N2 - Current Evidence:

*Is There Role for Surgery?*

*Is There a Role for Postop Radiation for Surprise N2?*

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Disclosures

• None personally

• Spouse’s financial relationships
  • Consultant for Atheromed (peripheral vascular catheter based interventions)
    – Advisory Board, Boston Scientific (peripheral vascular interventions)
    – Advisory Board, Abbott (peripheral vascular interventions)
    – Advisory Board, St. Jude (coronary interventions)
What is the best strategy for this patient?
A. Go straight to resection – this is the same as N1 disease
B. Mediastinoscopy, possible VATS then induction therapy
C. VATS node biopsy then induction therapy
D. Biopsy primary then give definitive chemoradiation
DEFINING STAGE IIIA LUNG CANCER
FOCUSING ON T1-3 N2

Stage IIIa

T4_{Inv} N0,1
T3_{Inv} N1
T3_{any} N1

T1a,b N2
T2a,b N2
T3_{Satell} N1

T4_{Ipsi} N0
T4_{Ipsi} N1

Stage IIIb

T4_{Inv} N2
T_{any} N3
T4_{Ipsi} N2

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Clinical Staging

Pathologic Staging
New Classification Scheme

• ACCP 2013 Guidelines:
  – Infiltrative Stage III (N2/N3)
    • Cannot distinguish individual nodes; encasement/invasion of great vessels, airway
  – Occult N2 despite adequate preoperative staging
    • cN0/pN2; “surprise N2”
  – Discrete N2 by CT or CT/PET
    • cN2/pN2 confirmed with biopsy
Schematic of types of patients included in studies using different treatment approaches:

- **Palliative Treatment (PS > 2)**
- **Curative-Intent Chemo-RT**
- **Neoadjuvant + Surgery**
- **Primary Surgery (Occult N2)**

↑ **Tumor Burden**

Stage III patient characteristics

↑ **Performance Status**
IS THERE A ROLE FOR SURGERY
ACCP 2013 Guidelines:

- Infiltrative Stage III (N2/N3)
  - Cannot distinguish individual nodes; encasement/invasion of great vessels, airway
  - May not be necessary to confirm with bx

- Occult N2 despite adequate preoperative staging
  - cN0/pN2; “surprise N2”

- Discrete N2 by CT or CT/PET
  - cN2/pN2 confirmed with biopsy

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Survival - Treatment Group

Cumulative Survival Probability

Time (months)

0.0 0.2 0.4 0.6 0.8 1.0

0 10 20 30 40 50 60

Median survival

25.3 months

15.9 months

Multimodality Treatment

Surgery Alone

P=0.004

*Martin LW et al. “The Evolution of Treatment Outcomes for Resected Stage IIIA NSCLC over 16 years at a Single Institution” JTCVS 2005
Survival by Lymph Node Stations Involved

Cumulative Survival Probability

Median Survival

- 1 Station: 25.3 months
- 2 Stations: 16.8 months
- >2 Stations: 15.5 months

Time (months)

Cumulative Survival Probability

P < 0.001

*Martin LW et al. “The Evolution of Treatment Outcomes for Resected Stage IIIA NSCLC over 16 years at a Single Institution” JTCVS 2005
ADJUVANT STRATEGIES FOR N2 NSCLC

- Induction Chemo ➔ Surgery ➔ RT
- Induction Concurrent Chemo/RT ➔ Surgery
- Surgery ➔ Adjuvant Chemo ➔ RT
- Surgery ➔ Concurrent Chemo/RT
- Surgery ➔ Adjuvant Chemo

cN2/pN2
ADJUVANT STRATEGIES FOR N2 NSCLC

Induction Chemo → Surgery → RT

Induction Concurrent Chemo/RT → Surgery

Surgery → Adjuvant Chemo → RT

Surgery → Concurrent Chemo/RT

Surgery → Adjuvant Chemo

\[\text{cN0/pN2}\]
INTERGROUP 0139 TRIAL
0139 Intergroup: Induction ChemoRT +/- Surgery
Stage IIIA

Stage IIIA Resectable N2 NSCLC

ChemoRT (45 Gy)

if no PD
Surgery
Chemo

ChemoRT (45 Gy)

if no PD
ChemoRT (61 Gy)
Chemo
INT 0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset

% Alive

Months from Randomization

Dead/Total

CT/RT/S 57/90
CT/RT 74/90

logrank p = 0.002

CT/RT/S 34 mos. 36%
CT/RT 22 mos. 18%

5 yr OS 36%

MS 34 mos.
POSTOPERATIVE RADIATION THERAPY FOR N2 DISEASE

WHAT IS THE EVIDENCE?
PORT – Why does it matter?

- We have entered a new era
- We are better at controlling distant disease now
- 20-60% local failure rate
- PORT reduces local recurrence 25-35%
Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

PORT Meta-analysis Trialists Group*

Interpretation Postoperative radiotherapy is detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients. The role of postoperative radiotherapy in the treatment of N2 tumours is not clear and may warrant further research.

Where do we stand on post-operative radiotherapy (PORT)?

- **Post-Operative RadioTherapy Overview**

- 2128 pts including 808 stage III pts in 9 randomized studies

  - Surgery alone (1072 pts)
    - 2-year Survival: 55%

  - Surgery + PORT (1056 pts)
    - 2-year Survival: 48%

Port Overview Lancet 1998
Subgroup Analysis for Survival

**Stage**
- 1
- 2
- 3

**Nodal Status**
- 0
- 1
- 2

Hazard Ratio

Test for trend
\( \chi^2 (1) = 13.194, \ p = 0.0003 \)

Test for trend
\( \chi^2 (1) = 5.780, \ p = 0.016 \)

PORT, Lancet 1998
### Table 1. Retrospective studies on postoperative radiation therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>n of patients</th>
<th>Dose (Gy)</th>
<th>Local recurrence (%)</th>
<th>Overall survival (%)</th>
<th>Follow-up method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astudillo and Connill [13]</td>
<td>IIIA</td>
<td>60</td>
<td>–</td>
<td>20%</td>
<td>28%</td>
<td>3-yr actuarial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86</td>
<td>45–50</td>
<td>13%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Green et al. [14]</td>
<td>I–IIIA</td>
<td>94</td>
<td>–</td>
<td>NR</td>
<td>NR</td>
<td>5-yr crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125</td>
<td>50–60</td>
<td>NR</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Choi et al. [15]</td>
<td>IIIA</td>
<td>55</td>
<td>40–56</td>
<td>31%</td>
<td>8%</td>
<td>5-yr actuarial</td>
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<tr>
<td></td>
<td></td>
<td>93</td>
<td></td>
<td>14%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Chung et al. [16]</td>
<td>I–IIIA</td>
<td>68</td>
<td>–</td>
<td>32%</td>
<td>28%</td>
<td>3-yr crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>46</td>
<td>10%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Paterson et al. [17]</td>
<td>T3N0–2</td>
<td>22</td>
<td>–</td>
<td>27%</td>
<td>30%</td>
<td>5-yr actuarial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>20–50</td>
<td>0</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Kirsh et al. [18]</td>
<td>IIIA</td>
<td>20</td>
<td>–</td>
<td>NR</td>
<td>0%</td>
<td>5-yr crude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td>50–60</td>
<td>NR</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Sawyer et al. [19]</td>
<td>IIIA</td>
<td>136</td>
<td>–</td>
<td>60%</td>
<td>22%</td>
<td>4-yr actuarial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>88</td>
<td>45–66</td>
<td>17%</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>

*The Oncologist* 2011;16:672–681  www.TheOncologist.com
### Table 2. Results of certain randomized studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>n of patients</th>
<th>Total dose/fraction size</th>
<th>LRR (%)</th>
<th>p</th>
<th>5-yr SR (%)</th>
<th>p (in favor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Houtte et al. [25]</td>
<td>T1–3N0</td>
<td>104</td>
<td>–</td>
<td>10.9%</td>
<td>NS</td>
<td>43%</td>
<td>&lt;.05 (surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
<td>60/2 Gy</td>
<td>1.2%</td>
<td></td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Lung Cancer Study Group [20]</td>
<td>II–III SCC</td>
<td>120</td>
<td>–</td>
<td>41%</td>
<td>.001</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110</td>
<td>50.4/1.8</td>
<td>3%</td>
<td></td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Dautzenberg et al. [22]</td>
<td>I–II–III</td>
<td>355</td>
<td>–</td>
<td>28%</td>
<td>NS</td>
<td>43%</td>
<td>.002 (surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>373</td>
<td>60/2–2.5</td>
<td>22%</td>
<td></td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Mayer et al. [29]b</td>
<td>I–II–III</td>
<td>72</td>
<td>–</td>
<td>20%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;.01</td>
<td>20.4%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83</td>
<td>50–56/2</td>
<td>7%&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>29.7%</td>
<td></td>
</tr>
<tr>
<td>Trodella et al. [26]b</td>
<td>T-2N0</td>
<td>53</td>
<td>–</td>
<td>23%</td>
<td>.19</td>
<td>58%</td>
<td>.048 (PORT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51</td>
<td>50.4/1.8</td>
<td>2.2%</td>
<td></td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Feng et al. [28]</td>
<td>II–III</td>
<td>182</td>
<td>–</td>
<td>33.2%</td>
<td>.01</td>
<td>40.5%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>183</td>
<td>60/2</td>
<td>12.7%</td>
<td></td>
<td>42.9%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Cumulative rate of local recurrences.

<sup>b</sup>Study not included in the meta-analysis published in 1998.

Abbreviations: LRR, local recurrence rate; NS, nonsignificant; PORT, postoperative radiation therapy; SCC, squamous cell carcinoma; SR, survival rate.
Surgery vs. Surgery + PORT

The evolution of treatment outcomes for resected stage IIIA non–small cell lung cancer over 16 years at a single institution

Linda W. Martin, MD,§ Arlene M. Correa, PhD,§ Wayne Hofstetter, MD,§ Waun Ki Hong, MD,§ Ritsuko Komaki, MD,§ Joe B. Putnam, Jr, MD,§ David C. Rice, MD,§ W. Roy Smythe, MD,§ Stephen G. Swisher, MD,§ Ara A. Vaporciyan, MD,§ Garrett L. Walsh, MD,§ and Jack A. Roth, MD§ JTCVS 2005

23.1 mo

15.9 mo

Figure E2. Survival comparing surgical intervention followed by radiation therapy (XRT; n = 156) with surgical intervention alone (n = 116). Ninety-five percent confidence intervals are displayed. Solid lines, postoperative radiation therapy; dashed lines, surgical intervention alone.
Since PORT publication, several studies supporting the necessity of a new PORT study

- No increase of Death from Intercurrent Disease with more modern RT from the US Intergroup trial (Wakelee, Lung Cancer 2005)

- AND better surgery, better selection of pts (PET-CT, Brain imaging), improvements of radiotherapy
IMPACT OF POSTOPERATIVE RADIATION THERAPY ON SURVIVAL IN PATIENTS WITH COMPLETE RESECTION AND STAGE I, II, OR IIIA NON–SMALL-CELL LUNG CANCER TREATED WITH ADJUVANT CHEMOTHERAPY: THE ADJUVANT NAVELBINE INTERNATIONAL TRIALIST ASSOCIATION (ANITA) RANDOMIZED TRIAL

JEAN-YVES DOUILLARD, M.D., PH.D.,* RAFAEL ROSELL, M.D.,† MARIO DE LENA, M.D.,‡ MARCELLO RIGGI, M.D.,.§ PATRICK HURTELLOUP, M.D.,§ AND MARC-ANDRE MAHE, M.D., PH.D.,* ON BEHALF OF THE ADJUVANT NAVELBINE INTERNATIONAL TRIALIST ASSOCIATION

*Centre R. Gauducheau, Nantes, France; †Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; ‡IRCCS Oncologico, Bari, Italy; and §Institut de Recherche Pierre Fabre, Boulogne, France

Purpose: To study the impact of postoperative radiation therapy (PORT) on survival in the Adjuvant Navelbine International Trialist Association (ANITA) randomized study of adjuvant chemotherapy.

Methods and Materials: ANITA is a randomized trial of adjuvant cisplatin and vinorelbine chemotherapy vs. observation in completely resected non–small-cell lung carcinoma (NSCLC) Stages IB to IIA. Use of PORT was recommended for pN+ disease but was not randomized or mandatory. Each center decided whether to use PORT before initiation of the study. We describe here the survival of patients with and without PORT within each treatment group of ANITA. No statistical comparison of survival was performed because this was an unplanned subgroup analysis.

Results: Overall, 232 of 840 patients received PORT (33.3% in the observation arm and 21.6% in the chemotherapy arm). In univariate analysis, PORT had a deleterious effect on the overall population survival. Patients with pN1 disease had an improved survival from PORT in the observation arm (median survival [MS] 25.9 vs. 50.2 months), whereas PORT had a detrimental effect in the chemotherapy group (MS 93.6 months and 46.6 months). In contrast, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (MS 23.8 vs. 47.4 months) and observation arm (median 12.7 vs. 22.7 months).

Conclusion: This retrospective evaluation suggests a positive effect of PORT in pN2 disease and a negative effect on pN1 disease when patients received adjuvant chemotherapy. The results support further evaluation of PORT in prospectively randomized studies in completely resected pN2 NSCLC. © 2008 Elsevier Inc.
pN2 Survival in the Anita Trial

Fig. 3. Overall survival according to treatment received in the pN2 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.
Postoperative Radiotherapy for Stage II or III Non–Small-Cell Lung Cancer Using the Surveillance, Epidemiology, and End Results Database

Brian E. Lally, Daniel Zelterman, Joseph M. Colasanto, Bruce G. Haffty, Frank C. Detterbeck, and Lynn D. Wilson

ABSTRACT

Purpose
To investigate the association between survival and postoperative radiotherapy (PORT) in patients with resected non–small-cell lung cancer (NSCLC).

Patients and Methods
Within the Surveillance, Epidemiology, and End Results database, we selected patients with stage II or III NSCLC who underwent a lobectomy or pneumonectomy. Only those patients coded as receiving PORT or observation were included. To account for perioperative mortality, we excluded patients who survived less than 4 months. As a result of our inclusion criteria, we selected a total of 7,465 patients, with a median follow-up time of 3.5 years for patients still alive.

Results
Predictors for the use of PORT included age less than 50 years, higher American Joint Committee on Cancer stage, T3-4 tumor stage, larger tumor size, advanced node stage, greater number of lymph nodes involved, and a ratio of lymph nodes involved to lymph nodes sampled approaching 1.00. On multivariate analysis, older age, T3-4 tumor stage, N2 node stage, male sex, fewer sampled lymph nodes, and greater number of involved lymph nodes had a negative impact on survival. The use of PORT did not have a significant impact on survival. However, in subset analysis for patients with N2 nodal disease (hazard ratio [HR] = 0.855; 95% CI, 0.762 to 0.959; P = .0077), PORT was associated with a significant increase in survival. For patients with N0 (HR = 1.176; 95% CI, 1.005 to 1.376; P = .0435) and N1 (HR = 1.097; 95% CI, 1.015 to 1.186; P = .0196) nodal disease, PORT was associated with a significant decrease in survival.

Conclusion
In a population-based cohort, PORT use is associated with an increase in survival in patients with N2 nodal disease but not in patients with N1 and N0 nodal disease.
Fig 5. Plot of overall survival for N2 patients stratified by postoperative radiotherapy (PORT) use. The solid line represents patients who received PORT, and the dashed line represents patients who did not receive PORT.
IS THERE A STANDARD FOR OPERABLE PATIENTS WITH N2 MEDIASTINAL INVOLVEMENT?

- Adjuvant chemotherapy has become a standard for IIIA patients in the last several years (Lancet 2010)

- Post-operative radiotherapy in completely resected NSCLC patients is a subject of debate
  - In pN0 and pN1 patients, PORT is not standard after the results of the PORT meta-analysis (Lancet 1998)
  - In pN2 patients, PORT should be the subject for further research (conclusion of PORT manuscript)

- **Need for a large randomized trial to assess the role of modern mediastinal radiotherapy**
LUNG ART TRIAL

Cecile LePechoux, MD – Principal Investigator
Institute Gustave Roussy
Rationale of a new LUNG Adjuvant Radiotherapy Trial

- Trial assessing the role of adjuvant radiotherapy in patients with proven N2 nodal involvement necessary
- As survival improves due to reduction of distant metastases with adjuvant CT, local control becomes an important issue
- Need to assess an improved technique of PORT but within an integrated multidisciplinary approach
- Quality control of both surgery and radiotherapy
Lung ART: Trial Design

- **Possibility pre-op CT**
  - Completely resected NSCLC with proven N2 involvement
  - Possibility Post-op CT
  - Random
    - No mediastinal PORT (Post-Operative RadioTherapy)
    - Conformal Mediastinal PORT 54 Gy/27 to 30 fr

- Primary endpoint: DFS
  - Secondary endpoints: Local control, OS, 2nd cancer, Late Toxicity

**Stratification factors**: Center, Administration of CT (no CT vs Post-op CT vs pre-op CT alone), Histology (SCC vs other), Extent of mediastinal lymph node involvement (0 vs 1 vs 2+), Histology (SCC vs others), use of pre-treatment PET-scan (yes/no)

**Statistical considerations**: 700 pts necessary to show a 10% DFS difference at 3 years (from 30% in the control arm to 40%) Power of 80%, Type one error of 5%, 2-sided log-rank test
Patients receiving radiation: Surgical Considerations

- Bronchial stumps covered with intercostal muscle flap
- Serratus flaps-pneumonectomies
Conclusions

- Stage IIIA – N2 disease is heterogeneous
- Survival rates vary from 9-50%
- Role of radiation is based on either outdated clinical data, or retrospective data
- **WE NEED A MODERN CLINICAL TRIAL TO DETERMINE THE ROLE OF PORT**
- Lung ART study ongoing in Europe, hopefully will open in North America soon via Alliance
What is the best strategy for this patient?
A. Go straight to resection – this is the same as N1 disease
B. Mediastinoscopy, possible VATS then induction therapy
C. VATS node biopsy then induction therapy
D. Biopsy primary then give definitive chemoradiation