ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

The Christie School of Oncology

ESMO-The CHRISTIE Preceptorship programme on Lung Cancer

3-5 February 2016, Manchester, UK

1-3 March 2017, Manchester, UK

Surgery for early stage NSCLC

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FACULTÉ DE MÉDECINE
PIERRE & MARIE CURIE

what is the impact of surgery on lung cancer survival ?

- is the patient operable ?
- is the tumour resectable?
- for this surgical patient, will surgery achieve better survival and quality of life
  - than no treatment?
  - than other treatments?
  - in the context of multimodal therapy compared to surgery alone, or no surgery?

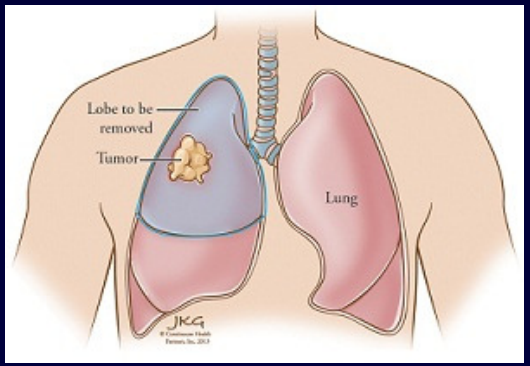
questions

	depends on
operable patient?	clinical performance
resectable tumour?	TNM staging
type of resection?	local invasion
which approach?	tumour size and location
therapeutic pathway?	state of the art
alternatives?	patient's condition or refusal

definitions

- **an "operable" patient has an acceptable risk of death or morbidity**

- a "resectable" tumour can be completely excised by surgery with clear pathological margins



is the patient operable ?

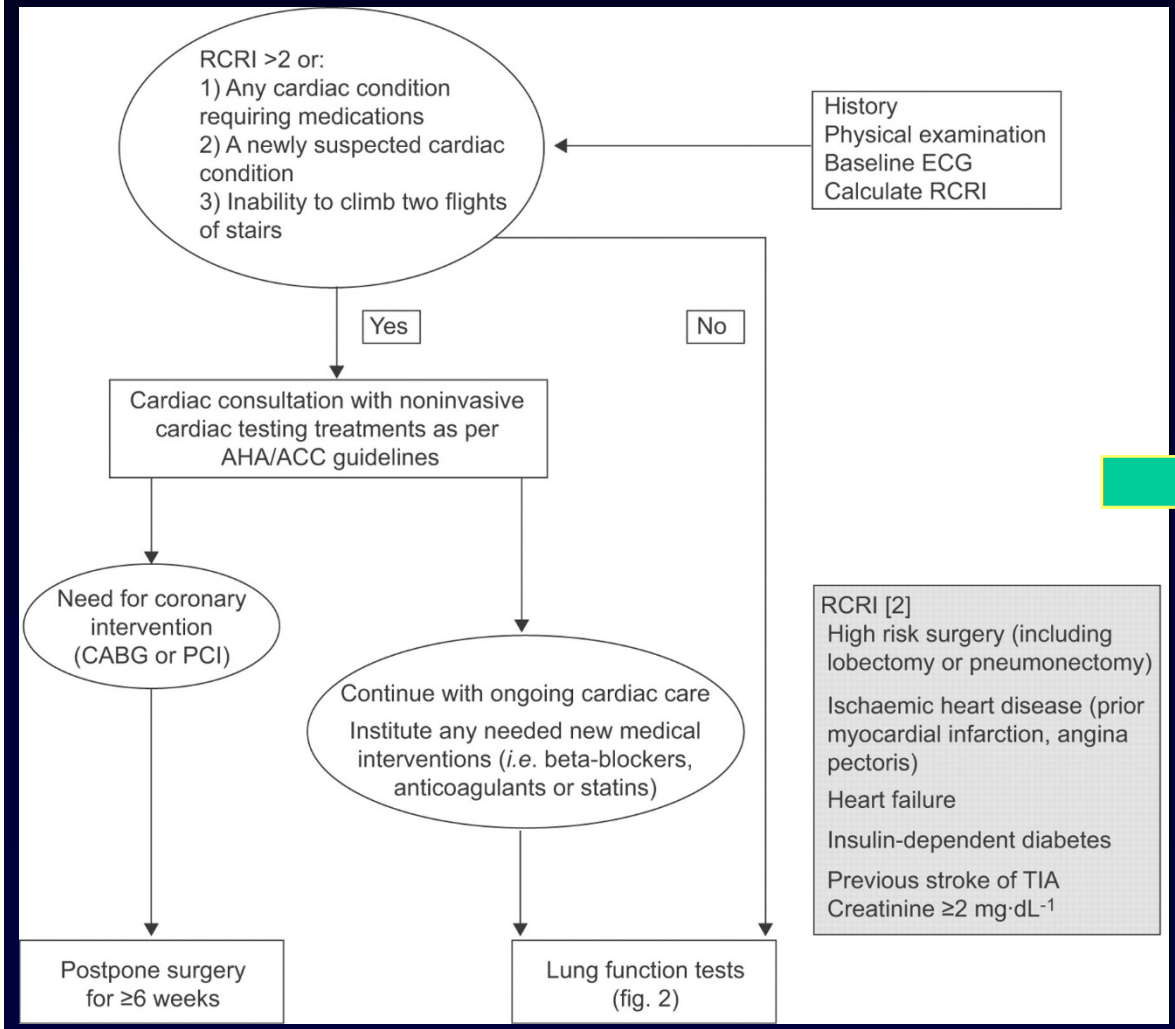
does the patient have the functional pulmonary reserve to tolerate the proposed resection to maintain a reasonable quality of life?

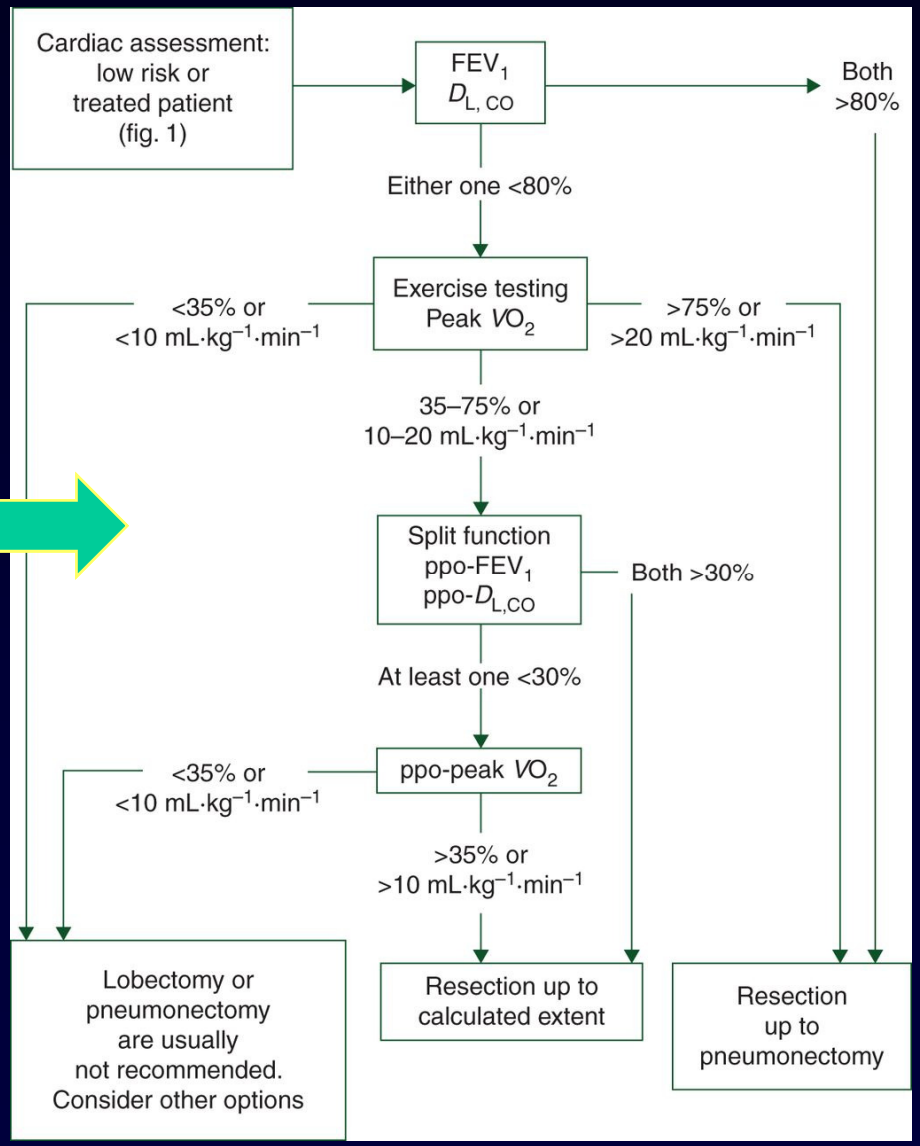
surgical resection offers little benefit if the patient suffers postoperative pulmonary insufficiency

Preoperative cardiac and respiratory evaluation (ERS-ESTS)

European Respiratory Journal

first : cardiac evaluation



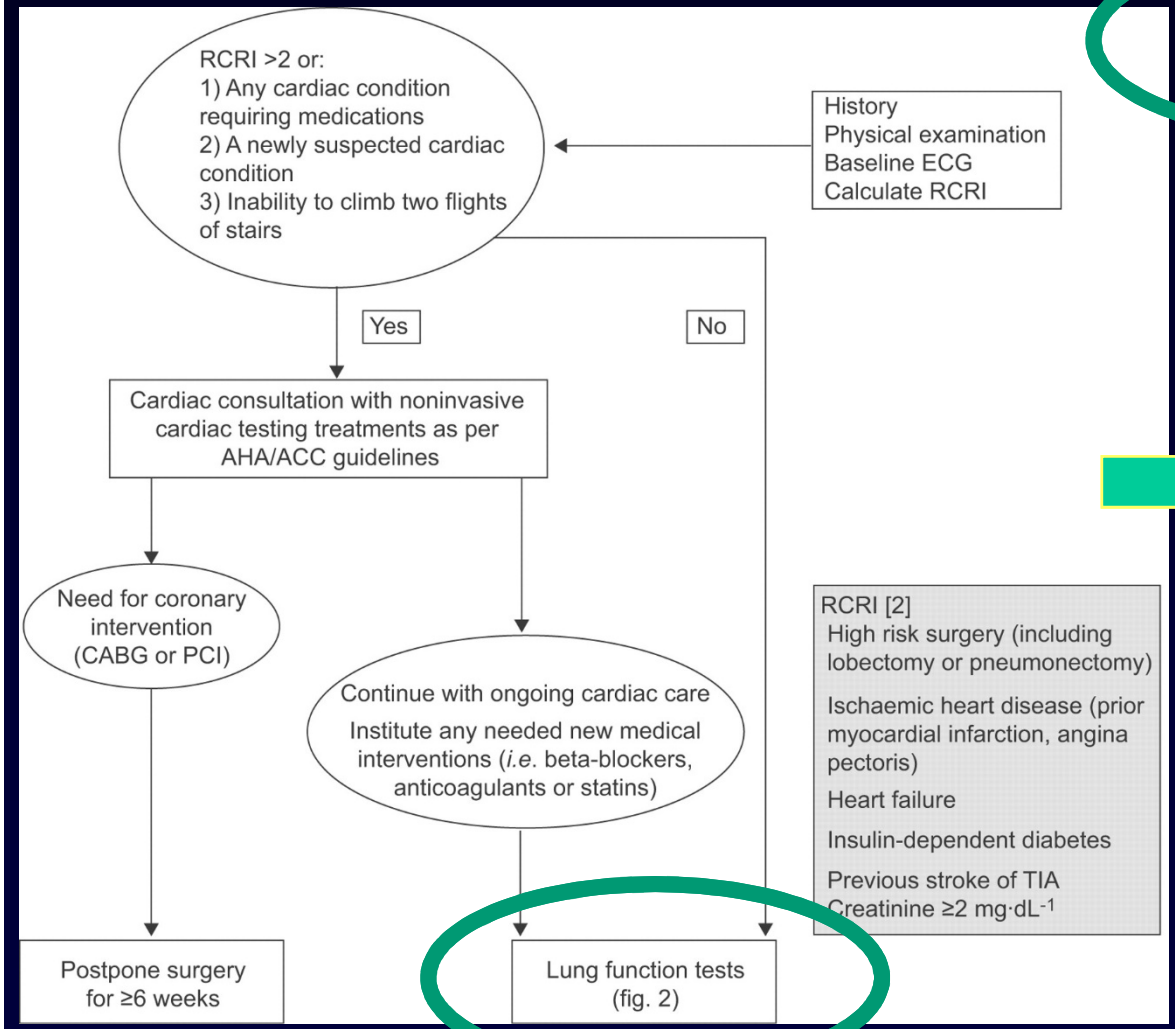


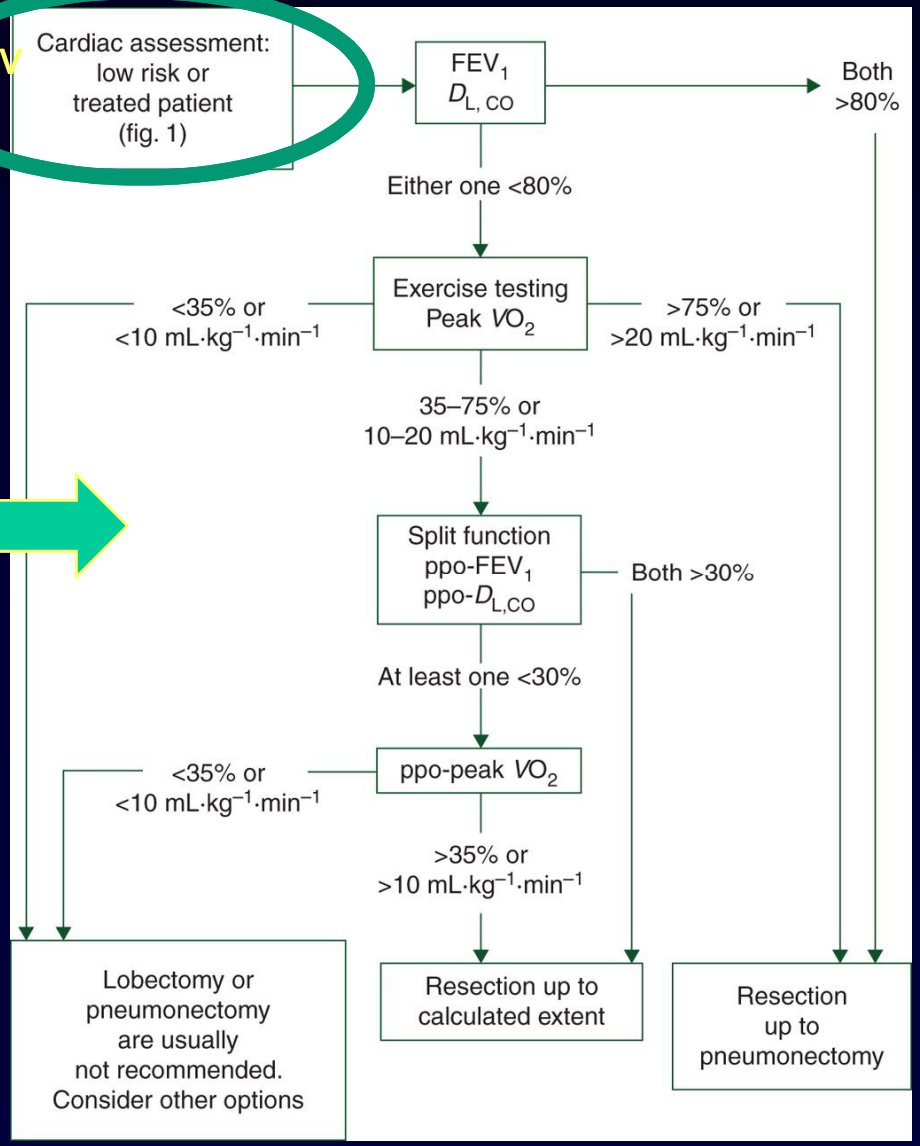
Brunelli , et al. Eur Respir J 2009;34:17-41

Preoperative cardiac and respiratory evaluation (ERS-ESTS)

European Respiratory Journal

2nd :respir. evaluation





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assessment by a multidisciplinary team (MDT)

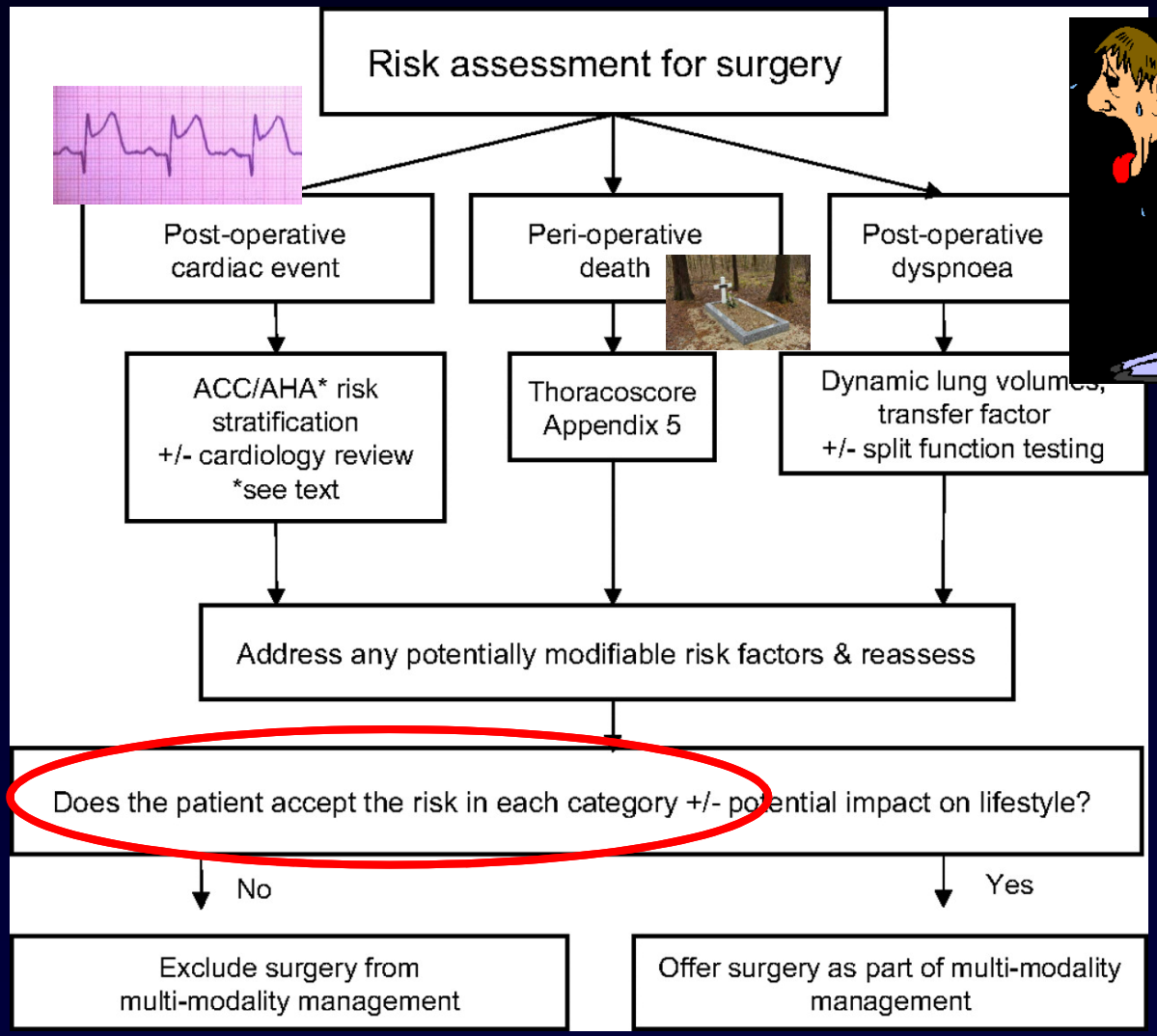
- thoracic surgery
- pulmonology
- oncology
- imaging
- nuclear medicine
- pathology

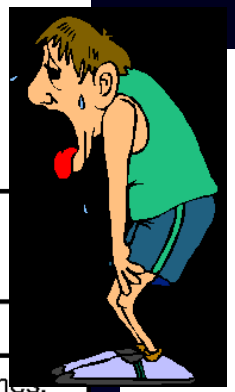
consideration of the patient's general condition

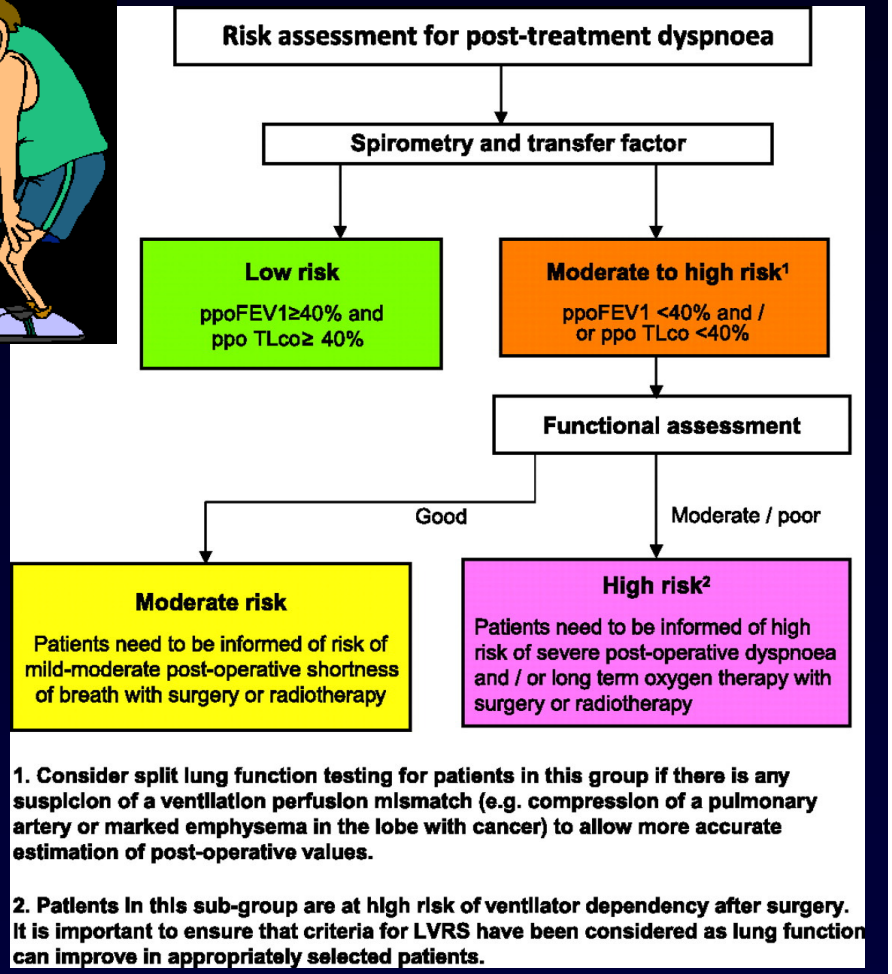
- comorbidity
- lung condition
- cardiac condition

diagnostic and therapeutic indications

Tripartite risk assessment (SCTS-BTS)







Eric Lim et al. Thorax 2010;65:iii1-iii27

assessment by a multidisciplinary team (MDT)

- the thoracic surgeon
- pulmonology
- oncology
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- nuclear medicine
- pathology

consideration of the patient's general condition

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and acceptance

diagnostic and therapeutic indications

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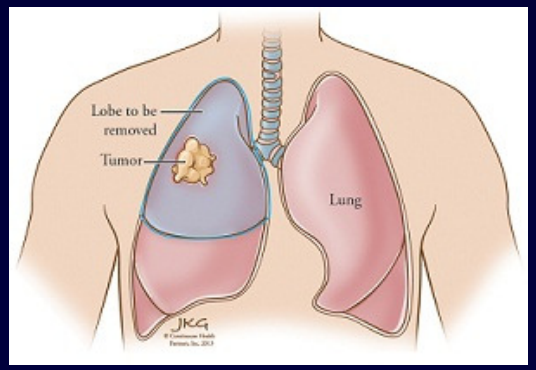
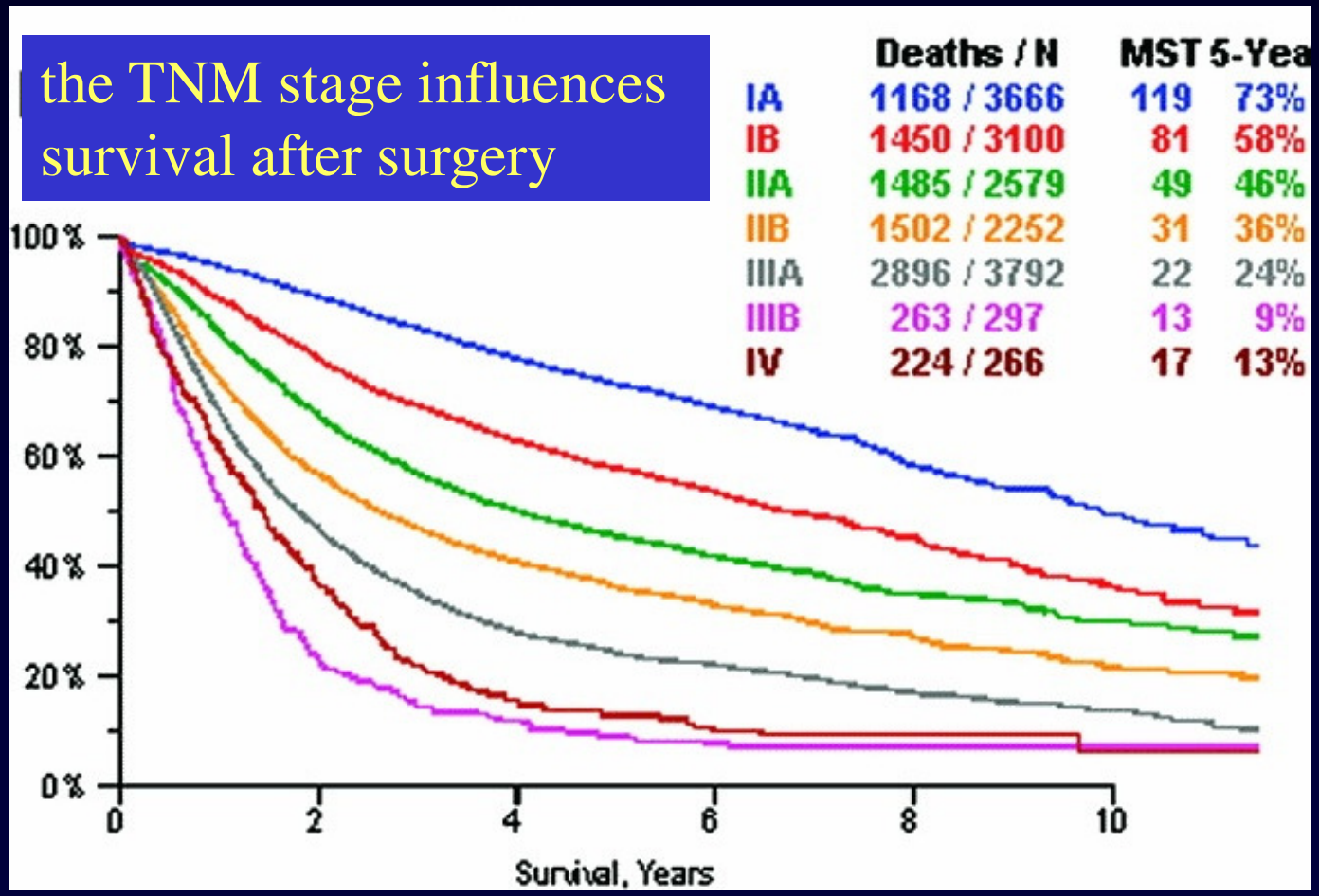


"early stage"

what is early stage lung cancer?

this refers to cancers that are caught early enough that they have the potential to be cured with surgery



Goldstraw P, et al. J Thorac oncol 2007;2:706-14

TNM Classification for Lung Cancer (8th Edition)

T Classification: importance of tumor size highlighted

T1 T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm)

T2 T2a (>3 to ≤4 cm) and T2b (>4 to ≤5 cm)

T3 (>5 to ≤ 7cm)

T4 > 7 cm (prev. T3)

T2 involvement of main bronchus regardless of distance from carina (prev. T2/3)

T2 partial and total atelectasis/pneumonitis (prev. T2/3)

T4 diaphragm invasion (prev. T3)

deletion of mediastinal pleural invasion as a T descriptor

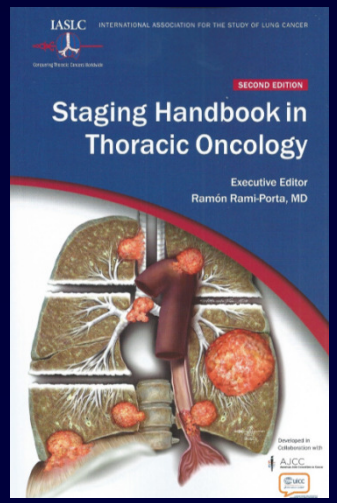
N Staging unchanged, new descriptors proposed for prospective testing and validation

p N1 single (pN1a) and multiple (pN1b) nodal station involvement

pN2 pN2a1 (single pN2 nodal station involvement without pN1 disease, "skip metastasis"

pN2a2 with single station pN2 and pN1 involvement

pN2b with involvement of multiple pN2 nodal stations



M Staging

M1a unchanged

M1b single metastasis in a single organ

M1c multiple metastases

stage groupings (8th edition)

Stage IA		N0 and ≤ 3 cm
IA1, IA2, IA3 (a category for each cm in size)		
Stage IB		N0 and >3 to ≤ 4 cm
Stage IIA		N0 and >4 to ≤ 5cm
Stage IIB		N0 and >5 to ≤ 7 cm
	or	N1 and smaller tumors
Stage IIIA		N0 and > 7cm or others T4
		N1 and T3-T4
		N2 and T1a-T2b
Stage IIIB		N2 and T3-4
		N3 and T1a-T2b
Stage IIIC		N3 and T3-T4
Stage IVA		Any T Any N with M1a and M1b
Stage IVB		> 1 extrathoracic metastasis (M1C)

8th edition TNM staging system

stage IA :	IA 1	T1a N0 M0 (≤1 cm)	
early	IA2	T1b N0 M0 (>1 to ≤ 2cm)	
	IA3	T1c N0 M0 (>2 to ≤3cm)	
stage IB :		T2a N0 M0 (>3 to ≤ 4cm)	
stage IIA :		T2b N0 M0 (>4 to ≤ 5 cm)	surgery
stage IIB :		T3 N0 M0 (>5 to ≤ 7cm)	
early		T1a-c N1 M0	
		T2a-b N1 M0	
stage IIIA :		T4 N0 M0	selected patients
locally advanced		T3-4 N1 M0	
		T1a-2b N2 M0	
stage IIIB		T3-4 N2 M0	no surgery
locally advanced		T1a-T2b N3 M0	
stage IVA-B :		Any T, any N, M1a-b-c	

questions

	depends on	
operable patient?	clinical performance	**YES**
resectable tumour?	TNM staging	**YES**
type of resection?	local invasion	
which approach?	tumour size and location	
therapeutic pathway?	state of the art	
alternatives?	patient's condition or refusal	

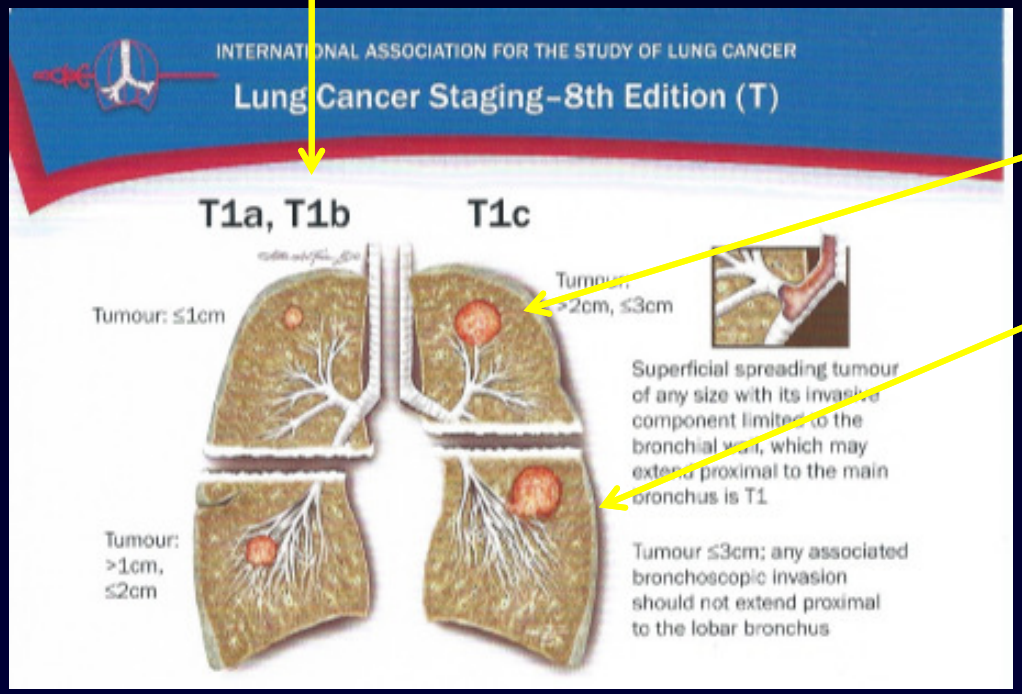
type of resection depends on local invasion (T factor)

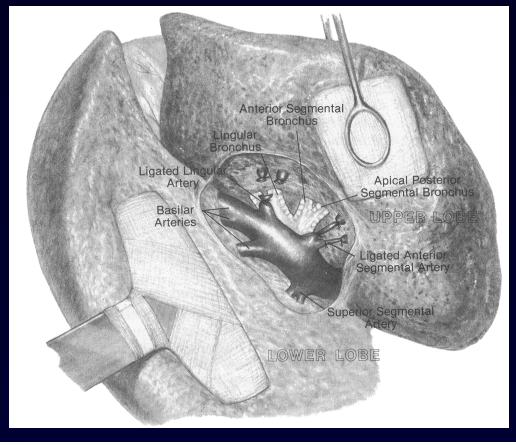
wedge resection

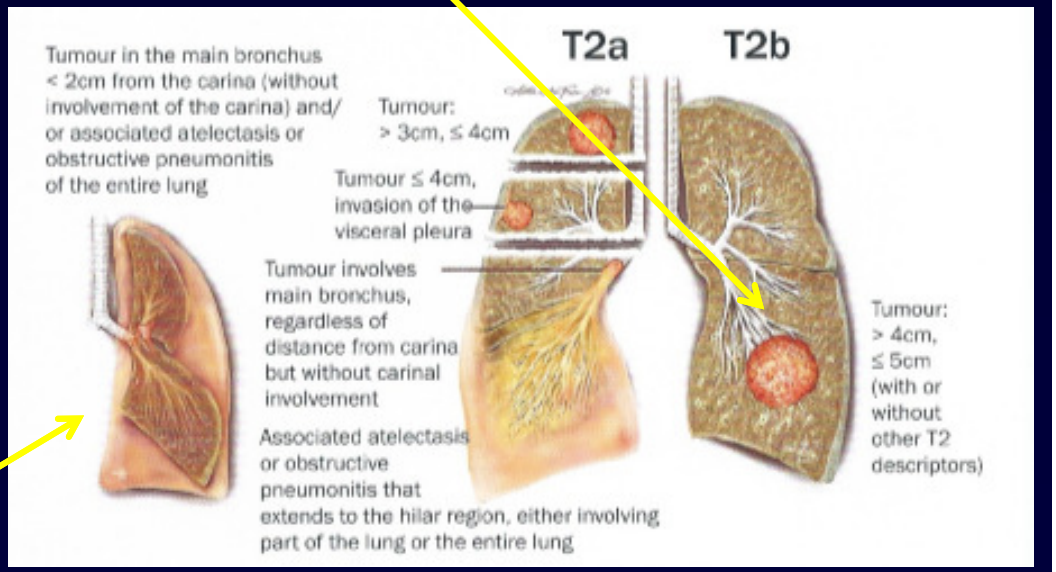
segmentectomy

lobectomy

pneumonectomy

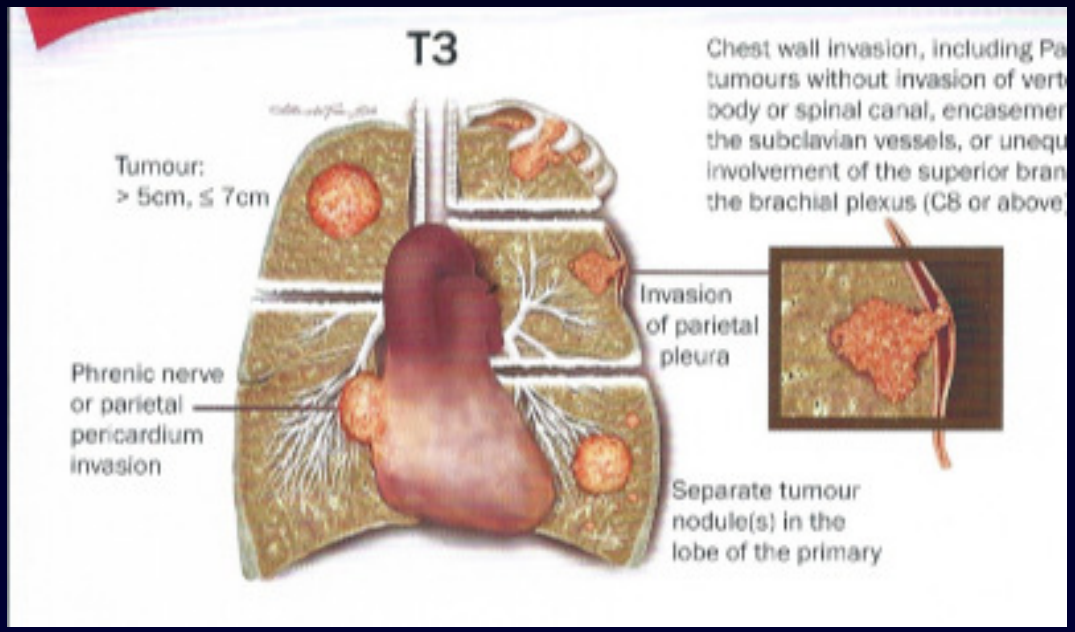






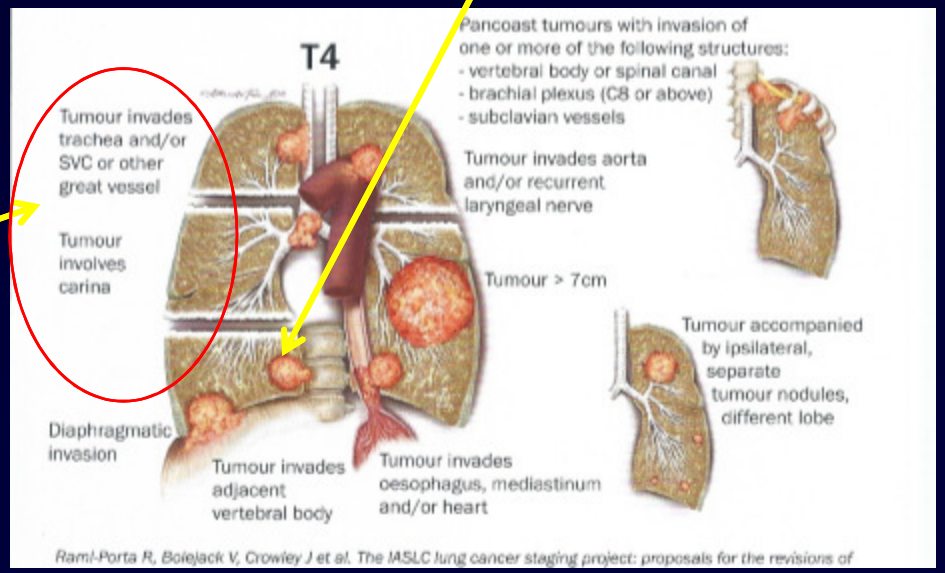
along with systematic en-bloc dissection of mediastinal lymph node stations!

type of resection depends on local invasion (T factor)

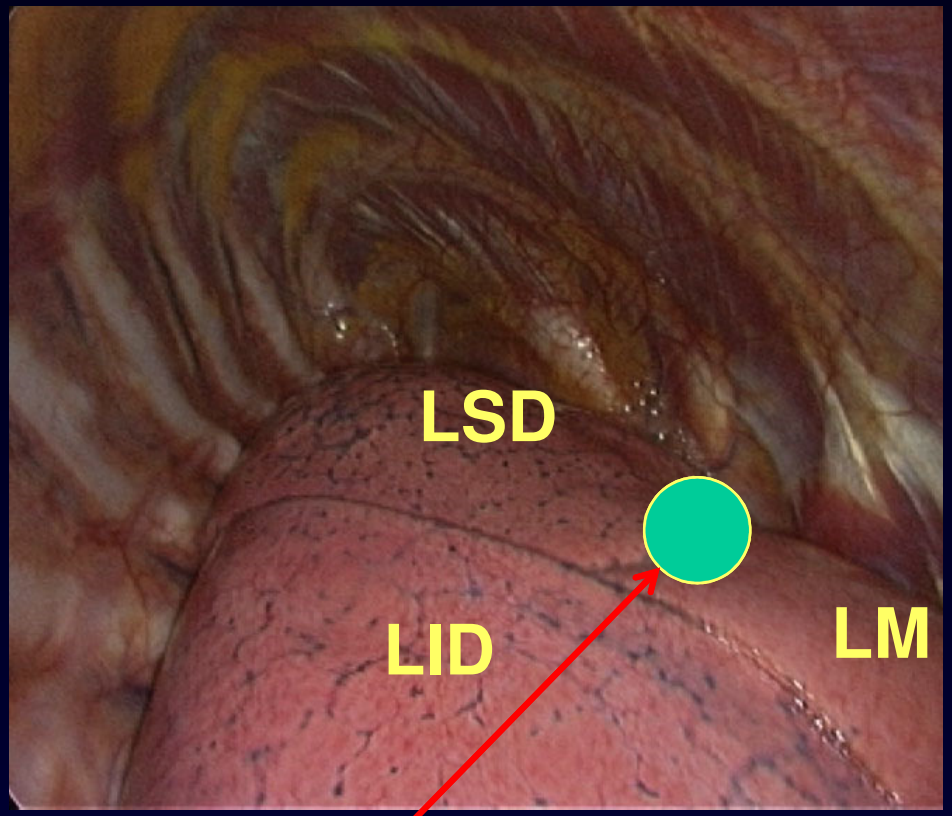


lobectomy
+ extended resection

extended pneumonectomy



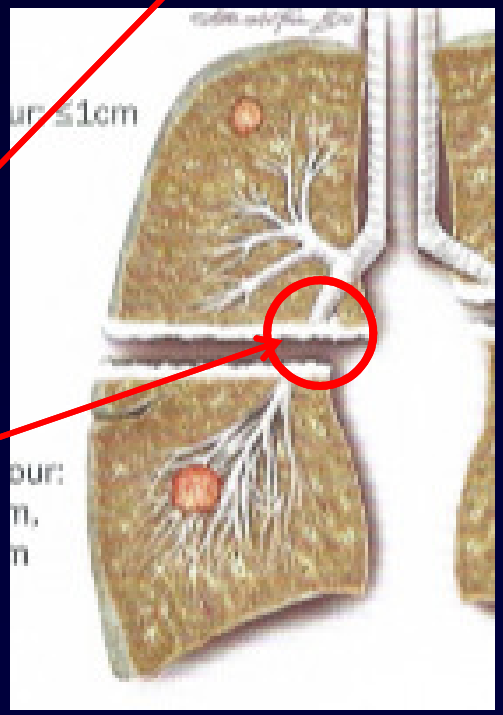
bilobectomy (right side)



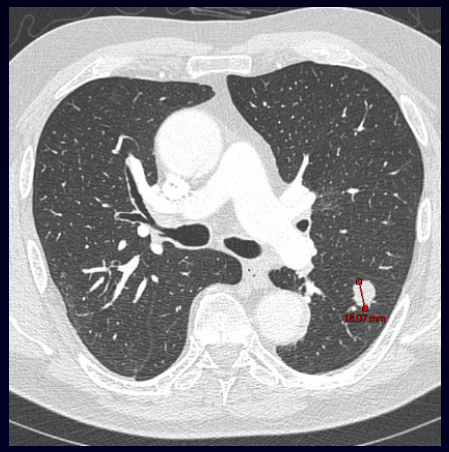
indication

parenchyma

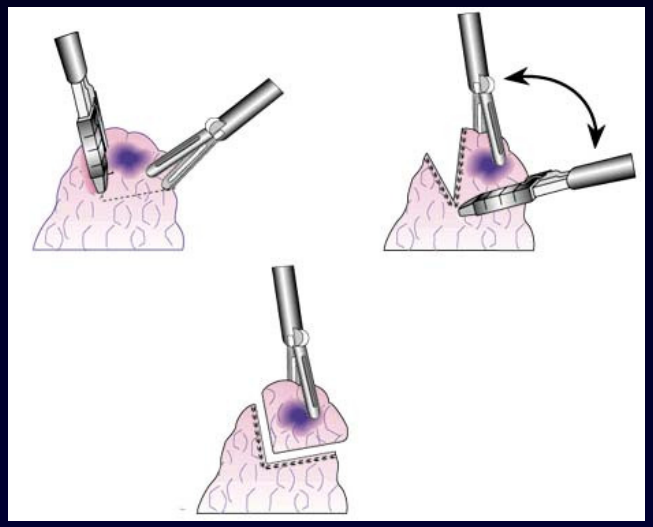
bronchus

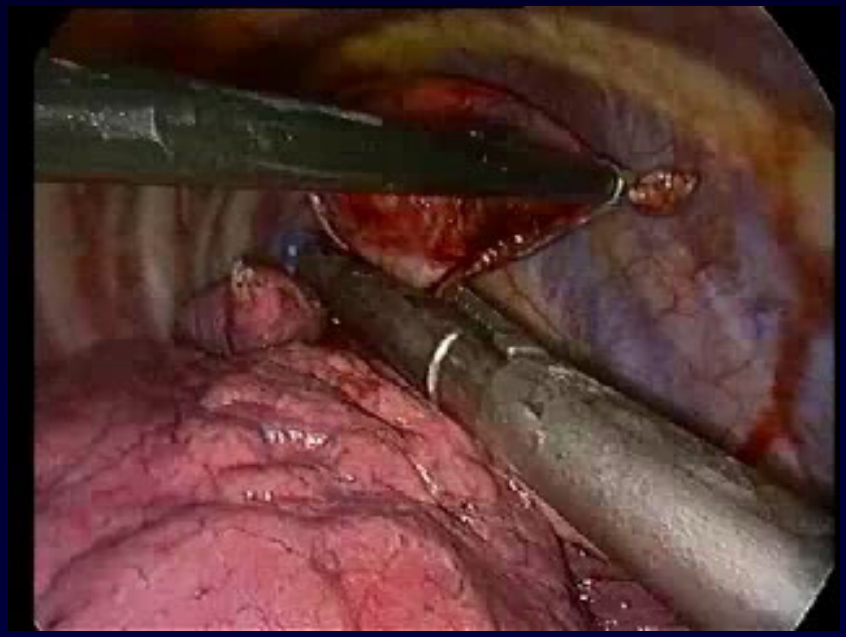


sublobar resection?

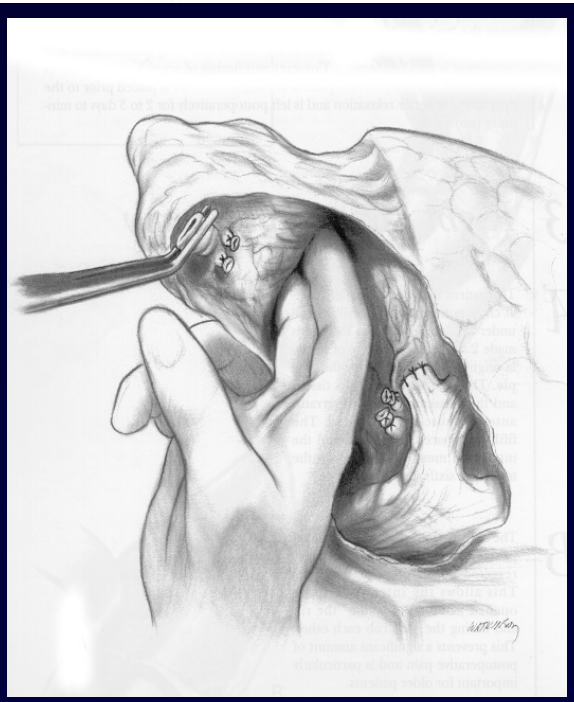


wedge resection





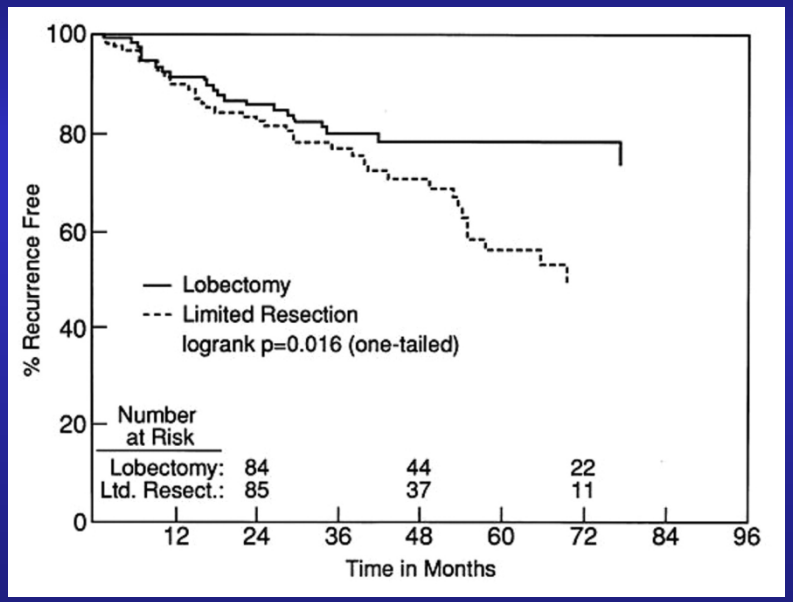
anatomical segmentectomy



stage I tumours (TNM 8th edition)

stage IA	:	IA 1	T1a N0 M0 (≤1 cm)
early		IA2	T1b N0 M0 (>1 to ≤ 2cm)
		IA3	T1c N0 M0 (>2 to ≤3cm)
stage IB	:		T2a N0 M0 (>3 to ≤ 4cm)

potential to be cured with surgery… alone



Ginsberg RJ and Rubinstein LV 1995

the gold standard in stage I is an anatomic lobar resection

an evolving paradigm?

sublobar resection: a movement from the Lung Cancer Study Group

1995 LCSG consensus : lobectomy = gold-standard (stage I nsclc)

enhancements in imaging technology
screening programs → larger cohorts of localized early-stage disease

minimally invasive surgical resection
reduced perioperative morbidity and mortality
equivalent oncologic effectiveness to open surgery

↓

challenging lobectomy as a standard for small tumors

Blasberg JD, et al. J Thorac Oncol 2010;5:1583-93

survival following lobectomy and limited resection for the treatment of stage I nsclc <= 1cm in size: a review of SEER data

(Surveillance, Epidemiology, and End Results registry)

stage I nsclc </=1 cm in size 2,090

limited resect. (segment. or wr) 688 (33%)

no difference in outcomes among patients treated with lobectomy vs limited resection

overall survival

HR : 1.12 (95% CI: 0.93-1.35)

lung cancer-specific survival

HR: 1.24 (95% CI: 0.95-1.61)

Kates M, et al. Chest 2010

sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules (International Early Lung Cancer Action Program)

nsclc with a diameter of 30 mm or less (stage 1) n=347

10-yr survival	sublobar res. (n=53)	85%	
	lobectomy (n=294)	86%	***P = .86***

cancers 20 mm or less in diameter ***P = .45***

sublobar resection and lobectomy have equivalent survival for patients with clinical stage IA nsclc in the context of computed tomography screening for lung cancer

Altorki NK, et al. J Thorac Cardiovasc Surg 2014;147:754-62 (I-ELCAP)

expected results of clinical trials

to determine whether patients with small peripheral NSCLC tumors can safely undergo sublobar resection while maintaining rates of survival and recurrence that are comparable to lobectomy

CALGB 140503
JCOG0802/WJOG4607L

Interactive CardioVascular and Thoracic Surgery 14 (2012) 816–820
doi:10.1093/icvts/ivs031 Advance Access publication 27 February 2012

BEST EVIDENCE TOPIC

Is limited pulmonary resection equivalent to lobectomy for surgical management of stage I non-small-cell lung cancer?

Maya K. De Zoysa[a,*], Dima Hamed[b], Tom Routledge[b] and Marco Scarci[a]

2012

16 papers / 116 (1 meta analysis, 1 RCT) represented the best evidence to answer the clinical question.

There is evidence that <u>wedge resections</u>, compared to segmentectomies and lobectomies, lead to lower survival and higher recurrence rates.

In conclusion, lobectomy is still recommended for younger patients with adequate cardiopulmonary function.

questions

	depends on	
operable patient?	clinical performance	**YES**
resectable tumour?	TNM staging	**YES**
type of resection?	local invasion	**DECIDED**
which approach?	**tumour size and location**	
therapeutic pathway?	state of the art	
alternatives?	patient's condition or refusal	

approach depends on tumor size and location

- open thoracotomy

- vats

- uniportal vats

video-assisted thoracoscopic versus open thoracotomy lobectomy in a cohort of 13,619 patients

Nationwide Inpatient Sample database

lobectomy thoracotomy (n = 12,860)

vats (n = 759)

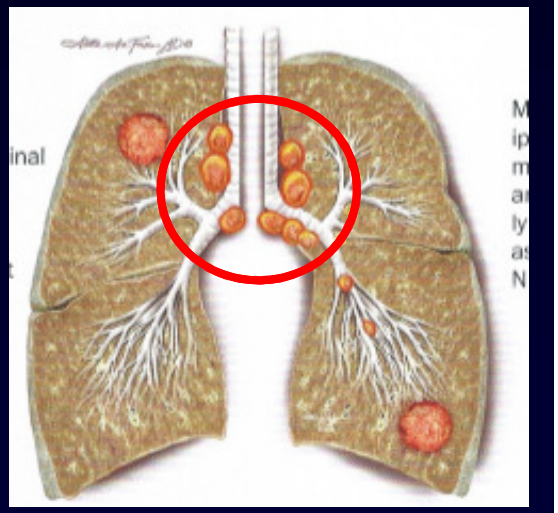
vats = higher incidence of intraoperative complications (p = 0.04)

Gopaldas RR, et al. Ann Thorac Surg 2010;89:1563-70

minimal incision = delay in control of bleeding

a national study of **nodal upstaging** after thoracoscopic versus open lobectomy for clinical stage I lung cancer

(nodal upstaging occurs when unsuspected lymph node metastases are found during the final evaluation of surgical specimens)



Danish Lung Cancer Registry

1,513 pts	VATS	717 (47%)
	thoracotomy	796 (53%)

nodal upstaging 281 pts (18.6%)

thoracotomy higher **N1 upstaging** (13.1% vs 8.1%; **p<0.001**)

N2 upstaging (11.5% vs 3.8%; **p<0.001**)

no difference in OS between VATS and thoracotomy

(hazard ratio, 0.98; 95% confidence interval, 0.80 to 1.22, p=0.88).

Licht PB, et al. Ann Thorac Surg 2013;96:943-9

video-assisted thoracic surgery for lung cancer: republication of a systematic review and a proposal by the guidelines committee of the Japanese Association for Chest Surgery 2014

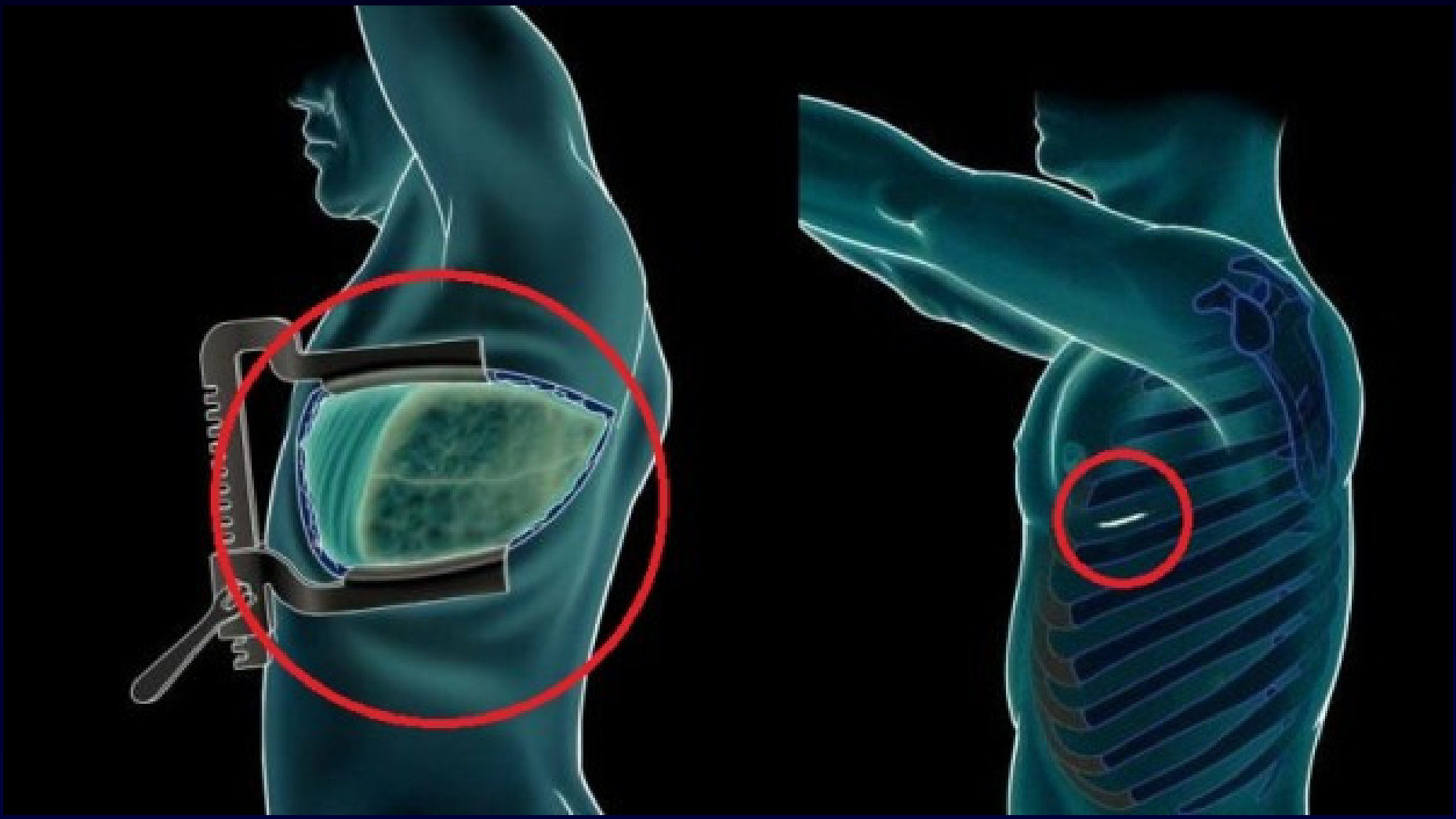
VATS lobectomy by an **experienced surgeon** may be considered and applied to patients with clinical stage I NSCLC, however, **well-established evidence is lacking**

VATS showed better or **at least equivalent outcomes** regarding intra- or postoperative complications compared with thoracotomy, with less invasiveness

long-term survival by VATS lobectomy was suggested to be **at least equivalent**, although there is a **lack of evidence** (Recommendation grade: Level C1).

Yamashita S, et al. Gen Thorac Cardiovasc Surg 2014:62:701-5

uniportal vats



Gonzales-Rivas D. WCLC 2016

Uniportal robotic platform

surgical resection of lung cancer - standard of care

stage IA :	IA 1	T1a N0 M0 (≤1 cm)	
early	IA2	T1b N0 M0 (>1 to ≤ 2cm)	
	IA3	T1c N0 M0 (>2 to ≤3cm)	
stage IB :		T2a N0 M0 (>3 to ≤ 4cm)	surgery
stage IIA :		T2b N0 M0 (>4 to ≤ 5 cm)	
stage IIB :		T3 N0 M0 (>5 to ≤ 7cm)	
early		T1a-c N1 M0	
		T2a-b N1 M0	

stage I & II tumours

- surgery
- open or vats
- lobar or sublobar?

surgical resection of lung cancer - standard of care

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type of resection?	local invasion	**DECIDED**
which approach?	tumour size and location	
therapeutic pathway?	**state of the art**	
alternatives?	patient's condition or refusal	

state of the art ? – controversial situations

stage III-N2

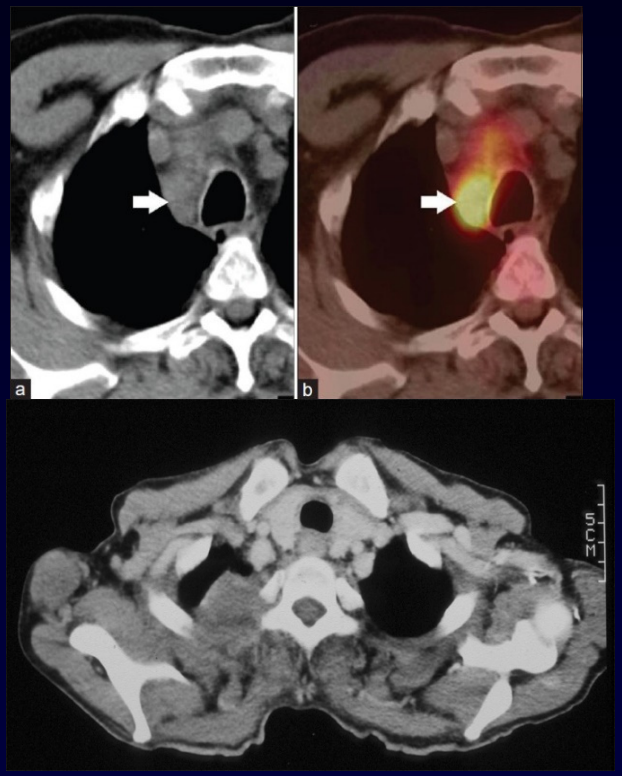
surgery or not ?

upfront surgery or induction ?

risks ?

locally advanced –T3/4

surgery ?



stage IIIA :	**T4 N0 M0**
locally advanced	**T3-4 N1 M0**
	T1a-2b N2 M0

selected patients

is there a role for surgery in locally advanced nsclc ?

what we know from evidence based medicine in N2 disease

- dramatic benefit with induction chemotherapy compared to surgery alone in two small-scale studies [*Roth, Rosell, 1994*]
- no benefit in large european randomized study in stage IIIA category [*Depierre, 2002*]
- stage IIIA benefits from adjuvant chemotherapy following "complete resection" [*Arriagada, 2004; Douillard, 2006*]
- nothing on radiotherapy (Lung-ART still ongoing)
- nothing on surgery

N2 disease – paradigms and opinions

- mediastinal downstaging from induction is the most powerful positive prognostic factor for survival after surgery [*Betticher, 2003; Albain, 2009]*
- rt should be considered the preferred locoregional treatment for pts with stage IIIA-N2 nsclc responders to induction ct [*Van Meerbeck, 2007]*
- good candidates for surgery may still be appropriately managed by using resection rather than radiation [*Vansteenkiste, 2007*]
- the role of surgery is not clearly defined [*Roy and Donington, 2007*]

no standard of care

outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials

main outcome = survival

805 publications ⟶ final 6 randomised trials (868 patients)

- 4 trials, patients randomised to surgery after chemotherapy

  HR = 1.01 (95% CI 0.82 1.23; P = 0.954)

- two trials, patients randomised to surgery after chemo-radiotherapy

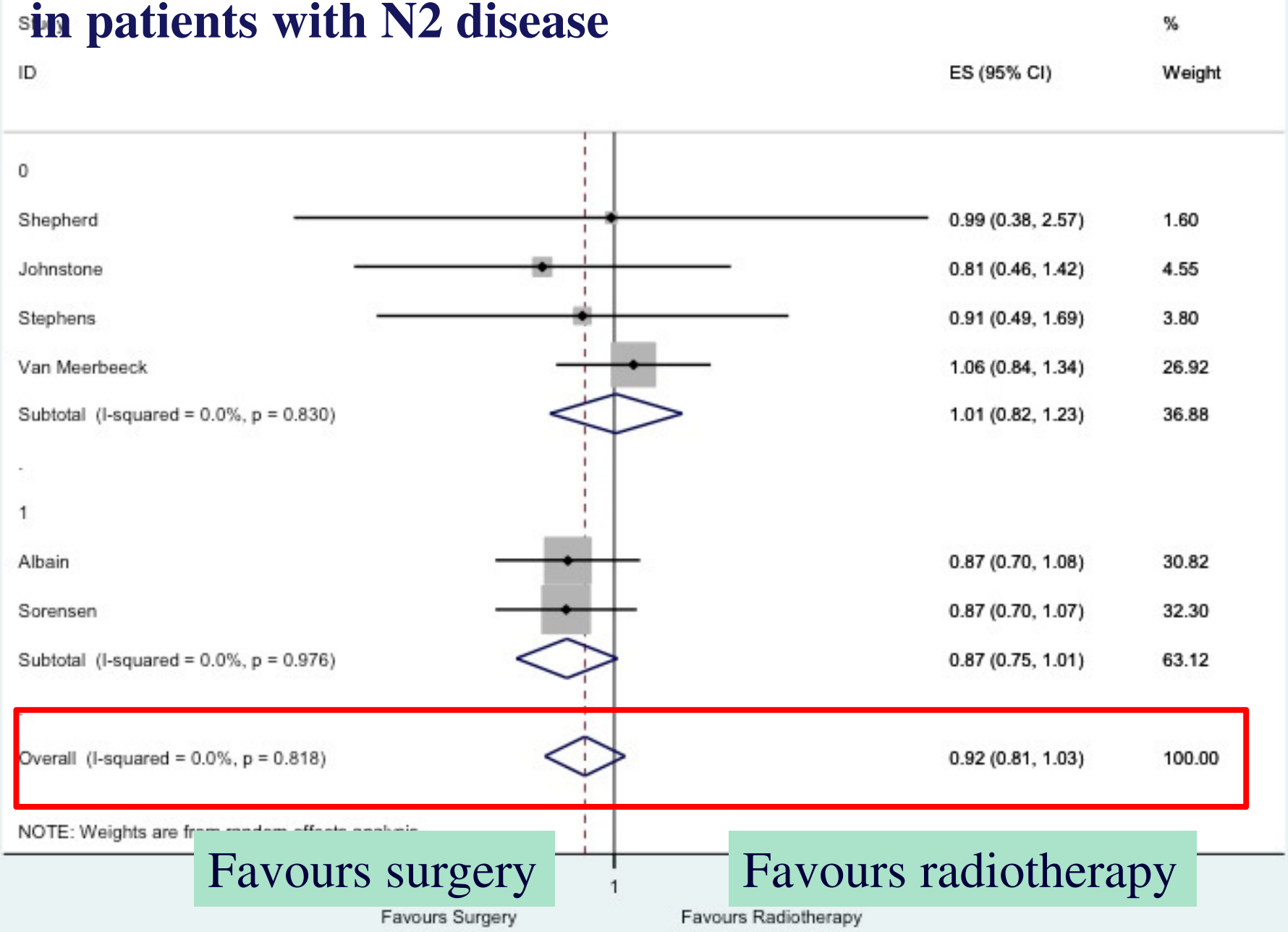
  HR = 0.87 (0.75 1.01; P = 0.068)

overall hazard ratio of all pooled trials = 0.92 (0.81 1.03; P = 0.157).

in trials where patients received surgery as part of trimodality treatment, the overall survival was better than chemo-radiotherapy alone

McElnay PJ, et al. Thorax. 2015;70:764-8

surgery versus radiotherapy after induction treatment in patients with N2 disease



By courtesy of PJ McElnay and E. Lim

questions

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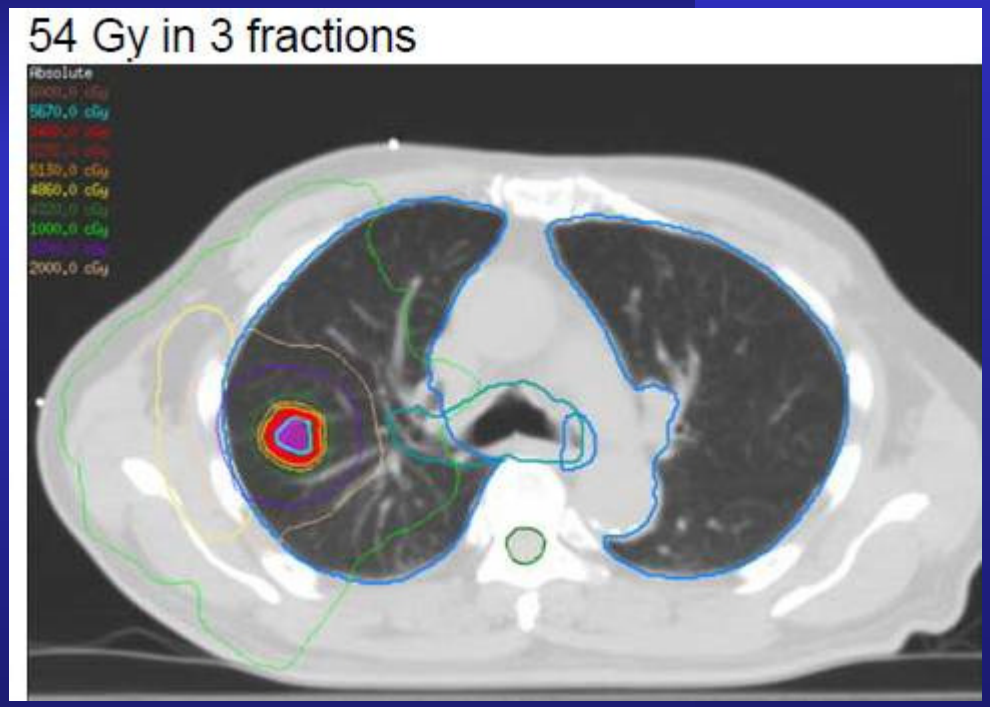
early		IA2	T1b N0 M0 (>1 to ≤ 2cm)
		IA3	T1c N0 M0 (>2 to ≤3cm)
stage IB	:		T2a N0 M0 (>3 to ≤ 4cm)

potential to be cured with surgery… alone

stereotactic ablative radiotherapy ?



Interactive CardioVascular and Thoracic Surgery 17 (2013) 845–853
doi:10.1093/icvts/ivt262 Advance Access publication 30 July 2013

BEST EVIDENCE TOPIC – THORACIC

Is stereotactic ablative radiotherapy equivalent to sublobar resection in high-risk surgical patients with Stage I non-small-cell lung cancer?

Sarah Mahmood[a], Haris Bilal[b], Corinne Faivre-Finn[c] and Rajesh Shah[b,*]

2013

19 / 318 papers provided the best evidence to answer the question.

Wedge resection and SABR are both reasonable alternatives to lobectomy in high-risk surgical patients.

SABR: reduced local recurrence compared to wedge resection (4 vs 20%; P = 0.07) and should be considered when a wedge resection is planned due to anatomical location and size of the primary tumour in a patient who is high-risk for surgery.

From Mueller, WCLC 2016

recommendations

- ESMO

  Vansteenkiste J, et al. Ann Oncol 2014;25:1462-74

- BTS-SCTS

  Lim E, et al. Thorax 2010;65:iii1-iii27

- ACCP

  Howington JA, et al. Chest 2013;143(5_suppl):e278S-e313S

guidelines on the radical management of patients with lung cancer. British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland.

offer radical treatment without further mediastinal lymph node sampling if there is no significant uptake in normal sized mediastinal lymph nodes on **PET-CT** scanning. **[C]**

evaluate PET positive mediastinal nodes by further mediastinal sampling. **[C]**

when obtaining diagnostic and staging samples, consider the adequacy of these in the context of selection of patients for targeted therapy. **[D]**

consider **EBUS/EUS-guided TBNA** to stage the mediastinum. **[C]**

confirm negative results obtained by TBNA and EBUS/EUS-guided TBNA by mediastinoscopy and lymph node biopsy where clinically appropriate. **[C]**

adequate TNM staging = the right treatment to the right patient

Lim E, et al. Thorax 2010;65:iii1-27

british guidelines (continued)

offer patients with T3N0–1M0 disease radical treatment. **[D]**

consider selected patients with T4N0–1M0 disease for radical multimodality treatment.**[D]**

consider surgery as part of multimodality management in patients with T1–3N2 (non-fixed, non-bulky, single zone) M0 disease. **[B]**

avoid pneumonectomy where possible by performing bronchoangioplastic resection or non-anatomical resection. **[C]**

consider patients with moderate to high risk of postoperative dyspnoea for lung parenchymal sparing surgery. **[D]**

consider bronchoangioplastic procedures in suitable patients to preserve pulmonary function. **[D]**

consider patients with limited pulmonary reserve for sublobar resection as an acceptable alternative to lobectomy. **[B]**

perform systematic nodal dissection in all patients undergoing resection for lung cancer.**[A]**

remove or sample a minimum of six lymph nodes or stations. **[D]**

Lim E, et al. Thorax 2010;65:iii1-27

treatment of stage I and II nsclc: diagnosis and management of lung cancer, 3rd ed: ACCP evidence-based clinical practice guidelines

surgical resection remains the primary and preferred approach to the treatment of stage I and II nsclc

lobectomy or greater resection remains the preferred approach to T1b and larger tumors

every patient should have systematic mediastinal lymph node sampling at the time of curative intent surgical resection, and mediastinal lymphadenectomy can be performed without increased morbidity

perioperative morbidity and mortality are reduced and long-term survival is improved when surgical resection is performed by a **board-certified thoracic surgeon**

Howington JA, et al. *Chest* 2013;143(5_suppl):e278S-e313S

2nd ESMO Consensus Conference on Lung Cancer: early-stage nsclc consensus on diagnosis, treatment and follow-up

recommendations

- a pre-surgical pathological diagnosis
- surgical resection for patients with a non-centrally located resectable tumour and absence of nodal metastasis on both CT and PET images [I,A]
- pathological confirmation for patients with suspect mediastinal lymph node metastasis on CT or PET images (unless bulky) [I, A]
- needle aspiration under endobronchial or endoscopic ultrasound guidance is the preferred first technique for pathological confirmation [I, A]
- before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to **estimate risk of operative morbidity** [III, A]

Vansteenkiste J, et al. Ann Oncol 2014;25:1462-74

2nd ESMO Consensus Conference on Lung Cancer (continued)

- comorbidities should be evaluated and optimised before surgery [III, A]
- surgery should be offered to patients with stage I and II NSCLC who are **willing to accept procedure-related risks** [III, A]
- **anatomical resection** (lobectomy) is preferred over lesser resections such as wedge or segment resection [I, A]
- sub-lobar resection is generally considered acceptable for pure GGO lesions or adenocarcinomas *in situ* or with minimal invasion [III, B] Lobectomy is still considered the standard surgical treatment of tumours ≤2 cm in size that have a solid appearance on CT [II, B]
- lymph node dissection should conform to IASLC specifications for staging [III, A]
- either open thoracotomy or VATS access can be utilised as appropriate to the **expertise of the surgeon** [III, A]

Vansteenkiste J, et al. Ann Oncol 2014;25:1462-74