How to improve stage III NSCLC multimodality treatment

Surgical techniques relevant for stage III disease

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I have no conflicts of interest to declare
The heterogenity in the subgroups of stage III disease demands an implications of patients selection. It is for the treatment choice and the prognosis of important significance

(Recommendation grade B)
Subgroups Stage IIIA/IIIB disease
(IASLC, UICC-TNM Classification 2010)

<table>
<thead>
<tr>
<th>IIIA</th>
<th>T1-2</th>
<th>N2</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td></td>
<td>N1-2</td>
<td>M0</td>
</tr>
<tr>
<td>T3 same lobe</td>
<td></td>
<td>N1-2</td>
<td>M0</td>
</tr>
<tr>
<td>T4 extension</td>
<td></td>
<td>N0-1</td>
<td>M0</td>
</tr>
<tr>
<td>T4 other lobe ipsilateral</td>
<td></td>
<td>N0-1</td>
<td>M0</td>
</tr>
</tbody>
</table>

| IIIB | T4 extension | N2 | M0 |
|      | T4 other lobe ipsilateral | N2 | M0 |
|      | N3 | M0 |

Surgical techniques relevant for stage III disease
Stage $T4$ N0-1 disease

Primary surgery or integration of surgery in a multimodality treatment is recommended for patients with functional and medical operability and involvement of

- carina / trachea
- heart (left atrium)
- great vessels (vena cava, pulmonary artery, aorta)
- vertebral body
- metastasis other lobe ipsilateral

(recommendation grade B)
Stage T4 N2 disease

For patients with acceptable performance status, combination of Chemotherapy and Radiation is the choice of treatment
(recommendation grade A)

For selected cases after induction CTx/RTx and good response the integration of surgery could be followed (if possible inside of studies)
(recommendation grade D)
T4 - Surgical management

Carina/ Trachea
Left Atrium
Superior Vena cava
Pulmonary artery
Aorta
Vertebral body
Metastasis other lobe ipsilateral
Carina/Trachea

In the last decades the number of patients needed a carinal resection significantly decreased because of the induction treatment and the down staging effect. Publications with large experience do not exactly define between T3 and T4 tumors. Induction treatment is not acceptable by all surgeons because of healing complications. Good long term results by R0-Resection und N0/N1 pathology are observed.
### Carina/Trachea

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Induction</th>
<th>R0</th>
<th>N2</th>
<th>Letality</th>
<th>5y Surv all</th>
<th>5y surv N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaggiari (2013)</td>
<td>33</td>
<td>23p CT</td>
<td>79%</td>
<td>42%</td>
<td>18%</td>
<td>22%</td>
<td>22% (N+)</td>
</tr>
<tr>
<td>Jiang (2009)</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2.4</td>
<td>26.8%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Liu (2009)</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9.4%</td>
<td>40.6%</td>
<td>NR</td>
</tr>
<tr>
<td>Yildizeli (2008)</td>
<td>92</td>
<td>21p. CT or CT/RT</td>
<td>98.5%</td>
<td>21%</td>
<td>6.7%</td>
<td>42.5%</td>
<td>17%</td>
</tr>
<tr>
<td>Rea (2008)</td>
<td>49</td>
<td>19p. CT</td>
<td>NR</td>
<td>NR</td>
<td>6.1%</td>
<td>27.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Chen (2006)</td>
<td>73</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5.5%</td>
<td>23.3%</td>
<td>NR</td>
</tr>
<tr>
<td>Macchiarini (2006)</td>
<td>50</td>
<td>18p. CT/RT</td>
<td>98%</td>
<td>36%</td>
<td>4%</td>
<td>51%</td>
<td>12%</td>
</tr>
<tr>
<td>De Perrot (2006)</td>
<td>100</td>
<td>29p CT or CT/RT</td>
<td>94%</td>
<td>27%</td>
<td>7.6%</td>
<td>44%</td>
<td>15%</td>
</tr>
<tr>
<td>Regnardt (2005)</td>
<td>65</td>
<td>11p. CT</td>
<td>94%</td>
<td>35%</td>
<td>7.7%</td>
<td>26.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Porhanov (2002)</td>
<td>151</td>
<td>NR</td>
<td>86%</td>
<td>20%</td>
<td>16%</td>
<td>24.7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Roviaro (2001)</td>
<td>48</td>
<td>22p.RT. CT or CT/RT</td>
<td>NR</td>
<td>25%</td>
<td>8.2%</td>
<td>24.5%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Surgical techniques relevant for stage III disease
Carina/Trachea – Technical details

**Type of resection**  
right sleeve pneumonectomy  
left sleeve Pneumonectomy  
RUL/carina sleeve  
Various carinal resections and reconstructions

**Technique of anastomosis**  
end to end  
end to side  
end to end and end to side

**Mediastinoscopy**  
to dissect the pretracheal plan to reduce tension at the anastomotic site

**Reinforcement**  
with omental flaps, muscle flap, or mediastinal fat

**Release maneuvers**

**Induction treatment**  
seems to improve survival if the mediastinal nodes can be sterilized before the lung resection. Some authors reported anastomotic healing problems after radiotherapy
Carina/Trachea - Neoadjuvant treatment

Before and after induction CT/RT

Surgical techniques relevant for stage III disease
Carina/Trachea - Resection

Surgical techniques relevant for stage III disease
Surgical techniques relevant for stage III disease

Stump protection with mediastinal fat

After right sleeve pneumonectomy

After RUL/sleeve lobectomy
Left atrium

Reports with small number and selected cases
Induction treatment is necessary in N2 disease and to reduce tumor size
NSCLC involves the left atrium either through direct tumor invasion or through tumor embolus in the pulmonary vein
Right sided tumors usually invade the left atrium widely, due to the shortness of the right upper pulmonary vein
Pneumonectomy rates between 66 and 95%
Cardiopulmonary bypass is seldom necessary
Mortality rate is low, morbidity acceptable
Residual tumor and lymph node status were factors significantly associated with survival
Left atrium
## Left atrium

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Resection</th>
<th>N2%</th>
<th>Letality</th>
<th>5y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galvaign (2014)</td>
<td>19</td>
<td>18PN/1</td>
<td>36%</td>
<td>10.5%</td>
<td>43.7%</td>
</tr>
<tr>
<td>Spaggiari (2013)</td>
<td>35</td>
<td>31PN/1Bilob/3Lob</td>
<td>45%</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Wang (2010)</td>
<td>25</td>
<td>NR</td>
<td>32%</td>
<td>NR</td>
<td>36%</td>
</tr>
<tr>
<td>Wu (2009)</td>
<td>46</td>
<td>30PN/8Bilob/8Lob</td>
<td>NR</td>
<td>0%</td>
<td>22%(28%N0, 23%N1, 18%N2)</td>
</tr>
<tr>
<td>Mu (2008)</td>
<td>32</td>
<td>22PN/10Lob</td>
<td>NR</td>
<td>6.2%</td>
<td>43%(70%N0, 45%N1, 15%N2)</td>
</tr>
<tr>
<td>Akopov (2007)</td>
<td>28</td>
<td>26PN/12Lob</td>
<td>NR</td>
<td>4%</td>
<td>17% MST 23 mo</td>
</tr>
<tr>
<td>Bobbio (2004)</td>
<td>23</td>
<td>22PN/1Lob</td>
<td>17%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Ratto (2004)</td>
<td>19</td>
<td>12PN/7Lob</td>
<td>57%</td>
<td>0%</td>
<td>14%</td>
</tr>
<tr>
<td>Fukuse (1997)</td>
<td>14</td>
<td>10PN/4Lob</td>
<td>22%</td>
<td>7.1%</td>
<td>14.3%, MST 10mo</td>
</tr>
<tr>
<td>Tsuchiya (1994)</td>
<td>44</td>
<td>29PN/15Lob</td>
<td>NS</td>
<td>8%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Left atrium


15 patients (2005), 35 patients (2013)
CT–scan, PET, transthoracic echocardiography, lung perfusion scan
For suspected N2 disease, EBUS-TBNA or mediastinoscopy was performed
Neoadjuvant treatment – N2 disease in nodal stations R4 and 7)
  - Reduce tumor size (risk of incomplete resection)
Resection - Satinski clamp to evaluate surgical feasibility and cardiocirculatory reduction of atrial volume
  - Sondergaard technique is used to lengthen the atrial cuff to about 2 cm
  - Atrial resection is performed after completion of lung resection
  - Suturing the defect with 2 running stitches of monofilament nonabsorbable sutures

Surgical techniques relevant for stage III disease
Superior Vena Cava

Only one report with large number of cases
Technical feasibility also without extracorporeal circulation
Induction treatment is recommended
Complementary operations, mostly carina resection or PA sleeve
Factors affecting significantly survival were advanced age (>60), N2-disease and R1/R2 resection
## SVC

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>N2</th>
<th>R0</th>
<th>Letality</th>
<th>5J Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaggiari (2013)</td>
<td>43</td>
<td>15(35%)</td>
<td>36(84%)</td>
<td>4.6%</td>
<td>26% (46%N0, 22%N+)</td>
</tr>
<tr>
<td>Lanuti (2009)</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>11.1%</td>
<td>30%</td>
</tr>
<tr>
<td>Yildizeli (2008)</td>
<td>39</td>
<td>13(33.3%)</td>
<td>33(85%)</td>
<td>7.7%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Politi (2007)</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
<td>6.25%</td>
<td>20 months</td>
</tr>
<tr>
<td>Misthos (2006)</td>
<td>9</td>
<td>5(56%)</td>
<td>NR</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Suzuki (2004)</td>
<td>40</td>
<td>NR</td>
<td>28(75%)</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Rendina (1999/2007)</td>
<td>9/140</td>
<td></td>
<td></td>
<td>11.1%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Thomas (1994)</td>
<td>15</td>
<td>6(40%)</td>
<td>12 (80%)</td>
<td>7%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Surgical techniques relevant for stage III disease
SVC – Technical aspects

Type of lung resection
- right PN or sleeve PN
- Bilobectomy or RUL
- Segmentectomy
- Wedge resection

Type of cava resection and reconstruction
Small involvement less than 50% of the vessels circumference
  - resection and direct repair using mechanical suture or side clamp and manual-suture with nonabsorbable filament
Larger involvement less than 50% of the vessels circumference
  - resection and autologous (pericardium) or synthetic patch
  - Azygos flap
Involvement more than 50% of the vessels circumference
  - Cross-clamping, cava segment resection and vascular prosthesis (PTFE – graft or custom-made bovine pericardial tube)
SVC

Remission after CT/RT

SVC and pericardial replacement after right sided pneumonectomy

Surgical techniques relevant for stage III disease
Pulmonary artery

Resection and reconstruction of the pulmonary artery is technically feasible. Early reports were associated with significant mortality and poor overall survival


Surgical techniques relevant for stage III disease
### Pulmonary artery

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Resection</th>
<th>Letality</th>
<th>5y survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akopov (2007)</td>
<td>28</td>
<td>16PN/12Lob</td>
<td>3.5%</td>
<td>17% /23 Months</td>
</tr>
<tr>
<td>Wu (2009)</td>
<td>46</td>
<td>30PN/16Lob</td>
<td>0%</td>
<td>22%(23%N1, 18%N2)</td>
</tr>
<tr>
<td>Mu (2008)</td>
<td>32</td>
<td>22PN/10Lob</td>
<td>6.2%</td>
<td>53%(70%N0, 45%N1, 15%N2)</td>
</tr>
<tr>
<td>Venuta (2009)</td>
<td>105</td>
<td>3PN/101Lob/1Bil</td>
<td>1%</td>
<td>25%IIIA, 12% IIIB</td>
</tr>
<tr>
<td>Berthet (2013)</td>
<td>10</td>
<td>10 Lob</td>
<td>0%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Galetta (2015)</td>
<td>150</td>
<td>56 Sleeve Lob, 94Lob</td>
<td>3.3%</td>
<td>50% all p., (61% N0/N1, 28%N2)</td>
</tr>
</tbody>
</table>

Surgical techniques relevant for stage III disease
Pulmonary artery - Technical details

**Infiltration** - partial infiltration
- more extensive infiltration
- circumferential infiltration

**CPB** (in some left sided tumors)

**Reconstruction technique**
- suture small defects
- patches with autologous or bovine pericardium
- sleeve and end-to-end anastomosis
- interposition of pericardial conduit
- cryopreserved arterial allografts

**Protection with** - omental flaps
- muscle flap
- mediastinal fat
Surgical techniques relevant for stage III disease


31 IIIA and 22 IIIB disease among 105 patients
CT–scan all patients, MRI and PET in selected cases
Neoadjuvant treatment – CT in all patients with N2 disease
Surgery – 47p. PA sleeve resection
  55p. reconstruction by pericardial patch
  3p. pericardial conduit
- 3PN, 65 bronchial sleeve lobectomies, 35 lobectomies, 1 bilobectomy
Mortality 1p. (0, 95%)
Morbidity 30p. (28.5%)
Pathology - R0 resection 101p (96%), R1 resection 4p. (4%)
  - 61p SCC, 38p. AdenoCa, 5 LargeCellCa, 1p. mixed
Adjuvant treatment 42p. (40%) receive CT,
Results - 5 years survival for stage IIIA 25%, for IIIB 12%
Pulmonary artery


32 pulmonary artery reconstructions in 178 centrally located NSCLC
X-ray, CT-scan, bronchoscopy, PET-scan
Type of PA reconstruction – 20 end-to-end anastomosis
  - 2 pericardial patch reconstructions
  - 10 PA replacements (harvesting cryopreserved vessels from multiorgan donors)
Cryopreserved allograft – descending aorta 3
  - pulmonary arteries 7
Neoadjuvant treatment by N2 disease 4/10p. (40%)
Resection – Lobectomy in 7 and bronchial sleeve in 3p.
Mortality 0%
Morbidity 4 p. (40%), 1p. Thrombosis Pneumonectomy
Pathology – 7p. SCC, 2p. AdenoCa, 1p. Atypical Carcinoid
  - 4p. pN0, 5p. pN1, 1p. pN2
  - R0-resection 100%
Results - 5 year survival 66.7%, MST 42 months
Cryopreserved arterial allografts can replace the PA, so that PN can be avoided

Surgical techniques relevant for stage III disease
Surgical techniques relevant for stage III disease

**Before CTx/RTx**

**After CTx//RTx**

Downstaging left PA after induction treatment
Pulmonary artery

Right pneumonectomy  Left bronchial and PA sleeve resection

Surgical techniques relevant for stage III disease
Surgical techniques relevant for stage III disease

T4-Aorta

Series with small number of cases
Radiologic findings on aortic infiltration may be unreliable in
differentiating invasion limited to the adventia or extending to the
medial or intima layers
Induction treatment is recommended
Thoracic aortic endografting allowed safe en bloc resection
For the prognosis important the R0 Resektion und N0/N1 disease
### T4-Aorta

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Induction</th>
<th>Site of invasion</th>
<th>Resection</th>
<th>Letality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klepetko (1999)</td>
<td>7</td>
<td>1p. CT</td>
<td>6 descending/ 1 arch</td>
<td>6PN/1LUL</td>
<td>0%</td>
</tr>
<tr>
<td>Ohta (2005)</td>
<td>16</td>
<td>10p. CT</td>
<td>7descending/ 9 arch</td>
<td>6PN/9LUL</td>
<td>12.5%</td>
</tr>
<tr>
<td>Misthos (2006)</td>
<td>13</td>
<td>No induction</td>
<td>13 descending</td>
<td>5PN/8LUL</td>
<td>0%</td>
</tr>
<tr>
<td>Collaud (2014)</td>
<td>5</td>
<td>4p. CT/RT</td>
<td>3 descending/ 2 arch</td>
<td>3PN/2LUL</td>
<td>0%</td>
</tr>
<tr>
<td>Yoshida (2015)</td>
<td>8</td>
<td>NR</td>
<td>5 descending/3 arch</td>
<td>5PN/3LUL</td>
<td>0%</td>
</tr>
<tr>
<td>Marulli (2015)</td>
<td>9</td>
<td>4p. CT</td>
<td>8 descending/1 arch</td>
<td>3PN/6LLL</td>
<td>0%</td>
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</tbody>
</table>

Surgical techniques relevant for stage III disease
Surgical techniques relevant for stage III disease

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>pTNM</th>
<th>Adjuvant</th>
<th>replacement</th>
<th>5J Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klepetko (1999)</td>
<td>7</td>
<td>2p. T4N0, 3p. T4N2</td>
<td>3p. CT, 1p. RT</td>
<td>5 tubular grafts, 2 patch</td>
<td>20% (4years)</td>
</tr>
<tr>
<td>Ohta (2005)</td>
<td>16</td>
<td>10p. T4N0, 6p. T4N2/3</td>
<td>4p. CT</td>
<td>10 prosthetic grafts, 5 patch, 1 suture</td>
<td>70% N0, 16.7% N2/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% N0, 37.5% N1, 0% N2</td>
</tr>
<tr>
<td>Collaud (2014)</td>
<td>5</td>
<td>NR</td>
<td>1p. CT/RT</td>
<td>5 Endograft/2 Reinforcement</td>
<td>All patients alive</td>
</tr>
<tr>
<td>Yoshida (2015)</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
<td>5 total grafts/3 patch</td>
<td>50%</td>
</tr>
<tr>
<td>Marulli (2015)</td>
<td>9</td>
<td>5 T4N0, 4 T4N1</td>
<td>5p. CT/1p. RT</td>
<td>9 Endograft/5 Reinforcement</td>
<td>62% (3year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1p. CT/RT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
T4-Aorta – Technical aspects

No bypass used
Passive shunt between ascending and descending aorta
Cardiopulmonary bypass

**Resection** of adventitia
  - media
  - intima
**Reconstruction** direct closure by suturing
  - Prosthetic patch
  - Prosthetic grafts
  - Aortic endografting (one or two stage procedures)

**Reinforcement** with synthetic patches
  - omental flaps
  - muscle flap

Surgical techniques relevant for stage III disease
T4-Aorta


9 patients
CT or MRI of the chest, PET/CT-scanning
EBUS_TBNA or mediastinoscopy only for PET-positive nodes
CT angiography (assess vessel size and anatomy)
Radiologic findings suggesting aortic invasion
  - Contact between aortic wall and tumor for more than 3cm
  - Obliteration of the fat plane between aorta and tumor
  - Contact by the tumor of more than 90° of aortic circumference
Neoadjuvant treatment – 4 patients (45%)
Resection – Pneumonectomy 4p. (45%)
  - Lobectomy 5p. (55%)
Surgical techniques relevant for stage III disease

T4-Aorta
Surgical techniques relevant for stage III disease

T4-Aorta

Left pneumonectomy with resection of aorta adventitia
T4 – Vertebral body

Experience with small number off patients
Most resections with Pancoast tumors
Resection after CTx/RTx
Cooperation with neurosurgeon/orthopedics necessary
Good long term results only by R0-Resection and N0/N1 pathology
Surgical techniques relevant for stage III disease

T4 – Vertebral body
## T4 – Vertebral body

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Induction</th>
<th>Letality</th>
<th>5J survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolton (2009)</td>
<td>39</td>
<td>CTx/RTx</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>Yokomise (2007)</td>
<td>7</td>
<td>CTx/RTx</td>
<td>0%</td>
<td>67,7%</td>
</tr>
<tr>
<td>Koizumi (2007)</td>
<td>8</td>
<td>CTx/RTx</td>
<td>0%</td>
<td>22,9%</td>
</tr>
<tr>
<td>Mazel (2003)</td>
<td>36</td>
<td>CTx-RTx*</td>
<td>2,7%</td>
<td>28%</td>
</tr>
<tr>
<td>Fadel (2002)</td>
<td>17</td>
<td>CTx-Rtx*</td>
<td>0%</td>
<td>20%</td>
</tr>
</tbody>
</table>

* Not all patients
**T4 – Vertebral body**

*Mara et al, ERS 2007*

**R0-resection and treatment concept**

**Survival and treatment concept**

Surgical techniques relevant for stage III disease
T4 other lobe ipsilateral

180p./100.869p. 5y survival 22%

5y surv 43% bilateral, 23% unilateral without N disease, 0% with lymph node metastasis

Watanabe S, Asamura H, Miyaoka E et al. Results of T4 surgical cases in the Japanese Lung Cancer registry Study: Should mediastinal fat tissue invasion really be included in the T4 category? J Thorac Oncol 2013;8:759-65
87p./11663 p. 5y surv 50.3% vs 19.9%, nodal status and age >70 years significant prognostic factors

Carefully selected patients may benefit from an aggressive surgical approach

Surgical techniques relevant for stage III disease
Stage N2A3- disease

Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with IIIA (N2) NSCLC

Albain KS et al., Lancet 2009;374:379-86
## Intergroup 0139 - Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CTx/RTx/Surgery</th>
<th>CTx/RTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>PFS</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>- primary tumor</td>
<td>2%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Albain KS. et al, Lancet 2009;374:379-86

Surgical techniques relevant for stage III disease
Stage N2A4 disease

For patients with acceptable performance status, combination of Chemotherapy and Radiation is the choice of treatment (recommendation grade A)

For selected cases after induction CTx/RTx and good response the integration of surgery could be followed (if possible inside of studies) (recommendation grade D)
### EORTC 08941 – Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CTx/RTx (n=165)</th>
<th>CTx/RTx/Surgery (n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up (mo)</strong></td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years (%)</td>
<td>17.5</td>
<td>16.4</td>
</tr>
<tr>
<td>5 years (%)</td>
<td>41</td>
<td>35</td>
</tr>
<tr>
<td><strong>Site of relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional</td>
<td>71 (54%)</td>
<td>37 (32%)</td>
</tr>
<tr>
<td>Distant</td>
<td>50 (39%)</td>
<td>70 (61%)</td>
</tr>
<tr>
<td>Both</td>
<td>9 (7%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mo)</td>
<td>11.3</td>
<td>9</td>
</tr>
<tr>
<td>2 years (%)</td>
<td>24</td>
<td>27</td>
</tr>
</tbody>
</table>


Surgical techniques relevant for stage III disease
## EORTC 08941 – Outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median</th>
<th>5 year(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extend of resection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bi-)Lobectomy</td>
<td>25.4</td>
<td>27</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>13.4</td>
<td>12</td>
</tr>
<tr>
<td><strong>Mediastinal nodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypN0-1</td>
<td>22.7</td>
<td>27</td>
</tr>
<tr>
<td>ypN2</td>
<td>14.9</td>
<td>12</td>
</tr>
<tr>
<td><strong>Type of resection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>24.1</td>
<td>27</td>
</tr>
<tr>
<td>Incomplete</td>
<td>12.1</td>
<td>7</td>
</tr>
</tbody>
</table>


Surgical techniques relevant for stage III disease
Different lymph nodes mapping

Naruke (1960)

Mountain-Dresler (1997)

IASLC (2009)

Surgical techniques relevant for stage III disease
Definition according the extension of LA

„Sampling“
Only suspected LN are removed after an individual interpretation of the surgeon

„Systematic LN dissection“ (Martini)
En bloc dissection of all ipsilateral compartments
Right side: 2R, 4R, 3, 7, 8, 9, 10, 11
Left side: 2L, 4L, 5, 6, 7, 8, 9, 10, 11

„Supraradical LN dissection“ (Naruke)
Additionally to systematic dissection, the anterior mediastinum (incl. thymus fat), contralateral 2 and 4 stations and the supraclavicular stations are removed
Sampling vs. Systematic LN dissection

1023 patients randomised
498p. sampling  525p. systematic LN dissection
Right side 2,4,7,10R
Left side 5,6,7, 10L
Died: 217(44%) sampling   218(42%) systematic LN d.
Median survival: 8,1y sampling  8,5y systematic LN d.
5y Survival: 64% sampling  68% systematic LN d.
Occult N2 21 patients in systematic LK dissection

Darling G et al. 2010
For lung cancer (UICC and AJCC)
CMountain CF, Dresler CM, Chest 1997)

Systematic lymphadenectomy (Martini)

Right side: 2R, 4R, 3, 7, 8, 9, 10, 11
Left side: 2L, 4L, 5, 6, 7, 8, 9, 10, 11
Why systematic lymph node dissection?

Systemic lymph node dissection is the only method to obtain a precise pathological staging (prognosis, adjuvant treatment et c.)

(Ogata 1987, Naruke 1996, Ginsberg 1997)
Why systematic lymph node dissection?

The incidence of the so-called „skip metastasis“ is too high (6-30%) to be ignored.

(Riquet 1995, Graham 1999, Passlick 2001)
Why systematic lymph node dissection?

The evidence of the importance of nodal micrometastasis enhances the limits of sampling

(Passlick 2002)
N3- disease

For N3 disease, treatment with neoadjuvant chemotherapy or chemoradiotherapy followed by surgery has been proved in limited phase II studies with a small number of cases. These trials showed that surgery is feasible and promising with long term survival only in selected downstaged patients. There are no phase III trial data available to document that surgery adds to survival (EORTC 08981 is failed). Therefore, this approach should be considered only inside of studies.
Supraradical lymphadenectomy (Naruke)

Right side: 2R, 4R, 3, 7, 8, 9, 2L, 4L
thymus fat, supraclavicular R/L
Left side: 2L, 4L, 5, 6, 7, 8, 9, 2R,
4R, thymus fat, supraclavicular R/L

For lung cancer (UICC and AJCC)
CMountain CF, Dresler CM, Chest 1997)
N3- disease

before induction CTx/RTx

before surgery

Surgical techniques relevant for stage III disease
## N3- Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Approach</th>
<th>Ipsilateral</th>
<th>Bilateral</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 8805 (Rusch VW 1994, Albain KS 1995)</td>
<td>27</td>
<td>Ipsilateral</td>
<td>53%</td>
<td></td>
<td>25% *</td>
</tr>
<tr>
<td>Stamatis et al, 1999</td>
<td>32</td>
<td>Ipsilateral-/Bilateral</td>
<td>25%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Grunenwald et al, 2001</td>
<td>18</td>
<td>Bilateral</td>
<td>30%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>DeCamp MM et al, 2003</td>
<td>21</td>
<td>Ipsilateral</td>
<td>30%</td>
<td>15%*</td>
<td></td>
</tr>
<tr>
<td>Ichinose Y et al, 2003</td>
<td>7</td>
<td>Bilateral</td>
<td>26%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Galetta D et al, 2003</td>
<td>5</td>
<td>Ipsilateral</td>
<td>-</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Yokomise H et al, 2007</td>
<td>4</td>
<td>Ipsilateral</td>
<td>25%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Stupp R (SAKK 2009)</td>
<td>15</td>
<td>Ipsilateral</td>
<td>13% ‡</td>
<td>40% ‡</td>
<td></td>
</tr>
<tr>
<td>Steger V et al (2012)</td>
<td>13</td>
<td>Ipsilateral-/Bilateral</td>
<td>66%</td>
<td>31mo †</td>
<td></td>
</tr>
<tr>
<td>Riquet M et al (2013)</td>
<td>11</td>
<td>Ipsilateral-/Bilateral</td>
<td>27.3%</td>
<td>54.5%</td>
<td></td>
</tr>
</tbody>
</table>

*2-years, ‡ all IIIB, † median survival

Surgical techniques relevant for stage III disease

elcc2016.org
Surgery for stage III disease

Inderdisciplinary approach of stage III disease is today the basis of successfully treatment

( recommendation grade A)