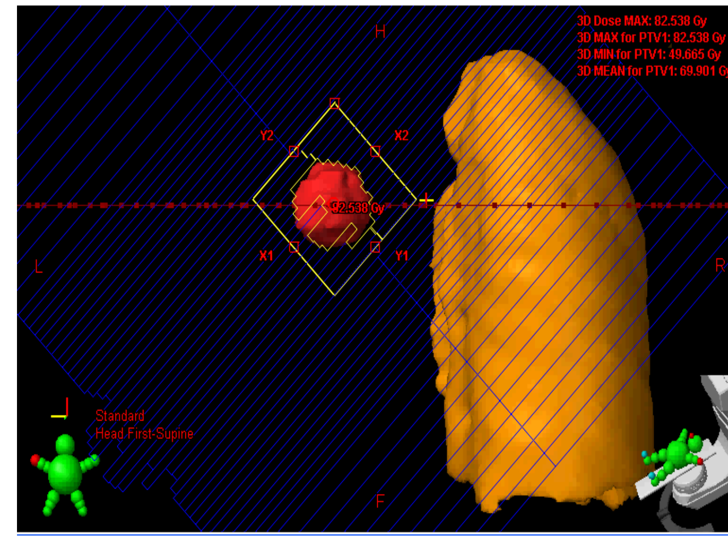
Image-guided radiotherapy technique at VUMC, Amsterdam



4-D imaging



CT scan on treatment couch

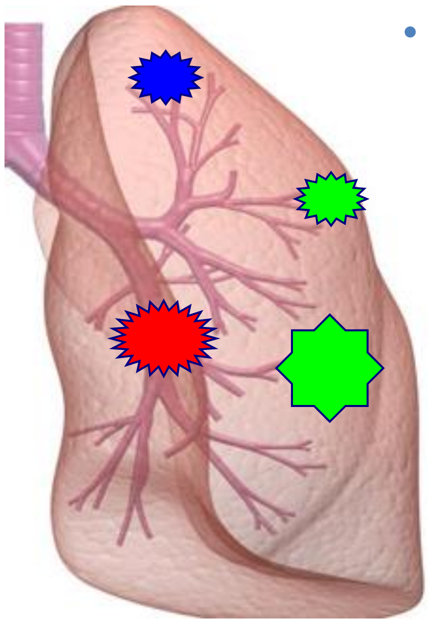


Delivery in <4 mins (Ong CL, 2012)

Many delivery platforms exist. No differences observed in either overall survival, or local progression-free survivals using different radiotherapy equipment [Solda F, Radiother Oncol 2013]

Planning and 'risk-adapted' delivery

Lagerwaard FJ, IJROBP 2008

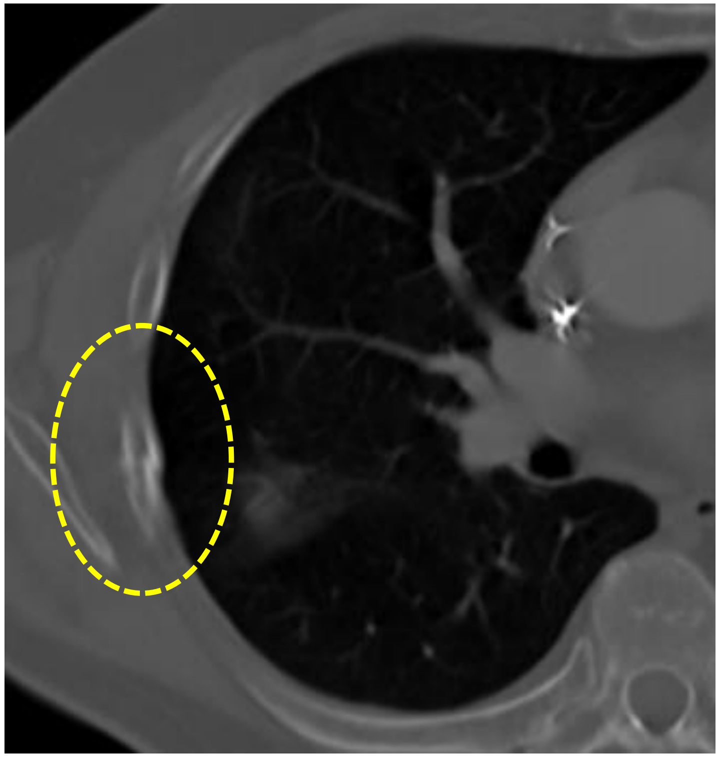


- **Risk adapted** fractionation (fr) scheme:
  - **3 fr of 18Gy** : T1 lesions, not adjacent to chest wall
  - **5 fr of 11Gy** : T1 lesions with broad chest wall contact, and T2 lesions
  - **8 fr of 7.5Gy** : central lesions showing limited overlap with mediastinal structures

- ITV = internal target volume encompasing all motion on 4DCT
- PTV = planning target volume = ITV + 5mm

SABR toxicity: chest wall

- 500 patients with T1-2N0 tumors (2003-2009)
- Median follow-up 33 months (13-86 months)
- Severe chest wall toxicity uncommon
  - severe pain in 2.2%,
  - rib fractures in 2.7%



Bongers E, JTO 2011

SABR toxicity: Lung, chest wall

- 505 lung tumors in 483 patients
- Median time to pneumonitis: 0.4 years

Pneumonitis grade	incidence
Grade 2 or higher	7%
Grade 3 or higher	2%
Grade 5	0.2%

Grills IS, JTO 2012

SABR and radiation pneumonitis

Japanese multi-institution analysis
Radiation pneumonitis ≥Grade 3 (CTCAE V3.0)

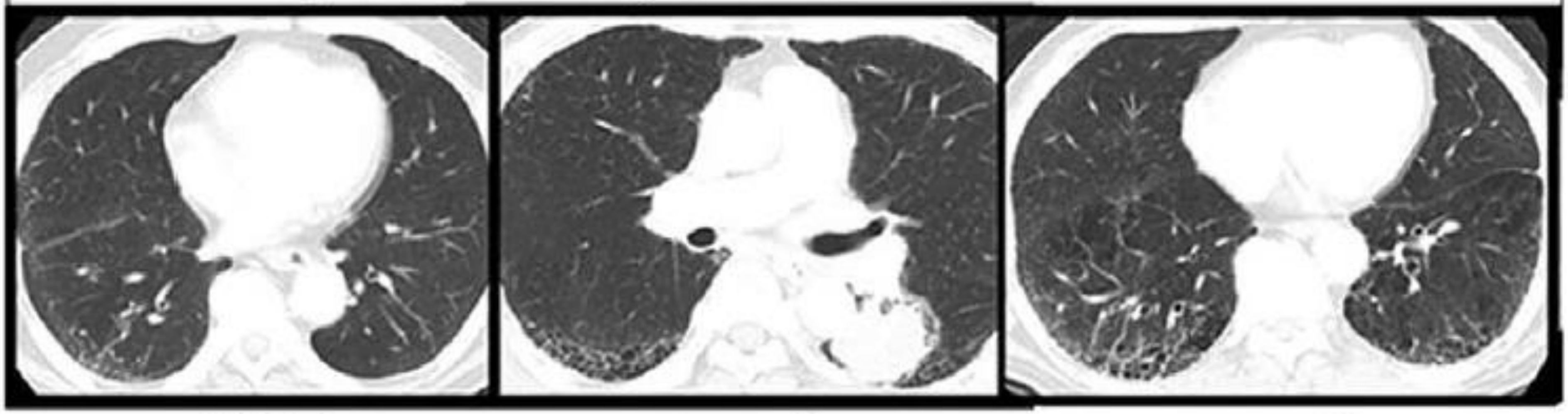
subgroup		Grade 3,4,5	Grade 5
All patients (n= 2278 pts)		3.3%	0.6%
Operable patients (n= 683 pts)		1.9%	0.4%
Pulmonary emphysema (+) (n= 449 pts)		4.4%	1.1%
Pulmonary fibrosis (+) (n= 243 pts)		11.9%	5.9%

No pathological diagnosis: 606 pts

Onishi H, Proc ASTRO 2013

Pulmonary fibrosis score

score	Pulmonary Fibrosis Score (PFS)
0	No fibrosis
1	Interlobular septal thickening; no descrete honeycombing
2	Honeycombing (with or without septal thickening) involving <25% of the lobe
3	Honeycombing involving 25 - 49% of the lobe
4	Honeycombing involving 50 - 75% of the lobe
5	Honeycombing involving > 75% of the lobe



score 1 score 2 score 3

Tsujino K, JTO 2014

Treatment without a tissue diagnosis

Dutch surgical series in FDG-PET era show a ≤6% likelihood of benign lesions in resected specimens

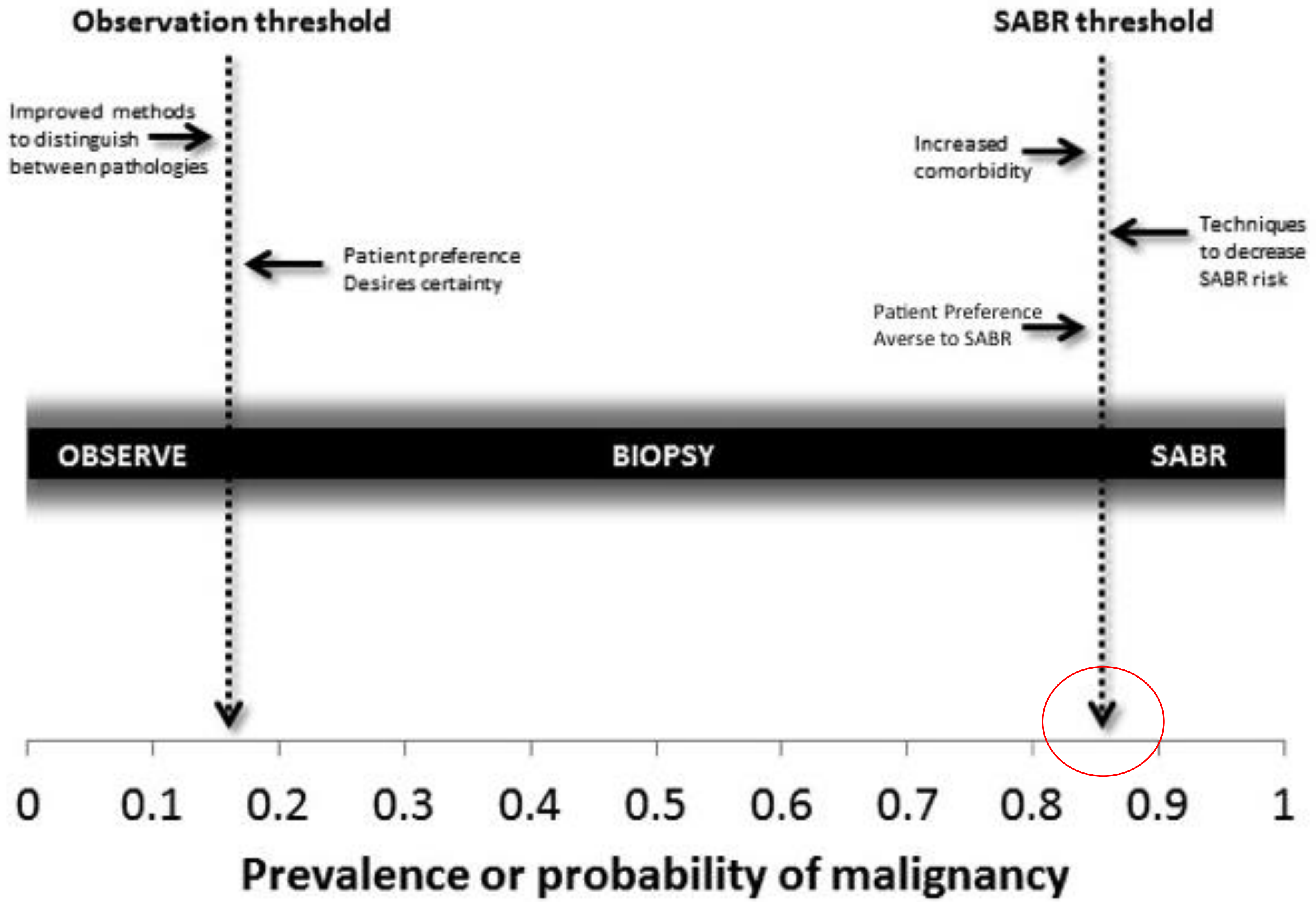
(Van Tinteren H, Lancet 2002; Herder G, JCO 2006; Verstegen N, Ann Oncol 2013)

Italian series of 1571 lung resections for suspicious lesions showed a final benign diagnosis in 22%

(Veronesi G, JTO 2014)

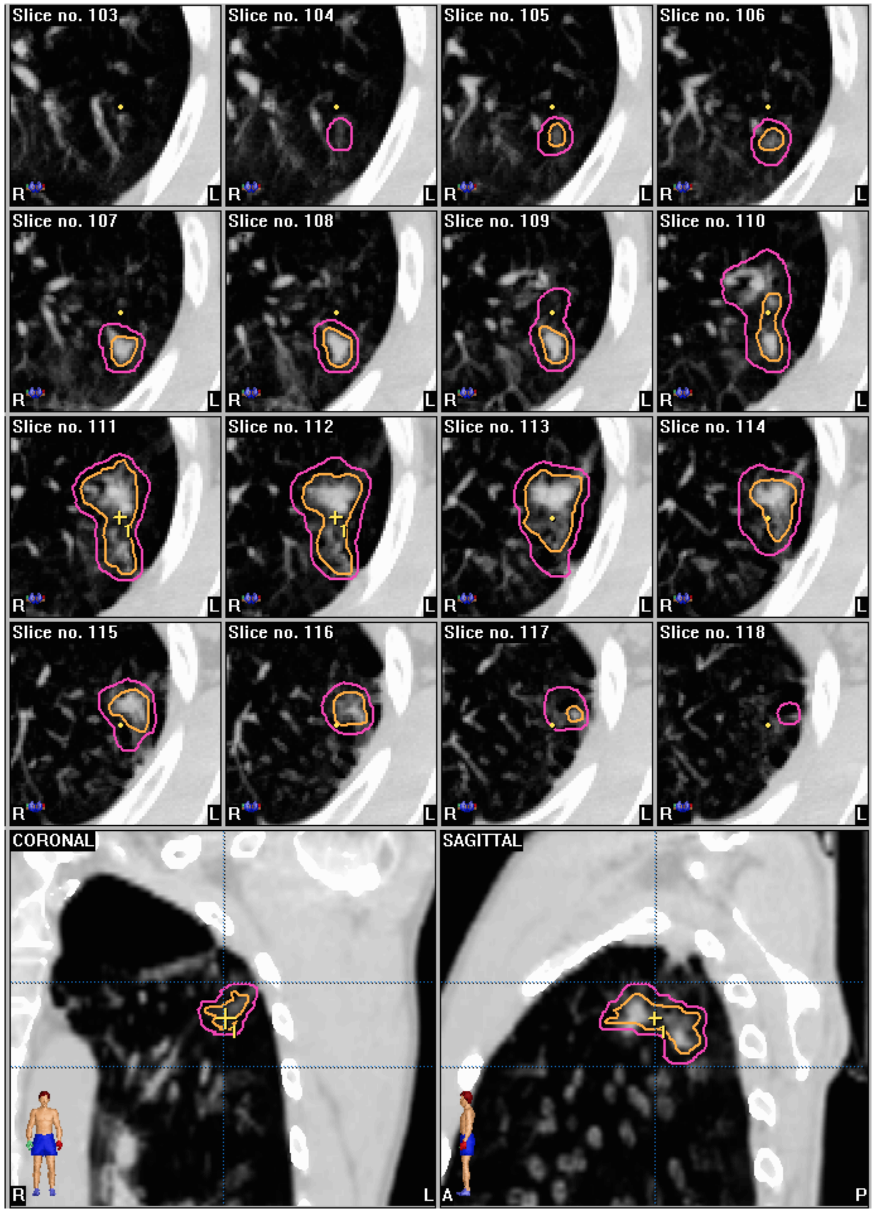
Establishing a pre-treatment diagnosis

When is a Biopsy-proven Diagnosis Necessary before Stereotactic Ablative Radiotherapy (SABR) for Lung Cancer? A Decision Analysis

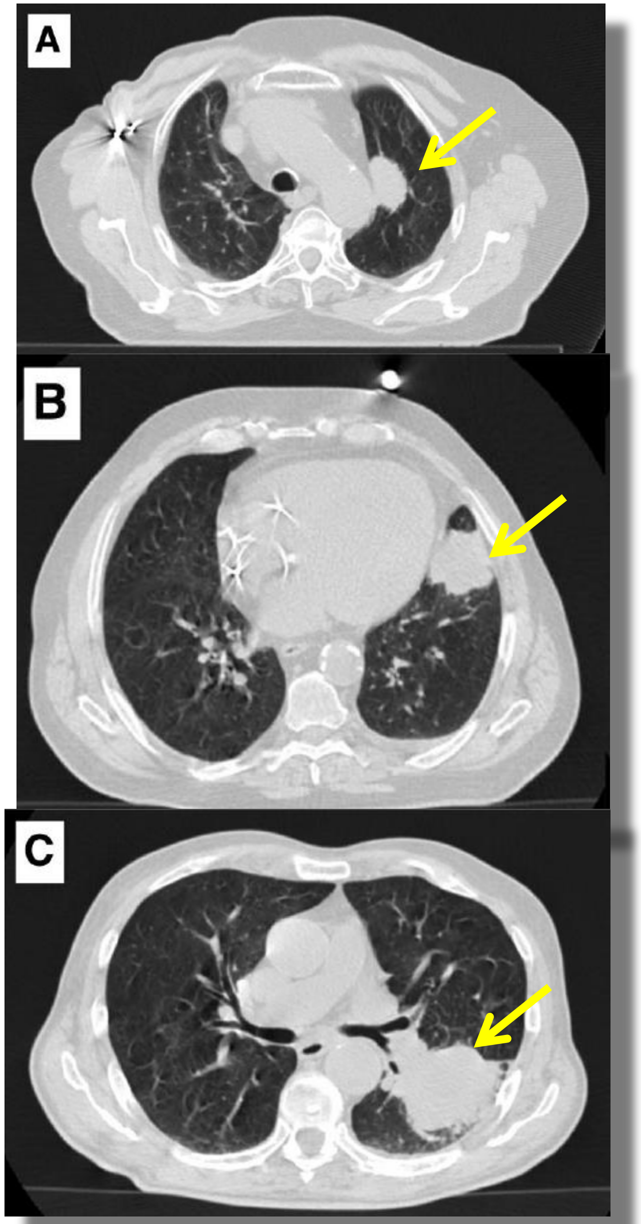


Louie AV, Chest 2014

SABR for central tumors?



Peripheral lung tumor



Central lung tumors
Haasbeek CJ, JTO 2011

SABR for central tumors

Systematic review of SABR for central tumors

20 publications: 563 central lung tumours (315 were early-stage NSCLC)

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

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

Grades 3-4 toxicities appear commoner following SABR for central tumours, but occurred in less than **9%** of patients.

Senthi S, Radioth Oncol 2013

Radiotherapy: Approach to central tumors

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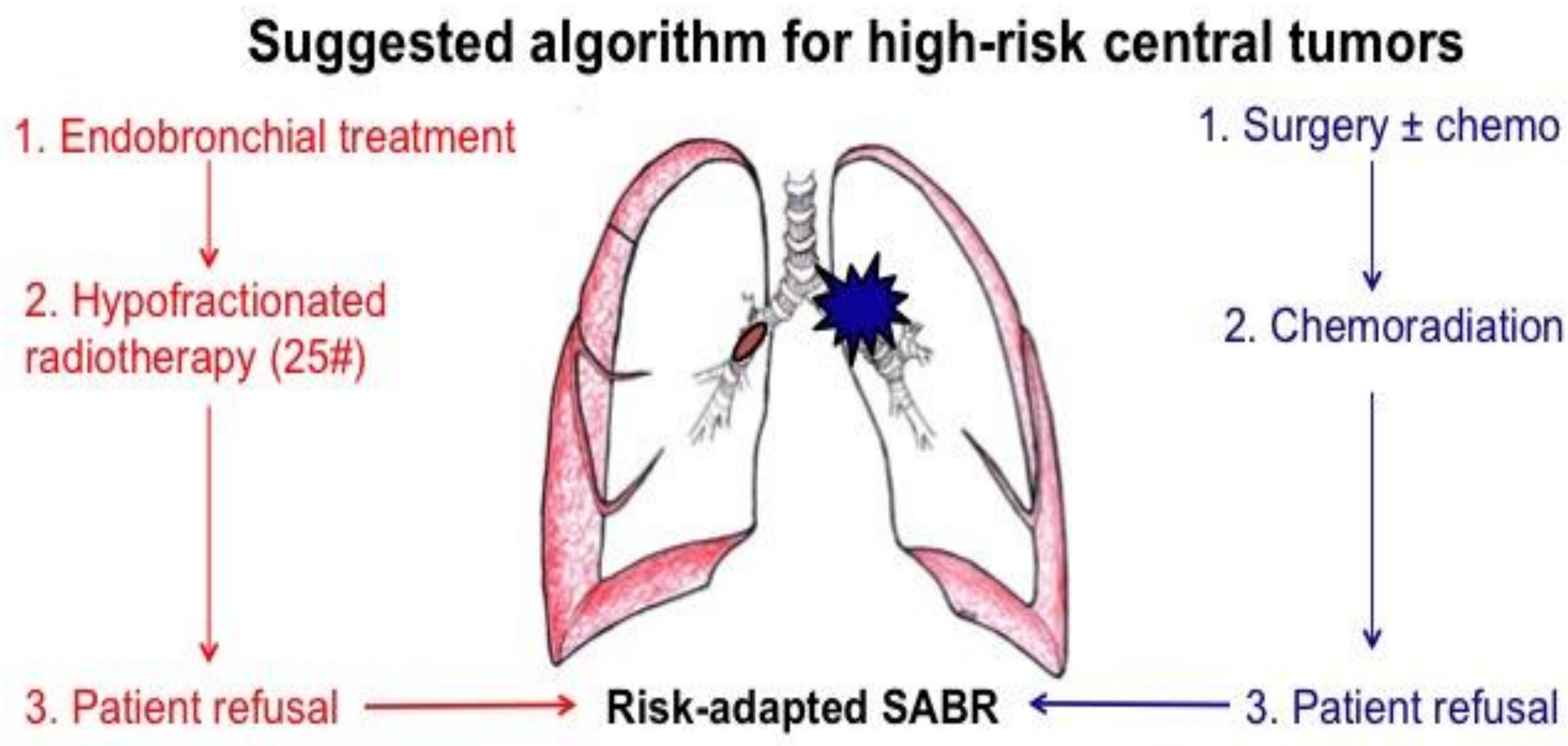


Louie AV, in press

Randomized trials of SABR vs. conventional RT

	SPACE NCT01920789	**CHISEL** NCT01014130
Study arms	SABR: 66 Gy in 3 frac (isocenter) CFRT: 66 Gy (2Gy frac)	SABR: 54 Gy in 3 frac CFRT: 60-66Gy (2Gy frac)
Primary End-point	Freedom from tumor progression at 36 mo.	Time to Local Failure at 24 mo.
Secondary end-points	OS at 36 mo. Toxicity, QoL	OS, CSS, Toxicity QoL
Total enrolled	102 pts (completed)	100 pts (76 enrolled)

Prospective RCT: SPACE trial

	A SBRT	B Conventional	All patients
Local recurrence	11 %	13 %	12 %
Regional recurrence	7 %	8 %	7 %
Distant metastases	24 %	23 %	23 %
Patients with progression	35 %	35 %	35 %

Fewer cases with pneumonitis (16 versus 34%) and esophagitis (9 versus 32%) in SBRT arm. Any G3-5 toxicity seen in 16 vs 18%

Nyman J, ESTRO 2014

SABR outcomes: Local control - survival

Table 37.2. Overview of Results of Sterotactic Ablative Radiotherapy after Delivery of Radiation at More than 106 Gy Biologic Effective Dose

Author (Year)	No. of Patients	Patients with Histopathologic Confirmation of NSCLC (%)	Overall Survival at 2-3 Years (%)	Freedom from Local Progression at 2-3 Years (%)
Prospective Phase II Trials				
Nagata et al. (2005)[71]	45	100	75	98
Baumann et al. (2009)[72]	57	67	60	92
Fakiris et al. (2009)[73]	70	100	43	88
Ricardi et al. (2010)[74]	62	65	51	88
Bral et al. (2010)[75]	40	100	52	84
Timmerman et al. (2010)[76]	54	100	56	98
All prospective studies[a]	*328*	*87.6*	55.1	*91.2*
Large Retrospective Series				
Grills et al. (2010)[77]	434	64	60	94
Senthi et al. (2012)[78]	676	35	55	95
Guckenberger et al. (2013)[79]	514	85	46 62[b]	80 93[b]
All retrospective studies[a]	*1,624*	*58.8*	*53.5*	*90.0*

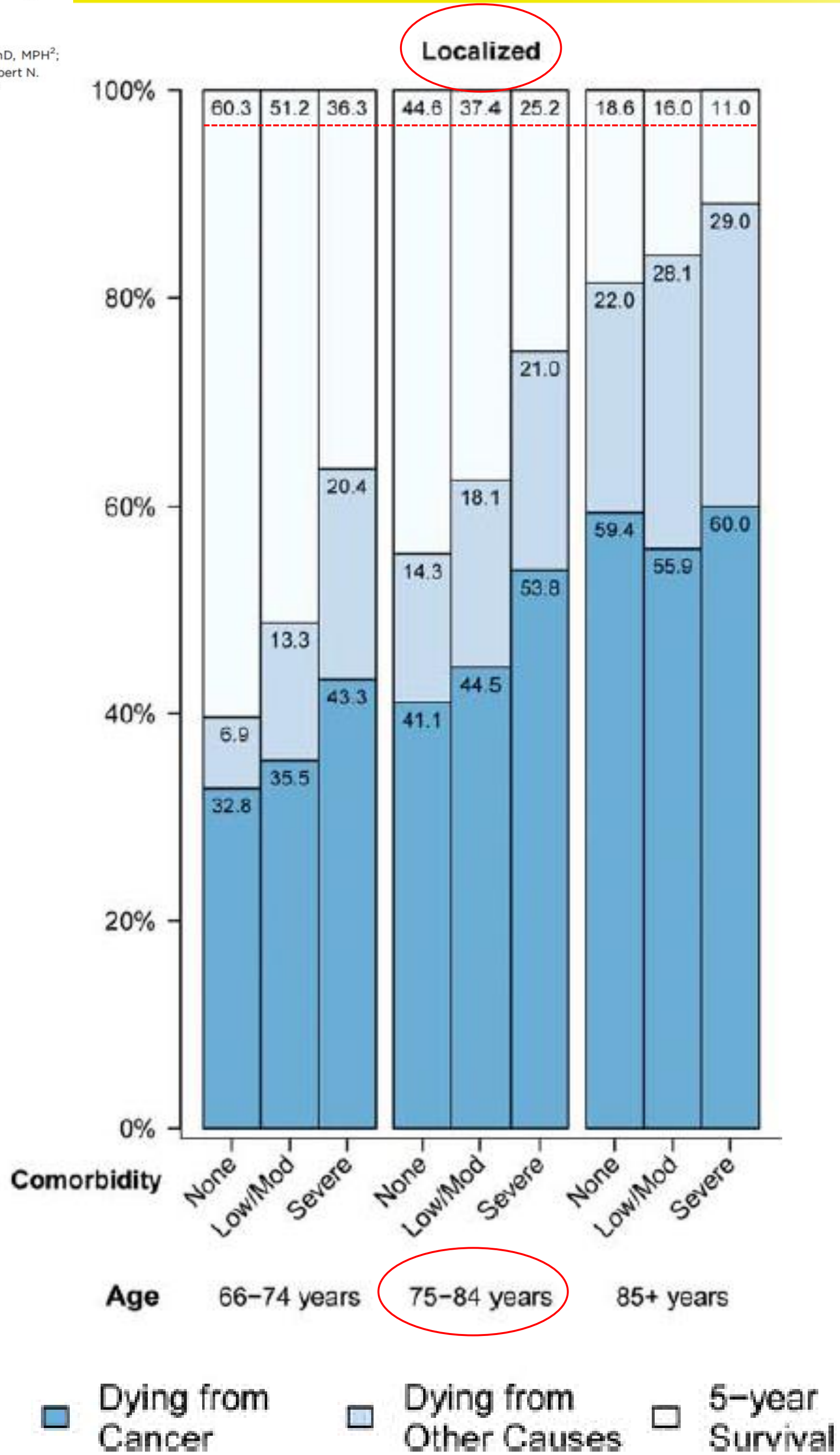
[a]The weighted average values are calculated for the summary of all prospective and retrospective studies.
[b]Subgroup of 164 patients treated with ≥106 Gy biologically effective dose.

Senan S, IASLC Multidisciplinary Approach to Thoracic Oncology 2014

Commentary

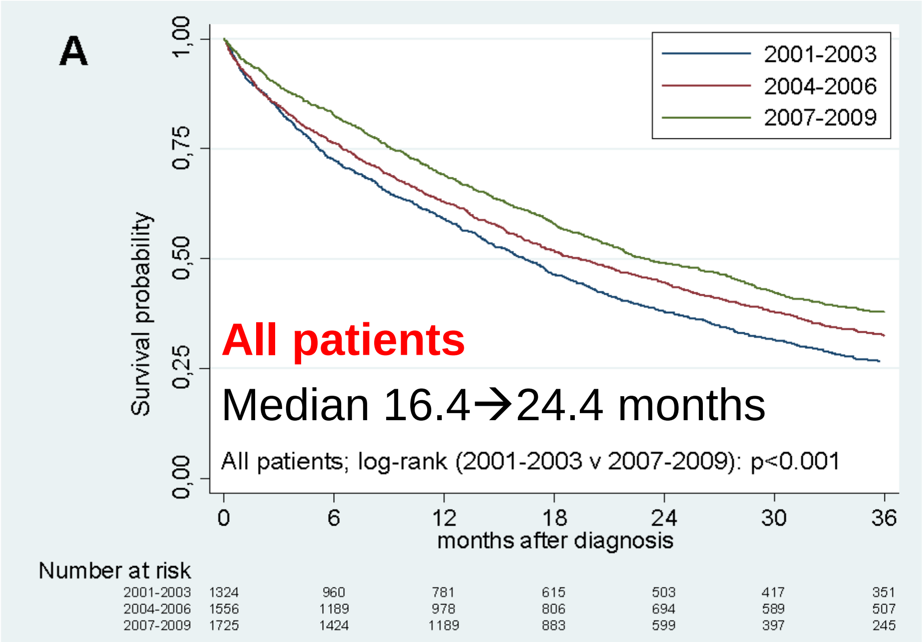
Annual Report to the Nation on the Status of Cancer, 1975-2010, Featuring Prevalence of Comorbidity and Impact on Survival Among Persons With Lung, Colorectal, Breast, or Prostate Cancer **(Cancer 2014)**

Brenda K. Edwards, PhD[1]; Anne-Michelle Noone, MS[1]; Angela B. Mariotto, PhD[1]; Edgar P. Simard, PhD, MPH[2]; Francis P. Boscoe, PhD[3]; S. Jane Henley, MSPH[4]; Ahmedin Jemal, DVM, PhD[2]; Hyunsoon Cho, PhD[1]; Robert N. Anderson, PhD[5]; Betsy A. Kohler, MPH[3]; Christie R. Eheman, PhD[4]; and Elizabeth M. Ward, PhD[2]



Dutch population study (2001-2009)

Survival in 4605 patients aged ≥75 years



Haasbeek C, Ann Oncol 2012

Comparative effectiveness research

Study	Study design	Number of patients	Surgical Procedure	Overall Survival Surgery	Overall Survival SABR	Conclusions/Comments
Crabtree [57]	Propensity-score matching	**Unmatched**: surgery = 458, SABR = 151 **Matched**: 112 / group	(Bi) lobectomy, 78% Sublobar, 19% Pneumonectomy, 4%	78%, 3 yrs 68%, 3yrs	47%, 3yrs 52%, 3yrs	Although surgical resection seems to result in better OS versus SABR, matching these patients remains challenging
Puri [47]	Propensity-	57 / group	Lobectomy, 81%			No significant difference in OS, however,
Shirvani [58						
Solda [59]						
Varlotto [60						
Verstegen [61]						
Grills [62]		SABR = 55		87%, 30m	72%, 30m	patients tended to be older with more comorbidities
Louie [63]	Markov Model	Lobectomy and SABR outcomes modelled from various sources		At 5 yrs, surgery 2-3% benefit in OS		Large patient numbers would be required to detect small differences in OS
Shah [46]	Markov Model	Lobectomy, wedge resection and SABR outcomes modelled from various sources		Not reported, model validated based on recurrence patterns		SABR is the dominant strategy when compared to wedge resection. In patients eligible for lobectomy, surgery is the most cost-effective option

Most suggest that local control / DFS after SABR is <u>at least equivalent,</u> if not better, than after surgery

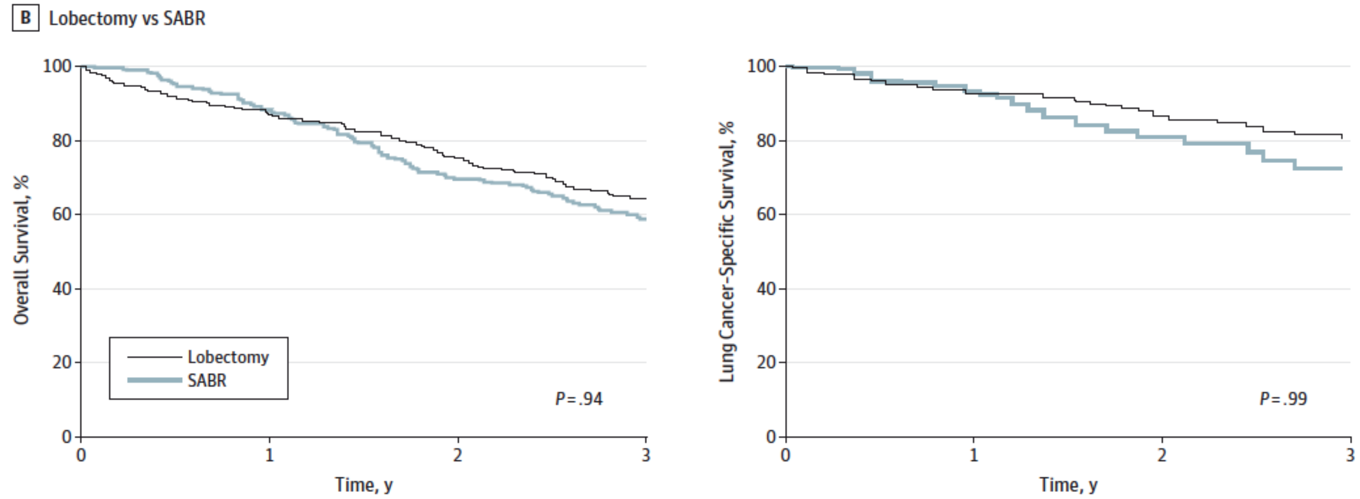
Most suggest that overall survival after SABR is <u>either equivalent or worse</u> than surgery cohorts (patient factors)

Louie A, *in preparation*

Comparative effectiveness research

DESIGN, SETTING, AND PARTICIPANTS The Surveillance, Epidemiology, and End Results database linked to Medicare was used to determine the baseline characteristics and outcomes of 9093 patients with early-stage, node-negative NSCLC who underwent definitive treatment consisting of lobectomy, sublobar resection, or stereotactic ablative radiotherapy (SABR) from January 1, 2003, through December 31, 2009.

Figure. Outcomes for Propensity Score-Matched Cohorts



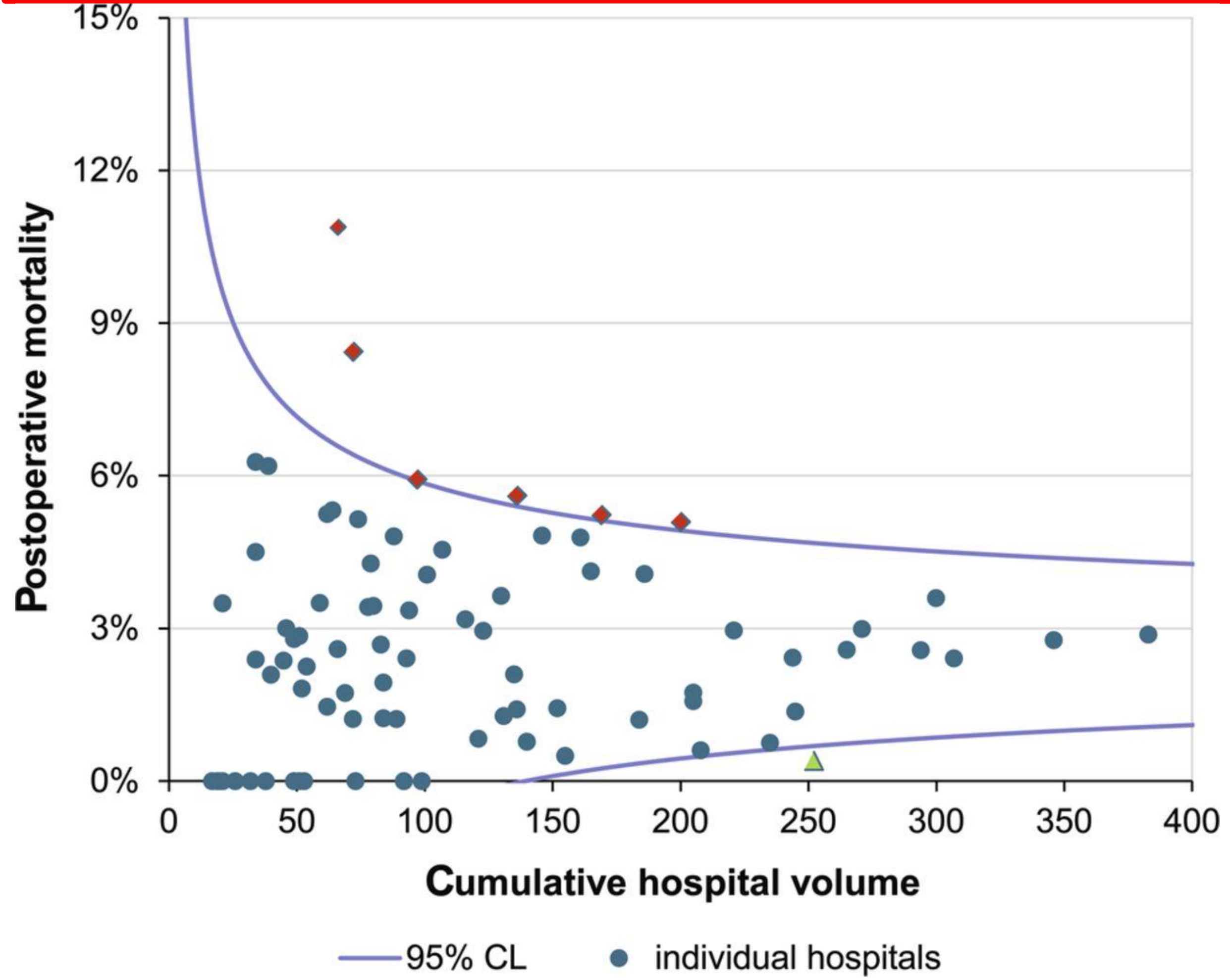
A, Comparison of groups treated with lobectomy and sublobar resection. B, Comparison of groups treated with lobectomy or stereotactic ablative radiotherapy (SABR).

Shirvani SM, JAMA Surgery *in press*

Dutch surgical mortality vs. age (2005-2010)

30-day post-operative mortality

		n	%	30-d (%)	OR
Leeftijd	20-59	2825	29	1,2	1
	60-69	3576	36	2,0	1,6
	70-79	3138	32	4,3	3,5
	80+	313	3	6,7	6,4



https://www.iknl.nl/cijfers-en-onderzoek/kankerzorg-in-beeld

Damhuis R A. Eur J Cardiothorac Surg 2014

30-day versus 90-day mortality

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90-day mortality is up to double that of the 30-day figure

Recent studies reporting 30-day and 90-day mortality following surgery or SABR.

Author	Type	Time	*n*	Stage I	Stage II	Sublobar resections	30-day (%)	90-day (%)	Ratio 90/ 30-day
Surgery									
Fernando (2011) [3]	Multi-centre RCT	2005–2010	222	100%	–	100% (all <3 cm)	1.4	2.7	1.9
Powell (2013) [13]	National registry	2004–2010	10,991	48%	17%	22%	3.0	5.9	2.0
Haasbeek (2012) [14]	National registry	2001–2009	1698	100%	–	6%	5.4	9.3	1.7
Rueth (2012) [4]	State registry	2000–2005	4171	100%	–	0%	4.2	6.3	1.5
Cheung (2009) [15]	State registry	1998–2002	13,469	59% 'local' 35% 'regional'		14%	2.3	6.3	2.7
Damhuis (2013) [16]	Regional registry	1997–2008	2668	Not reported		0%	4.5	7.5	1.7
Rivera2011 [17]	Voluntary registry	2004–2008	1969	74%	26%	8%	3.6	4.7	1.3
Greillier (2007) [18]	Single-centre prospective	2002–2004	110	55%	27%	0%	3.2	9.5	3.0
Bryant (2010) [2]	Single-centre retrospective	2002–2008	1845	Not reported		39%	4.1	6.4	1.6
He (2011) [6]	Single-centre retrospective	2000–2007	1058	41%	28%	5%	2.7	4.1	1.5
Schuchert 2012 [5]	Single-centre retrospective	2002–2010	785	81%	8%	100%	1.1	3.0	2.7
St Julien (2012) [19]	Single-centre retrospective	2005–2010	78	100%		89%	3.8	6.4	1.7
Stereotactic ablative radiotherapy									
Crabtree (2013) [20]	Multi-centre prospective	2004–2006	59	100%	–	–	0.0	0.0	–
Verstegen (2013) [21]	Single-centre retrospective	2003–2012	64	100%	–	–	0.0	0.0	–

Senthi S, Eur J Cancer 2013

Impact of nodal upstaging

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Schematic demonstrating **the number needed to treat** (NNT) when considering surgery to guide adjuvant chemotherapy decision-making for stage I NSCLC at 5 years.

Conversely, number needed to harm (NNH) when considering post-operative mortality of at least 1%, is 100 or less.

Benefit of surgical resection to stage the mediastinum?

100 patients with stage I NSCLC undergoing surgery

↓

~ 15 upstaged to N1 or N2 (ATS/Danish cancer registries)

↓

10 (⅔) receive adjuvant chemo (NATCH randomized control trial)

↓

0.5 more patients alive at 5 years (5% benefit LACE meta-analysis)

↓

NNT = 200
NNH < 100

Louie AV, *in preparation*

2nd primary lung cancers

5% had a second primary in same lobe [I-ELCAP, Altorki N, 2014]

9.1% had multifocal disease [COSMOS trial, Veronesi G, 2014]

7% (VATS) and **12%** (thoracotomy) had synchronous primary tumors identified at the initial operation [MSKCC, Flores RM 2011]

Treatment guidelines in stage I NSCLC

- Surgery is preferred if patients accept procedure-related risks
- In patients who are unfit, stereotactic ablative radiotherapy (SABR) is the preferred treatment because of low toxicity and low failure rates

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Thank you for your attention.