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?
<table>
<thead>
<tr>
<th>questions</th>
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<tbody>
<tr>
<td>operable patient?</td>
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<td>patient’s condition or refusal</td>
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</tbody>
</table>
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)

first: cardiac evaluation

RCRI >2 or:
1) Any cardiac condition requiring medications
2) A newly suspected cardiac condition
3) Inability to climb two flights of stairs

Cardiac consultation with noninvasive cardiac testing treatments as per AHA/ACC guidelines

RCRI [2]
- High risk surgery (including lobectomy or pneumonectomy)
- Ischaemic heart disease (prior myocardial infarction, angina pectoris)
- Heart failure
- Insulin-dependent diabetes
- Previous stroke of TIA
- Creatinine ≥2 mg·dL⁻¹

Need for coronary intervention (CABG or PCI)

Postpone surgery for ≥6 weeks

Lung function tests (fig. 2)

Cardiac assessment:
- Low risk or treated patient (fig. 1)

FEV₁

Either one <80%

<35% or <10 mL·kg⁻¹·min⁻¹

Exercise testing
Peak VO₂

≥75% or ≥20 mL·kg⁻¹·min⁻¹

35–75% or 10–20 mL·kg⁻¹·min⁻¹

Split function

ppo-FFV₁

ppo-DL CO

Both >30%

At least one <30%

<35% or <10 mL·kg⁻¹·min⁻¹

ppo-peak VO₂

>35% or >10 mL·kg⁻¹·min⁻¹

Lobectomy or pneumonectomy are usually not recommended. Consider other options

Resection up to calculated extent

Resection up to pneumonectomy

Preoperative cardiac and respiratory evaluation (ERS-ESTS)

2nd respir. evaluation

Cardiac assessment: low risk or treated patient (fig. 1)

- FEV$_1$
- $D_L$ co

Either one <80%

Exercise testing
Peak VO$_2$

- <35% or <10 mL·kg$^{-1}$·min$^{-1}$
- >75% or >20 mL·kg$^{-1}$·min$^{-1}$

35–75% or 10–20 mL·kg$^{-1}$·min$^{-1}$

Split function
pno-FFV$_1$
ppD$_L$ co

Both >30%

At least one <30%

<35% or <10 mL·kg$^{-1}$·min$^{-1}$

>35% or >10 mL·kg$^{-1}$·min$^{-1}$

Lobectomy or pneumonectomy are usually not recommended. Consider other options

Resection up to calculated extent

Resection up to pneumonectomy

RCRI $>$ 2 or:
1) Any cardiac condition requiring medications
2) A newly suspected cardiac condition
3) Inability to climb two flights of stairs

Yes

Cardiac consultation with noninvasive cardiac testing treatments as per AHA/ACC guidelines

No

Need for coronary intervention (CABG or PCI)

Continue with ongoing cardiac care
Institute any needed new medical interventions (i.e. beta-blockers, anticoagulants or statins)

Postpone surgery for ≥ 6 weeks

Lung function tests (fig. 2)

RCRI [2]
High risk surgery (including lobectomy or pneumonectomy)
Ischaemic heart disease (prior myocardial infarction, angina pectoris)
Heart failure
Insulin-dependent diabetes
Previous stroke of TIA
Creatinine ≥ 2 mg·dL$^{-1}$

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)

Risk assessment for surgery

- Post-operative cardiac event
- Peri-operative death
- Post-operative dyspnoea

- ACC/AHA* risk stratification +/− cardiology review +/− split function testing
- Thoracoscope Appendix 5
- Dynamic lung volumes, transfer factor +/− split function testing

Address any potentially modifiable risk factors & reassess

Does the patient accept the risk in each category +/− potential impact on lifestyle?

- No
  - Exclude surgery from multi-modality management
- Yes
  - Offer surgery as part of multi-modality management

Risk assessment for post-treatment dyspnoea

- Spirometry and transfer factor
  - Low risk
    - ppoFEV1 ≥40% and ppo TLco ≥ 40%
  - Moderate to high risk
    - ppoFEV1 <40% and/or ppo TLco <40%

Functional assessment

- Good
- Moderate / poor

Moderate risk
- Patients need to be informed of risk of mid-moderate post-operative shortness of breath with surgery or radiotherapy

High risk
- Patients need to be informed of high risk of severe post-operative dyspnoea and/or long-term oxygen therapy with surgery or radiotherapy

1. Consider split lung function testing for patients in this group if there is any suspicion of a ventilation perfusion mismatch (e.g. compression of a pulmonary artery or marked emphysema in the lobe with cancer) to allow more accurate estimation of post-operative values.

2. Patients in this sub-group are at high risk of ventilator dependency after surgery. It is important to ensure that criteria for LVRS have been considered as lung function can improve in appropriately selected patients.
assessment by a multidisciplinary team (MDT)

the thoracic surgeon
pulmonology
oncology
imaging
nuclear medicine
pathology

consideration of the patient’s general condition
comorbidity
lung condition
cardiac condition

and acceptance

diagnostic and therapeutic indications
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

"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.

The TNM stage influences survival after surgery.

TNM Classification for Lung Cancer (8th Edition)

**T Classification: importance of tumor size highlighted**

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

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

T3  
\((>5\ to\ \leq 7cm)\)

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)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size/Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>N0 and ≤ 3 cm</td>
</tr>
<tr>
<td>IA1, IA2, IA3</td>
<td>(a category for each cm in size)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>N0 and &gt;3 to ≤ 4 cm</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>N0 and &gt;4 to ≤ 5 cm</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>N0 and &gt;5 to ≤ 7 cm</td>
</tr>
<tr>
<td></td>
<td>or N1 and smaller tumors</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>N0 and &gt; 7 cm or others T4</td>
</tr>
<tr>
<td></td>
<td>N1 and T3-T4</td>
</tr>
<tr>
<td></td>
<td>N2 and T1a-T2b</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>N2 and T3-4</td>
</tr>
<tr>
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<td>N3 and T1a-T2b</td>
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<tr>
<td>Stage IIIC</td>
<td>N3 and T3-T4</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>Any T Any N with M1a and M1b</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>&gt; 1 extrathoracic metastasis (M1C)</td>
</tr>
<tr>
<td>Stage</td>
<td>IA (≤1 cm)</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>IA1</td>
<td>T1a N0 M0</td>
</tr>
<tr>
<td>IA2</td>
<td>T1b N0 M0</td>
</tr>
<tr>
<td>IA3</td>
<td>T1c N0 M0</td>
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**Early Stages:**

- IA1 (≤1 cm)
- IA2 (≥1 to ≤2 cm)
- IA3 (≥2 to ≤3 cm)
- IIA (≥3 to ≤4 cm)
- IIIB (≥4 to ≤5 cm)

**Locally Advanced Stages:**

- IIIA (≥3 to ≤4 cm)
- IIIB (≥4 to ≤5 cm)

**Any Stages:**

- IV A-B (any T, any N, M1a-b-c)

**Surgery:**

- Yes for early stages
- No for locally advanced stages
- No for any stages
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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 ≤2 cm)
IA3 T1c N0 M0 (>2 to ≤3 cm)
stage IB : T2a N0 M0 (>3 to ≤4 cm)

potential to be cured with surgery... alone

the gold standard in stage I is an anatomic lobar resection

Ginsberg RJ and Rubinstein LV 1995
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

survival following lobectomy and limited resection for the treatment of stage I nsclc \(\leq 1\text{ cm in size}:\) a review of SEER data (Surveillance, Epidemiology, and End Results registry)

- stage I nsclc \(\leq 1\text{ cm in size}:\) 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)

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

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

There is evidence that *wedge resections*, 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.
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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)


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, \(p=0.88\)).

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).

uniportal vats

Gonzales-Rivas D. WCLC 2016
Uniportal robotic platform
### Stage IA - early IA2 - IA3
- IA 1: T1a N0 M0 ($\leq 1$ cm)
- IA2: T1b N0 M0 ($>1$ to $\leq 2$ cm)
- IA3: T1c N0 M0 ($>2$ to $\leq 3$ cm)

### Stage IB
- T2a N0 M0 ($>3$ to $\leq 4$ cm)

### Stage IIA
- T2b N0 M0 ($>4$ to $\leq 5$ cm)

### Stage IIB
- T3 N0 M0 ($>5$ to $\leq 7$ cm)

### 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>IA1</th>
<th>IA2</th>
<th>IA3</th>
<th>IB1</th>
<th>IIA1</th>
<th>IIB1</th>
<th>Early IA1</th>
<th>Early IA2</th>
<th>Early IA3</th>
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<td>IA</td>
<td>T1a</td>
<td>T1b</td>
<td>T1c</td>
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<td>T3</td>
<td>T1a-c</td>
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<td>T2a-b</td>
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<tr>
<td>IA</td>
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<td>N0</td>
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<td>N0</td>
<td>N1</td>
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<tr>
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<td>T1a-c N1 M0</td>
<td>T2a-b N1 M0</td>
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stage I & II tumours

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- open or vats
- lobar or sublobar?
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<th>T1c-N0-M0 (2 to ≤3 cm)</th>
<th>T2a-N0-M0 (≥3 to ≤4 cm)</th>
<th>T2b-N0-M0 (≥4 to ≤5 cm)</th>
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<td>IA 2</td>
<td>IA 3</td>
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<tr>
<td>Early</td>
<td>T1a-N0-M0 (≤1 cm)</td>
<td>T1b-N0-M0 (1 to ≤2 cm)</td>
<td>T1c-N0-M0 (2 to ≤3 cm)</td>
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**Stage I & II Tumours**

- **surgery**
- **open or vats**
- **lobar or sublobar?**

*surgical resection of lung cancer - standard of care*
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</table>
state of the art? – controversial situations

**stage III-N2**
surgery or not?
upfront surgery or induction?
risks?
locally advanced – T3/4

**stage IIB**
T3 N0 M0
>5 to ≤ 7 cm
locally advanced – T3-4 N2 M0

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

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
  \[ HR = 1.01 \text{ (95\% CI 0.82 1.23; } P = 0.954) \]
- two trials, patients randomised to surgery after chemo-radiotherapy
  \[ HR = 0.87 \text{ (0.75 1.01; } P = 0.068) \]

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

surgery versus radiotherapy after induction treatment in patients with N2 disease

<table>
<thead>
<tr>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd</td>
<td>0.99 (0.38, 2.57)</td>
<td>1.60</td>
</tr>
<tr>
<td>Johnstone</td>
<td>0.81 (0.46, 1.42)</td>
<td>4.55</td>
</tr>
<tr>
<td>Stephens</td>
<td>0.91 (0.49, 1.69)</td>
<td>3.80</td>
</tr>
<tr>
<td>Van Meerbeeck</td>
<td>1.06 (0.84, 1.34)</td>
<td>26.92</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.830)</td>
<td>1.01 (0.82, 1.23)</td>
<td>36.88</td>
</tr>
<tr>
<td>Albain</td>
<td>0.87 (0.70, 1.08)</td>
<td>30.82</td>
</tr>
<tr>
<td>Sorensen</td>
<td>0.87 (0.70, 1.07)</td>
<td>32.30</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.976)</td>
<td>0.87 (0.75, 1.01)</td>
<td>63.12</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.818)</td>
<td>0.92 (0.81, 1.03)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

By courtesy of PJ McElnay and E. Lim

Favours surgery

Favours radiotherapy
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<tr>
<td>Stage</td>
<td>Sub-stage</td>
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<tr>
<td>stage IA</td>
<td>IA 1</td>
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<td></td>
<td>early IA2</td>
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<td>IA3</td>
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<tr>
<td>stage IB</td>
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Potential to be cured with surgery... alone

Stereotactic ablative radiotherapy?
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

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

• ACCP

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

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 bronchoangioplastastic resection or non-anatomical resection. [C]
consider patients with moderate to high risk of postoperative dyspnoea for lung parenchymal sparing surgery. [D]
consider bronchoangioplastastic 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]
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.

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]

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]