Klinik RADIOONKOLOGIE
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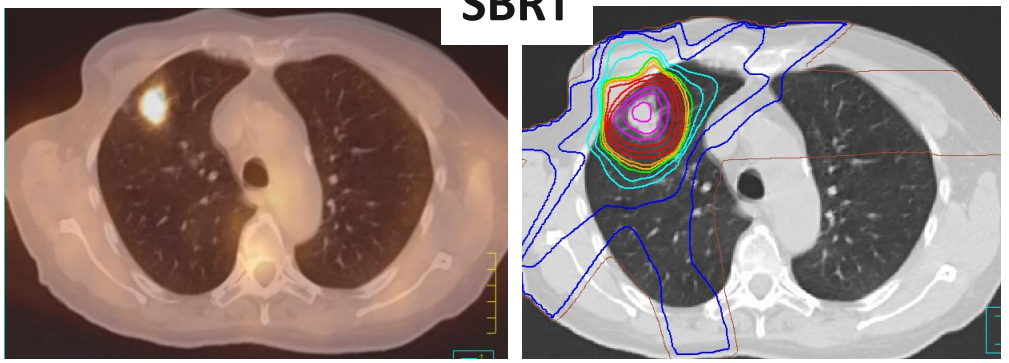
SBRT in operable patients – here comes the existing evidence

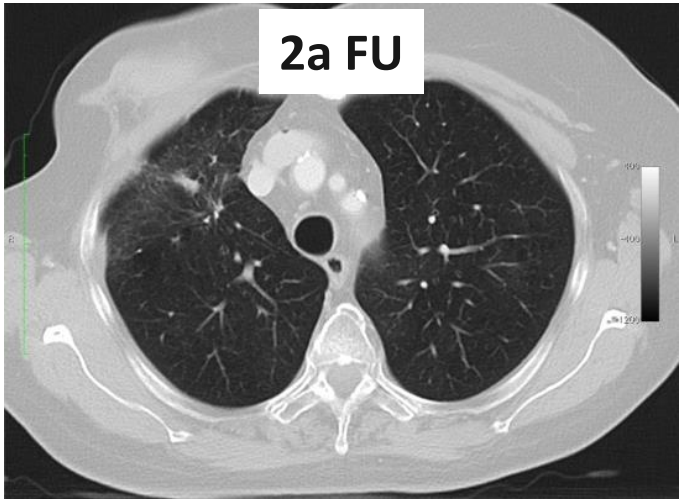
Matthias Guckenberger

Mission impossible ? !

The typical case …

SBRT



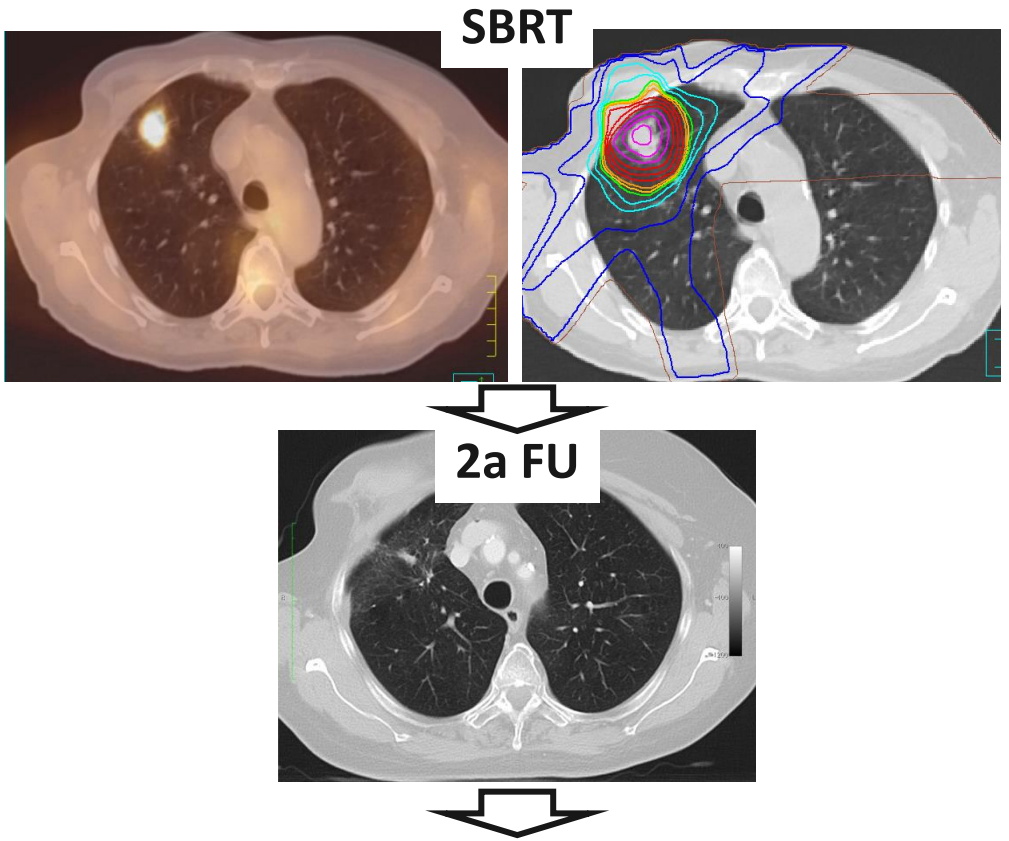


60 pack years
O2 supply in rest: 1.5 l/min
COPD GOLD IV
Pulmonary emphysema

And he lived happily ever after

Real word, not a fairy tale …

60 pack years
O2 supply in rest: 1.5 l/min
COPD GOLD IV
Pulmonary emphysema



Dead after 2.5a
bacterial pneumonia

Spectrum of stage I NSCLC patients

SBRT

No treatment | **Conv. RT** | **Sublobar resection** | **Lobar resection**

Health / Fitness of the patients

Outcome of SBRT in inoperable patients

Study	Year	# patients	OS @ 2-3a	LC @ 2-3a
Nagata	2005	45	75%	98%
Baumann	2009	57	60%	92%
Fakiris	2009	70	43%	88%
Ricardi	2010	62	51%	88%
Bral	2010	40	52%	84%
Timmerman	2010	54	38%	98%
Prospective studies		**328**	**52.1%**	**91.2%**

Highly consistent results in prospective and retrospective studies

Spectrum of stage I NSCLC patients

SBRT

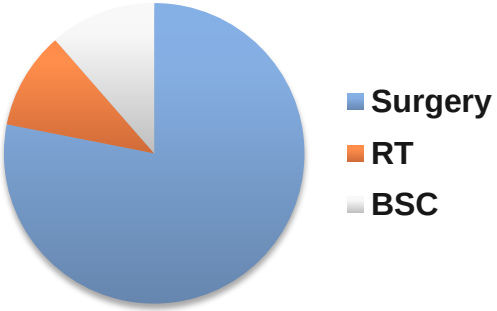
No treatment | **Conv. RT** | **Sublobar resection** | **Lobar resection**

Health / Fitness of the patients

Proportion of patients remaining untreated

Total population

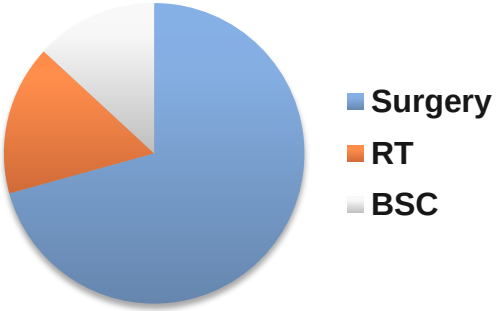
11%



Raz Chest 2007

SEER > 65 years

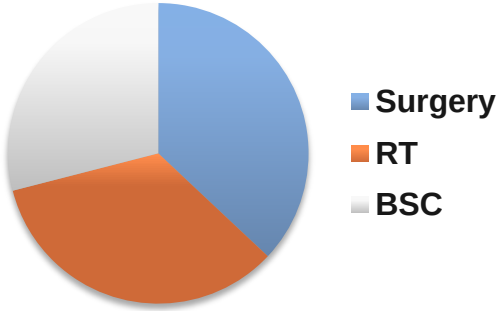
13%



Shirvani IJROBP 2012

Netherlands >75a

29%



Haasbeek Ann Oncol 2012

- **Large proportion of elderly patients remaining untreated**
- **Proportion of patients will increase with aging societies**

Safety of SBRT in elderly patients

	Patients	Median Age
Takeda 2013	109	83
Sandhu 2013	24	85
Haasebeek 2010	193	79

- **Very low mortality and morbidity despite very old age**
- **Excellent safety profile**

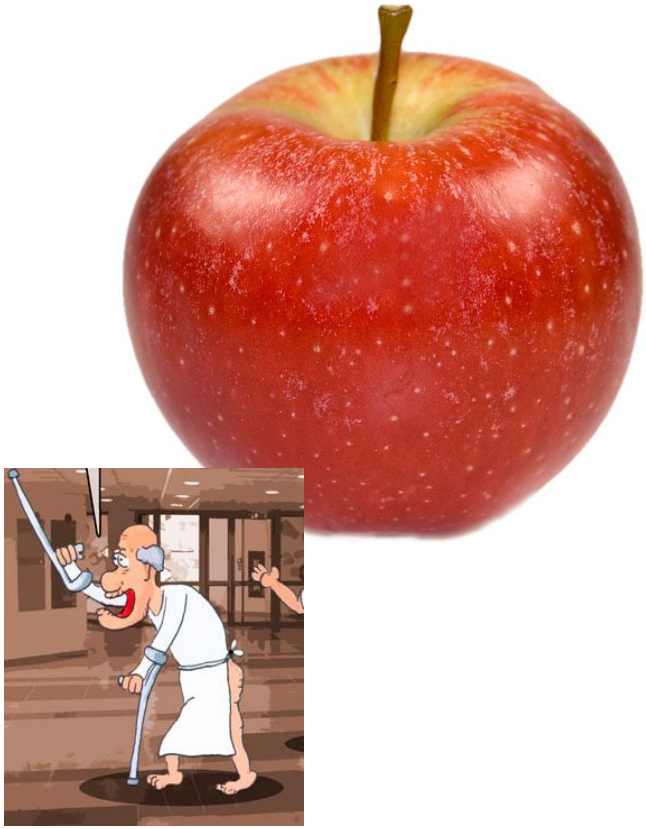
Spectrum of stage I NSCLC patients

SBRT →

No treatment | **Conv. RT** | **Sublobar resection** | **Lobar resection**

Health / Fitness of the patients

SBRT



Surgery

The evidence:

randomized trials comparing surgery and SBRT

Rosel

STAR

RTOG 1021

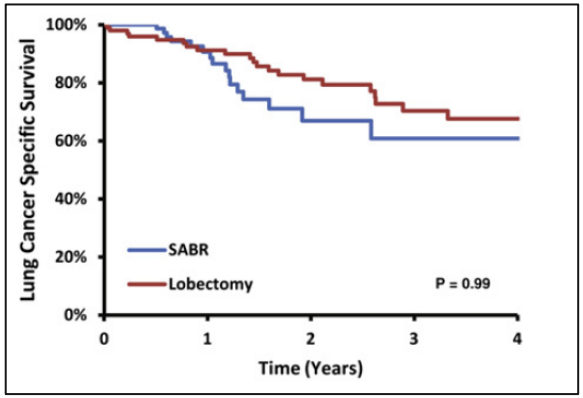
Enrollment: 68 / 2410 (2.8%)

- Was it successfull — certainly no !!!
- Was it for nothing — certainly no !!!

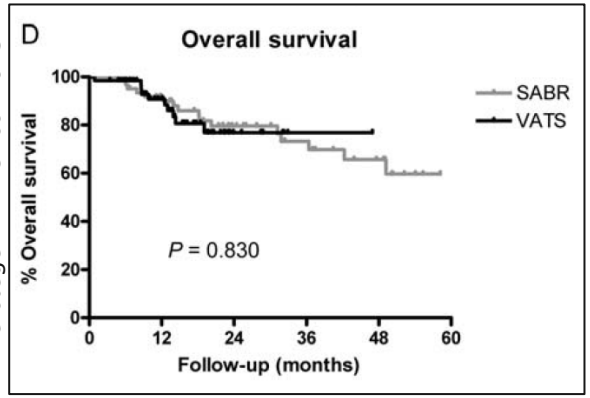
The evidence:
there is more that RCT

The next level of evidence:
Propensity Score Matched Analyses, systematic reviews

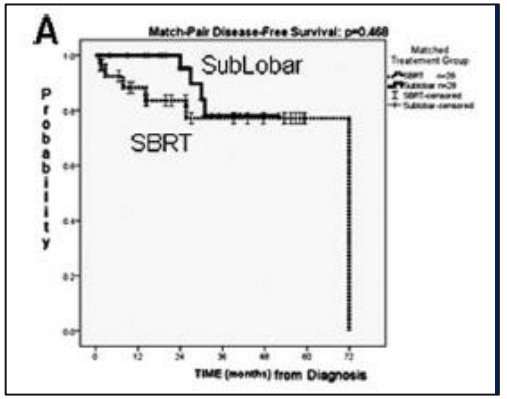
Shirvani IJROBP 2012



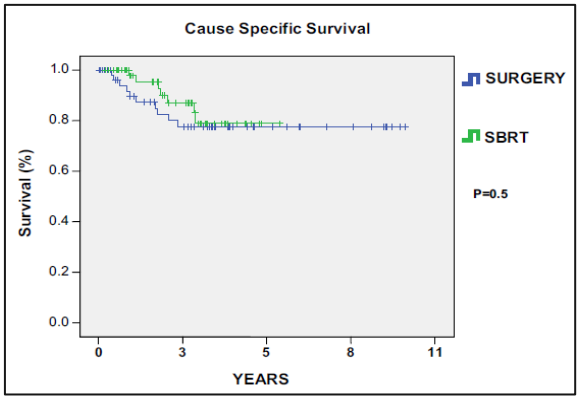
Verstegen Ann Oncol 2013



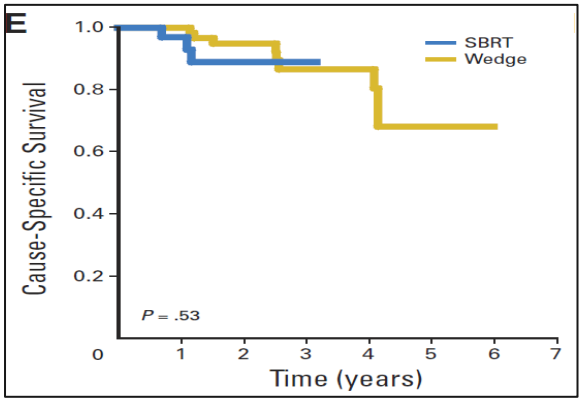
Varlotto Cacner 2013



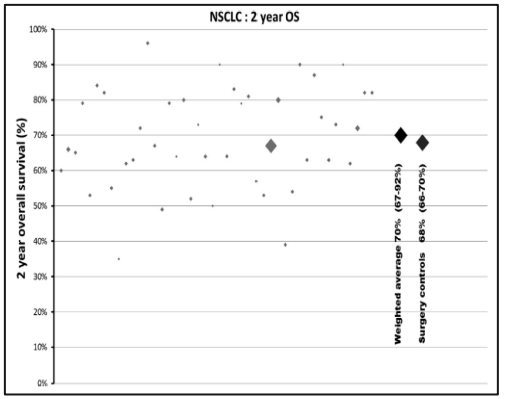
Puri JTCS 2012



Grills JCO 2010



Solda Rediother Oncol 2013



Consistently no difference in (intermediate term) OS / CSS

SBRT: results of population based studies

SEER database: stage I NSCLC, age ≥65a: n=10.923

Shirvani IJROBP 2012

	Safety: 90 day death rate	Efficacy: OS	Efficacy: CSS
SBRT	0.8 %		
SLR	5.6 %		
LE	4.1 %		

SLR

LE

SBRT as low-risk option for patients >65 years old

SBRT: multicenter comparison of SBRT and VATS LE

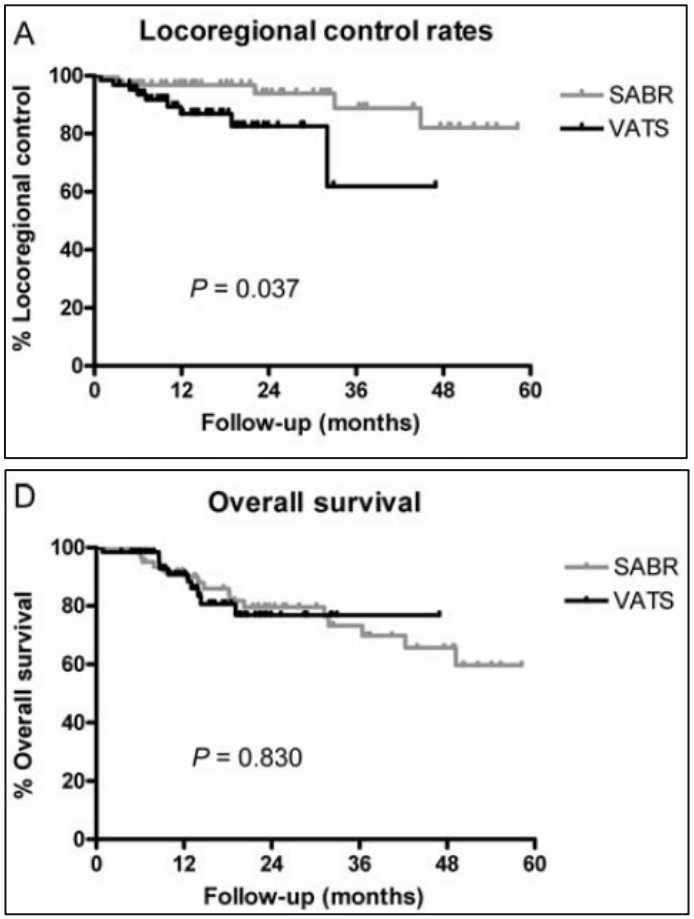
SBRT: n=64

Propensity Score matched:

- cTNM stage
- Age
- Gender
- Charlson comorbidity score
- Lung function
- Performance score

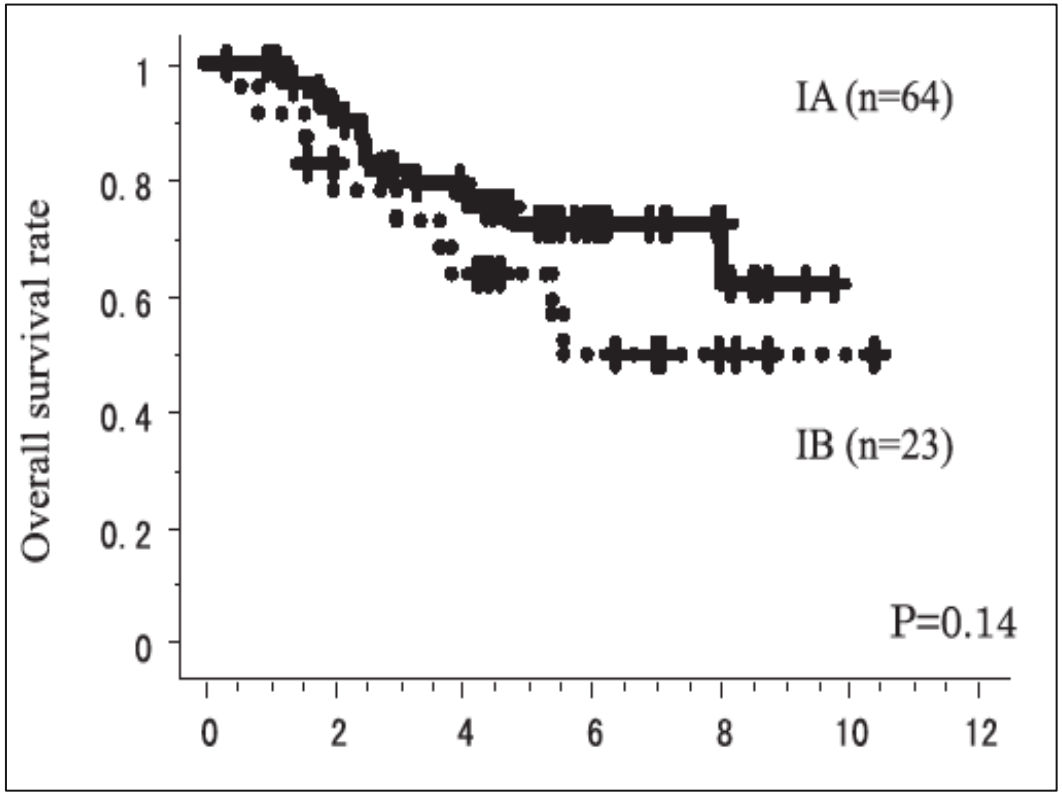
VATS LE: n=64

Verstegen Ann Oncol 2013



Superior LRC and equivalent OS after SBRT compared to VATS LE

SBRT in patients who refused surgery



5a OS	IA	IB
SBRT	72%	62%

Onishi IJROBP 2011

No apparent difference in OS between SBRT and IASLC data

Controversy: Histophathological confirmation

Do we predominantly treat and "cure" benign nodules?

Study		Biopsy
Nagata	2005	100%
Baumann	2009	67%
Fakiris	2009	100%
Ricardi	2010	65%
Bral	2010	100%
Timmerman	2010	100%
Prospective studies		**87.6%**
Senthi	2012	35%
Guckenberger	2013	85%
Grills	2013	59%
Retrospective studies		**57.6%**

- Histological confirmation should be obtained prior SBRT
- SBRT justified in case of high-risk patients

Controversy: Histophathological confirmation

Do we predominantly treat and "cure" benign nodules?

Proportion of benign disease after clinical **CT and FDG-PET** diagnosis:

Operable NSCLC	**0%**
Stage I NSCLC	**8 – 10%**

Fischer 2009, Herder 2006
Meyers 2006, Kozower 2008

- High PPV of CT and FDG-PET based staging
- Accuracy decreased in regions with high incidence of granulomatous diseases

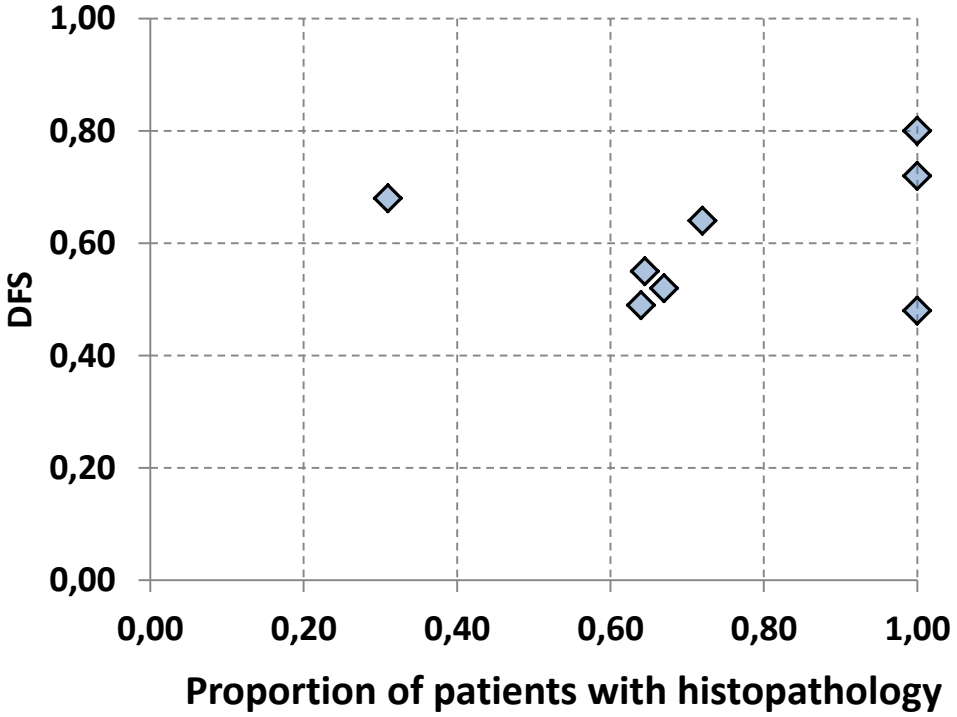
Controversy: Histophathological confirmation

Do we predominantly treat and "cure" benign nodules?

Literature review

- All prospective SBRT studies
- Large retrospective studies

Correlation between
- % of patients with biopsy
- DFS



No difference in DFS (and any other endpoint) whether biopsy had been performed or not

Controversy: No treatment of lymph nodes

How good is clinical nodal staging ?

Surgical series

	CT
False negative	~ 25%
References	*D'Cunha 2005*

SBRT series

	CT & FDG-PET
Nodal recurrences	~ 10%
References	*Chi 2010*

Consistent rate of 10% regional recurrences after PET staging

- Further improvement with EBUS / EUS ?
  - NPV of 98.9% in clinical stage I NSCLC *Herth 2008*

Controversy: No treatment of lymph nodes

Compliance with nodal staging in surgery ?

	Database	LN sampling / dissection
Little 2005	*ACR*	58%
Osarogiagbon 2012	SEER	38% - 51%
Verhagen 2012	Netherlands	75%

- **Poor compliance with guideline recommended LN dissection**
- **Potential advantage of surgery minimized**

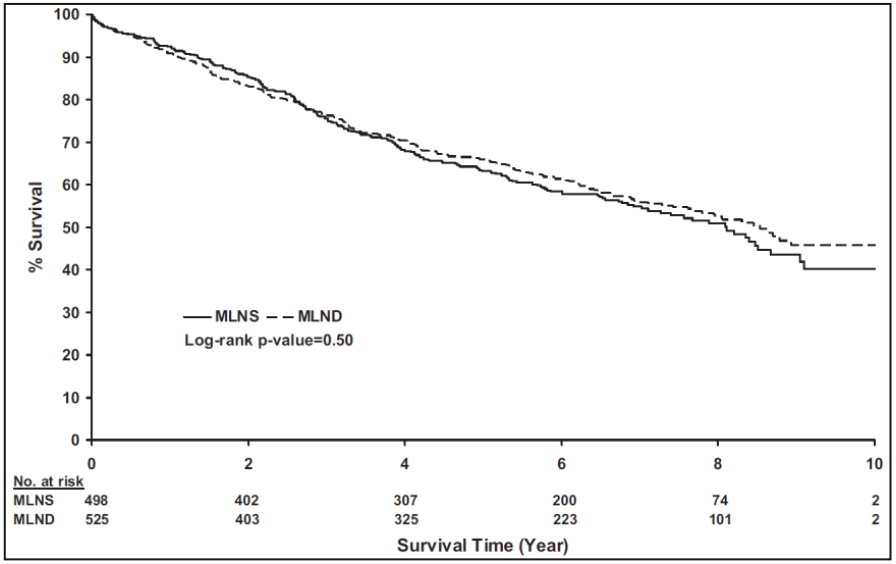
Controversy: No treatment of lymph nodes

What is the clinical benefit of LN sampling / dissection?

ACOSOC Z0030

cN0, nonhilar cN1,cT1, cT2
Randomization:

- MLN sampling (n=498)
- MLN dissection (n=525)



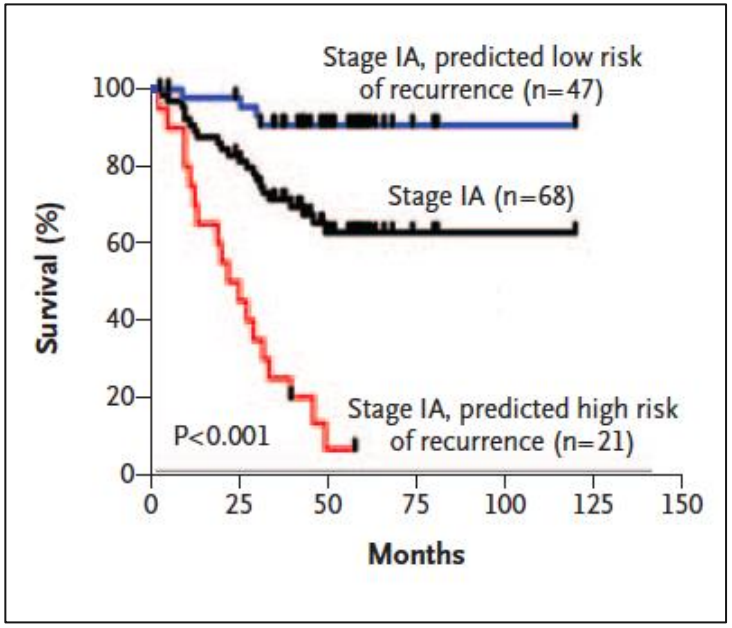
Darling 2011

- Value of Lymph node sampling / dissection:

➢ **Diagnostic or Therapeutic?**

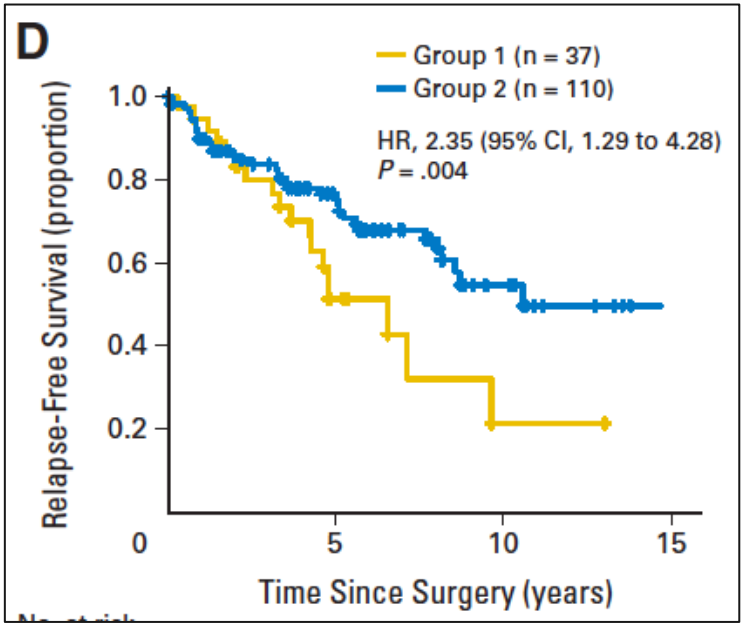
Beyond the discussion about local therapy

Gene expression profiling



Potti NEJM 2006

DNA Methylation Signature



Sandoval JCO 2013

CONCLUSIONS

- **NO** RCT demonstrates equivalence of SBRT and surgery for stage I NSCLC
- **Existing** evidence shows equivalence of SBRT and sublobar resection
- SBRT
  - Mandatory component of interdisciplinary management of NSCLC
  - Excellent alternative for patients refusing surgery
  - Routine discussion with elderly patients with comorbidities not undergoing lobectomy

➢ Integration of **SBRT AND surgery** into innovative multimodal treatment concepts