

# Developments in early NSCLC

## Stereotactic ablative radiation therapy (SABR)



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- The Department of Radiation Oncology at VUMC has a research agreement with Varian Medical Systems.
- S Senan has received speakers honoraria from Varian Medical Systems.



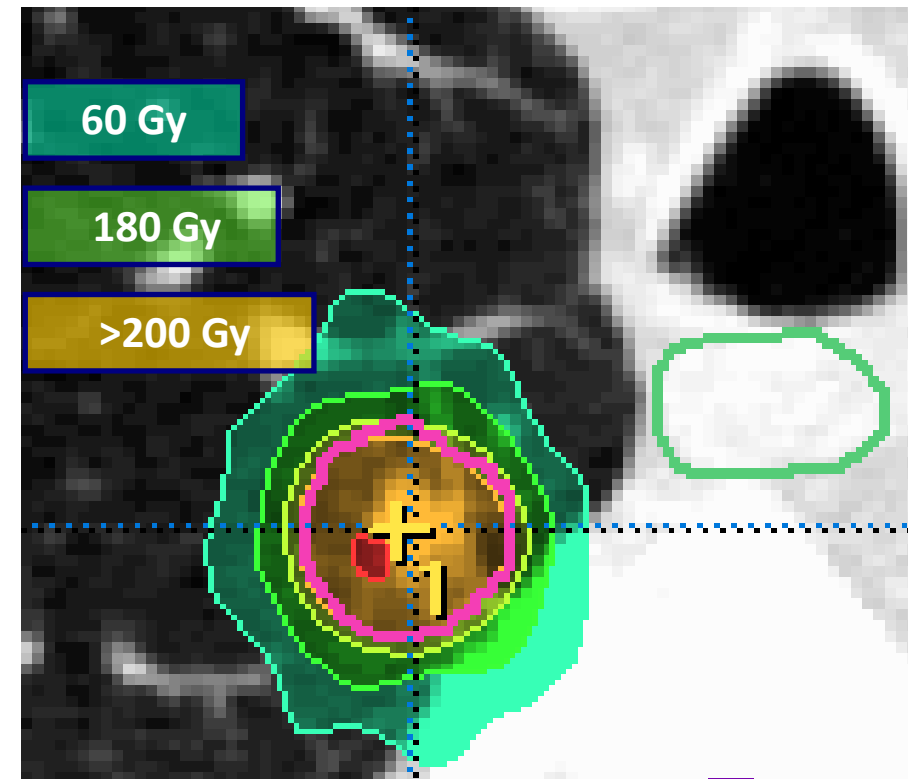
**SABR = SBRT** (stereotactic body radiotherapy)

**High-precision image-guided RT characterized by:**

- Accurate target definition
- Reproducible tumor positioning
- Multiple fixed beams or arc delivery

## **Features of SABR delivery**

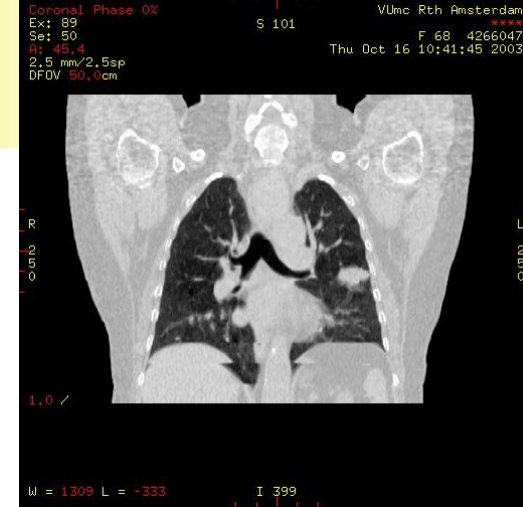
- Very high biological doses
- Delivery in 3-8 sessions
- Steep dose-gradients



# SABR in stage I NSCLC

## Current guidelines and patterns of care

- Standard of care for medically inoperable patients in Japan and The Netherlands
- National Comprehensive Cancer Network guidelines (v3.2012): *non-surgical treatment of choice*
- NHS 'radiotherapy implementation report' 2011: *available to all ..... with early lung cancer and contraindications to surgery*
- Editorial, Lancet Oncol 2012: *..with mature evidence at hand, SABR should be regarded as standard of care for patients with inoperable stage I NSCLC*



Phase 2 North American multi-center study in stage I NSCLC  
[Timmerman R, 2010]

Biopsy-proven lesions measuring  $\leq 5$  cm

- 3-year in-field tumor control was 97.6% (95% CI, 84.3%-99.7%)
- 3-year local-regional control was 87.2% (95% CI, 71.0%-94.7%)

Phase 2 Scandinavian multi-center study in stage I NSCLC  
[Baumann P, 2009]

70% of patients had a tissue diagnosis of malignancy

- 3 year local control rates of 92%.
- Local relapse in 7%; regional relapses in 5%



## Pathology confirmed stage I NSCLC results at VUMC

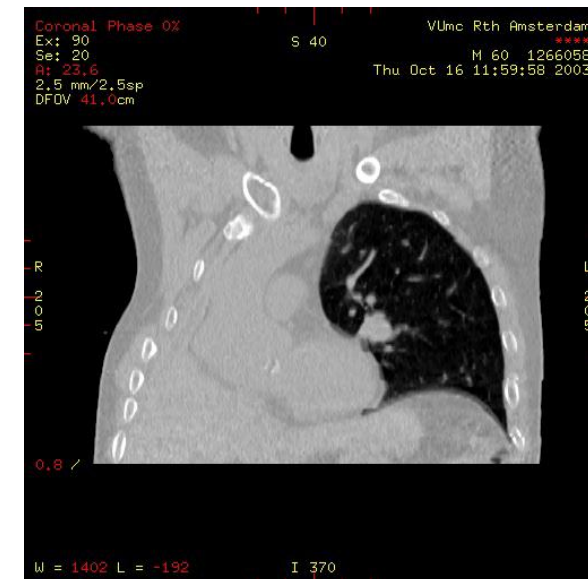
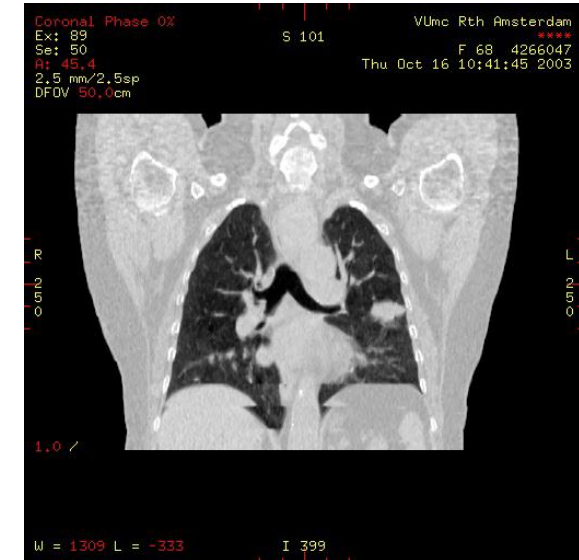
3 year endpoints	PA + (n=209)
Overall survival	55.4%
Local control	90.4%
Regional control	90.3%
Distant control	79.6%
Disease free survival	72.1%

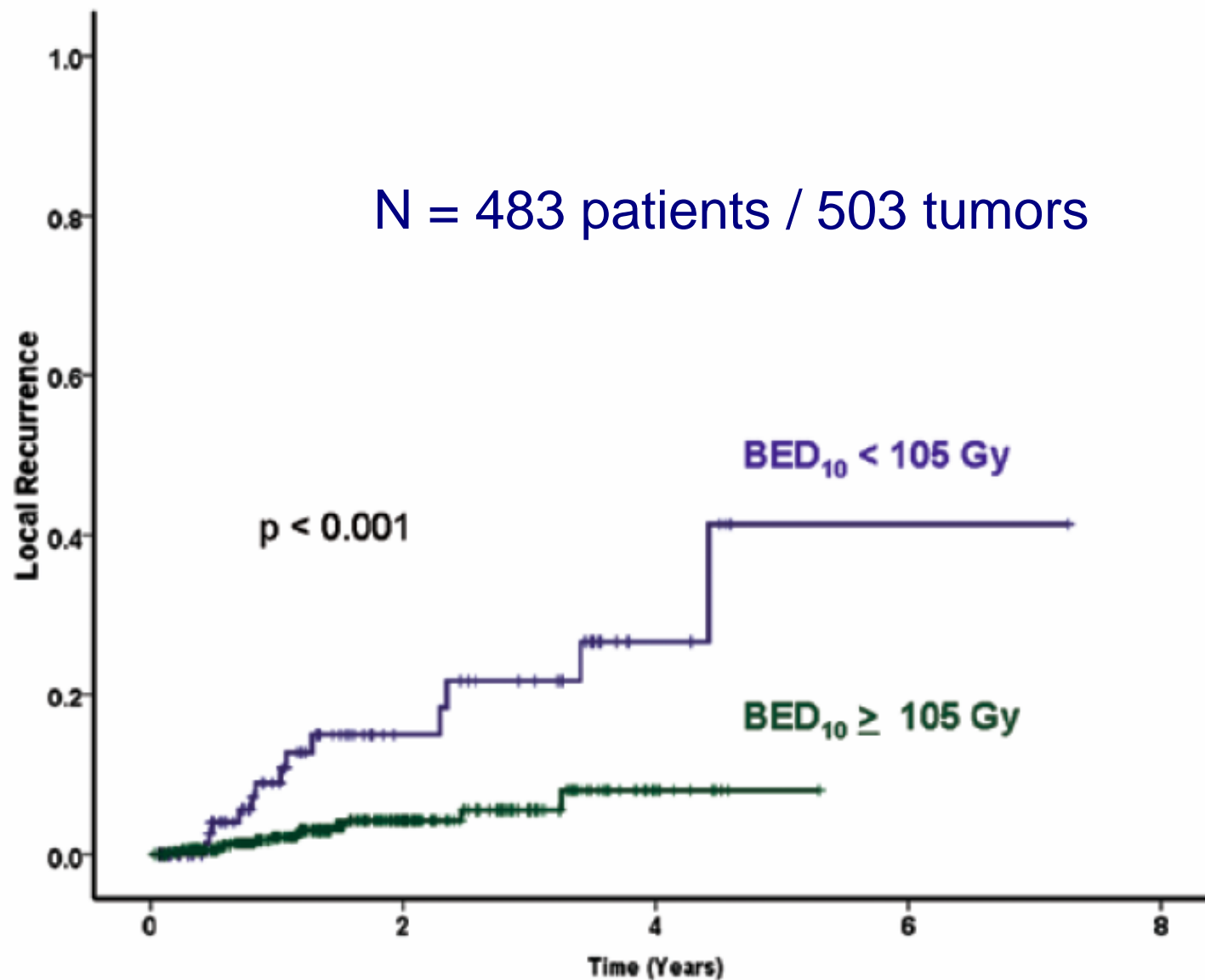


# 'Risk-adapted' SABR protocols

- T1 tumors ( $\leq 3$  cm), without extensive contact with thoracic wall or mediastinum
  - 3 fractions of 18 Gy in 1 week (BED 180 Gy)
- T1 tumors in broad contact with thoracic wall or mediastinum, and T2 tumors
  - 5 fractions of 11 Gy in 1.5 weeks (BED 132 Gy)
- Tumors adjacent to pericardium or hilus
  - 8 fractions of 7.5 Gy, 3 fx/week (BED 105 Gy)

*Doses prescribed to encompass isodose (95% prescription isodose to encompass PTV, 99% of PTV to receive a minimum of 90% of prescription dose)*





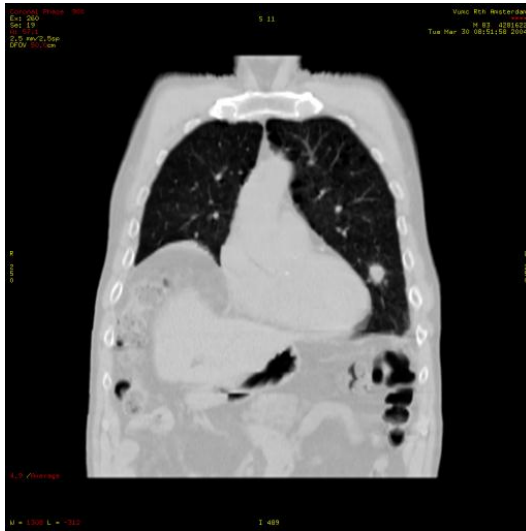
**FIGURE 3.** Local recurrence according to prescription biological equivalent doses.



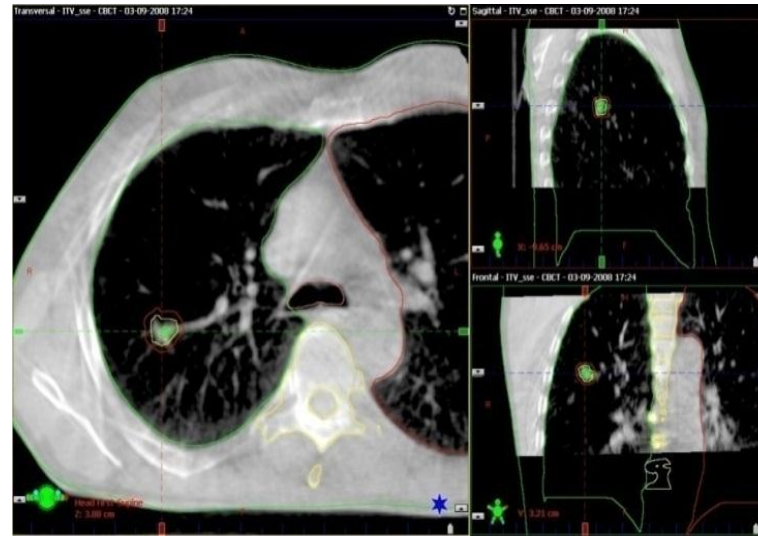


# SABR for stage I NSCLC at VUMC

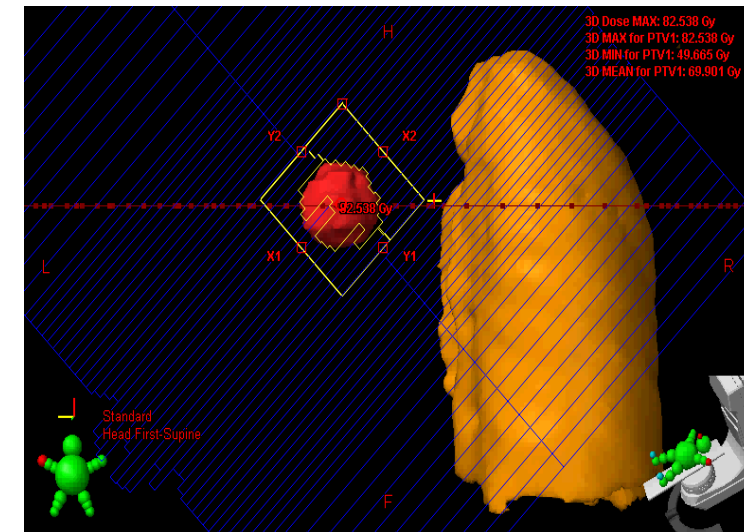
## Image guided ablative radiotherapy in 3-8 sessions



4-D imaging



CT scan on treatment couch



Delivery in 4 mins (Ong CL, 2012)



Verstegen NE, 2011

No pathological diagnosis

3 year endpoints	PA + (n=209)	PA – (n=393)	
Overall survival	55.4%	54.4%	P = .93
<b>Local control</b>	<b>90.4%</b>	<b>91.5%</b>	<b>P = .92</b>
Regional control	90.3%	87.9%	P = .83
Distant control	79.6%	79.8%	P = .95
<b>Disease free survival</b>	<b>72.1%</b>	<b>73.2%</b>	<b>P = .98</b>

Calculated mean probability of malignancy [Herder GJ, CHEST 2005]

**94.8%**  
(95% CI 94.3-95.4%)

**92.5%**  
(95% CI 91.8-93.3%)

*... availability of an effective non-operative therapy should lead to greater efforts to obtain a pathological diagnosis before SABR, because **a diagnosis based on CT scans and <sup>18</sup>F-FDG-PET might not be appropriate outside the Netherlands.*** Senthil S, 2012



# Recurrences following SABR (n=676 pts)

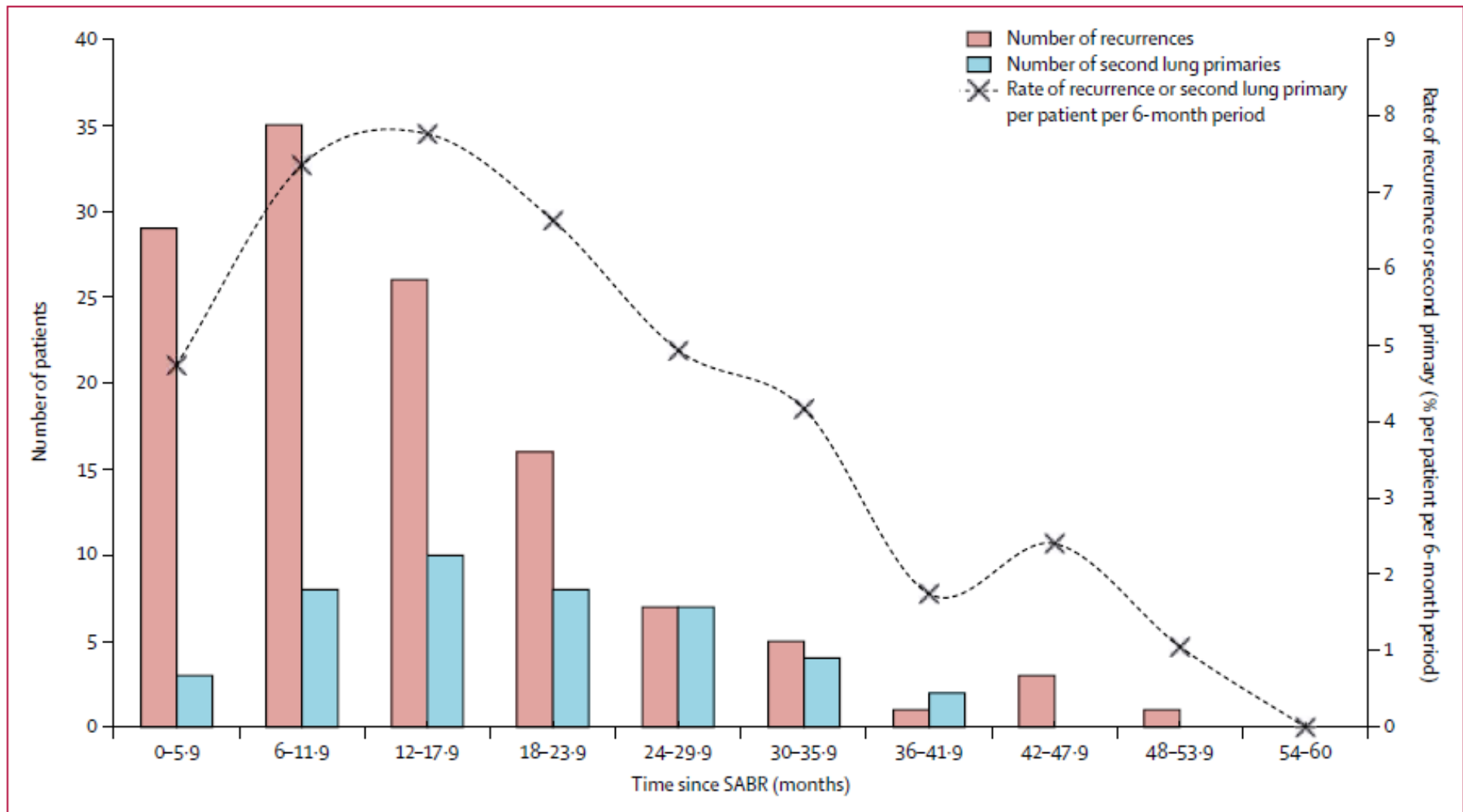
	Local	Regional	Distant
Actuarial 2-year rates	4.9%	7.8%	14.7%
Actuarial 5-year rates	10.5%	12.7%	19.9%

	Median time to event
Distant recurrence	9.6 months (95% CI 6.8-12.4)
Regional recurrence	13.1 months (95% CI 7.9-18.3)
Local recurrence	14.9 months (95% CI 11.4-18.4)
2nd primary tumors	18 months (95% CI 12.5-23.5)

- Stage I-II NSCLC (2003-2011); median follow-up **32.9 months**;
- 66% of recurrences were distant (DR); isolated DR made up 46% of recurrences



# Recurrences following SABR (n=676 pts)

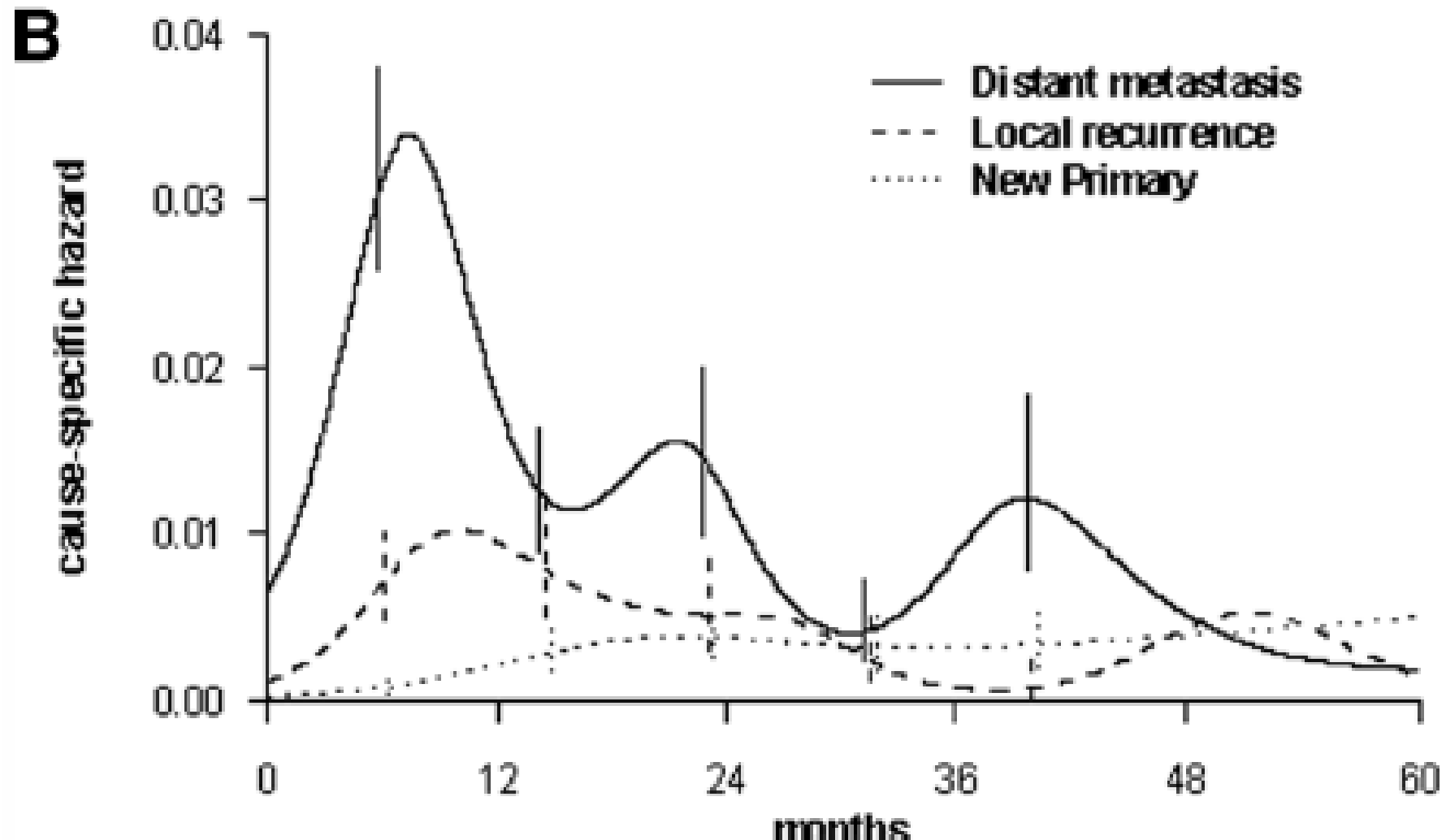


**Figure 3: Number of recurrences and second primary lung cancers per patient per 6-month follow-up period after SABR**

The rate of combined events per patient per 6-month period was identified by the number of patients beginning each period (line). SABR=stereotactic ablative radiotherapy.

Stage I-II NSCLC (2003-2011); median follow-up **32.9 months** (IQR 14.9 - 50.9)



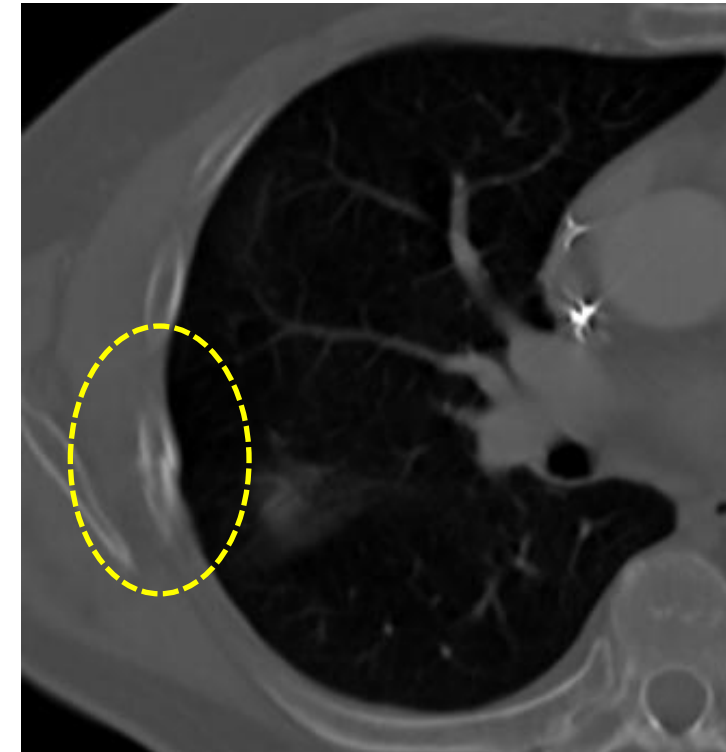


N = 1506 patients. Cause-specific hazard rates estimates following surgery for early-stage NSCLC. Hazard rate obtained by the piecewise exponential regression approach.



Bongers E, 2011

- 500 pts 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%



EORTC recommendations [De Ruysscher 2010]: For chest wall, a dose of <30 Gy, delivered in three to five fractions on a volume of <30 mL, recommended.



- 505 lung tumors in 483 patients
- Median follow-up: 1.6 years
- Median time to pneumonitis: 0.4 years

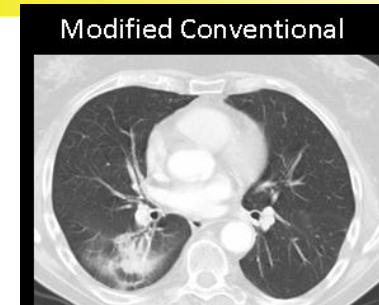
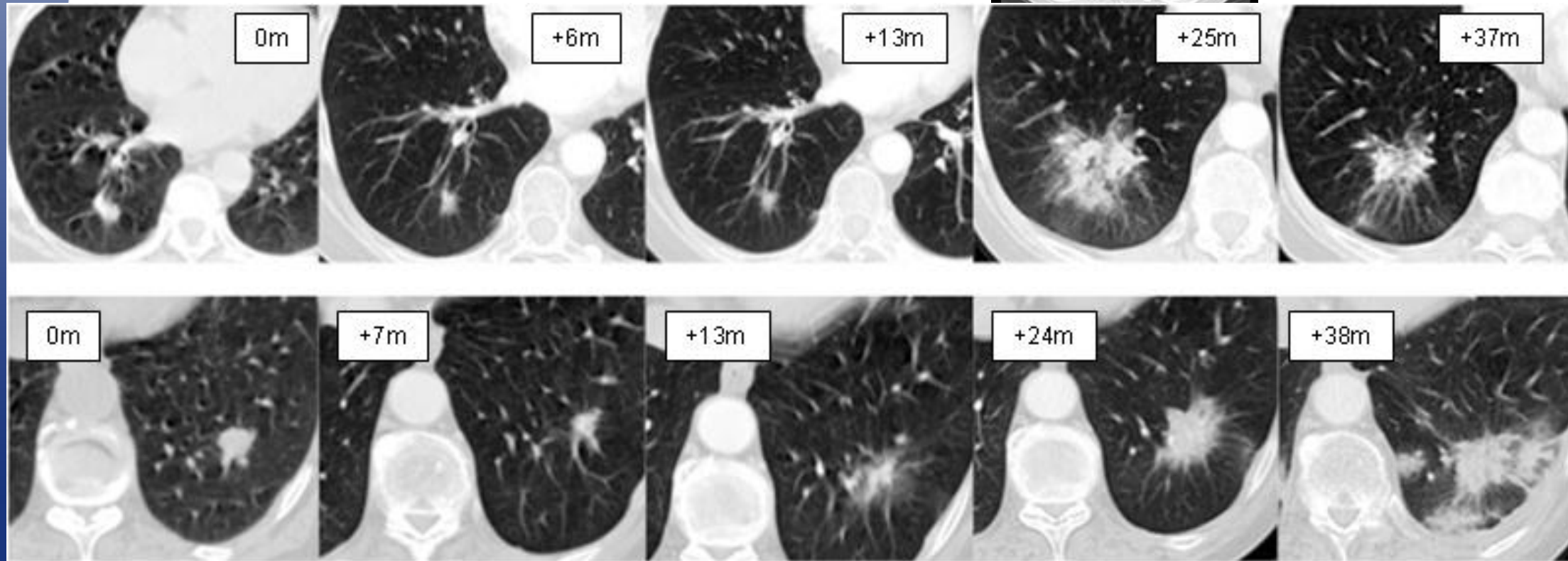
Pneumonitis (NCI-CTC v3 )	incidence
Grade 2 or higher	7%
Grade 3 or higher	2%
Grade 5	0.2%



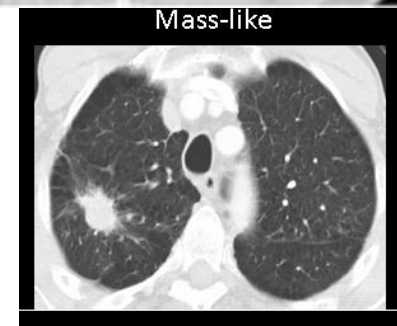


# CT changes after SABR

Patient A



Patient B





- Evidence for superiority of SABR over conventional radiotherapy (30-33 fractions, 6-7 weeks)?
- Approach to '**borderline operable**' patients (age  $\geq 75$  years & severe COPD)

Improving Outcomes for High-Risk Patients  
With Early-Stage Non-Small-Cell Lung Cancer:  
Insights from Population-Based Data and the  
Role of Stereotactic Ablative Radiotherapy

David A. Palma,<sup>1</sup> Suresh Senan<sup>2</sup>

*Clinical Lung Cancer*, Vol. xx, No. x, xxx © 2012 Elsevier Inc. All rights reserved.



## Randomized clinical trials

- SPACE - phase II trial  
SABR (3 x15 Gy at periphery or  
3x22 Gy to center) versus  
70Gy in 7 weeks.  
Accrual completed (100 pts)
- CHISEL study (TROG)  
SABR (3 x18 Gy) versus 60-  
66Gy in 6-6.5 weeks.  
Accrual ongoing

## Population-based studies

IKA-North Holland (3 mil),  
Palma D, JCO 2010

Netherlands Cancer Registry  
(16 mil), Haasbeek CJ, Ann  
Oncol 2012

SEER-Medicare (19,923 pts):  
HR 1.97 (95% C.I. 1.31-2.96)  
for conv. RT versus SABR  
(Shervani SM, IJROBP 2012)



<http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/>

1. Randomized controlled trials and meta-analysis
2. Controlled trials where allocation is non-random (e.g allocation by birth date or chart number)
- 3. Population-based consecutive series**
4. Others

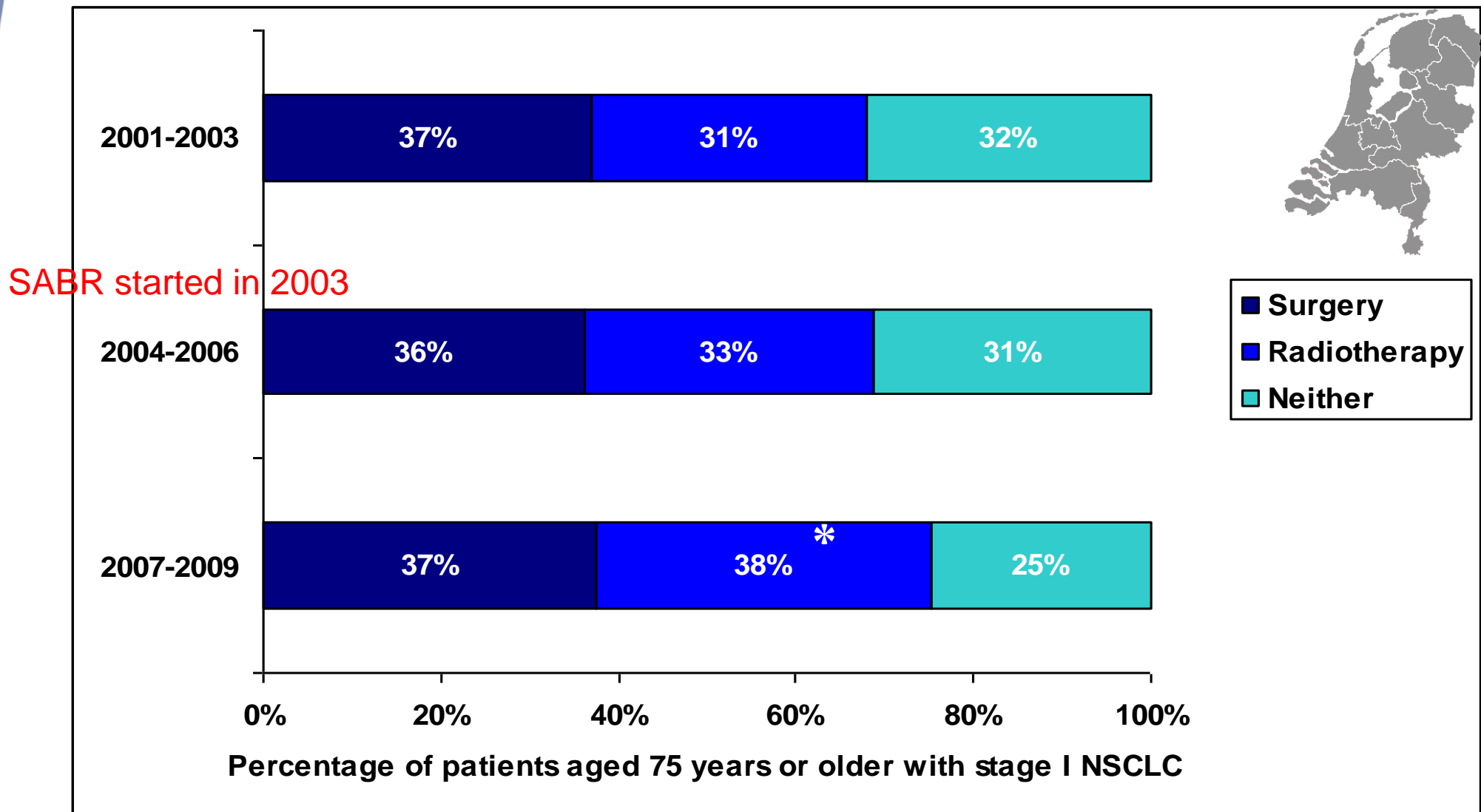
## Population-based studies

Reflect real-world outcomes; patients in randomized studies are systematically different from those who are not treated in trials [Van Spall HG, 2007]

Unselected registries are the only way to examine the generalizability of results from randomized trials

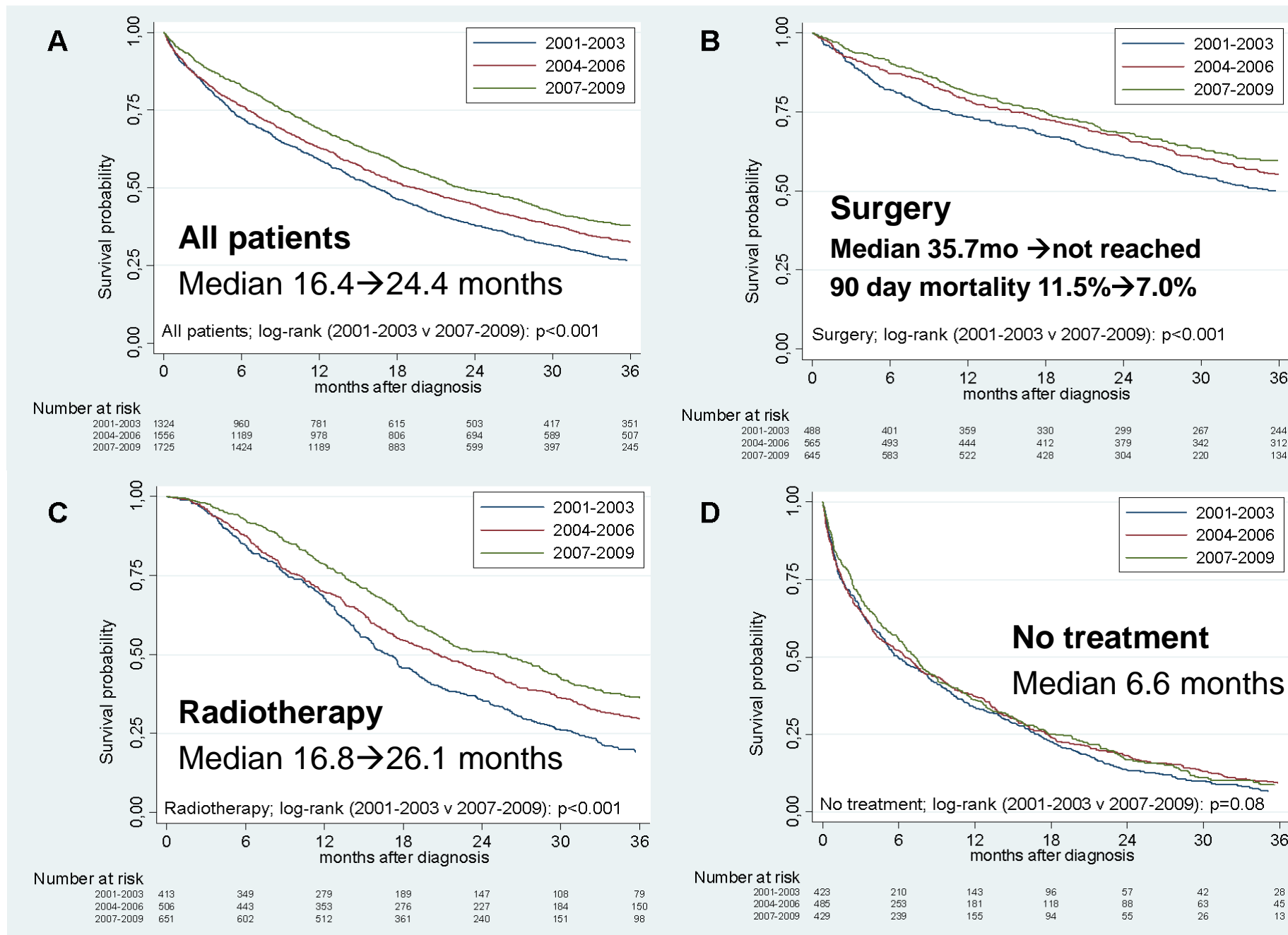


4605 stage I NSCLC patients aged  $\geq 75$  years

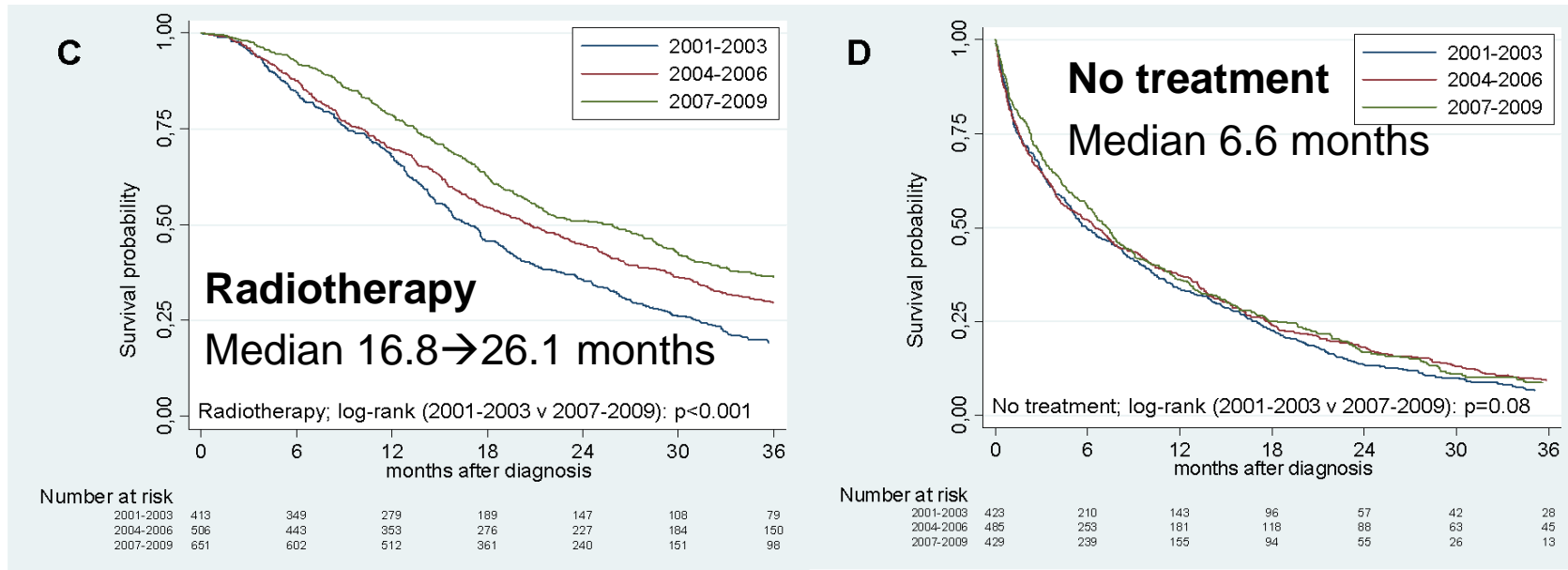


# Dutch national study (2001-2009)

Survival in 4605 stage I NSCLC patients aged  $\geq 75$  years



Haasbeek C, 2012

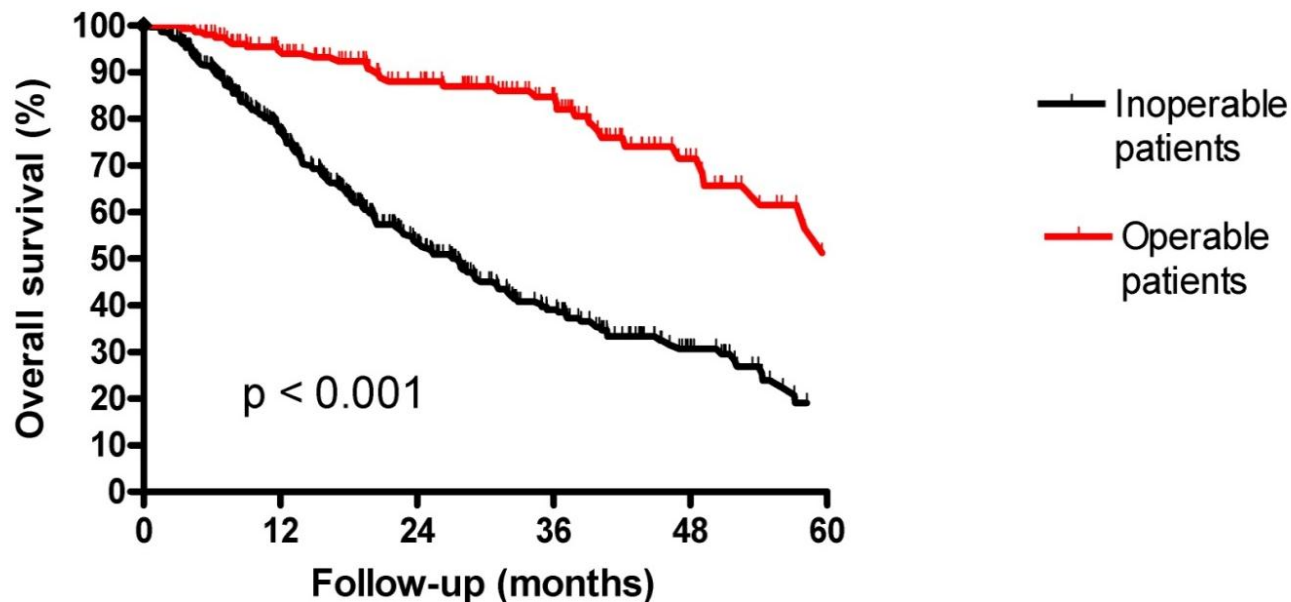


- SABR can be rapidly implemented at national level
- Survival gains of 9.3 months attained in the unfit elderly
- Quality of life did not decline in >500 patients post-SABR (*van der Voort van Zyp NC, 2010; Widder J, 2011; Lagerwaard F, 2012*)



177 patients (24% of referrals to VUmc)

Survival: operable vs. inoperable pts



## Operable patients

Median survival	5.1 years
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30-day mortality	0%
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2-year survival	88%
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3 year survival	85%
-----------------	-----

5 year survival	51%
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Predicted 30-day mortality for lobectomy (Thoracoscopic): 2.6%



Danish Cancer registry: 3152 resected cases (2005-2010)

Table 4

Five-year survival by pathological tumour size (pT) and nodal status (pN) stage and Charlson comorbidity score.

Stage	Charlson score 0			Charlson score 1–2			Charlson score 3+
	5-year survival	95% CI		5-year survival	95% CI		5-year survival
pT1	0.69	0.62	0.75	0.54	0.45	0.62	0.38
pT2	0.50	0.45	0.55	0.41	0.35	0.48	0.30
pT3	0.40	0.31	0.50	0.25	0.10	0.45	
pT4	0.23	0.09	0.40	0.30	0.17	0.45	
pN0	0.61	0.57	0.65	0.51	0.45	0.57	0.38
pN1	0.46	0.37	0.55	0.34	0.21	0.47	
pN2	0.24	0.17	0.33	0.16	0.07	0.28	0.12

CI: confidence interval.





- Nationwide Inpatient Sample, 1994 to 2003 (Finlayson E, 2006)

**Table 1.** Characteristics of Patients Undergoing Operations (Nationwide Inpatient Sample 1994–2003)

Cancer	Age (y)						p Value*
	65–69		70–79		80+		
	n	%	n	%	n	%	
Lung							
Weighted n	70,416	31.8	125,967	57.0	24,804	11.2	

**Table 2.** Short-Term Outcomes by Age (Nationwide Inpatient Sample 1994–2003)

Cancer	Age (y)			p Value*
	65–69	70–79	80+	
Lung				
Operative mortality (%)	3.7	5.2	6.9	<0.0001
Length of stay (mean no. of days)	9.8	10.6	11.2	<0.0001
Discharge disposition (%)				
Home	93.1	87.4	75.4	<0.0001
Short-term hospital	0.4	0.6	0.7	<0.0001
Skilled nursing facility	3.9	7.9	15.8	<0.0001
Intermediate care facility	0.3	0.5	1.2	<0.0001
Another type of facility	2.2	3.6	6.8	<0.0001



First author	Institution	Publication year	Accrual period	n	Treatment
<b>Surgery</b>					
Magdeleinat (26)	Hopital Hotel Dieu and Lannelongue Surgical centre, Paris, France	2005	1983–2003	58	Segmentectomy or wedge (n = 15)
Lau (19)	Glenfield Hospital, Leicester, UK	2010	1997–2009	63	Lobectomy or greater (n = 43) Open segmentectomy or VATS procedure (n = 43) Open lobectomy (n = 20)
<b>SBRT</b>					
Henderson (27)	Indiana University, USA	2008	2002–2004	33	60–66 Gy/3 fractions
Stephans (28)	Cleveland Clinic, USA	2009	2004–2007	42	50 Gy/10 fractions to 60 Gy/3 fractions
Palma (current study)	VU University Medical centre, Netherlands	2010	2003–2010	176	60 Gy/3–8 fractions

*Abbreviations:* n = number of patients; RT = radiotherapy; SBRT = stereotactic body radiotherapy; VATS = video-assisted thoracoscopic surgery.

- Systematic review
- Mean 30-day mortality: **0% post-SBRT** and **10% post-surgery**
- Local or loco-regional control >89% after both treatments
- Survival at 1- and 3-years comparable between treatments



## Potential gains to be achieved

Reduce mortality  
of initial treatment

Survival with  
acceptable QoL

Fitness to  
undergo Rx for  
2<sup>nd</sup> tumors and  
recurrences

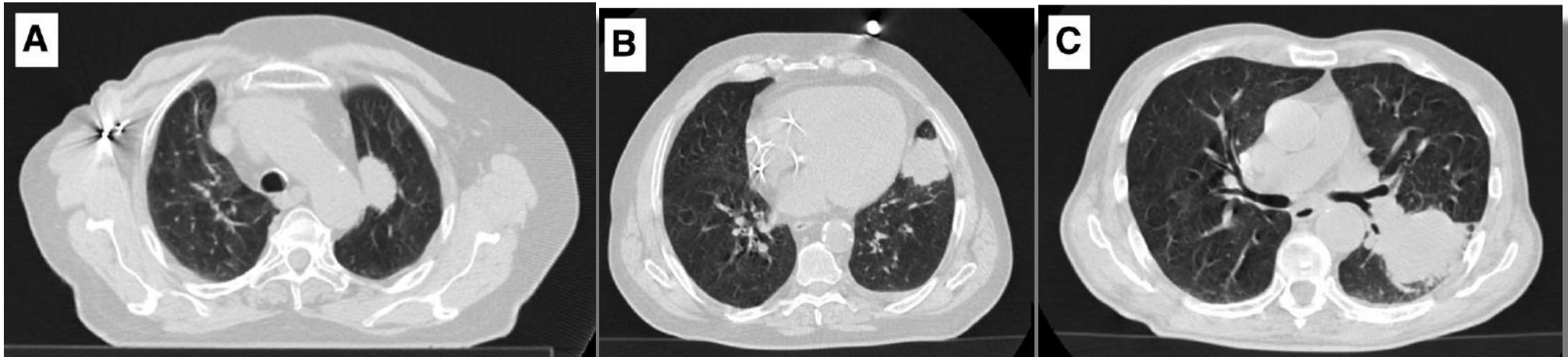
### SEER data [Surapaneni R, 2012]

Risk of second lung cancer highest in 1<sup>st</sup> year with the O/E at **6.78** (CI: 6.29–7.31) and continues to be high at 10 years (O/E **4.12**; CI: 4.44–4.80)



# Central tumors *can* be treated safely

Central tumors: 8 fractions of 7.5 Gy



N = 63 patients

Median follow-up: 35 months

Median survival: 47 months

3-year local control : 92.6%

3-year overall survival: 64.3%

Haasbeek CJ, 2011





# SABR versus surgery: A gladiatorial contest?



# Local failure after complete resection of N0–1 NSCLC

**Table 4**

The crude local–regional failure rates, and locations, by number of mediastinal stations sampled.

Number of mediastinal stations sampled	Local–regional failure										Total	
	Ipsilateral lung		Stump		Hilum		Mediastinum		Chest wall			
	n <sup>a</sup>	%	n <sup>a</sup>	%	n	%	n	%	n	%	n	%
0	1/14	7	1/14	7	0/14	0	3/14	21	1/14	7	4/14	29
1	4/45	9	4/45	9	3/45	7	5/45	11	1/45	2	11/45	24
2	12/94	13	3/94	3	1/94	1	10/94	11	2/94	2	20/94	21
3	7/77	9	7/77	9	2/77	3	9/77	12	1/77	1	17/77	22
4	5/59	8	5/59	8	3/59	5	13/59	22	2/59	3	18/59	31
≥5	8/46	17	4/46	9	2/46	4	9/46	20	0/46	0	14/46	30
Total	35/84	42	24/335	7	11/335	3	49/335	15	7/335	2	84/335	25

<sup>a</sup> Patient number.



## Propensity score-matched analysis of stage I-II NSCLC treated using either SABR or VATS-lobectomy

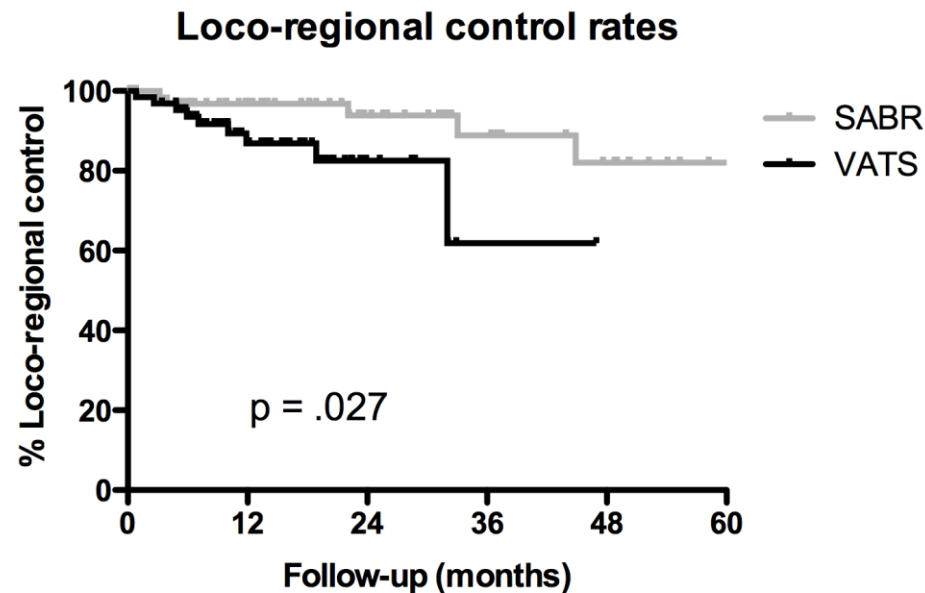
- 86 VATS-lobectomy and 527 SABR patients eligible
- Nodal staging in VATS group in accordance with ESTS guidelines
- Matching covariates:
  - *Gender*                      - *Age*
  - *cTNM*                        - *Tumor diameter*
  - *Histology*                  - *Tumor location*
  - *FEV 1%*                    - *WHO score*
  - *Charlson comorbidity*



- 64 VATS patients
- 3 pts (4.7%) converted to open lobectomy
- Median sampled nodes/patient: 8.5 (1-24),
- Median number of stations sampled: 4 (1-6)
- Disease upstaged in 12 pts (18.8%): 4 pts - N1, 8 pts - N2 disease; adjuvant therapy delivered in 8 pts
- Final diagnosis of benign disease in 4 pts (6.3%)
  
- 64 SABR patients
- Risk-adapted fractionation schemes delivered using either 3 fractions (36%), 5 fractions (52%), 8 fractions (9%) or 12 fractions (3%)
  
- Median follow-up: SABR 30 months; VATS 16 months

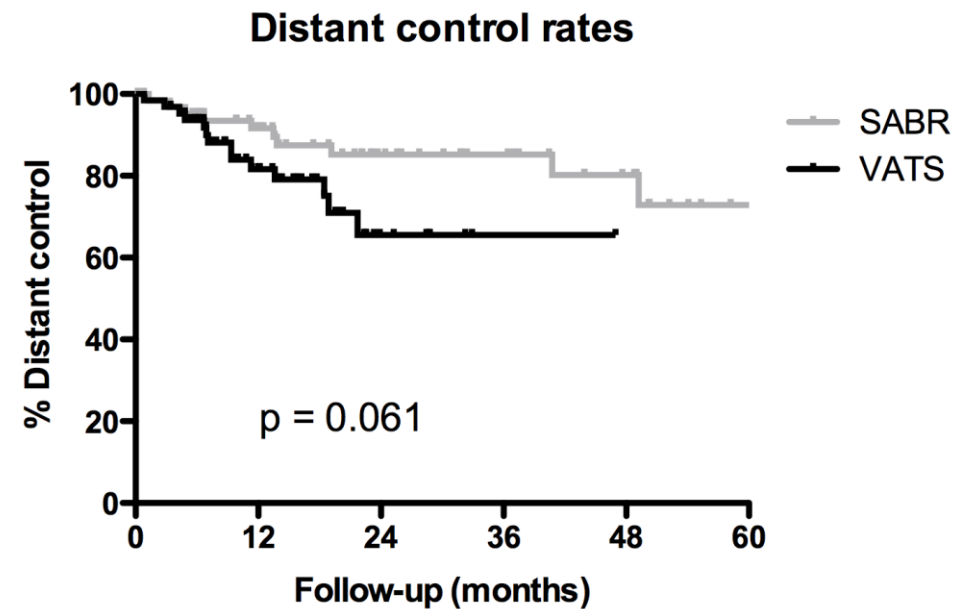






**Pts at risk**

<b>SABR:</b>	64	48	28	18	11	3
<b>VATS:</b>	64	35	8	1	0	0

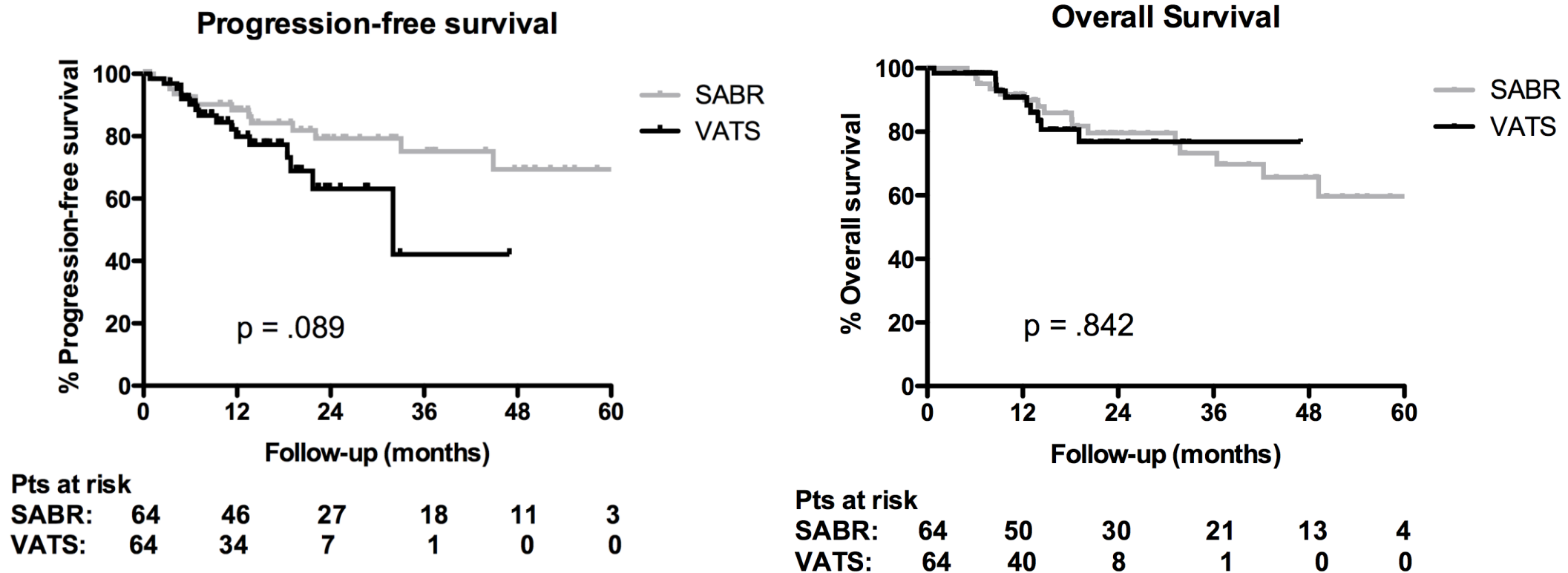


**Pts at risk**

<b>SABR:</b>	64	48	29	21	13	4
<b>VATS:</b>	64	35	7	1	0	0

- Loco-regional control was significantly better after SABR, with actuarial LRC rates after SABR at 1- and 3 years of 96.8% and 93.8%, compared to a 1- and 3-year LRC after VATS-lobectomy of 86.9% and 82.6% (p = .03)
- Distant recurrence rates did not significantly differ between groups, with 1- and 3- year distant control rates of 91.6% and 85.2%, compared to 81.7% and 65.5% at 1 and 3 years after VATS lobectomy (p = .06,





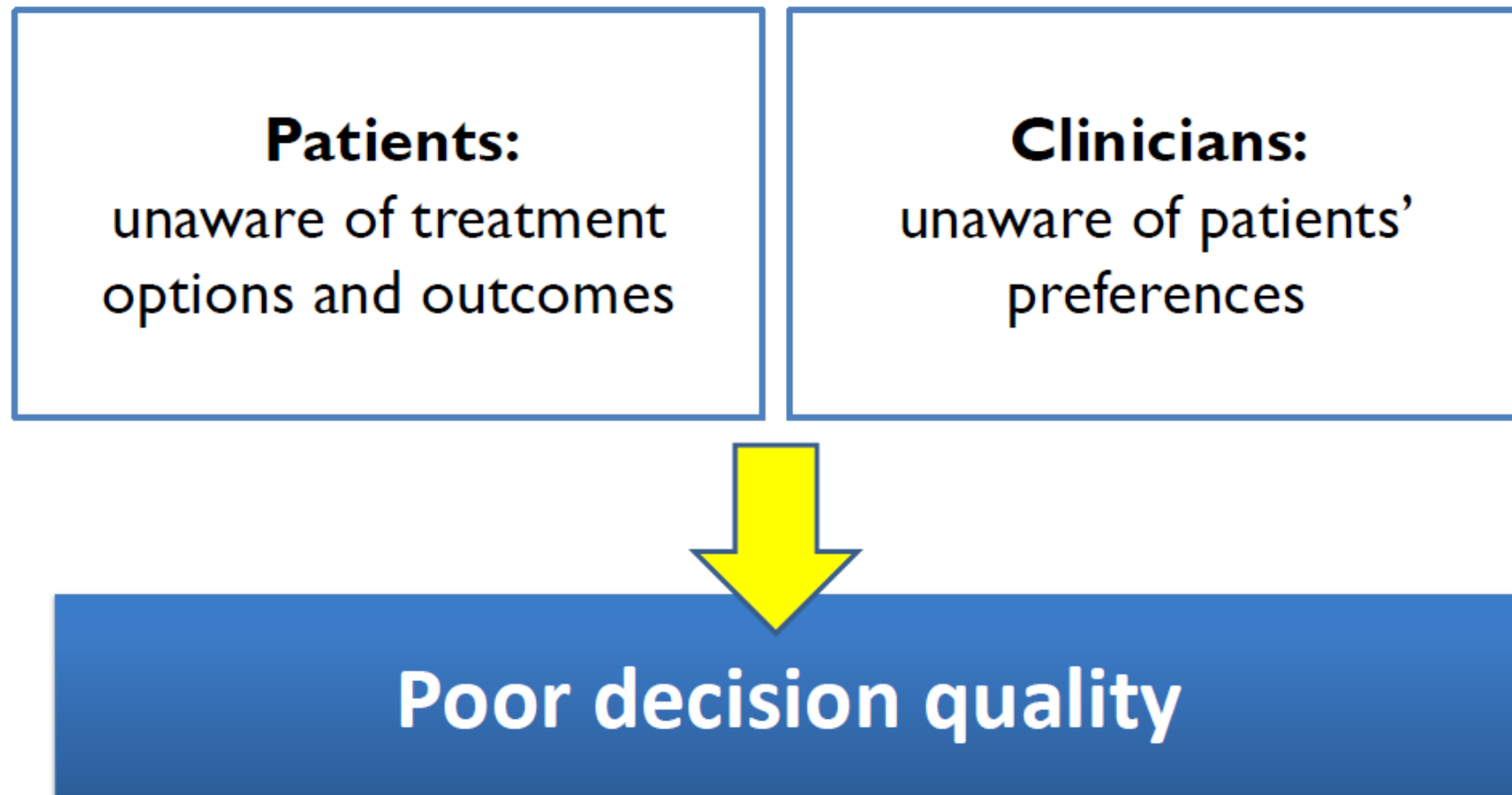
Progression-free survival (PFS) did not significantly differ between the groups.

Overall survival (OS) was similar in both cohorts, with 1- and 3-year OS rates after SABR of 91.8% and 79.6% and 1- and 3-year OS rates after VATS lobectomy of 90.8% and 76.9% ( $p = .84$ )





## The clinical decision problem



Sharing decisions, as opposed to clinicians making decisions on behalf of patients, is gaining prominence in health care policy.

SDM aims to empower patients by 1) providing information and 2) supporting the decision making process.



## **The Patient-Centered Outcomes Research Institute — Promoting Better Information, Decisions, and Health**

A. Eugene Washington, M.D., and Steven H. Lipstein, M.H.A. NEJM 2010

## **Getting the Methods Right — The Foundation of Patient-Centered Outcomes Research**

Sherine E. Gabriel, M.D., and Sharon-Lise T. Normand, Ph.D.

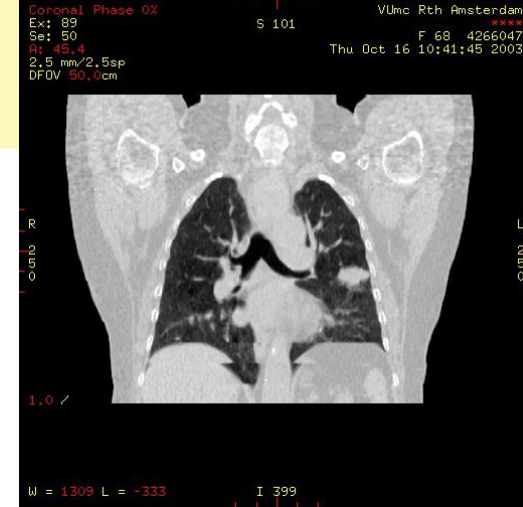
NEJM 2012



# SABR in stage I NSCLC

## Current guidelines and conclusions

- Standard of care for inoperable patients (Japan, Netherlands)
- National Comprehensive Cancer Network guidelines (v3.2012): *non-surgical treatment of choice*
- NHS 'radiotherapy implementation report' 2011: *available to all ..... with early lung cancer and contraindications to surgery*
- For borderline operable cases, a randomized trial of SABR versus surgery is in progress (ACOSOG-RTOG)



# Thank you for your attention

