Stereotactic radiosurgery for operable lung cancer

Con

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LOK Antwerpse Longartsen – TOGA 15/03/11

Specifc topics

- discuss the role of surgical treatment for early stage lung cancer
- determine important factors for long-term survival
- develop treatment algorithm for “small” lung cancers

- list major concerns when applying stereotactic radiotherapy *(radiosurgery)* to operable lesions

Against SRT in operable tumors

- surgical treatment for stage I lung cancer
  - complete resection: definition
  - lymph node staging
  - limited resection
- stereotactic radiotherapy as new treatment modality
  - how to obtain a pathological diagnosis?
  - how to determine nodal staging?
  - how to evaluate response and local recurrence rate?
  - how to select patients for adjuvant therapy?
  - radiotherapy issues

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SURGICAL THERAPY

- very effective therapy early stage lung cancer
  no large randomized studies
- only applicable in 1/4 of cases
- resectability :
  - stage: clinical, surgical
  - medical status: respiratory
    cardiac
- final aim = complete resection

COMPLETE RESECTION

depending on R = residual disease

- **R0 no residual tumor**
- **R1 microscopic residual tumor**
- **R2 macroscopic residual tumor**
- **R uncertain (to be tested prospectively)**

Rami-Porta R et al. Lung Cancer 2005; 49:25

IASLC
Complete Resection Subcommittee
Complete resection R0

- free resection margins proved microscopically
- systematic or lobe-specific systematic nodal dissection:
  ≥ 6 nodes (3 mediastinal)
- no extracapsular extension in nodes removed separately or at the margin of the lung specimen
- highest mediastinal lymph node must be negative

Rami-Porta R et al. Lung Cancer 2005; 49:25

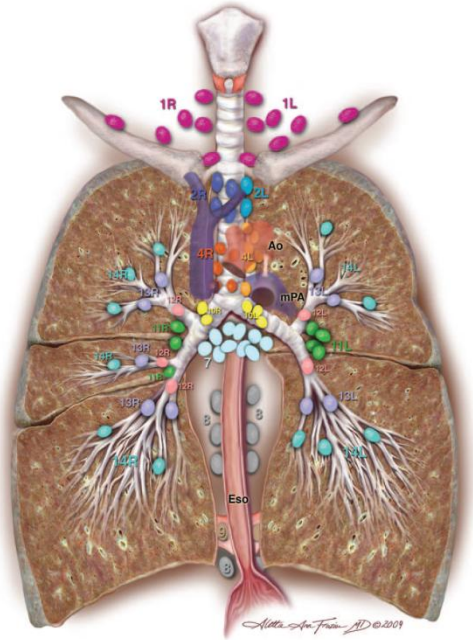
Lymph node staging

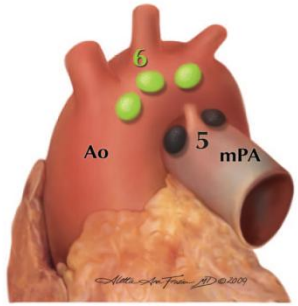
When there are no distant metastases lymph node involvement will determine prognosis!

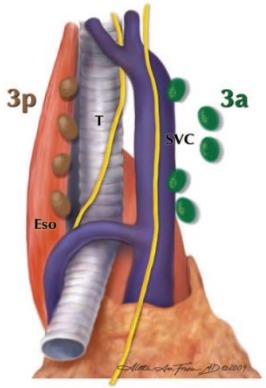
Peroperative staging utmost important!

Meta-analysis: lymph node dissection ↑ survival

Wright G. Thorax 2006; 61:597
Rusch VW. J Thorac Oncol 2009; 4:568







Supraclavicular zone
1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

AORTIC NODES

AP zone
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
7 Subcarinal

Lower zone
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
10 Hilar
11 Interlobar

Peripheral zone
12 Lobar
13 Segmental
14 Subsegmental

Systematic nodal dissection

- dissection of mediastinal, hilar and lobar LN in a systematic fashion
- 240 pts cT1-3 N0-1 NSCLC
- 3 % expl. thoracotomy - 20 % N2 disease
- skip metastases : 34 % N2 disease
- no subgroup 0 % incidence of N2 metastases

Graham A. J Thorac Cardiovasc Surg 1999; 117:246

Systematic nodal dissection

- **peripheral tumors < 2 cm. : 24 % LN mets**
- ***necessary for accurate staging NSCLC***
- ***gold standard for mediastinal staging***
- **confusion : radical lymphadenectomy**
  lymph node sampling
- **R : 4,3,2 7,8,9 L : 5,6,4 7,8,9**

Graham A. J Thorac Cardiovasc Surg 1999; 117:246

Accuracy PET - CT scanning anno 2009

- 200 patients operated lung cancer
- PET-CT followed by staging mediastinoscopy and resection, if appropriate
- PET-CT

correct staging	99 pts	49.5 %
under-staged	59	29.5 %
over-staged	42	21 %

- superior mediastinal nodes not correctly staged in 19 %

Carnochan FM, Walker WS. Eur J Cardiothorac Surg 2009; 35:781

Is lobectomy standard therapy?

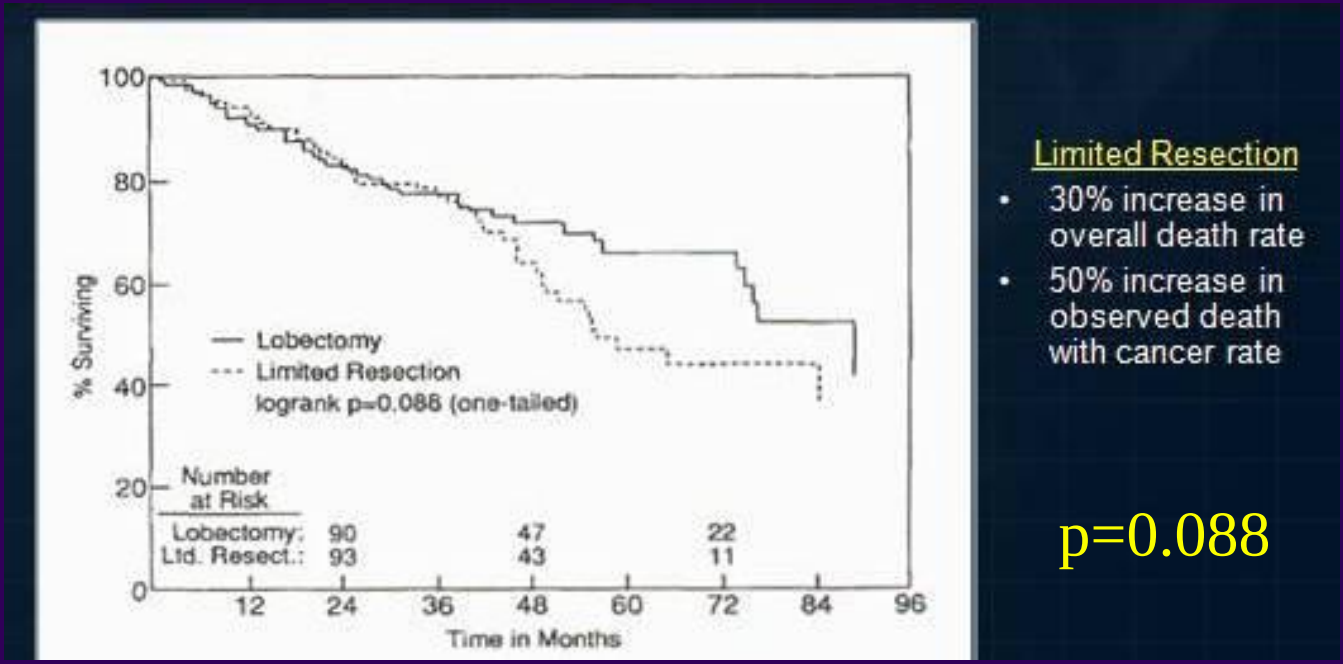
- LCSG : prospective randomized trial
  lobectomy versus lesser resection

  - peripheral cT1N0 < 3cm
  - 50 % contra-indication to randomization :

    not T1 (size, pleura) not N0 (25% mediastinal LN involvement !)
  - postop. morbidity and mortality equal

Ginsberg RJ. Ann Thorac Surg 1995; 60:615

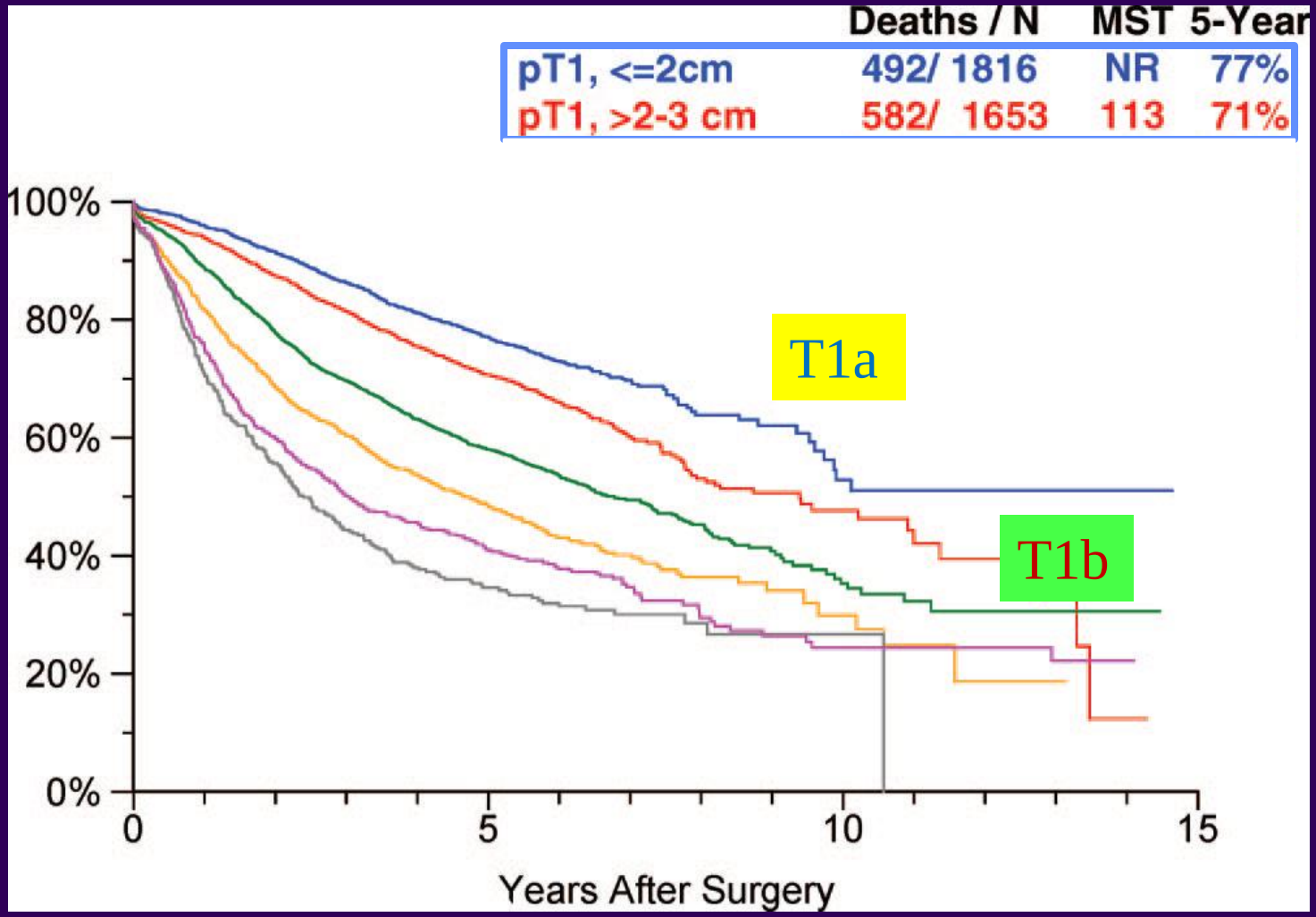
Role of limited resection ?



minimal resection = lobectomy

Ginsberg RJ. Ann Thorac Surg 1995; 60:615

Survival pT1



Rami-Porta R. J Thorac Oncol 2007; 2:593

T1a peripheral lung lesions

Treatment algorithm

- prospective single centre trial, T1a ≤ 2 cm
- inclusion ≤ 2 cm on HRCT
  hilar, mediastinal LN ≤ 1 cm (cN0)
- 179 pts proven or suspected lung cancer - 10/97 and 09/02

- lesions: ≤ 10, 11-15, 16-20 mm
- % GGO: ≥ 50% GGO type, < 50% solid type
- procedures: wide wedge resection, segmentectomy, lobectomy

Kodama K. Eur J Cardiothorac Surg 2008; 34:1068

T1a peripheral lung lesions

Treatment algorithm

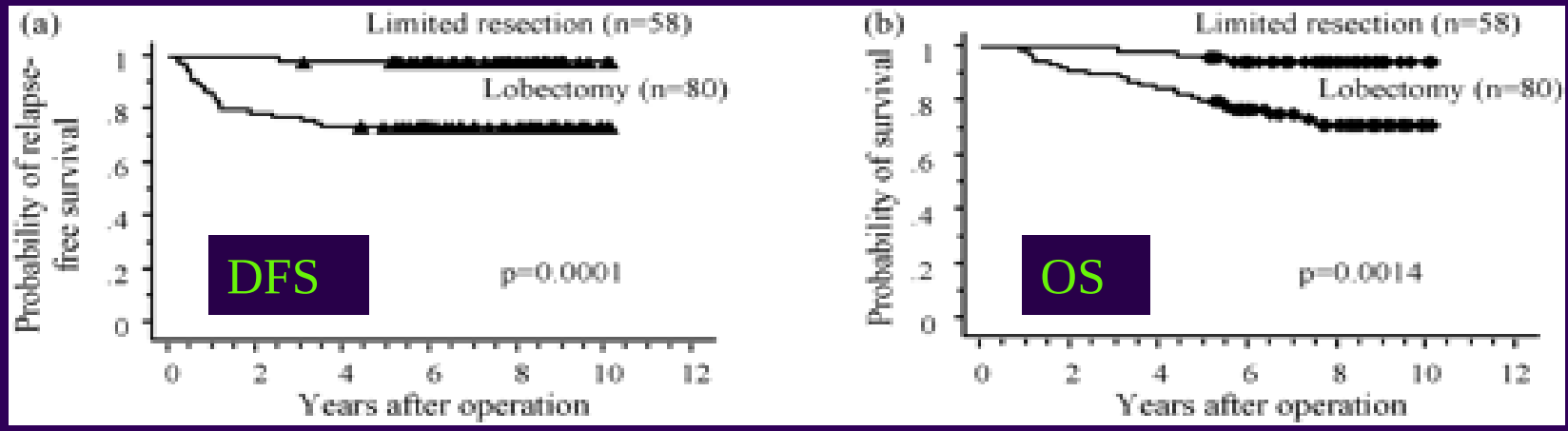
ø	type	procedure
≤ 10 mm	any type	observation → ↑ size, density
any size	pure GGO	wedge
		segmentectomy
		(VATS) lobectomy
11-15 mm	GGO	segmentectomy + LN sampling
	solid	segmentectomy + LN dissection
16-20 mm	GGO	
	solid	lobectomy + LN dissection

Kodama K. Eur J Cardiothorac Surg 2008; 34:1068

T1a peripheral lung lesions

Follow-up

- limited resection: no locoregional recurrences
- lobectomy: 5 (metastatic pleuritis, resection margin, LN)



5-year	limited resection	98%
	lobectomy	74%

5-year	limited resection	97%
	lobectomy	80%

Mortality lung resection

- lobectomy open 2 → 1% recent series
  VATS < 1%

- pneumonectomy 4-8%
  R > L (bronchopleural fistula)
  ↑ induction chemoradiotherapy

Shields T. General Thoracic Surgery, 6th ed. 2005, chapter 106
Pennathur A. Curr Opin Pulm Med 2007; 13:267
Altorki K. Therapeutic modalities for small stage I lung cancers. ASCO 2008

Morbidity lung resection

- **overall morbidity: 6 – 22%**

  ↑ *induction therapy*

  up to 60% complex pneumonectomies

- **complications** **respiratory**

  cardiac

  surgical

Shields T. General Thoracic Surgery, 6th ed. 2005, chapter 106
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Long-term results

- 5-year survival lobectomy stage I 60-70%
- local control 65-90%
- limited resection similar results peripheral T1 ≤ 2cm N0
- surgical treatment guidelines well established
- *lobectomy = gold standard for comparison*

Shields T. General Thoracic Surgery, 6th ed. 2005, chapter 106
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Against SRT in operable tumors

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- **stereotactic radiotherapy as new treatment modality**
  - **how to obtain a pathological diagnosis?**
  - **how to determine nodal staging?**
  - **how to evaluate response and local recurrence rate?**
  - **how to select patients for adjuvant therapy?**
  - **radiotherapy issues**

Against SRT in operable tumors

New treatment modalities

- radiofrequency ablation (RFA)
- stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS)

  adopted from brain irradiation *but: lung is moving target !*

  does not equal surgery: radiosurgery
- meta-analysis medically *inoperable* patients stage I NSCLC classical radiotherapy: 5-year survival 21%
  local recurrence: most common reason treatment failure

  Qiao X. Lung Cancer 2003; 41:1
- new fascinating strategies developed, hypofractionation
- non-randomized studies: local control ≈ surgery
- *operable* early stage I NSCLC? *major concerns!!!*

Against SRT in operable tumors

How to obtain a pathological diagnosis?

- peroperative frozen section analysis
- SRT: no precise histological diagnosis, up to 70% of patients

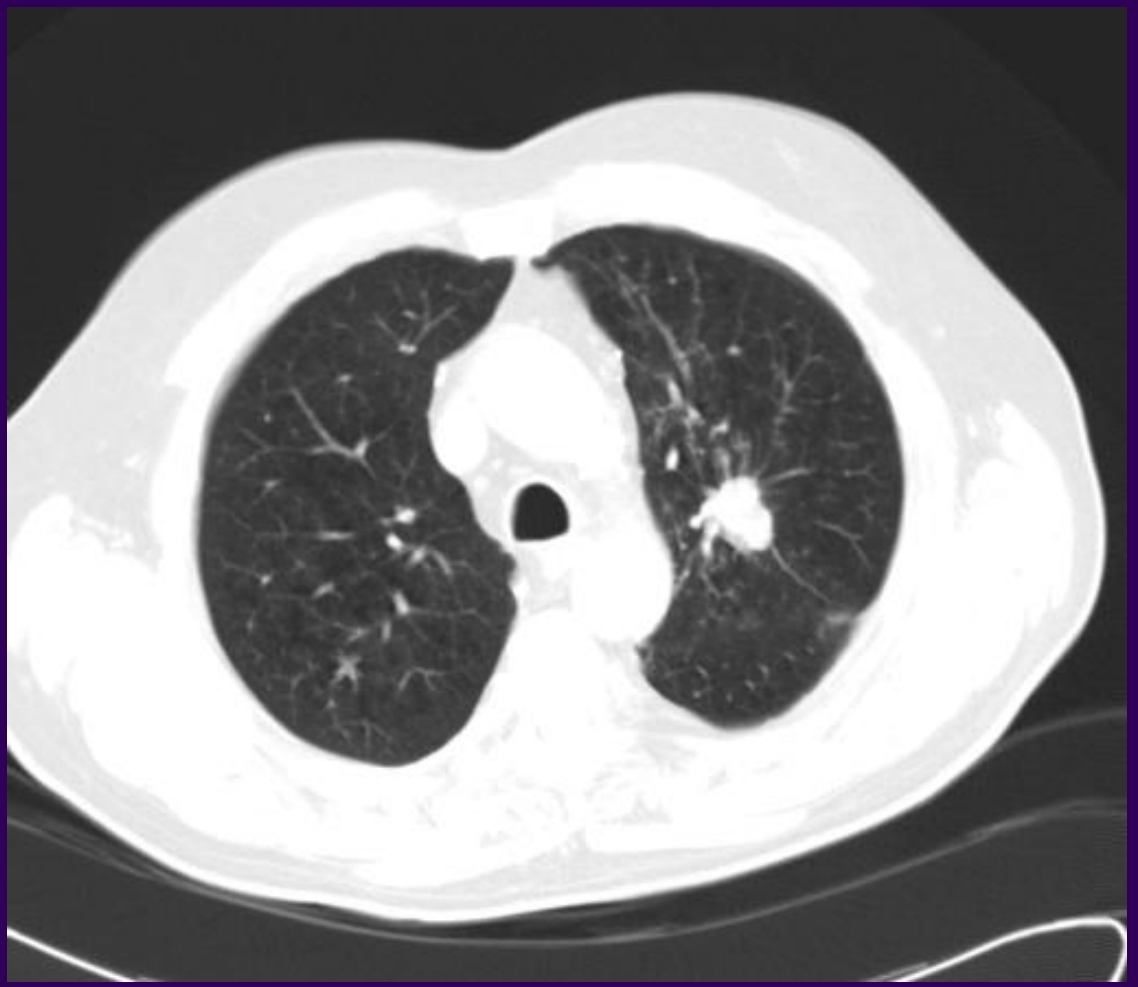
  Lagerwaard FJ. Int J Radiat Oncol Biol Phys 2008; 70:685
- ROSEL trial (Radiotherapy Or Surgery for operable Early stage non-small cell Lung cancer): no histology required; new or growing lesion with + PET sufficient *study currently stopped*
- what is irradiated? what is compared to surgery? benign lesion/cancer/ mixed or heterogeneous lesions?

Against SRT in operable tumors

74-year-old

suspect lesion LUL

aspergilloma!



Against SRT in operable tumors

65-year-old

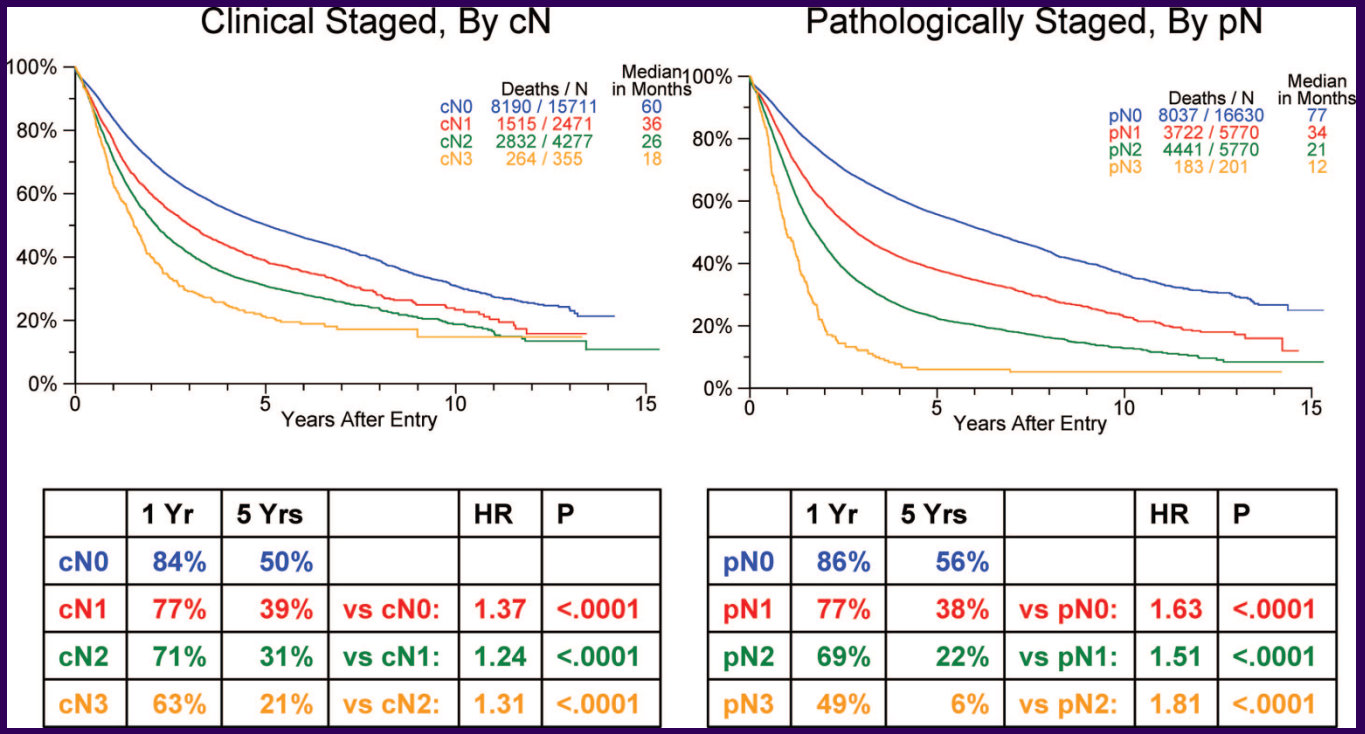
tumor RLL

tuberculoma!

Against SRT in operable tumors

How to determine nodal staging?

- clinical staging not reliable
- clinical ≠ pathological staging; survival difference cTNM and pTNM



	1 Yr	5 Yrs		HR	P
cN0	84%	50%			
cN1	77%	39%	vs cN0:	1.37	<.0001
cN2	71%	31%	vs cN1:	1.24	<.0001
cN3	63%	21%	vs cN2:	1.31	<.0001

	1 Yr	5 Yrs		HR	P
pN0	86%	56%			
pN1	77%	38%	vs pN0:	1.63	<.0001
pN2	69%	22%	vs pN1:	1.51	<.0001
pN3	49%	6%	vs pN2:	1.81	<.0001

Graham A. J Thorac Cardio-vasc Surg 1999; 117:246

Rusch VW. J Thorac Oncol 2007; 2:603

Precise information on nodal staging will never be available!

Against SRT in operable tumors

How to evaluate response and local recurrence rate?

- radiotherapy: fibrosis, radiopneumonitis
- evaluation of response? CT-PET?
- modified RECIST criteria lesion size
  quality of lesion
  uptake on PET

Pennathur A. J Thorac Cardovasc Surg 2009; 137:597

- no uniform agreement, no prospective validation

Against SRT in operable tumors

How to select patients for adjuvant therapy?

- pN1 or pN2 involvement: adjuvant chemo- or chemoradiotherapy
- how to select after SRT?
- no optimal treatment given
- long-term survival compromised?

Wakelee H. Semin Thorac Cardiovasc Surg 2008; 20:198

Against SRT in operable tumors

Radiotherapy issues

- no clear guidelines
- no precise selection: central lesions ↑ toxicity and †

  2-year freedom from toxicity 54% ↔ 83% peripheral

  Timmerman R. J Clin Oncol 2006; 24:4833
- *1ary endpoint?* local control ↔ overall and *disease-free* survival
- *exact dose?* steep dose-response relationship

  local failure up to 42%

  Pennathur A. J Thorac Cardiovasc Surg 2009; 137:597

- *movement of target lesion?* no definite solution

Against SRT in operable tumors

Radiotherapy issues

- *long-term safety SRT?* radiation pneumonitis
  rib fractures
  chronic pain

Haasbeek CJ. Oncologist 2008; 13:309

- many concerns remain in *operable* patients
- compromises: diagnosis, staging, response, long-term evaluation
- thoracic surgeons co-investigators randomized trials
- currently, SRT ≠ surgery for resectable, early stage lung cancer

Against SRT in operable tumors
CONCLUSIONS

Aim = complete resection

complete irradiation? radiosurgery

- **preoperative cT and cN factor unreliable**
- **peroperative staging : T and N factor "surgical stage"**
- **T1a: lobectomy vs. sublobar resection vs. SRT**
- **SRT operable lesions:**

  many concerns remain ≠ complete resection

  compromises: diagnosis, staging, response
  long-term evaluation

Against SRT in operable tumors

- **lobectomy gold standard**
  - **↓ incision** — **VATS** → **wedge excision**
  - **↓ resection** — **sublobar** → **segmentectomy**
  - ***+ brachytherapy***
- **stereotactic radiotherapy (SRT)** → **salvage surgery**
- **RFA** ***+ SRT*** → **salvage surgery**

Van Schil P. J Thorac Oncol 2010; 5:1881-2