EVIDENCE BASED MANAGEMENT OF STAGE III NSCLC

MILIND BALDI
Overview

• Introduction
• Diagnostic work up
• Treatment
  • Group 1
  • Group 2
  • Group 3
Stage III lung cancer

• Historically was defined as
  – locoregionally advanced disease
    • attributed to primary tumor extension into extrapulmonary structures (T3 or T4)
    • Or mediastinal lymph node involvement (N2 or N3)
    • Without evidence of distant metastasis (M0)
<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a,b</th>
<th>N2</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2a,b</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N0, N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III B</td>
<td>T1a,b</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>T2a,b</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N2</td>
<td>M0</td>
<td></td>
</tr>
</tbody>
</table>
• IASCLC data base

20% patients $\rightarrow$ cIII A $\rightarrow$ 5 year survival $\rightarrow$ 16%

3% patients $\rightarrow$ cIII B $\rightarrow$ 5 year survival $\rightarrow$ 7%
• Stage III represents a heterogeneous population
<table>
<thead>
<tr>
<th>IASLC</th>
<th>TNM subset</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
</table>
| III A | T1-3, N2   | Occult N2  | Found at surgery  
• Microscopic N2  
• Macroscopic N2 |
<p>| III A | T1-3, N2   | Potentially resectable | Minimal N2 |
| III A | T1-3, N2   | Potentially resectable, but at risk of incomplete resection | Pancoast subset, Centrally located III A |
| III A | T1-3, N2   | Unresectable N2 | Bulky N2 |
| III A | T4, N0-1   | Potentially resectable, but at risk of incomplete resection | Pulmonary artery, carina, spine, trachea, vena cava, right atrium |</p>
<table>
<thead>
<tr>
<th>IASLC</th>
<th>TNM subset</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>III B</td>
<td>T4 N0-1</td>
<td>Unresectable T4</td>
<td>Oesophagus, heart, aorta, pulmonary veins</td>
</tr>
<tr>
<td>III B</td>
<td>T1-4, N3</td>
<td>Unresectable N3</td>
<td>N3 nodes at staging</td>
</tr>
</tbody>
</table>
### Heterogeneity

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td>Squamous, adenocarcinoma, large cell</td>
</tr>
<tr>
<td><strong>Tumor location and extension</strong></td>
<td>T4N0 vs T1N3</td>
</tr>
</tbody>
</table>
| **Individual patient risk profile** | Smokers vs non smokers  
Cardiopulmonary risks |
| **Inter institution diversity** | Expertise in  
• Thoracic surgery  
• Radiation oncology |

J Clin Oncol 2005; 23: 2955–2961  
J Thorac Oncol 2009; 4: 62–68  
Eur Respir J 2009; 34: 17–41
Treatment of Stage III Non-small Cell Lung Cancer


doi: 10.1093/annonc/mdv197
Published online 20 April 2015

2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer


NCCN.org
Three readily identifiable groups

1. Patients with **infiltrative stage III** (N2/N3) tumors
2. Patients with **occult N2** node involvement despite thorough preoperative staging, and
3. Patients with **discrete** clinically evident (by CT or CT-PET scan) N2 involvement.
Infiltrative stage III (N2/N3) tumors

- Patients with infiltrative N2/N3 involvement have N2 or N3 disease where discrete nodes can no longer be clearly distinguished and measured
- invasive proof of mediastinal involvement is not necessary
Occult N2 node involvement despite thorough preoperative staging

- Patients with occult N2 disease despite thorough preoperative staging are found intraoperatively or postoperatively to have positive N2 nodes.
- The thoroughness of the preoperative staging and intraoperative mediastinal assessment is critical.
Discrete evident (by CT or CT-PET scan) N2 involvement

- Discrete N2 involvement denotes patients in whom individual mediastinal nodes can be distinguished.
- These nodes may be enlarged or normal sized and may be suspected by PET uptake.
- Mediastinal stage suggested by imaging in these patients must be confirmed thorough invasive staging.
Best managed by...

• Multidisciplinary team
• High volume centers
• in a clinical trial

J Clin Oncol 2013; 31: 3141–3146
multidisciplinary team including

• pulmonologists
• thoracic/ medical oncologists
• radiation oncologists
• thoracic surgeons
• integrated radiologists and nuclear medicine physicians and pathologists
Diagnostic work up

- Positron emission tomography–computed tomography (PET-CT)
- Invasive mediastinal staging (transbronchial needle aspiration / EBUS/EUS/ mediastinoscopy)
- Brain MRI/brain CT
Positron emission tomography–computed tomography (PET-CT)

- For initial staging of stage III NSCLC patients
- Rule out extracerebral metastases
- To initiate mediastinal lymph node sampling

Lancet. 2002 Apr 20;359(9315):1388-93
Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial.

Cerfolio RJ¹, Bryant AS, Ojha B, Eloubeidi M.

Abstract

BACKGROUND: Clinical stage affects the care of patients with nonsmall cell lung cancer.

METHODS: This is a prospective trial on patients with suspected resectable nonsmall cell lung cancer. All patients underwent integrated positron emission tomographic scanning and computed tomographic scanning, and all suspicious metastatic sites were investigated. A, T, N, and M status was assigned. If N2, N3 and M1 were negative, patients underwent thoracotomy and complete thoracic lymphadenectomy.

RESULTS: There were 383 patients. The accuracy of clinical staging using positron emission tomographic scanning and computed tomographic scanning was 68% and 66% for stage I, 84% and 82% for stage II, 74% and 69% for stage III, and 93% and 92% for stage IV, respectively. N2 disease was discovered in 115 patients (30%) and was most common in the subcarinal lymph node (30%). Unsuspected N2 disease occurred in 28 patients (14%) and was most common in the posterior mediastinal lymph nodes (subcarinal, 38%; posterior aortopulmonary, 15%). It was found in 9% of patients who were clinically staged I (58% in the posterior mediastinal lymph nodes) and in 26% of patients clinically staged II (86% in posterior mediastinal lymph nodes).

CONCLUSIONS: Despite integrated positron emission tomographic scanning and computed tomographic scanning, clinical staging remains relatively inaccurate for patients with nonsmall cell lung cancer. Recent studies suggest adjuvant therapy for stage Ib and II nonsmall cell lung cancer; thus the impact on preoperative care is to find unsuspected N2 disease. Unsuspected N2 disease is most common in posterior mediastinal lymph nodes inaccessible by mediastinoscopy. Thus one should consider endoscopic ultrasound fine-needle aspiration, especially for patients clinically staged as I and II, even if the nodes are negative on positron emission tomographic scanning and computed tomographic scanning.
Invasive mediastinal staging

- In case of suspicious lesions invasive mediastinal staging may still be indicated despite PET negativity
  - primary tumour of $>3$ cm large axis,
  - central tumours,
  - CT-enlarged lymph nodes with small axis $>1$ cm
• Endoscopic methods should be preferred as the initial interventional procedure whenever feasible.

Table 1. Characteristics of the Studies Included in the Present Meta-Analysis

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Patients (No.)</th>
<th>Average Age (y)</th>
<th>Study Design</th>
<th>Patient Enrollment</th>
<th>Confirmation of EBUS-TBNA-Positive Results</th>
<th>Stations Examined by EBUS-TBNA</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yasufuku [16]</td>
<td>2004</td>
<td>108</td>
<td>65.3</td>
<td>Prospective</td>
<td>ND</td>
<td>Open thoracotomy, thoracoscopy, or clinical follow-up</td>
<td>2, 3, 4, 7</td>
<td>94.6</td>
<td>100</td>
</tr>
<tr>
<td>Yasufuku [17]</td>
<td>2006</td>
<td>102</td>
<td>67.8</td>
<td>Prospective</td>
<td>ND</td>
<td>Thoracotomy with complete mediastinal lymph node dissection</td>
<td>1, 2, 4, 5, 7</td>
<td>92.3</td>
<td>100</td>
</tr>
<tr>
<td>Yasufuku [18]</td>
<td>2011</td>
<td>153</td>
<td>66.8</td>
<td>Prospective</td>
<td>ND</td>
<td>Mediastinoscopy</td>
<td>2, 4, 7</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>Lee [15]</td>
<td>2008</td>
<td>102</td>
<td>64.3</td>
<td>Prospective</td>
<td>ND</td>
<td>Operation</td>
<td>2, 4, 7</td>
<td>69.8</td>
<td>100</td>
</tr>
<tr>
<td>Jhun [12]</td>
<td>2012</td>
<td>151</td>
<td>65</td>
<td>Retrospective</td>
<td>ND</td>
<td>Operation</td>
<td>1, 2, 3, 4, 7</td>
<td>91.9</td>
<td>98.4</td>
</tr>
<tr>
<td>Ye [19]</td>
<td>2011</td>
<td>101</td>
<td>57.4</td>
<td>Prospective</td>
<td>ND</td>
<td>Cytopathology, surgical results, and/or clinical follow-up</td>
<td>2, 4, 7, 8</td>
<td>95.08</td>
<td>100</td>
</tr>
<tr>
<td>Herth [13]</td>
<td>2006</td>
<td>100</td>
<td>58.9</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>Mediastinoscopy or thoracotomy</td>
<td>2, 4, 7</td>
<td>92.3</td>
<td>100</td>
</tr>
<tr>
<td>Herth [14]</td>
<td>2008</td>
<td>97</td>
<td>52.9</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>Mediastinoscopy or thoracotomy</td>
<td>4, 7</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Vincent [10]</td>
<td>2008</td>
<td>152</td>
<td>59.9</td>
<td>Retrospective</td>
<td>Consecutive</td>
<td>Mediastinoscopy or lung resection</td>
<td>2, 3, 4, 7</td>
<td>99.1</td>
<td>100</td>
</tr>
</tbody>
</table>

a All of the studies had patients selected on the basis of positive results on computed tomography or positron emission tomography.

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; ND = not defined.
• In case of negative endoscopic findings, and high suspicion of mediastinal node involvement, surgical staging is indicated
ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

Paul De Leyn a,*, Didier Lardinois b, Paul E. Van Schil c, Ramon Rami-Porta d, Bernward Passlick e, Marcin Zielinski f, David A. Waller g, Tony Lerut a, Walter Weder b

a Department of Thoracic Surgery, University Hospitals Leuven, Belgium
b Department of Thoracic Surgery, University Hospital of Zurich, Switzerland
c Department of Thoracic Surgery, University Hospital of Antwerp, Belgium
d Department of Thoracic Surgery, Hopital Mutua de Terrasa, Spain
e Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Germany
f Department of Thoracic Surgery, Pulmonary Hospital Zakopane, Poland
g Department of Thoracic Surgery, Glenfield Hospital Leicester, United Kingdom

Received 12 November 2006; received in revised form 28 January 2007; accepted 29 January 2007; Available online 19 April 2007
a: In central tumors, tumors with low FDG uptake, tumors with LNs ≥ 1.6 cm and/or PET N1 disease invasive staging remains indicated
b: Endoscopic techniques are minimally invasive and can be the first choice
c: Due to its higher NPV mediastinoscopy remains indicated
If surgical staging of the mediastinum is indicated:

- video-assisted mediastinoscopy (VAMS) is the preferred technique for upper mediastinal lymph nodes
- video-assisted thoracoscopic (VATS) is preferred for aortopulmonary lymph nodes
5. Conclusion

This retrospective study of a consecutive cohort of patients suggests that there is no additive value of post contrast MRI when $^{18}$FDG-PET-CT with CE-CT is performed in the diagnostic work-up of neurologically asymptomatic stage III NSCLC patients in screening for brain metastases. However, brain metastases is still an important problem as 13% of patients developed symptomatic brain metastases within 1 year after treatment with curative intent. Due to the possible impact of these findings on clinical practice a prospective trial (NTR3628) using up-to-date imaging techniques to validate these data has started.

Screening for small cell lung cancer: Is there additive value of magnetic resonance imaging above a contrast-enhanced computed tomography of the brain?

Lizza E.L. Hendriks$^{a,b,*}$, Gerben P. Bootsma$^a$, Dirk K.M. de Ruysscher$^{c,d}$, Nicole A.M. Scheppers$^a$, Paul A.M. Hofman$^e$, Boudewijn T. Brans$^f$, Anne-Marie C. Dingemans$^b$
Brain MRI/Brain CT

- Patients with T4 tumours and N2 or N3 nodes have a high risk of brain metastases. (10–30%)

Table 5. Impact of limited brain MRI screening on stage determination

<table>
<thead>
<tr>
<th>Stage</th>
<th>Before the detection of brain metastasis</th>
<th>After the detection of brain metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>13 (-2)</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
<td>13 (-3)</td>
</tr>
<tr>
<td>IIIA</td>
<td>38</td>
<td>32 (-6)</td>
</tr>
<tr>
<td>IIIB</td>
<td>42</td>
<td>38 (-4)</td>
</tr>
<tr>
<td>IV</td>
<td>72</td>
<td>87 (+15)</td>
</tr>
</tbody>
</table>

Overall upstaging rate: 15/111 (13.5%).
Upstaging rate in patients initially considered resectable surgically: 11/69 (15.9%).

Assessing relevant comorbidities

• Cardio-pulmonary functions are relevant for multidisciplinary treatment decisions.

• If surgery is planned:
  – Cardiac function: ECG, echocardiography, stress ECG, stress echocardiography or coronary angiography
  – Pulmonary function: spirometry and diffusion capacity, exercise tests (in particular, peak oxygen consumption)

• Post-radiotherapy lung function cannot be readily predicted
ERS/ESTS TASK FORCE

ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy)

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

History
Physical examination
Baseline ECG
Calculate RCRI

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

FEV1

Either one < 80%

Exercise testing
Peak VO2

< 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 ppo-FEV1
ppo-DL,CO

Both > 30%

Lobectomy or pneumonectomy are usually not recommended. Consider other options

Resection up to calculated extent

Resection up to pneumonectomy
• Number of preop functioning/obstructed segments should be taken into account when calculating post op predicted values.

  – T = 19 - number of obstructed segments (estimated by image techniques and/or bronchoscopy)
  – R = T - number of functioning segments to be resected
  – Pred post op values = (pre-operative value/T) x R
• In an obstructed right lower lobe with right pneumonectomy planned
• \( T = 19 - 5 = 14 \)
• \( R = 14 - 5 = 9 \)
• Post op pred = preop x 9/14
• Comorbidities are of paramount importance
The potential risk of toxicity/morbidity/mortality should be balanced with the potential benefit of any aggressive curative-intent treatment strategy
• For curative-intent management, patients should be able to undergo platinum-based chemotherapy (preferably cisplatin)
• Cisplatin can be easily administered to the majority of patients excluding only those few with significant renal failure or heart failure
Group 1: Infiltrative disease
• Goal in treating the patient with stage III lung cancer seems simple:
  – to eradicate both visible, intrathoracic disease and
  – to reduce the incidence of subsequent systemic, extrathoracic metastases.
• Local control can be achieved through radiotherapy

• Systemic chemotherapy is used for two reasons:
  – As a radiosensitizing agent and
  – as a cytotoxic agent, the aim is to eradicate unsuspected or prevent de novo development of systemic metastasis
• Concurrent vs sequential?
• Induction vs consolidative vs none?
• Optimal dose, duration?
## Concurrent vs sequential

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Number of patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auperin (2010)</td>
<td>1,205</td>
<td>significant benefit of concomitantly radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; P = .004)</td>
</tr>
<tr>
<td>O’Rourke (2010)</td>
<td>1,024</td>
<td>A significant benefit of concurrent treatment was shown in overall survival (HR 0.74, 95% CI 0.62 to 0.89;</td>
</tr>
<tr>
<td>Curran (2011)</td>
<td>610</td>
<td>Five-year survival: significantly higher for patients treated with the concurrent regimen vs sequential treatment (5-year survival: sequential: 10%; concurrent, 16% [31 patients], P = .046)</td>
</tr>
</tbody>
</table>

J Clin Oncol 2010;28:2181-2190  
Cochrane Database Syst Rev 2010:CD002140  
J Natl Cancer Inst 2011;103:1452-1460
### Analysis 2.1. Comparison 2 Concurrent vs Sequential chemoradiotherapy, Outcome 1 Overall survival.

Review: Concurrent chemoradiotherapy in non-small cell lung cancer

Comparison: 2. Concurrent vs Sequential chemoradiotherapy

Outcome: 1. Overall survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Concurrent chemoRT</th>
<th>Sequential chemoRT</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV</th>
<th>Random,95% CI</th>
<th>Weight</th>
<th>Hazard Ratio IV</th>
<th>Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curran 2003</td>
<td>200</td>
<td>199</td>
<td>-0.24 (0.11)</td>
<td></td>
<td>73.8 %</td>
<td>0.79 [0.63, 0.98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourmel 2001</td>
<td>100</td>
<td>101</td>
<td>-0.4 (0.34)</td>
<td></td>
<td>7.7 %</td>
<td>0.67 [0.34, 1.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zatloukal 2003</td>
<td>52</td>
<td>50</td>
<td>-0.49 (0.22)</td>
<td></td>
<td>18.5 %</td>
<td>0.61 [0.40, 0.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>352</strong></td>
<td><strong>350</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.74 [0.62, 0.89]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.0; Chi² = 1.13, df = 2 (P = 0.57); I² = 0.0%

Test for overall effect: Z = 3.16 (P = 0.0016)

Test for subgroup differences: Not applicable

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Cochrane Database Syst Rev 2010:CD002140
**Arm 1:**
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
 cisplatin 100 mg/m² IV over 30-60 minutes, days 1 & 29

(starting day 50)
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

**Arm 2:**
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
 cisplatin 100 mg/m² IV over 30-60 minutes, days 1 & 29
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

**Arm 3:**
oral etoposide 50 mg twice daily x 10 only on RT treatment days 1-5, 8-12, 29-33 and 36-40 (75 mg/day if body surface area < 1.7 m²)
cisplatin 50 mg/m² IV over 30-60 minutes on days 1 and 8 and 29 and 36
69.6 Gy/6 wks/58 x 1.2 Gy twice-daily fractions (at least 6 hours apart)
<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Arm 1 (n = 195)</th>
<th>Arm 2 (n = 195)</th>
<th>Arm 3 (n = 187)</th>
<th>Total (n = 577)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 y</td>
<td>82 (42)</td>
<td>90 (46)</td>
<td>72 (39)</td>
<td>244 (42)</td>
</tr>
<tr>
<td>≥60 y</td>
<td>113 (58)</td>
<td>105 (54)</td>
<td>115 (62)</td>
<td>333 (58)</td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
<td>60</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>122 (63)</td>
<td>125 (64)</td>
<td>124 (66)</td>
<td>371 (64)</td>
</tr>
<tr>
<td>Women</td>
<td>73 (37)</td>
<td>70 (36)</td>
<td>63 (34)</td>
<td>206 (36)</td>
</tr>
<tr>
<td>KPS, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–80</td>
<td>45 (23)</td>
<td>47 (24)</td>
<td>45 (24)</td>
<td>137 (24)</td>
</tr>
<tr>
<td>90–100</td>
<td>150 (77)</td>
<td>148 (76)</td>
<td>142 (76)</td>
<td>440 (76)</td>
</tr>
<tr>
<td>Histology, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>75 (38)</td>
<td>75 (38)</td>
<td>70 (37)</td>
<td>220 (38)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>53 (27)</td>
<td>73 (37)</td>
<td>52 (28)</td>
<td>178 (31)</td>
</tr>
<tr>
<td>Large Cell</td>
<td>29 (15)</td>
<td>27 (14)</td>
<td>23 (12)</td>
<td>79 (14)</td>
</tr>
<tr>
<td>Combined</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>8 (4)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Carcinoma NOS</td>
<td>34 (17)</td>
<td>18 (9)</td>
<td>30 (16)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>AJCC stage, No. (%)</td>
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<td>3 (2)</td>
<td>4 (2)</td>
<td>11 (2)</td>
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<td>81 (42)</td>
<td>84 (43)</td>
<td>75 (40)</td>
<td>240 (42)</td>
</tr>
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<td>IIIB</td>
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<td>108 (55)</td>
<td>108 (58)</td>
<td>326 (57)</td>
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<td>Race, No. (%)</td>
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<td>161 (86)</td>
<td>499 (86)</td>
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<td>2 (1)</td>
<td>2 (1)</td>
<td>7 (1)</td>
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<td>17 (9)</td>
<td>56 (10)</td>
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<td>1 (&lt;1)</td>
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<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>3 (1)</td>
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Figure 3. Five-year survival results for patients assigned to receive standard radiation with concurrent chemotherapy compared with patients assigned to receive sequential chemotherapy and radiotherapy. Hazard ratio for death = 0.812, 95% confidence interval = 0.663 to 0.996, \( P = .046 \), two-sided log-rank test. Total dead at any time: Arm 1 = 189 and Arm 2 = 185. Slash marks indicate censored observations.
• But all of the above mentioned trials have also found increased toxicity with concurrent treatment.
Analysis 2.6.  Comparison 2 Concurrent vs Sequential chemoradiotherapy, Outcome 6 Toxicity.


Comparison: 2 Concurrent vs Sequential chemoradiotherapy

Outcome: 6 Toxicity

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Concurrent</th>
<th>Sequential</th>
<th>Risk Ratio M-H,Random,95% CI</th>
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<tr>
<td>Curran 2003</td>
<td>6/201</td>
<td>4/201</td>
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<td>41.6%</td>
<td>1.50 [ 0.43, 5.24 ]</td>
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<tr>
<td>Fournel 2001</td>
<td>10/93</td>
<td>3/100</td>
<td></td>
<td>41.0%</td>
<td>3.58 [ 1.02, 12.62 ]</td>
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<tr>
<td>Reinfuss 2005</td>
<td>2/84</td>
<td>2/89</td>
<td></td>
<td>17.3%</td>
<td>1.06 [ 0.15, 7.35 ]</td>
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<tr>
<td>Wu 2006</td>
<td>0/40</td>
<td>0/40</td>
<td></td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Zatloukal 2003</td>
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<td>0/50</td>
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<td>Not estimable</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>470</strong></td>
<td><strong>480</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.02 [ 0.90, 4.52 ]</strong></td>
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Total events: 18 (Concurrent), 9 (Sequential)

Heterogeneity: Tau² = 0.0; Chi² = 1.45, df = 2 (P = 0.48); I² =0.0%

Test for overall effect: Z = 1.71 (P = 0.088)
2 Acute pneumonitis

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<th>Study</th>
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<th>Event Rate</th>
<th>Control Rate</th>
<th>Event Rate 95% CI</th>
<th>Control Rate 95% CI</th>
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<td>8/201</td>
<td>14/201</td>
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<td>0.57 [0.25, 1.33]</td>
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<tr>
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<td>2/89</td>
<td>12.5%</td>
<td>2.65 [0.53, 13.28]</td>
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<td>30.2%</td>
<td>1.63 [0.76, 3.49]</td>
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<tr>
<td>Zatloukal 2003</td>
<td>2/51</td>
<td>1/48</td>
<td>6.7%</td>
<td>1.88 [0.18, 20.09]</td>
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<td></td>
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Subtotal (95% CI) 469/478 100.0% 0.99 [0.51, 1.91]

Total events: 33 (Concurrent), 36 (Sequential)
Heterogeneity: $\tau^2 = 0.22; \text{Chi}^2 = 6.81, df = 4 (P = 0.15); I^2 = 41\%$
Test for overall effect: $Z = 0.02 (P = 0.98)$

3 Acute oesophagitis

<table>
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<tr>
<th>Study</th>
<th>Events</th>
<th>Controls</th>
<th>Event Rate</th>
<th>Control Rate</th>
<th>Event Rate 95% CI</th>
<th>Control Rate 95% CI</th>
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</thead>
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<tr>
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<td>50/201</td>
<td>8/201</td>
<td>27.3%</td>
<td>6.25 [3.04, 12.84]</td>
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<tr>
<td>Fourmell 2001</td>
<td>30/93</td>
<td>3/100</td>
<td>20.7%</td>
<td>10.75 [3.40, 34.05]</td>
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<tr>
<td>Reinfuss 2005</td>
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<td>0/89</td>
<td>6.8%</td>
<td>15.88 [0.92, 273.84]</td>
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<tr>
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<td>10/40</td>
<td>28.8%</td>
<td>1.90 [1.01, 3.65]</td>
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<tr>
<td>Zatloukal 2003</td>
<td>9/51</td>
<td>2/48</td>
<td>16.4%</td>
<td>4.24 [0.96, 18.62]</td>
<td></td>
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</table>

Subtotal (95% CI) 469/478 100.0% 4.96 [2.17, 11.37]

Total events: 115 (Concurrent), 23 (Sequential)
Heterogeneity: $\tau^2 = 0.52; \text{Chi}^2 = 11.81, df = 4 (P = 0.02); I^2 = 66\%$
### Neutropenia

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<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Curran 2003</td>
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<td>113/201</td>
<td>29.6%</td>
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<td>31.0%</td>
<td>0.88 [ 0.77, 1.00 ]</td>
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<tr>
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<td>1/89</td>
<td>1.5%</td>
<td>4.24 [ 0.48, 37.15 ]</td>
</tr>
<tr>
<td>Wu 2006</td>
<td>26/40</td>
<td>17/40</td>
<td>18.5%</td>
<td>1.53 [ 1.00, 2.34 ]</td>
</tr>
<tr>
<td>Zatloukal 2003</td>
<td>33/51</td>
<td>19/48</td>
<td>19.4%</td>
<td>1.63 [ 1.09, 2.45 ]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)** 469 478 100.0% 1.18 [ 0.90, 1.55 ]

Total events: 252 (Concurrent), 238 (Sequential)

Heterogeneity: Tau² = 0.06; Chi² = 17.59, df = 4 (P = 0.001); I² = 77%

Test for overall effect: Z = 1.19 (P = 0.23)

### Anaemia

<table>
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<tr>
<th>Study or subgroup</th>
<th>Concurrent</th>
<th>Sequential</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Fourmel 2001</td>
<td>19/93</td>
<td>28/100</td>
<td>71.6%</td>
<td>0.73 [ 0.44, 1.21 ]</td>
</tr>
<tr>
<td>Zatloukal 2003</td>
<td>6/51</td>
<td>3/48</td>
<td>28.4%</td>
<td>1.88 [ 0.50, 7.11 ]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)** 144 148 100.0% 0.95 [ 0.41, 2.21 ]

Total events: 25 (Concurrent), 31 (Sequential)

Heterogeneity: Tau² = 0.19; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%

Test for overall effect: Z = 0.11 (P = 0.91)
Guidelines

unresectable IIIA (N2) disease and IIIB disease patients

National Comprehensive Cancer Network®

Non-Small Cell Lung Cancer

PRINCIPLES OF RADIATION THERAPY (2 of 10)

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II (node positive) and stage III is concurrent chemotherapy/RT.\(^{16-18}\)
- Sequential chemotherapy/RT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.\(^{19,20}\)
- Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).\(^{21,22}\)

- RT has a role before or after surgery.
- Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)\(^{23}\) and is recommended for resectable superior sulcus tumors.\(^{24,25}\)
- Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.\(^{26,27}\)
- The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.\(^{28,29}\)
- The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Up front multidisciplinary consultation is particularly important when considering surgical treatment of stage III NSCLC.

- In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.\(^{30,31}\)
- Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients\(^{32-34}\) and is
Induction vs consolidation chemotherapy

treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A).

Remark: We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question.

Remark: We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question.
• GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a setup margin for positioning and mechanical variability
• Commonly used dose for conventionally fractionated RT with or without chemotherapy is 60-70 Gy with a fraction size of 2 Gy over 6-7 weeks

• Dose escalation in RT alone, sequential chemoRT, or concurrent chemoRT is associated with better survival in non-randomized comparisons

• Improved survival was demonstrated with accelerated fractionation RT regimens
• In PET-CT staged patients omitting elective nodal irradiation has been shown to improve survival, probably because of escalated dose.
Chemotherapy vs no chemotherapy

• Objective:
  – To evaluate the effect of cytotoxic chemotherapy on survival in patients with non-small cell lung cancer

• Selection criteria:
  – Trials comparing primary treatments of surgery, surgery + radiotherapy, radical radiotherapy or supportive care versus the same primary treatment, plus chemotherapy were eligible

• Results:
  – Data from 52 trials and 9387 patients were included. The results for modern regimens containing cisplatin favoured chemotherapy in all comparisons and reached conventional levels of significance when used with radical radiotherapy and with supportive care.

• Plain language summary
  – Chemotherapy can improve survival rates for non-small cell lung cancer

Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD002139
What agent?

A

B

Survival (%)

Time to Progression (%)

0 10 20 30 40

0 5 10 15 20 25 30

Cisplatin and paclitaxel
Cisplatin and gemcitabine
Cisplatin and docetaxel
Carboplatin and paclitaxel

paclitaxel, 225 mg/m² over 3-hr period on day 1
carboplatin, AUC 6.0 mg/ml/min on day 1
3-wk cycle

All patients (N = 1,722)
Age < 65 years (n = 1,116)
Age ≥ 65 years (n = 606)
Female (n = 514)
Male (n = 1,208)
White (n = 1,346)
East/Southeast Asian (n = 220)
Other origin (n = 156)
Ever-smoker (n = 1,265)
Never-smoker (n = 250)
ECOG PS 0 (n = 612)
ECOG PS 1 (n = 1,110)
Histologic diagnosis (n = 1,145)
Cytologic diagnosis (n = 577)
Stage IIIB (n = 414)
Stage IV (n = 1,308)
Adenocarcinoma (n = 846)
Large-cell carcinoma (n = 153)
Squamous cell carcinoma (n = 473)
Other histologic diagnosis (n = 250)
A systematic review of first-line treatment in NSCLC with local cell lung cancer

Gerlinde Pilking, Rumona Dickson

Results
NSCLC population with squamous disease
In the squamous disease population, vinorelbine (oral or intravenous) doublets were shown not to be cost effective in either price scenario due to relatively poor outcomes. Paclitaxel, gemcitabine and docetaxel all lie on the efficiency frontier, but ICERs comparing interventions with better outcomes to paclitaxel exceed levels considered to be cost effective in the UK. The choice of platinum compound changes from cisplatin (base case) to carboplatin when contract drug prices are used, indicating that when drug costs are reduced, the location (and therefore cost) of administration influences cost-effectiveness estimates.

NSCLC population with non-squamous disease
In the non-squamous population, pemetrexed+cisplatin was shown to be a valid comparator to standard treatments and provides strong evidence of improved OS. However, its much higher price leads to non-competitive cost-effectiveness results.
**Chemotherapy combination**

**Recommendation 5.2:** Most comparative studies of concurrent chemoradiotherapy versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine). There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered perioperatively, cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].

Radiotherapy alone may be used for patients ineligible for combined modality treatment; it may offer better tolerability, but poorer survival.

Postoperative radiotherapy may be recommended for patients with complete resection of N2 disease to improve local control, but should be delivered sequentially after adjuvant chemotherapy.
Number of cycles

• In the stage III disease chemoradiotherapy strategy, two to four cycles of concomitant chemotherapy should be delivered.
• There is no evidence for further induction or consolidation chemotherapy.
• In the perioperative setting, three to four cycles of cisplatin-based chemotherapy are recommended.
• Aim for a total cumulative dose of at least 300 mg/m² of cisplatin in the adjuvant setting.
Summary for group 1

IMAGING: CT-SCAN

INVASIVE LN RESULT

CATEGORY OF N2

THERAPEUTIC APPROACH

Extensive mediastinal N2 infiltration → Not required → Unresectable N2 → Non-surgical multimodality treatment
Group 2: Occult N2 Involvement Despite Thorough Preoperative Staging

- Occult N2
- Incidental N2
- Unforeseen N2
- Unexpected N2
- Unsuspected N2

- must differentiate from
  - Ignored N2 (enlarged or PET scan positive but no biopsy specimen)
  - underappreciated N2 (known high risk of false negative CT or PET findings but no biopsy specimen)
• True unsuspected N2
  – found intra op or post operatively
  – occurs in about 10% of surgical patients (5%-16%)
• If N2 nodal involvement is found at the time of surgical resection and all the involved lymph nodes and the primary tumor are technically resectable, then the surgeon should proceed with the planned lung resection along with a mediastinal lymphadenectomy.

• If a complete resection is not possible, the planned lung resection should be aborted because the average 5-year survival is < 5%.
Intraoperative handling of the mediastinum

- complete mediastinal lymph node dissection (MLND)
- systematic node sampling or
- selective sampling
• A formal MLND involves removal of all the node bearing tissues, leaving only the skeletonized trachea, phrenic nerves, aorta, and superior vena cava.

• A systematic mediastinal node sampling means that the pleura overlying each ipsilateral node station is opened and explored and representative biopsy specimens of nodes obtained.

• A selective sampling involves biopsy of only selected mediastinal nodes that are believed to be abnormal.
Existing guidelines consistently recommend either systematic lymph node sampling or complete MLND
NSCLC adjuvant studies that included patients with stage III disease

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<th>% stage III</th>
<th>Chemo-therapy</th>
<th>RT (both arms)</th>
<th>Survival</th>
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<th></th>
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**Randomized trials**

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</tr>
<tr>
<td>Holmes</td>
<td>1993</td>
<td>130</td>
<td>-</td>
<td>CAP</td>
<td>RT</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>(29)</td>
<td>(18)</td>
</tr>
<tr>
<td>Pisters</td>
<td>1994</td>
<td>72</td>
<td>-</td>
<td>PVd</td>
<td>RT</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>17</td>
<td>30</td>
</tr>
</tbody>
</table>

**Average**

<table>
<thead>
<tr>
<th></th>
<th>MST (mo)</th>
<th>2 yr (%)</th>
<th>5 yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj</td>
<td>Control</td>
<td>Adj</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>30</td>
<td>54</td>
</tr>
</tbody>
</table>

**Meta-analyses**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Stage</th>
<th>RT (both arms)</th>
<th>Overall 5 year survival benefit of 5.0%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>1995</td>
<td>1,394</td>
<td>I-III</td>
<td>P-based</td>
<td>Overall 5 year survival benefit of 5.0%</td>
<td>0.08</td>
</tr>
<tr>
<td>LACE</td>
<td>2008</td>
<td>4,584</td>
<td>27</td>
<td>P-based</td>
<td>Overall 5 year survival benefit of 5.4%</td>
<td>0.005</td>
</tr>
</tbody>
</table>
• greatest effect were observed in stage III compared with stage II and stage I NSCLC

• No RCTs have addressed which chemotherapy regimen is optimal, how many cycles should be given, or when this should start

• It is suggested that adjuvant chemotherapy involving cisplatin-based doublets for three to four cycles started within 12 weeks of surgery should be given
• In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.

• Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy.

• PORT with concurrent chemotherapy can be administered safely in medically fit patients and is recommended for positive resection margins.
Summary for group 2

IMAGING: CT-SCAN
-No enlarged LNs and peripheral tumour

INVASIVE LN RESULT
-Not required if negative LNs on PET

CATEGORY OF N2
-Surgery: unforeseen N2

THERAPEUTIC APPROACH
-Adjuvant chemotherapy (radiotherapy)
Group 3: Potentially resectable IIIA(N2) disease

- Discrete N2 involvement
- must undergo a careful staging evaluation
Fig. 3. Progression-free survival rates estimated from time of random- zization using Kaplan-Meier analyses. P value (two-sided) was calculated using the log-rank test. O = number of deaths; N = number of patients. Hazard ratio = 1.06, 95% confidence interval = 0.85 to 1.33; P = .605.

Fig. 1. The different populations included in the study analysis: registered (n = 582), eligible (n = 579), and randomly assigned (n = 332). Patients were allocated and actually treated as per protocol with either surgery or radiotherapy.
Abstract

**Background**—Concurrent chemotherapy plus radiation therapy (chemoRT) is the standard treatment for stage IIIA(N2) non-small cell lung cancer (NSCLC), a common disease entity. Phase II studies demonstrated feasibility of resection after chemoRT with encouraging survival rates. This phase III trial compared both approaches.

**Methods**—Patients with stage T1-3pN2M0 NSCLC were randomized before induction chemoRT (2 cycles of cisplatin and etoposide [PE] concurrent with 45 Gy RT). If no progression, arm 1 underwent resection, and arm 2 continued RT uninterrupted to 61 Gy. Two additional cycles of PE were given. The primary endpoint was overall survival (OS).

**Findings**—Progression-free survival for 396 eligible patients was superior in arm 1: median 12.8 versus 10.5 months, \( p=0.017 \), hazard ratio (HR) 0.77 (0.62,0.96); 5-yr 22.4% versus 11.1%. Median OS was 23.6 versus 22.2 months, \( p=0.24 \), HR 0.87 (0.70,1.10). Five-year survivals were arm 1, 27.2% and arm 2, 20.3%; odds ratio 0.63 (0.36,1.10, \( p=0.10 \)). N0 status at thoracotomy predicted median OS of 33.5 months (5-year, 41.8%). Major chemoRT toxicities were neutropenia and esophagitis. Treatment-related death occurred in 16 (7.9%) patients on arm 1, of which 14 were post-pneumonectomy; and in 4 (2.1%) on arm 2. An exploratory analysis showed improved OS for patients who underwent lobectomy versus a matched cohort on chemoRT alone, but not for those undergoing pneumonectomy (matched similarly).

**Interpretation**—There was no significant survival advantage to surgery after chemoRT, despite improved PFS. Both chemoRT with definitive RT and chemoRT followed by resection (preferably lobectomy) are options for patients with stage IIIA(N2) NSCLC.
A questionnaire was submitted to the NCCN Member Institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

a) Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
b) Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%)
c) Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%)
d) Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
e) Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%)
• In potentially resectable superior sulcus tumors, concurrent chemoradiotherapy induction followed by definitive surgery is the treatment of choice.

• The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres.

• In both situations, surgery should be carried out within 4 weeks after the end of radiotherapy.
• Possible strategies include several options:
  – induction chemotherapy followed by surgery,
  – Induction chemoradiotherapy followed by surgery
  – concurrent definitive chemoradiotherapy.
Guidelines

potentially resectable IIIA(N2) disease

preoperative diagnosis of IIIA(N2)

3.5.3. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended (except as part of a clinical trial) (Grade 1C).

given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].
Summary for group 3

**IMAGING:**
CT-SCAN

**INVASIVE LN RESULT**
- N0–N1
- N2
- N3

**CATEGORY OF N2**
- Potentially resectable N2

**THERAPEUTIC APPROACH**
- Dedicated multidisciplinary assessment
  - Surgical multimodality treatment
  - Non-surgical multimodality treatment
Prophylactic cranial irradiation

• May reduce incidence of brain metastasis but none of the studies have found a survival benefit
• One of the study has shown some benefit is squamous histology
• Further studies are warranted
• No role of PCI in NSCLC
Targeted therapy

<table>
<thead>
<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
</tr>
</thead>
</table>
| **BRAF V600E mutation** *             | vemurafenib\(^1,2\)  
dabrafenib\(^2,3\)  
dabrafenib + trametinib\(^4\) |
| High level MET amplification or MET exon 14 skipping mutation | crizotinib\(^5,6,7,8\) |
| RET rearrangements                    | cabozantinib\(^9,10\) |
| ROS1 rearrangements                   | crizotinib\(^11\) |
| HER2 mutations                        | trastuzumab\(^12\) (category 2B)  
afatinib\(^13\) (category 2B) |

*Non-V600E mutations have variable kinase activity and response to these agents.*
Targeted therapy in early stage NSCLC

- EGFR MUTATION-POSITIVE NSCLC
- Two trials: RADIANT and SELECT
Targeted therapy in early stage NSCLC

- SELECT
- phase II, single arm trial
- included patients with stage I to IIIA surgically resected
- standard-of-care, followed by adjuvant erlotinib at 150 mg per day.
- n = 100
- 24 patients recurred, but only 2 of them during erlotinib treatment and the rest 22 after stop of erlotinib treatment, in time of 1 to 2 years.

journal of the American Society of Clinical Oncology. 2014; 32 (suppl; abstr 7514)
Targeted therapy in early stage NSCLC

- The RADIANT study was a randomized study of 2 years of adjuvant erlotinib vs. placebo that enrolled a broader population of lung cancer patients among which 16% harbored EGFR mutations.

- Though the overall study was negative, the subgroup analysis of EGFR mutants suggested that erlotinib provided a disease-free survival advantage with HR = 0.61 (95% CI 0.38, 0.98) but no OS advantage in this preliminary study.

official journal of the American Society of Clinical Oncology. 2014; 32 (suppl; abstr 7501)
Targeted therapy in early stage NSCLC

Overall survival was longer in both the studies in nivolumab arm
Subgroup analysis for III B is not available

Disease stage | Squamous | Non Squamous
---|---|---
III B | 29 (21%) | 20 (7%)
IV | 105 (78%) | 272 (93%)

Targeted therapy in early stage NSCLC

- Targeted therapy are yet to find a mention in guidelines for stage III NSCLC
Take home slide

**IMAGING: CT-SCAN**
- No enlarged LNs and peripheral tumour
- No enlarged N2 nodes but central tumour or hilar LNs
- Enlarged discrete N2 LNs
- Extensive mediastinal N2 infiltration

**INVASIVE LN RESULT**
- Not required if negative LNs on PET
- N0–N1
- N2
- N3
- Not required

**CATEGORY OF N2**
- Surgery: unforeseen N2
- Potentially resectable N2
- Unresectable N2

**THERAPEUTIC APPROACH**
- Adjuvant chemotherapy (radiotherapy)
- Dedicated multidisciplinary assessment
- Surgical multimodality treatment
- Non-surgical multimodality treatment