Thoracoscopic Lobectomy for Stage IIIA Lung Cancer

10th Annual Masters in Minimally Invasive Thoracic Surgery

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Disclosures

Consultant, Scanlan Instruments

No conflicts of interest related to this presentation
Stage IIIA (N2) NSCLC

Controversial issues

• Mediastinal staging of c-N0 patients and restaging after induction therapy
• Single-vs multi-station; Microscopic vs bulky
• Induction chemotherapy vs Induction ChemoRT
• VATS vs thoracotomy vs Definitive ChemoRT
Stage IIIA (N2) NSCLC

Objectives

1. Understand the importance of surgical staging and restaging of the mediastinum for patients with potentially resectable N2 NSCLC
2. Review the data on the optimal induction therapy strategy for N2 disease
3. Improve selection of operable patients
4. Explore the role of Thoracoscopic Lobectomy
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4. Explore the role of Thoracoscopic Lobectomy
Stage IIA (N2) NSCLC

**NCCN Guidelines Version 3.2017**
Non-Small Cell Lung Cancer

**CLINICAL ASSESSMENT**

- **Stage IIA** (peripheral T1ab, N0)
  - PFTs (if not previously done)
  - Bronchoscopy (intraoperative preferred)
  - Consider pathologic mediastinal lymph node evaluation
  - FDG PET/CT scan (if not previously done)

- **Stage IIB** (T2, N0)
  - PFTs (if not previously done)
  - Bronchoscopy
  - Pathologic mediastinal lymph node evaluation
  - FDG PET/CT scan (if not previously done)
  - Brain MRI with contrast (Stage II, IIIA)
  - (Stage IB [optional])

**PRETREATMENT EVALUATION**

- **Operable**
  - Negative mediastinal nodes
  - Medically inoperable

- **Operable**
  - Negative mediastinal nodes
  - Medically inoperable

**INITIAL TREATMENT**

- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Definitive RT including stereotactic ablative radiotherapy (SABR)

**See Stage IIA (NSCL-7) or Stage IIIB (NSCL-11)**

- Surgical exploration and resection + mediastinal lymph node dissection or systematic lymph node sampling
- Consider adjuvant chemotherapy (category 2B) for high-risk stages IB-IIIB
- Definitive chemoradiation

**See Stage IIA (NSCL-7) or Stage IIIB (NSCL-11)**

*Note: NSCL-3, NSCL-7, NSCL-11 refer to specific sections in the NCCN Guidelines.*
## c-Stage I Mediastinal Staging with PET

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iowa¹</td>
<td>237</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>Duke University Medical Center²</td>
<td>203</td>
<td>64%</td>
<td>77%</td>
</tr>
<tr>
<td>ACOSOG Z0050³</td>
<td>287</td>
<td>61%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>727</td>
<td><strong>68%</strong></td>
<td><strong>81%</strong></td>
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*Stage IIIA (N2) NSCLC*
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<td>727</td>
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25% of c-stage I patients are incorrectly staged without EBUS or mediastinoscopy.


*Stage IIIA (N2) NSCLC*
Strategy of Induction Therapy and Re-staging

• Standard of care for resectable IIIA

• Induction chemo tests the biology of the tumor: patients who do not respond have poor prognosis

• If RT is also used, the strategy of re-staging to determine operability is meaningless
Restaging after Induction

CT (None)
CT/PET
EBUS
Restaging after Induction

CT (None)
CT/PET
EBUS

Not Effective

Stage IIIA (N2) NSCLC
Restaging after Induction

CT (None)
CT/PET
EBUS
Mediastinoscopy/Re-mediastinoscopy
VATS

Stage IIIA (N2) NSCLC
Repeat Mediastinoscopy after Induction Rx

- More difficult than primary mediastinoscopy
- Higher complication rate
- Higher false negative rate
- Not mandatory to rely on frozen section
- Not adequate for 5, 6, 8, 9
Postinduction Video-mediastinoscopy Is Accurate and Safe In Patients with Potentially Operable NSCLC


- 219 patients underwent mediastinoscopy
- 24 patients after induction therapy

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Accuracy</th>
<th>Cx</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rx</td>
<td>87%</td>
<td>96%</td>
<td>4%</td>
</tr>
<tr>
<td>Induction</td>
<td>81%</td>
<td>91%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Stage IIIA (N2) NSCLC*
Accuray and Survival Of Repeat Mediastinoscopy After Induction Therapy For NSCLC

- Remediastinoscopy 104 pts after induction Rx
- Feasible in all but 1 who died due to bleeding
- Re-mediastinoscopy was (+) in 40 and (-) in 64; the latter group underwent thoracotony
- 17 false-negative re-mediastinoscopies
- Sensitivity 71%, accuracy 84%
Remediastinoscopy in Restaging Of Lung Cancer After Induction Therapy

- 104 pts (stage IIIA/B) re-mediastinoscopy
- Feasible in 98% of cases, with no mortality and low morbidity (1.9%)
- LN down-staging (N0) was observed in 84 patients
- Persistent N2/3 in 20 patients
- Sensitivity 61%, NPV 85%, *accuracy 88%*
Repeat mediastinoscopy in all its indications: experience with 96 patients and 101 procedures


- 1992 -2009, 96 patients underwent reMS:
  - 84 restaging after induction therapy for N2 disease
- reMS for restaging after induction therapy
  - Sensitivity 74%, NPV 79%, Accuracy 87%

- Median survival after restaging mediastinoscopy
  - True negative 51.5 months
  - Positive/false-negative 11 months ($p = 0.0001$)

*Stage IIIA (N2) NSCLC*
Stage IIIA (N2) NSCLC

Survival curve after reMS showing true negative and combined positive and false negative subgroups.

Mediastinal Node Clearance After Induction Chemotherapy Is Prognostic of Survival in Patients With Stage IIIA (N2) NSCLC


- 90 pts with potentially operable stage IIIA (pN2)
- 3 cycles chemo (docetaxel/cisplatin) + resection
- Multivariable analyses for improved survival:
  - Mediastinal downstaging (HR= 0.22; $P = 0.0003$)
  - Complete resection (HR=0.26; $P = 0.0006$)
Survival and p-N status


Stage IIIA (N2) NSCLC
VATS Restaging

- Evaluates 2R, 4R, 5, 6, 7, 8, 9, 10, 11, 12 + pleura
- Easier to get adequate tissue
- Rely on frozen section
- Facilitates the intended resection

Stage IIIA (N2) NSCLC
VATS Restaging After Induction Therapy for IIIA NSCLC (Prospective Phase II CALGB 39803)

- 70 patients accrued from 10 institutions
- 57% met restaging criteria
  - 19 with 3 (-) nodal stations, 21 with persistent disease
- 19% obliteration of nodal tissue
- 76% were restaged accurately
- Sensitivity 75%, specificity 100%, NPV 76%
VATS Re-Staging

- Difficult to compare 1st report of VATS re-staging to the experience of re-mediastinoscopy
- While some believe that re-staging is not necessary, the survival advantage of down-staged patients suggests that re-staging is useful
- VATS re-staging enables MLND, not just biopsy
- VATS re-staging significantly facilitates lobectomy
Mediastinal Lymph Node Staging Options

1. PET
2. EBUS
3. Induction Chemo
4. Mediastinoscopy
5. Down-staging?
6. Resection

1. PET
2. Mediastinoscopy
3. Induction Chemo
4. VATS Re-staging
5. Down-staging?
6. Resection
Objectives

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Stage IIIA (N2) NSCLC

NCCN Guidelines Version 3.2017
Non-Small Cell Lung Cancer

**MEDIASTINAL BIOPSY FINDINGS**

- T1-3, N0-1 (including T3 with multiple nodules in same lobe)
  - Resectable\(^{k,n}\)
  - Medically inoperable

- T1-2, T3 (other than invasive), N2 nodes positive, M0

**INITIAL TREATMENT**

- Surgical resection\(^k\) + mediastinal lymph node dissection or systematic lymph node sampling

- Definitive concurrent chemoradiation\(^{l,q}\) (category 1)
  - Or
  - Induction chemotherapy\(^{o,w} \pm RT^{l}\)

- Definitive concurrent chemoradiation\(^{l,q}\)

**ADJUVANT TREATMENT**

- See Adjuvant Treatment (NSCL-3)

- Surgery\(^k\) ± chemotherapy\(^o\) (category 2B) ± RT\(^l\) (if not given)

- No apparent progression

- Local
  - RT\(^l\) (if not given) ± chemotherapy\(^o\)

- Progression
  - Systemic
  - See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)
Induction Chemoradiotherapy is not Superior to Induction Chemotherapy Alone in Patients with Stage IIIA(N2) NSCLC: A Systematic Review and Meta-Analysis

WCLC, Amsterdam, 2011
Ann Thorac Surg 2012; 93: 1807-12

Asad A. Shah, Mark F. Berry, Ching Tzao, Mihir Gandhi, Mathias Worni, Dimple Rajgor, Ricardo Pietrobon, Thomas A. D’Amico
Duke Cancer Institute, Durham, NC, USA
Non-Randomized Studies

Stage IIIA (N2) NSCLC

Forest Plot for 3-Year Survival
Randomized Studies

Forest Plot for 3-Year Survival

Stage IIIA (N2) NSCLC
Randomized Studies

No advantage to adding RT to Induction Chemotherapy

Forest Plot for 3-Year Survival

Stage IIIA (N2) NSCLC
Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

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

Number at risk

Chemoradiotherapy group 117 57 27 13 7 5 2 0
Chemotherapy group 115 53 28 15 7 2 0 0
Conclusions: Induction Regimens

- The addition of radiation therapy to induction chemotherapy regimens for stage IIIA(N2) NSCLC is not supported by published evidence.
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Stage IIIA (N2) NSCLC
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Non-Small Cell Lung Cancer

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T1-2, T3 (other than invasive), N2 nodes positive, M0
- Definitive concurrent chemoradiation (category 1)
  - or
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T3 (invasion), N2 nodes positive, M0
- Definitive concurrent chemoradiation

INITIAL TREATMENT

Surgical resection + mediastinal lymph node dissection or systematic lymph node sampling

See Treatment according to clinical stage (NSCL-2)

ADJUVANT TREATMENT

See Adjuvant Treatment (NSCL-3)

Surgery ± chemotherapy (category 2B)

Local RT (if not given) ± chemotherapy

Progression

Systemic

See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)
Stage IIA (N2) NSCLC

Is There a Role for Surgery After Induction Chemotherapy?
ChemoRT With or Without Surgical Resection for Stage III NSCLC (RTOG 9309/Intergroup 0139)

429 patients randomized (+/- Surgery)

Cisplatin (50 mg/m² IV) + Etoposide (50 mg/m² IV)
RT (4500 cGy)

Group 1: Surgical Resection (202)

Group 2: RT Boost: 61 Gy Total (194)

Consolidation Cisplatin + Etoposide (2 cycles)

Stage IIIA (N2) NSCLC

## Stage IIIA (N2) NSCLC

### Chemo/RT+ Surgery vs Chemo/RT

<table>
<thead>
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<th>C/RT+Surg</th>
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<th>P Value</th>
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<tbody>
<tr>
<td><strong>Median PFS</strong></td>
<td>12.8 m</td>
<td>10.5 m</td>
<td>.02</td>
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<td><strong>5-year PFS</strong></td>
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<td>11%</td>
<td>.02</td>
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<td><strong>Median OS</strong></td>
<td>23.6 m</td>
<td>22.2 m</td>
<td>.24</td>
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<tr>
<td><strong>5-year OS</strong></td>
<td>27%</td>
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<td>.1</td>
</tr>
<tr>
<td><strong># Alive-5 years</strong></td>
<td>37 (27%)</td>
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**Stage IIIA (N2) NSCLC**

RTOG 9309/INT 0139

- OS not improved with surgery
- OS improved for lobectomy (not pneumonectomy; but this is an unplanned subset analysis)
- Mortality: Pneumonectomy 26%; Lobectomy 1%
- CT/RT+S: More are alive without PD (P = .008), but more died without PD (P = 0.02)
- 5-year OS  ypN0: 41%  ypN1-3: 24%
Stage IIIA (N2) NSCLC

Failed/Total
159/202
172/194

CT/RT+S
CT/RT

Progression-Free Survival

Stage IIIA (N2) NSCLC

Overall Survival

Overall Survival
Pneumonectomy Subset

Logrank \( P = \text{NS} \)

CT/RT
CT/RT + S

Stage IIIA (N2) NSCLC

Stage IIIA (N2) NSCLC

Overall Survival
Lobectomy Subset

CT/RT+S

CT/RT

Logrank $P = .002$

Overall Survival by Nodal Status

N0

N1-3

No Surgery

$P < .0001$

Stage IIIA (N2) NSCLC

RTOG 9309/INT 0139: Conclusions

- Improved PFS but not OS for surgery after CT/RT in patients with stage IIIA(N2) NSCLC
- Tri-modality approach not optimal when pneumonectomy is required
- Lobectomy is a reasonable approach as is associated with superior survival
- N0 status at surgery predicts survival and restaging prior to surgery should be standard
Stage IIIA (N2) NSCLC

NCCN Guidelines Version 3.2017
Non-Small Cell Lung Cancer

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  - or
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T3 (invasion), N2 nodes positive, M0
- Definitive concurrent chemoradiation\textsuperscript{l,q}

Progression
  - Local
    - RT\textsuperscript{l} (if not given) ± chemotherapy\textsuperscript{0}
  - Systemic
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Long-term Survival Following Open vs Thoracoscopic Lobectomy after Induction Therapy for Non-small Cell Lung Cancer


Jeffrey Yang, Ryan Meyerhoff, Terry Singhapricha, Paul Speicher, Matthew Hartwig, Mark Onaitis, Betty Tong, David Harpole, Thomas D'Amico, Mark Berry
Long-term Survival Following Lobectomy After Induction Therapy for NSCLC: VATS Approach Does Not Compromise Outcomes

- 273 patients: lobectomy after induction chemo: 70 (26%) VATS and 203 (74%) thoracotomy
- Compared to thoracotomy patients, VATS pts
  - Higher stage (p=0.03)   Older (p<0.001)
  - Greater BMI (p=0.01)
  - More CAD (p=0.008)   More COPD (p=0.02)
- Induction RT more common in open patients

Stage IIIA (N2) NSCLC
Operative Approach by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Open</th>
<th>VATS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-2001</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>2002-2007</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2008-2012</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

Number of Patients
Lobectomy After Induction Therapy: VATS Approach Does Not Compromise Outcomes

• Univariate analysis: VATS patients had improved 3-year survival compared with thoracotomy (61% vs 43%; p=0.008)

• Multivariable analysis: VATS approach was associated with improved overall survival (p=0.04)
Peri-operative Outcomes: Conversions

- 7 (10%) VATS cases converted to thoracotomy:
  - Difficult dissection: fibrotic tissue, adhesions (n=5)
  - Bleeding (n=2)

- None of these conversions led to periop deaths
## Peri-operative Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thoracotomy (N = 203)</th>
<th>VATS (N = 69)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day Mortality (%)</td>
<td>4%</td>
<td>3%</td>
<td>0.69</td>
</tr>
<tr>
<td>Overall Complications (%)</td>
<td>48%</td>
<td>41%</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Complications: Thoractomy vs VATS

No significant difference

- Post-op bleeding requiring blood transfusion
- Post-op bleeding requiring reoperation
- Atrial Fibrillation
- Prolonged Air Leak
- Respiratory Failure
- Pneumonia

Stage IIIA (N2) NSCLC
# Peri-operative Outcomes

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<th>VATS (N = 69)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube duration (days) Median (IQR)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Length of hospitalization (days) Median (IQR)</td>
<td>5 (4-7)</td>
<td>4 (4-5)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Overall Survival Stratified by Surgical Approach

Thoracotomy 43%
VATS 61%
p = 0.01
Propensity-Matched Survival Stratified by Surgical Approach

Thoracotomy

VATS

Median Survival (months)

Approach

Thoracotomy 30.2
VATS 36.3

p = 0.56

Number at risk

Open 30 21 13 8 6 3
VATS 30 25 19 12 9 6
Impact of Patient Selection and Treatment Strategies on Outcomes after Lobectomy for Stage II A(N2) Non-Small Cell Lung Cancer

May 20, 2015


Jeffrey Yang, Ryan Meyerhoff, Syed Adil, Kevin Anderson, Matthew Hartwig, Betty Tong, Mark Onaitis, Thomas D'Amico, Mark Berry, David Harpole Jr.
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 111</th>
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<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>62 ± 9.6</td>
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<tr>
<td>Male (%)</td>
<td>63%</td>
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<tr>
<td>Coronary Artery Disease (%)</td>
<td>15%</td>
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<tr>
<td>TIA/CVA (%)</td>
<td>8%</td>
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<tr>
<td>Hypertension (%)</td>
<td>49%</td>
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<tr>
<td>History of diabetes (%)</td>
<td>17%</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>76 ± 20</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>74 ± 18</td>
</tr>
<tr>
<td>Multi-station N2 disease (%)</td>
<td>24%</td>
</tr>
</tbody>
</table>

Stage IIIA (N2) NSCLC
Stage IIIA (N2) NSCLC

 Radiation Use Stratified by Operative Year

Number of Patients

Operative Year

1996-2001

2002-2007

2008-2012

No Radiation

Radiation
Stage IIIA (N2) NSCLC

Surgical Approach

Number of Patients

Operative Year

1996-2001
2002-2007
2008-2012

Thoracotomy
VATS
Invasive Mediastinal Restaging Strategy

Number of Patients

- Invasive Mediastinal Restaging Performed, no residual N2
- Invasive Mediastinal Restaging Performed, residual N2
- No Invasive Mediastinal Restaging Performed

Stage IIIA (N2) NSCLC

1996-2012
Overall Survival of Patients with Stage IIIA pN2 Following Induction Therapy and Lobectomy

**Median Survival**: 30.1 months

**5-year Survival**: 39%

Number at risk:
- 113 at 0 months
- 82 at 12 months
- 55 at 24 months
- 41 at 36 months
- 34 at 48 months
- 23 at 60 months
Overall Survival Stratified by Induction

Stage IIIA (N2) NSCLC

Overall Survival (Probability)

- No radiation
- Induction Radiation

No. at risk
- No radiation: 55, 47, 31, 23, 18, 10
- Induction Radiation: 56, 35, 24, 18, 16, 13

p = 0.03

Time (months)
Overall Survival Stratified by Induction

Stage IIIA (N2) NSCLC

Overall Survival (Probability)

Time (months)

No. at risk

<table>
<thead>
<tr>
<th>Radiation Type</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tr>
<td>No radiation</td>
<td>55</td>
<td>47</td>
<td>31</td>
<td>23</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Induction Radiation</td>
<td>56</td>
<td>35</td>
<td>24</td>
<td>18</td>
<td>16</td>
<td>13</td>
</tr>
</tbody>
</table>

aHR: 1.38 (95% CI: 0.81-2.34), p = 0.24

p = 0.03
Overall Survival Stratified by Invasive Mediastinal Restaging Approach

Stage IIIA (N2) NSCLC

Overall Survival (Probability)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0.00</th>
<th>0.25</th>
<th>0.50</th>
<th>0.75</th>
<th>1.00</th>
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<tr>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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No. at risk

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p < 0.01
# Multivariable Analysis

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<th>Predictor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
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<td>Operative year</td>
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*Stage IIIA (N2) NSCLC*
## Multivariable Analysis

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*Stage IIIA (N2) NSCLC*
Conclusion

- Invasive mediastinal restaging prior to lobectomy was associated with improved survival, even with multi-station N2
- No improvement in survival in patients with the addition of RT to induction chemotherapy
- Survival after VATS and thoracotomy approaches equivalent
Duke Approach

1. Mediastinal staging: mediastinoscopy or EBUS
2. If single station N2 or non-bulky multi-station N2, proceed with induction chemotherapy
3. Restaging: PET + mediastinoscopy or VATS
4. If evidence of down-staging (radiographic or pathologic), proceed with resection
5. If minimal down-staging but no evidence of progression proceed with lobectomy
Final Conclusions

- Surgical staging and restaging for patients with potentially resectable N2 lung cancer is critical
- Identify N2 for induction; exclude N3; restaging
- Operable N2: Induction chemo + surgery + RT
- Restaging and demonstration of down-staging is powerful prognostic factor
- Lobectomy after induction therapy is optimal
- Thoracoscopic Lobectomy: at least equivalent
11th Annual Masters in Minimally Invasive Thoracic Surgery

September 21-22, 2018
Waldorf Astoria
Orlando, Florida

Stage IIIA (N2) NSCLC