surgical approach for resectable NSCLC

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University of Paris VI. France
SUCCESSFUL REMOVAL OF AN ENTIRE LUNG FOR CARCINOMA OF THE BRONCHUS

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AND

J. J. SINGER, M.D.

ST. LOUIS

Carcinoma of the bronchus in recent years has become a problem of major importance. It is now known that primary carcinoma of the lung, which almost always arises in a bronchus, constitutes between 5 and 10 per cent of all carcinomas. In frequency, therefore, it is comparable with carcinoma of the large intestine, and it is much more frequent than the malignant tumors of some other organs that have received much more comment. The problem of primary carcinoma of the lung is of special importance, since up to the present time at least the prognosis has been almost uniformly bad because of the complete futility of any methods of treatment other than surgical excision. There is no record in the literature of the successful treatment by radiotherapy of a single case in which the pathologic evidence has been incontrovertible and in which a five year interval without recurrence has
is it reasonable to sacrifice a vital organ for treating a molecular disorder???
what is the impact of surgery on lung cancer survival?

- is the tumour resectable?
- is the patient operable?
- 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?

"early stage"
definitions

- A "resectable" tumour can be completely excised by surgery with clear pathological margins.
- An "operable" patient has an acceptable risk of death or morbidity.
what is early stage lung cancer?

when lung cancer is defined in this way, it is often referring to cancers that are caught early enough that they have the potential to be cured with surgery

if you are wondering whether or not something you hear about “early stage lung cancer” applies to your particular situation, share your questions with your oncologist

http://lungcancer.about.com/od/glossary/g/Early-Stage-Lung-Cancer.htm
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the TNM stage influences survival after surgery

post-surgery survival by pTNM
(7th edition stage grouping)
<table>
<thead>
<tr>
<th>Stage</th>
<th>IA</th>
<th>T1a-b N0 M0 (&lt;2cm;&lt;3cm)</th>
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</thead>
<tbody>
<tr>
<td>early IA</td>
<td>IB</td>
<td>T2a N0 M0 (&lt;5cm)</td>
</tr>
<tr>
<td>Stage II</td>
<td>IIA</td>
<td>T1a-b N1 M0</td>
</tr>
<tr>
<td>early</td>
<td>IIB</td>
<td>T2a N1 M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b N0 M0 (&lt;7cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 N0 M0</td>
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<tr>
<td>Stage III</td>
<td>IIIA</td>
<td>T1-2 N2 M0</td>
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<td></td>
<td>T3 N1-2 M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4 N0-1 M0</td>
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<tr>
<td>locally advanced</td>
<td></td>
<td>IIIIB</td>
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<tr>
<td></td>
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<td>T1-4 N3 M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, any N, M1a-b</td>
<td></td>
</tr>
</tbody>
</table>

**is the tumour resectable?**

surgery

selected patients

no surgery
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
risks from surgery increase with age and comorbidities

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 … or death
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
Preoperative cardiac and respiratory evaluation (ERS)

Cardiac assessment: low risk or treated patient (fig. 1)
- FEV₁
- Dₐₐ₃,co

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-FEV₁
- ppo-Dₐₐ₃,co

Both > 30%

At least one < 30%

< 35% or < 10 mL·kg⁻¹·min⁻¹

Resection up to calculated extent

Resection up to pneumonectomy

Lobectomy or pneumonectomy are usually not recommended. Consider other options

Tripartite risk assessment

Risk assessment for surgery

- Post-operative cardiac event
  - ACC/AHA* risk stratification
    +/- cardiology review
    *see text

- Peri-operative death
  - Thoracoscore Appendix 5

- Post-operative dyspnoea
  - 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 mild-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.

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consideration of the patient’s general condition
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- cardiac condition

and acceptance

diagnostic and therapeutic indications
surgical resection of lung cancer controversial situations

stage I tumours
- surgery, SABR, or nothing?
- open or vats?
- lobar or sublobar?

stage III-N2
- surgery or not?
- upfront surgery or induction?
- risks?

locally advanced – T3/4
potential to be cured with surgery... alone

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>IB</td>
<td>IIA</td>
<td>IIB</td>
</tr>
<tr>
<td>T1a N0</td>
<td>T2a N0</td>
<td>T1a N1</td>
<td>T2b N1</td>
</tr>
<tr>
<td>T1b N0</td>
<td></td>
<td>T1b N1</td>
<td>T3 N0</td>
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<tr>
<td></td>
<td></td>
<td>T2a N1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b N0</td>
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<td>T2b N0</td>
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<td></td>
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<td>T3 N2</td>
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<td>T4 N0</td>
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<td>T4 N1</td>
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</tr>
<tr>
<td>T2b N0</td>
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<td>T4 N2</td>
<td>any T N3</td>
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<td></td>
<td>any T N3</td>
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<td></td>
<td></td>
<td>any T</td>
<td>any N M1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>any T</td>
<td>any N M1b</td>
</tr>
</tbody>
</table>
the reality

• no randomised trial comparing resection vs. no treatment in early stage nsclc
• risks from surgery increase with age and comorbidities
• in 20% of patients with stage IA, the cancer will recur within 5 years of surgery
better survival and quality of life than no treatment?
better survival and quality of life than other treatments?

sbrt = on-site destruction
direct comparison of sbrt and sublobar resection is difficult

stereotactic body radiotherapy has become established as an effective modality for treating peripheral cancer in medically inoperable patients

low toxicity and excellent local control rates

different definitions of recurrence

different populations of patients

different methods of classifying morbidity

imaging follow-up not standardized

ACOSOG Z4099/RTOG 1021

a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer

Fernando HC, Timmerman R. J Thorac Cardiovasc Surg 2012;144:S35-8
direct comparison of SBRT and sublobar resection is difficult

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Fernando HC, Timmerman R. J Thorac Cardiovasc Surg 2012;144:S35-8
surgery = extirpation
open or vats* ?

* video-assisted thoracoscopic surgery


open or vats*? 

* video-assisted thoracoscopic surgery 

safety?
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**

<table>
<thead>
<tr>
<th></th>
<th>VATS</th>
<th>Thoracotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>pts</td>
<td>717 (47%)</td>
<td>796 (53%)</td>
</tr>
<tr>
<td>nodal upstaging</td>
<td>281 pts (18.6%)</td>
<td></td>
</tr>
<tr>
<td>thoracotomy higher N1 upstaging</td>
<td>13.1% vs 8.1%; p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N2 upstaging</td>
<td>11.5% vs 3.8%; p&lt;0.001</td>
</tr>
</tbody>
</table>

**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).

Time to recurrence (excluding second primaries) by treatment for 247 eligible patients

Ginsberg RJ and Rubinstein LV 1995

a sublobar resection?
the gold standard in stage I is an anatomic lobar resection

Time to recurrence (excluding second primaries) by treatment for 247 eligible patients

Ginsberg RJ and Rubinstein LV 1995
an evolving paradigm?

sublobar resection: a movement from the Lung Cancer Study Group

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

eenhancements in imaging technology
screening programs

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

larger cohorts of localized early-stage disease

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
\[
\text{HR} : 1.12 \ (95\% \ CI: 0.93-1.35)
\]
lung cancer-specific survival
\[
\text{HR}: 1.24 \ (95\% \ CI: 0.95-1.61)
\]

recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I nsclc: a propensity-matched analysis

matched cohorts (n = 312 pts per group)

<table>
<thead>
<tr>
<th></th>
<th>segmentectomy (%)</th>
<th>lobectomy (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>periop. mortality</td>
<td>1.2</td>
<td>2.5</td>
<td>0.38</td>
</tr>
<tr>
<td>locoreg. recurr.</td>
<td>5.5</td>
<td>5.1</td>
<td>1.00</td>
</tr>
<tr>
<td>distant recurr.</td>
<td>14.8</td>
<td>11.6</td>
<td>0.29</td>
</tr>
<tr>
<td>overall recurr.</td>
<td>20.2</td>
<td>16.7</td>
<td>0.30</td>
</tr>
<tr>
<td>5-yr DFS</td>
<td>70</td>
<td>71</td>
<td>0.467</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>54</td>
<td>60</td>
<td>0.258</td>
</tr>
</tbody>
</table>

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

the surgical management of stage I and stage II lung cancer

"anatomic lobectomy combined with hilar and mediastinal lymphadenectomy constitutes the oncologic basis of surgical resection"

"however, the role of sublobar pulmonary resection, either anatomic segmentectomy or nonanatomic wedge resection, in patients with subcentimeter nodules may become important"

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
surgical resection of lung cancer
standard of care

**Stage I & II tumours**

- surgery
- open or vats
- **lobar** or sublobar?
surgical resection of lung cancer
controversial situations

stage III-N2
- surgery or not?
- upfront surgery or induction?
- risks?

locally advanced – T3/4
- surgery?
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]
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• the role of surgery is not clearly defined [Roy and Donington, 2007]
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

induction chemoradiotherapy

Favours surgery

Favours radiotherapy

By courtesy of PJ McElnay and E. Lim
surgery versus radiotherapy after induction treatment in patients with N2 disease

Favours surgery

Favours radiotherapy

By courtesy of PJ McElnay and E. Lim
algorithm for surgery in c-stage IIIa N2

- **pet**
  - **negative**
  - **positive**
    - **Histological documentation**
      - **negative**
      - **positive**
        - **st. 7 - (subcar.)**
        - **st. 7 +**
          - **induction ct**
            - **CT-scan**
              - **induction ct**
                - **rt or rt-ct**

- **primary surgery with Ind**
  - **adjuvant ct (cisplatin-vinorelbine)**
  - **inclusion in adjuvant RT trial**

- **N2 clearance**
  - **surgery**
  - **lungART**

algorithm for surgery in c-stage IIIa N2

**pet**

- **negative**
  - primary surgery with Ind
  - adjuvant ct (cisplatin-vinorelbine)
  - inclusion in adjuvant RT trial

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  - **Histological documentation**
    - **negative**
    - **positive**
      - st. 7 - (subcar.)
      - st. 7 +
        - induction rt ct
          - CT-scan

  - **N2 clearance**
    - surgery lungART
  - **persistent N2**
    - rt or rt-ct

locally advanced NSCLC are not "surgical", an evolving paradigm?

locally advanced T3-4 superior sulcus tumor
superior sulcus tumors
surgery versus no surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>5-Year OS</th>
<th>5-Year DFS</th>
<th>5-Year LRC</th>
<th>p</th>
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<tbody>
<tr>
<td>Surgery with ind. or adj. treatment</td>
<td>139</td>
<td>35%</td>
<td>38%</td>
<td>62%</td>
<td>&lt; 0.0001</td>
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<tr>
<td>rt +/- ct without surgery</td>
<td>96</td>
<td>8%</td>
<td>15%</td>
<td>38%</td>
<td>&lt; 0.0001</td>
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induction ct-rt and surgical resection for superior sulcus nsclc

<table>
<thead>
<tr>
<th>author</th>
<th>year</th>
<th>no.</th>
<th>R0 (%)</th>
<th>pCR (%)</th>
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<td>Rusch</td>
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<td>76</td>
<td>56</td>
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<td>Marra</td>
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<td>29</td>
<td>94</td>
<td>nr</td>
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<td>Kunitoh</td>
<td>2008</td>
<td>57</td>
<td>51</td>
<td>16</td>
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<tr>
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<td>2009</td>
<td>22</td>
<td>22</td>
<td>62</td>
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<td>yr</td>
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<td>MDA</td>
<td>Toronto</td>
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<tr>
<td>R0 res. (%)</td>
<td>88</td>
<td>56</td>
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<tr>
<td>mortality (%)</td>
<td>3</td>
<td>5</td>
<td>6</td>
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<tr>
<td>5-yr surv. (%)</td>
<td>24</td>
<td>27</td>
<td>61</td>
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</tr>
</tbody>
</table>

* unpublished
an old myth, or a paradigm?

1993 neoadjuvant therapy for lung cancer: a note of caution Rusch VW, Benfield JR


2001 right pneumonectomy is at risk Martin J, et al.

2003 surgery is toxic in INT0139 trial Albain KS, et al.

2007 radiotherapy preferred (lower morbidity) Van Meerbeeck J, et al.
an old myth, or a paradigm?

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is "adjuvant" surgery risky?

is surgical toxicity a restricting factor?

should surgical toxicity influence therapeutic strategy?


retrospective analysis of patients who underwent pneumonectomy after neoadjuvant therapy in 2 centers

pneumonectomies 176
induction ct 35 20%
induction ct-rt 141 80%
extended resections 138 78%
perioperative mortality 6 3%
90-day major complications 22 13%
5-year survival 38%

by courtesy of Dr. W. Weder, MD
where is the truth?

- surgery adds mortality when compared with no surgery
- mortality rates are lower in retrospective analyses of academic centers compared with multicenter randomised studies
- evidence from INT0139 cannot be applied to academic centers
- whether addition of rt to induction ct increases surgical complications is not demonstrated yet
- pneumonectomy *per se* is a risk factor for mortality
- whether the side (right/left) does matter is not proven
duties of the surgeon

the patient has to stay on
- alive at 30 days after operation
- in good condition at 3 months
- without local recurrence at 1 year

the dearest wish:
- alive and dis.-free at 5 yrs

pffffffff!!!!!!!
what a challenge!!!!!!!!!!
blood-borne cancer cells in pulmonary veins in surgical non-small cell lung cancer

• venous blood is collected from the pulmonary vein in the operating room

• circulating tumor cells are detected in 81% of the patients
the future challenges

• to pursue efforts in aggressive surgery
• to improve all modalities (morbidity, mortality)
• to optimize multimodality combinations
• to improve knowledge on predictive factors, biomarkers, circulating tumor cells, new targets
• to apply customized therapy in perioperative setting

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

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]

recommendations

• ESMO

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

• ACCP