Optimal treatment of potentially resectable stage IIIA/N2 disease

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Conflicts of Interest disclosure

• **Advisor to company**: AstraZeneca, Novartis, Chugai, Boehringer-Ingeleheim, Pfizer, Roche, Synta, Clovis, MSD

• **Lecture fees**: AstraZeneca, Chugai, Boehringer-Ingeleheim, Pfizer, Taiho, Eli-Lilly, Daiichi-Sankyo

• **Research expenses**: AstraZeneca, Chugai, Boehringer-Ingeleheim, Pfizer, Taiho, Ono, Daiichi-Sankyo, Eli-Lilly
2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt¹, D. De Ruysscher², W. Weder³, C. Le Péchoux⁴, P. De Leyn⁵, H. Hoffmann⁶, V. Westeel⁷, R. Stahel⁸, E. Felip⁹, S. Peters¹⁰ & Panel Members†

incidental IIIA(N2) (unforeseen N2)  potentially resectable IIIA(N2) disease  unresetable IIIA (N2) disease and IIIB disease patients
Exploratory analyses of survival for pN1 and pN2 according to the number of metastatic nodal stations (single versus multiple, skip metastasis versus non-skip metastasis) for R0.

The IASLC Lung Cancer Staging Project, Asamura et al., JTO 2015
State of the art: Chemoradiation for cN2

- **WJTOG0105** (MVP+RT/CBDCA+PTX+RT/CDDP+CPT+RT) Yamamoto et al., JCO, 2010
  - MST: 19.8-22mo, 5YSR: ca20%

- **OLCSG0007** (MVP+RT/CDDP+DTX+RT) Segawa et al., JCO, 2010
  - MST: 23.7-26.8mo, 5YSR: ca20%
  - Local recurrence: 37.6-38.4%

- **RTOG 0617** (CBDCA+PTX+74/60Gy, ± Cetuximab) Bradley et al., Lancet Oncol, 2015
  - MST: 60Gy group 28.7mo, 74Gy group 19.5mo
  - Local rec: 60Gy group 25%, 74Gy group 34%
  - No benefit in 74Gy group
  - No benefit of addition of Cetuximab

- **PROCLAIM** (CDDP+PEM+RT vs.CSSP+ ETP +RT) Senan et al., ASCO, 2015
  - MST: ETP 25.0mo, PEM 26.8mo
  - No benefit of CDDP+PEM

Courtesy of Dr. Horinouchi
7506: Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC) – Senan S et al ASCO 2015

HR (95%CI) 0.98 (0.79, 1.20)
Log-rank p=0.831

Median OS (95%CI), months
Pemetrexed + cisplatin: 26.8 (20.4, 30.9)
Etoposide + cisplatin: 25.0 (22.2, 29.8)
what are the optimal multi-modality combinations for the different stage III disease sub-stages?

incidental IIIA(N2) (unforeseen N2)

Recommendation 4.1: If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant chemotherapy [I, A]. In case of complete resection, addition of post-operative radiotherapy is not routinely recommended, but may be an option following individual risk assessment [V, C].

potentially resectable IIIA(N2) disease

preoperative diagnosis of IIIA(N2)

Recommendation 4.2.1: Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].

unresectable IIIA (N2) disease and IIIB disease patients

Recommendation 4.3: Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible—for any reason—sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A].

Pictures are from ACCP guideline for non-invasive mediastinal staging, 2007
T1-2, T3 (other than invasive), N2 nodes positive:

- Brain MRI
- PET/CT scan, if not previously done

Positive

• Brain MRI

Negative for M1 disease

• Definitive concurrent chemoradiation\(^{k,p}\) (category 1)
• Induction chemotherapy\(^{n}\) ± RT\(^{k}\)

No apparent progression

Surgery\(^{j}\) ± chemotherapy\(^{n}\) (category 2B)
± RT\(^{k}\) (if not given)

Local

RT\(^{k}\) (if not given) ± chemotherapy\(^{n}\)

Systemic

See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-15)
Role of surgery?
Radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC: a phase III randomized controlled trial (INT0139)
Albain et al., Lancet 2009

Progression free survival
HR 0.77 (95% CI 0.62-0.96): p=0.017

Overall survival (primary endpoint)
HR 0.87 (95% CI 0.70-1.10): p=0.24
Radiotherapy plus chemotherapy with or without surgical resection for stage III NSCLC: a phase III randomized controlled trial (INT0139)  
Albain et al., Lancet 2009
Phase III study of surgery vs. definitive concurrent chemoradiotherapy boost in patients with operable (stage IIIA(N2)/selected IIIb (sel IIIB) NSCLC following induction chemotherapy and concurrent CRTx (ESPATUE).
Eberhardt et al., Abstr 7510 et al. ASCO 2014
Phase III study of surgery vs. definitive concurrent chemoradiotherapy boost in patients with operable (stage IIIA(N2)/selected IIIb (sel IIIB) NSCLC following induction chemotherapy and concurrent CRTx (ESPATUE).
Eberhardt et al., Abstr 7510 et al. ASCO 2014

Conclusions

- Long-term OS at 5 y in rand OP+ pts was excellent with both Tx.
- These high-volume center data confirm earlier trials: Both options are acceptable and should be discussed with individual pts.
- In the ITT population 87.8% were treated with a definitive approach. 5-y-OS of 34.1% in all 246 initially recruited patients are amongst the best published data, so far.
Role of surgery?
Randomized controlled trial of resection vs. radiotherapy after induction chemotherapy in stage IIA-N2 NSCLC van Meerbeeck et al., J Natl Cancer Inst, 2007

Eligible patients
- cytologic or histologic proof of unresectable stage IIIA-N2

Guidelines for unresectability
- any N2 involvement by a non-sq
- in case of sq ca, any N2 nodal involvement exceeding level 4R for a right-sided tumor and level 5 and 6 for a left-sided tumor.
Randomized controlled trial of resection vs. radiotherapy after induction chemotherapy in stage IIA-N2 NSCLC

van Meerbeeck et al., J Natl Cancer Inst, 2007

Overall survival

Table 5. Exploratory analyses in 154 patients in the resection surgery arm

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median OS, months (95% CI)</th>
<th>5-year OS, %</th>
<th>P, Univariate analysis</th>
<th>P, Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bi-)lobectomy</td>
<td>68</td>
<td>25.4 (17.7 to 48.9)</td>
<td>27</td>
<td>.009</td>
<td>.03</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>72</td>
<td>13.4 (11.1 to 19.5)</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>Mediastinal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ypN0-1</td>
<td>64</td>
<td>22.7 (17.6 to 42.7)</td>
<td>29</td>
<td>&lt;.001</td>
<td>.04</td>
</tr>
<tr>
<td>ypN2</td>
<td>86</td>
<td>14.9 (11.2 to 18.5)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>77</td>
<td>24.1 (16.7 to 42.4)</td>
<td>27</td>
<td>&lt;.001</td>
<td>.01</td>
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<tr>
<td>Incomplete</td>
<td>76</td>
<td>12.1 (9.5 to 17.1)</td>
<td>7</td>
<td></td>
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<tr>
<td>No PORT</td>
<td>92</td>
<td>14.1 (11.2 to 19.9)</td>
<td>19</td>
<td>.6</td>
<td>.004</td>
</tr>
<tr>
<td>PORT</td>
<td>62</td>
<td>18.0 (15.0 to 25.9)</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OS = overall survival; PORT = postoperative radiotherapy; CI = confidence interval; ypN = pathologic N after induction therapy. P values were calculated using a two-sided logrank test.

Only 57% of the patients were randomized due to PD, toxicity
Role of surgery?
Surgery for NSCLC stages T1-3N2M0 having preoperative pathologically verified N2 involvement: A prospective randomized multinational phase III trial by Nordic Thoracic Oncology Group Sorensen, JB, et al., ASCO 2013 abstr 7504
Surgery for NSCLC stages T1-3N2M0 having preoperative pathologically verified N2 involvement: A prospective randomized multinational phase III trial by Nordic Thoracic Oncology Group Sorensen, JB, et al., ASCO 2013 abstr 7504

Conclusions: Formally negative but surgery may be beneficial for T1N2 or in Adnocarcinoma
Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials

P J McElnay, A Choong, E Jordan, F Song, E Lim

Thorax 2015

Bi-modality trials

Tri-modality trials

<-Favors surgery

Favors radiotherapy->
Trimodality vs Bimodality
Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer


- Resectable stage IIIA/IIIB NSCLC
- PS 0–1
- Age < 70
- N = 558

R 1:1

N = 279

N = 264

N = 279

N = 260

N = 142

N = 264

N = 154

N = 260

N = 49

N = 187

<table>
<thead>
<tr>
<th>EORTC 08943* (stage IIIA: N2)</th>
<th>INT 0239** (stage IIIA: N2)</th>
<th>GLC33 (stage IIIA or IIIB)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT response, randomisation, surgery vs RT</td>
<td>Randomisation, CT/RT vs CT/RT, surgery, CT</td>
<td>Randomisation, CT, CT/RT, surgery</td>
<td>Randomisation, CT, CT/RT, surgery, CT</td>
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<tr>
<td>Patients initially eligible n</td>
<td>579</td>
<td>396</td>
<td>264</td>
</tr>
<tr>
<td>Patients initially allocated to surgery, n</td>
<td>262</td>
<td>264</td>
<td>260</td>
</tr>
<tr>
<td>Patients allocated to surgery after induction, n</td>
<td>177</td>
<td>202</td>
<td>226</td>
</tr>
<tr>
<td>Patients undergoing surgery, n</td>
<td>154</td>
<td>142</td>
<td>154</td>
</tr>
<tr>
<td>Patients with negative resection margins, %</td>
<td>37</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>Patients with complete resection, %</td>
<td>50</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Patients with exploratory thoracotomy, %</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Patients with lobectomy or bilobectomy, %</td>
<td>38</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Patients with pneumonectomy, %</td>
<td>47</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Surgical mortality, %</td>
<td>4</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>After lobectomy or bilobectomy</td>
<td>7</td>
<td>26</td>
<td>140</td>
</tr>
<tr>
<td>After pneumonectomy</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

SAKK 16/00 trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walser Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrapas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bidjelovic, Adrian Ochsenbein, Urs R Meier, Christoph Marnot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

Interpretation Radiotherapy did not add any benefit to induction chemotherapy followed by surgery
A Phase 3 Study of Induction Treatment With Concurrent Chemoradiotherapy vs Chemotherapy Before Surgery in Patients With Pathologically Confirmed N2 Stage IIIA NSCLC (WJTOG9903)
Katakami N, Tada H, Mitsudomi T, et al., Cancer 2012
preoperative chemotherapy

**Pro**
- resectability
- local control
- micromets

**Con**
- delay surgery
- increased morbidity

VS.
A RANDOMIZED TRIAL COMPARING PREOPERATIVE CHEMOTHERAPY PLUS SURGERY WITH SURGERY ALONE IN PATIENTS WITH NON–SMALL-CELL LUNG CANCER

Rafael Rosell, M.D., Ph.D., José Gómez-Codina, M.D., Ph.D., Carlos Camps, M.D., José Maestre, M.D., Ph.D., José Padré, M.D., Antonio Cantó, M.D., José Luis Mate, M.D., Shankong Li, M.D., Jorge Roig, M.D., Ph.D., Ángel Olazábal, M.D., Ph.D., Mercedes Canela, M.D., Ph.D., Aurelio Ariza, M.D., Ph.D., Zdeněk Skácel, M.D., José Morera-Prat, M.D., Ph.D., and Albert Abad, M.D., Ph.D.

Figure 2. Kaplan–Meier Plot of Overall Survival in Patients with Stage IIIA Lung Cancer Treated with Surgery Alone (Dashed Line) or Chemotherapy plus Surgery (Solid Line).
Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data

NSCLC Meta-analysis Collaborative Group*

The Lancet, 2014; 383, 1561 - 1571

Clinical stage (IA, IB, II, III)
9 trials, 2171 patients
Greater treatment effect with higher clinical stage

<table>
<thead>
<tr>
<th></th>
<th>Preoperative chemotherapy*</th>
<th>Control*</th>
<th>O-E</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 1990</td>
<td>8/13</td>
<td>8/13</td>
<td>0.32</td>
<td>3.97</td>
</tr>
<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
</tr>
<tr>
<td>Spain 1994</td>
<td>19/29</td>
<td>27/30</td>
<td>-8.88</td>
<td>9.65</td>
</tr>
<tr>
<td>MIP-91</td>
<td>136/179</td>
<td>146/176</td>
<td>-12.99</td>
<td>70.22</td>
</tr>
<tr>
<td>SWOG 59015</td>
<td>3/5</td>
<td>12/16</td>
<td>-1.04</td>
<td>2.94</td>
</tr>
<tr>
<td>JCOG 9209</td>
<td>28/31</td>
<td>25/31</td>
<td>2.25</td>
<td>12.97</td>
</tr>
<tr>
<td>Finland 2003</td>
<td>19/30</td>
<td>19/22</td>
<td>-0.59</td>
<td>9.48</td>
</tr>
<tr>
<td>MRC BLT</td>
<td>4/5</td>
<td>3/5</td>
<td>1.26</td>
<td>1.60</td>
</tr>
<tr>
<td>MRC LU22</td>
<td>153/258</td>
<td>158/261</td>
<td>-2.92</td>
<td>77.01</td>
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<tr>
<td>SWOG 59000</td>
<td>93/180</td>
<td>103/174</td>
<td>-9.31</td>
<td>48.84</td>
</tr>
<tr>
<td>China 2002</td>
<td>26/32</td>
<td>18/23</td>
<td>1.42</td>
<td>10.78</td>
</tr>
<tr>
<td>China 2005</td>
<td>8/39</td>
<td>14/21</td>
<td>-3.31</td>
<td>5.44</td>
</tr>
<tr>
<td>ChEST</td>
<td>45/129</td>
<td>61/141</td>
<td>-30.27</td>
<td>26.39</td>
</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.31</td>
<td>51.95</td>
</tr>
<tr>
<td>Total</td>
<td>682/1178</td>
<td>745/1207</td>
<td>-50.62</td>
<td>351.78</td>
</tr>
</tbody>
</table>

Overall HR 0.87 (0.78-0.96), p=0.007 (fixed effect)
0.86 (0.75-0.98), p=0.03 (random effect)
Heterogeneity: χ²=18.75, df=14, p=0.18, I²=25%

Greater treatment effect with lower clinical stage 0.96 (0.83-1.12), p=0.64, heterogeneity p=0.22

HR=0.87, p=0.007

27
Discrete mediastinal node involvement

In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA),

3.5.2. either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A).

3.5.3. primary surgical resection followed by adjuvant therapy is not recommended (Grade 1C).
Postoperative adjuvant chemotherapy vs.
HR 0.89 (95% CI, 0.82 to 0.96; P = .005)

5-year absolute benefit of 5.4%
LACE Meta-analysis (OS)

<table>
<thead>
<tr>
<th>PERFORMANCE STATUS</th>
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<tbody>
<tr>
<td>PS = 0</td>
<td>881</td>
<td>1,769</td>
</tr>
<tr>
<td>PS = 1</td>
<td>829</td>
<td>1,533</td>
</tr>
<tr>
<td>PS = 2</td>
<td>108</td>
<td>183</td>
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<table>
<thead>
<tr>
<th>HISTOLOGY</th>
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<tr>
<td>Squamous cell</td>
<td>1,124</td>
<td>2,231</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>971</td>
<td>1,817</td>
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<tr>
<td>Other</td>
<td>140</td>
<td>257</td>
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<table>
<thead>
<tr>
<th>STAGE</th>
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<tbody>
<tr>
<td>Stage IA</td>
<td>104</td>
<td>347</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515</td>
<td>1,371</td>
</tr>
<tr>
<td>Stage II</td>
<td>893</td>
<td>1,616</td>
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<tr>
<td>Stage III</td>
<td>878</td>
<td>1,247</td>
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<table>
<thead>
<tr>
<th>TYPE OF SURGERY</th>
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<tbody>
<tr>
<td>Pneumonecetomy</td>
<td>783</td>
<td>1,346</td>
</tr>
<tr>
<td>Other type of surgery</td>
<td>1,420</td>
<td>2,926</td>
</tr>
</tbody>
</table>

However, how many of these patients were discrete N2 is unknown

Pignon et al., JCO 2008
Adjuvant Cisplatin and Vinorelbine for Completely Resected Non-small Cell Lung Cancer

Subgroup Analysis of the Lung Adjuvant Cisplatin Evaluation

Jean-Yves Douillard, MD, PhD,* Hélène Tribodet, MSc,† Delphine Aubert, MSc,‡
Frances A. Shepherd, MD,§ Rafael Rosell, MD, PhD,‖ Keyue Ding, PhD,¶ Anne-Sophie Veillard, MSc,†
Lesley Seymour, PhD,‖ Thierry Le Chevalier, MD,# Stephen Spiro, MD,** Richard Stephens,‖‖
Jean Pierre Pignon, MD, PhD,† and on behalf of the LACE Collaborative Group

** Absolute benefit in OS:
- At 3-year: 6.8% (±2.3%)
- At 5-year: 8.9% (±2.5%)

- Cisplatin-vinorelbine
- No chemotherapy

Time from randomization (Years)

+1.8%
+11.6%
+14.7%
Preop vs postop chemotherapy

Pros
- improve resectability
- sterile micromets
- in vivo sensitivity test
- better tolerability, dose intensity

Cons
- delay surgery
- increase morbidity?
Conclusions:
The relative hazards of postoperative compared with preoperative chemotherapy was 0.99 (0.81–1.21; p 0.91).
In patients with resectable lung cancer, there was no evidence of a difference OS and DFS between postoperative versus preoperative CTx.
624 patients with stage IA (tumor size 2 cm), IB, II

In early-stage patients, no statistically significant differences in disease-free survival were found with the addition of preoperative or adjuvant chemotherapy to surgery.
Summary...
Peri-operative chemo/radiotherapy for N2 disease

LACE meta-analysis < JT0 metaanalysis ≒ Lancet meta-analysis

≥ Nordic

Conclusion
Something is better than nothing !?
However N2 is very heterogeneous...
Patient subsets between the trials are not same
Clinical practice?
Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

Matthew Koshy, MD,*† Stacey A. Fedewa, MPH,‡ Renu Malik, MD,† Mark K. Ferguson, MD,§¶ Wickii T. Vigneswaran, MD,§ Lawrence Feldman, MD,¶ Andrew Howard, MD,*† Khaled Abdelhady, MD,# Ralph R. Weichselbaum, MD,*† and Katherine S. Virgo, PhD, MBA†**

Journal of Thoracic Oncology® • Volume 8, Number 7, July 2013

TABLE 1. Patient, Facility and Area-Level Characteristics by Treatment Type among Clinical Stage IIIA-N2 Non–Small-Cell Lung Cancer Patients, National Cancer Database (NCDB) 1998–2004

<table>
<thead>
<tr>
<th>Categories</th>
<th>Total</th>
<th>Neoadjuvant Chemoradiotherapy + Lobectomy</th>
<th>Neoadjuvant Chemoradiotherapy + Pneumonectomy</th>
<th>Lobectomy + Adjuvant Therapy</th>
<th>Pneumonectomy + Adjuvant Therapy</th>
<th>Definitive Concurrent Chemoradiotherapy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 11242</td>
<td>n = 564 (4.94)</td>
<td>n = 188 (1.65)</td>
<td>n = 510 (4.46)</td>
<td>n = 123 (1.08)</td>
<td>n = 9857 (86.28)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2. Multivariate Cox Proportional Hazard Models Predicting 5-year Overall Survival among Clinical Stage IIIA-N2 NSCLC Patients, NCDB 1998–2004 (n = 10,058)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive chemoradiation</td>
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<td></td>
</tr>
<tr>
<td>Neoadjuvant chemoradiotherapy + lobectomy</td>
<td>0.51</td>
<td>(0.45–0.58)</td>
</tr>
<tr>
<td>Neoadjuvant chemoradiotherapy + pneumonectomy</td>
<td>0.77</td>
<td>(0.63–0.95)</td>
</tr>
<tr>
<td>Lobectomy + adjuvant therapy</td>
<td>0.66</td>
<td>(0.59–0.75)</td>
</tr>
<tr>
<td>Pneumonectomy + adjuvant therapy</td>
<td>0.69</td>
<td>(0.54–0.88)</td>
</tr>
</tbody>
</table>
Questionnaire survey by JCOG lung cancer surgical group (Sep, 2013)

- **Surgeons**
  - Surgery->CTX
  - CRTx->Surg
  - Surg+other
  - CRTx

  - 29 institutions
  - 10 single N2
  - 3 CRTx
  - 0 Surg+other

- **Medical Oncologist**
  - Surgery->CTX
  - CRTx->Surg
  - Surg+other
  - CRTx

  - 24 institutions
  - 7 single N2
  - 1 CRTx
  - 6 Surg+other

Courtesy of Dr. Horinouchi
Treatment decision in the continuum of N2 disease

incidental
minimal
skip
single
discrete
multiple
bulky
extranodal
unresectable
2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt¹, D. De Ruyscher², W. Weder³, C. Le Péchoux⁴, P. De Leyn⁵, H. Hoffmann⁶, V. Westeel⁷, R. Staehler⁸, E. Felip⁹, S. Peters¹⁰ & Panel Members¹

potentially resectable IIIA(N2) disease
preoperative diagnosis of IIIA(N2)

Recommendation 4.2.1: Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].

3.5.1. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), it is recommended that the treatment plan should be made with the input from a multidisciplinary team (Grade 1C).
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