Advances in Internal Medicine
LUNG CANCER
What’s old, what’s new, and what to expect

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Objectives

• Recognize the changing epidemiology of lung cancer
• Understand the treatment options for early and advanced disease
• Recognize the role of targeted agents and their toxicities
• Recognize the heterogeneity of lung cancer and tumor biology based individualized treatments

NSCLC Epidemiology

Statistics for 2008

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Incidence</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>108,070</td>
<td>49,960</td>
</tr>
<tr>
<td>Breast</td>
<td>184,450</td>
<td>40,930</td>
</tr>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>28,660</td>
</tr>
<tr>
<td>Total</td>
<td>478,840</td>
<td>119,550</td>
</tr>
<tr>
<td>Lung</td>
<td>215,020</td>
<td>161,840</td>
</tr>
</tbody>
</table>

Jemal, CA Cancer J Clin 2008; 58: 71
Prototypical U.S. Lung Cancer patient 1950’s-60’s

- 60-70 Year Old Males
- Long Smoking History
- Large Squamous Cell Tumors
- Cowboy Image
- Started in 1950s

The Changing Face of Lung Cancer in the U.S.

Annual Age-adjusted Cancer Death Rates, US 1930-2002

Etiology

Smoking and lung cancer incidence
Etiology:

*Environmental causes*

- **Smoking:**
  - Tars, tobacco, aromatic amines, Polycyclic aromatic hydrocarbons
- **Environmental:**
  - Second hand smoke, radon
- **Occupational:**
  - Asbestos, uranium, beryllium, vinyl chloride, nickel chromates, coal products, mustard gas, chloromethyl ethers, gasoline, diesel exhaust

**Smoking cessation and mortality in women**

**Nurses Health Study**
- 104,519 subjects
- Lung CA OR Current smokers: 21.87 (17.85-26.80)
  - Past smokers: 4.93 (4.00-6.08)

**Effect of smoking cessation**

Lung cancer mortality:
- First 5 yrs: 21% ↓
- 20-30 yrs: 87% ↓
- ≥ 30 yrs: 93% ↓

**All cause mortality:** Level of non-smoker 20yrs

Kenfield, JAMA 2008; 299: 2037

**Lung cancer in never smokers**

- Women are more likely than men to have non-smoking related cancer
- Incidence rates/100,000:
  - **Women 15-20**: Men 4-13.7
  - Higher frequency of adenocarcinoma

Wakelee et al, J Clin Oncol, 2007; 25: 472

**Gender differences and risk of lung cancer (LC) with smoking**

- OR LC in smokers: women 1.2-1.7 times higher than men when adjusted for tobacco dose exposure
- RR for LC in smokers: women 27.9 and men 9.6

Zang, JNCI 1996;88:183
Schoenberg, Am J Epi. 1989;130:688
Gender differences in biology

- CYP and GSTM 1 (glutathione S-transferases): 2 enzyme systems for the metabolism of PAH and intermediate products of tobacco smoke.
- CYP1A1 *2A and *2B assoc with inc risk of LC (OR 4.7 CI 1.2-19)
- GSTTI null phenotype OR 1.2 (CI 1.0-1.6) 
  F –OR 3.0 (1.09-8.4) M – OR 1.4 (.5-4.0)
- Higher levels of DNA adducts

Taioli, Int J Epi 2003:32:60

Gender differences in biology

- Hormones and lung cancer
- Estrogen receptors are present in lung tumors
- Estradiol promotes growth of lung tumors in preclinical models
- Conflicting reports on the influence of hormones on development of LC in case control and cohort studies
- HRT adversely affects treatment outcomes (MS 79 vs 39 mo p=0.02)

Dubey, Lancet Oncol, 2006, 7:416
Ganti, JCO 2005, 24:59

SCREENING

Lung Cancer Stage Distribution at Time of Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>36%</td>
</tr>
<tr>
<td>III</td>
<td>37%</td>
</tr>
<tr>
<td>I/II</td>
<td>16%</td>
</tr>
<tr>
<td>Unstaged</td>
<td>8%</td>
</tr>
</tbody>
</table>

Screening

• IELCAP (Early Lung Cancer Action Program)

• 31,567 H/O tobacco use, second hand, occupational exposure, radon.
• Baseline and annual CT screening
• 5500 Positive results requiring further w/u
• 535 required biopsy
• Lung cancer detected in 484 (1.6%) of which 85% stage I.

NEJM 2006, 357, 17

Screening

• NLST (National lung screening trial)
• Randomized comparison of CT and CXR
• 50,000 enrolled and closed to accrual
• Endpoint: survival
• Results expected ~ 2009

Principles of Cancer Therapy

• Diagnosis
• Stage
• Medical condition (performance status, co-morbid diseases)
Performance status

<table>
<thead>
<tr>
<th>Karnofsky Scale</th>
<th>Zubrod Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no evidence of disease</td>
<td>Normal activity</td>
</tr>
<tr>
<td>Able to perform normal activity with only minor</td>
<td>100</td>
</tr>
<tr>
<td>symptoms</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort, some symptoms</td>
<td>Symptomatic and ambulatory</td>
</tr>
<tr>
<td>Able to care for self but unable to do</td>
<td>80</td>
</tr>
<tr>
<td>normal activities</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance, cares for most needs</td>
<td>Ambulatory &gt;50% of time</td>
</tr>
<tr>
<td>Requires considerable assistance</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>Occasional assistance</td>
</tr>
<tr>
<td>Disabled, requires special assistance</td>
<td>Ambulatory ≤50% of time</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>40</td>
</tr>
<tr>
<td>Very sick, requires active supportive treatment</td>
<td>20</td>
</tr>
<tr>
<td>Moribund</td>
<td>Bedridden</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Treatment of NSCLC

- Practically 3 groups:
  - Local: stage I, II, some IIIA → surgery
  - Regional: some IIIA, IIIB, → RT ± chemo
  - Metastatic: Systemic Rx (cytotoxics and targeted agents)

Evolution In Approach To Surgery
Open or Closed: Does Size Matter?

- Thoracotomy
- Thoracoscopy

• Early NSCLC
Surgery

- Advances in surgery:
- Videoscopic Assisted Thoracoscopic Surgery
- Speciality training
- Shorter hospital stay
- Earlier recovery

NSCLC: 5-year Survival by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>TMN</th>
<th>5-yr Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1NOMO</td>
<td>~70%</td>
</tr>
<tr>
<td>IB</td>
<td>T2NOMO</td>
<td>~60%</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1MO</td>
<td>55%</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1MO</td>
<td>~40%</td>
</tr>
<tr>
<td></td>
<td>T3N0MO</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-3N2MO</td>
<td>~25%</td>
</tr>
<tr>
<td></td>
<td>T3N1M0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>Any T4,N3, MO</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>IV</td>
<td>Any M1</td>
<td>1%</td>
</tr>
</tbody>
</table>


Systemic therapy for a local disease ???

- Elimination of micrometastases
- Reduction of recurrence
- Improvement of survival

- Adjuvant chemotherapy
- Neoadjuvant chemotherapy

Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Chemo</th>
<th>5yrS %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3590</td>
<td>II and IIIA</td>
<td>TRT VS TRT/CDDP+E Obs Vs MVP</td>
<td>42 38</td>
</tr>
<tr>
<td>ALPI</td>
<td>I-IIIA</td>
<td></td>
<td>44 48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IALT</td>
<td>IB-IIIIB</td>
<td>CDDP based Obs</td>
<td>44.5 40.4</td>
</tr>
<tr>
<td>NCIC BR10</td>
<td>IB-IIIB</td>
<td>CDDP + Vin Obs</td>
<td>69 54</td>
</tr>
<tr>
<td>ANITA</td>
<td>IB-III A</td>
<td>Cis/Vin</td>
<td>52 42</td>
</tr>
<tr>
<td>JLCRG</td>
<td>IA/IB IB</td>
<td>UFT Vs obs</td>
<td>88 vs 85 85 vs 73</td>
</tr>
<tr>
<td>CALGB</td>
<td>IB</td>
<td>Carboplatin+ P Obs</td>
<td>59 57(4yrS)</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy in the elderly

- OS for >65 was better with chemo vs obs
  HR 0.61 (CI 0.38-0.98) p=0.04
- OS lesser for patients >75 compared to those aged 66-74
  HR 1.95 (CI 1.11-3.41, p=0.02)

Early Lung cancer
What’s new?

- VATS procedures can reduce surgical morbidity
- Adjuvant chemotherapy is the Standard of Care for resected NSCLC
  Good Performance Status
  Should be offered to >65 yrs
  Those over the age of 75 require further study
• Advanced disease

Progress in the Treatment of Advanced NSCLC: Baby steps

<table>
<thead>
<tr>
<th></th>
<th>Median survival</th>
<th>One year survival</th>
<th>Two year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>4-6 months</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>“Older” chemotherapy</td>
<td>6 months</td>
<td>20%</td>
<td>?</td>
</tr>
<tr>
<td>“Newer” chemotherapy</td>
<td>8 - 12 months</td>
<td>30% - 50%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Sources:
- American Cancer Society: Cancer Facts and Figures 2005
- National Cancer Institute: Cancer Research Funding, 2005
• Treatment of advanced disease
  Cytotoxic chemotherapy
  Targeted agents

NSCLC - Chemotherapy
Platinum Chemotherapy Versus Supportive Care in NSCLC

First line chemotherapy for NSCLC
Survival by Treatment Group
All Randomized Cases

65 yr old male with lung cancer and good PS progresses after 4 cycles of carboplatin and paclitaxel. What would you recommend?

1. 2 more cycles of same chemo just in case more is better
2. Different single agent cytotoxic chemotherapy
3. Single agent targeted therapy
4. Refer to hospice
**Relapsed disease**

- **Cumulative probability**
- **Docetaxel 75 mg/m² (n=55)**
- **Best supportive care (n=49)**
- **Response(%)**
- **Median survival (months)**
- **1-year-survival (%)**

**QOL with Docetaxel**

- **Shepherd, J Clin Oncol 2000, 18:2095**

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**Single agents used in second line therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Survival (median)</th>
<th>1-yr OS</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>8.3 mos</td>
<td>29.7%</td>
<td>0.99 (0.82-1.20)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>7.9 mos</td>
<td>29.7%</td>
<td>1.00 (0.82-1.20)</td>
</tr>
</tbody>
</table>

**Second Line Therapy**

- **Pemetrexed vs. Docetaxel**
- **MST 8.3 mos**
- **1-yr OS: 29.7%**

**Single agents used in second line therapy**

- **JCO 2004, 18:3722**

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**Notes**

- **Shepherd, J Clin Oncol 2000, 18:2095**
- **Hanna JCO, 2004, 22:1589**
• Treatment of advanced disease
  Cytotoxic chemotherapy
  Targeted therapy

“Normalizing” Tumor Vasculature with Anti-angiogenic Therapy

“Pruning” of abnormal immature vessels with chemo. Results in better delivery of therapeutics

Bevacizumab Blocks Angiogenesis

Recombinant humanized monoclonal antibody to VEGF-A
E4599. Ph III RCT: Bevacizumab and CP vs CP in non-squamous NSCLC

- **Paclitaxel 200 mg/m² IV + Carboplatin AUC 6 IV q 3 wk X6 cycles**
- **Paclitaxel 200 mg/m² IV + Carboplatin AUC 6 IV q 3 wk X6 cycles**
- **Bevacizumab 15 mg/kg q3 wk till PD**

**Stratification by:**
- Stage (IIIB or IV)
- Geographic region

Sandler, NEJM 2006; 355: 2542

**Bevacizumab related toxicity**

<table>
<thead>
<tr>
<th></th>
<th>PC</th>
<th>PCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 4/5 Neutropenia</td>
<td>16.4%</td>
<td>24%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7%</td>
<td>6%</td>
</tr>
<tr>
<td>Gr ¾</td>
<td>3%</td>
<td>3.8%*</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Rx related deaths</td>
<td>2</td>
<td>9 (5 due to hemoptysis)</td>
</tr>
</tbody>
</table>

* p=NS

**Survival by Treatment**

- PC: 12 mo 43.7% 24 mo 18.3%
- PCB: 16.1% 22.1%
- HR 0.77 (0.55, 0.99)
- P = 0.037

Medians: 10.2, 12.5

Sandler, ASCO annual meeting, 2005, LBA4

**Epidermal Growth Factor Receptor (EGFR)**

Tyrosine Kinase Inhibitors

- Gefitinib: EGFR, NSCLC
- Erlotinib: EGFR, NSCLC
- Imatinib: PDGF/C-kit/Bcr-Abl, CML, GIST
- Sunitinib: VEGF, PDGF, CKIT, RET, RCC, GIST
- CI1033: Pan ERBB (irreversible)
- GW572016: EGFR/ErbB-2
- EKB 569: EGFR
- PTK 787: VEGF, PDGF
- AMG 706: VEGF PDGF CKIT RET

Erlotinib (Tarceva)- Phase III
BR 21

- ECOG PS 1,2,3
- Prior 1-2 regimens
- Erlotinib 150 mg/d
- Placebo 150 mg/d

Stratification:
- PS: 0/1 vs 2/3
- Prior chemo: 1 vs 2
- Prior response to chemo: CR vs PR vs SD

Shepherd et al. NEJM, 2005, 353:123

Radiographic responses to erlotinib can be dramatic and sustained

Shepherd et al. ASCO 2004 # 7022
**Significant Clinical predictors to response**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Male</th>
<th>Female</th>
<th>Overall response %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>6</td>
<td>6</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Adenoca</td>
<td>14</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic group</td>
<td>Asian</td>
<td>19</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current or ever</td>
<td>12</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Toxicities of EGFR -TKIs**

- Acneiform rash 60%
- Diarrhea 50%
- Transaminitis
- Anorexia
- Wt loss
- Interstitial lung disease <2%

Rx: moisturizing lotions, sun screen, topical steroids, clindamycin, Doxycycline

**Erlotinib**

**Survival by rash**

- Grade 2/3 (n=17)
- Grade 1 (n=26)
- No rash (n=14)

<table>
<thead>
<tr>
<th>Rash Level</th>
<th>Median survival (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rash</td>
<td>1.5 (1–2.2)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>9.5 (4.8–14.8) p&lt;0.0001*</td>
<td></td>
</tr>
<tr>
<td>Grade 2/3</td>
<td>19.6 (10.8–22.1+) p&lt;0.0001*</td>
<td></td>
</tr>
</tbody>
</table>

*vs no rash


**SPECIAL POPULATIONS**

- The elderly
Age in Lung Cancer Relationship to Prognosis ?????

- MSKCC (JCO 4:1604, 1986)
- ECOG (JCO 4:702, 1986)
- ECOG (JCO 23:175, 2005)
  - prognosis not related to age
  - Elderly experience more toxicities
- SWOG (JCO 1991:3:1618)
  - Elderly – favorable survival

Randomized Trial of Vinorelbine vs. BSC in the Elderly

The ELVIS Trial

<table>
<thead>
<tr>
<th>Chemo-naive</th>
<th>N</th>
<th>MS</th>
<th>1 yr Survival</th>
<th>OOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine</td>
<td>80</td>
<td>28 wks</td>
<td>32%</td>
<td>Better</td>
</tr>
<tr>
<td>BSC</td>
<td>81</td>
<td>21 wks</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

Gridelli, Oncologist 2001;6(S1) 4-7

Treatment in advanced disease

- Conclusions
  - Multiple cytotoxic chemotherapy available
  - Options also include targeted agents
  - Treatment is associated with prolongation of survival and improved symptoms
  - Treatment choice is dependent on performance status, co-morbidities

- Conclusions
  - Be aware of toxicities of targeted agents
  - Age is not a discriminator in treatment decisions. Elderly “fit” should be offered anti-cancer treatments.
Individualized therapy - Genomic predictors?

Potential Biomarkers for Lung Cancer Treatment

- Platinum – ERCC1
- Taxanes – BRCA1
- Gemcitabine – RRM1
- Pemetrexed – TS expression
- Gene expression
- EGFR – EGFR mutation, FISH
- VEGF - ??

Excision Repair Cross Complementing-1 Enzyme (ERCC1)

- Involved in DNA repair after damage from cisplatin
- High levels of DNA repair enzyme are linked to cisplatin resistance

Effect of adjuvant chemotherapy on survival in patients with ERCC1 negative tumors

Adjusted HR=0.65, 95%CI [0.50-0.86], p = 0.002

Soria, ASCO 2006, Abstr # 7010
Lung cancer - What have we learned?

- Early disease: Adjuvant chemotherapy improves survival

- Advanced disease: Systemic therapy improves survival and QOL

Lung cancer - What have we learned?

- Recognize the unique toxicity profile of targeted agents

- Biomarkers will provide the platform for personalized treatment

- Have I missed anything?
• Back up slides

Lung Metagene Prognosis

Incorporate LMP into prospective clinical trials of adjuvant chemotherapy

Future Plan

Biomarker Selection for EGFR Inhibitors:

- EGFR protein expression by immunohistochemistry
- EGFR gene copy number by FISH
- EGFR Mutational status

Structure of the EGFR-ATP Binding Site

Exons 18, 19, 20 and 21 - Tyrosine kinase domain

In frame deletions and missense mutations

**EGFR mutation and response**

<table>
<thead>
<tr>
<th></th>
<th>RR %</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR WT</td>
<td>10</td>
<td>No significant difference</td>
</tr>
<tr>
<td>EGFR MT</td>
<td>46</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>

Bell, JCO 2005;23:8081

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**Biomarkers**

- **Conclusions**
  - EGFR biomarkers:
    - Gene copy number predicts response and survival to EGFR-TKIs.
    - Mutation predicts response but not improved survival
  - Ongoing and planned biomarker trials will evaluate biomarker based treatment approach

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**Lung cancer - What have we learnt?**

- **Early disease**: Adjuvant chemotherapy improves survival
- **Locally advanced disease**: Combined chemoradiation improves survival
- **Advanced disease**: Systemic therapy improves survival and QOL
- Biomarkers will provide the platform for personalized treatment

---

**FISH predicts benefit of EGFR-TKIs**

- **ISEL FISH +**
  - Proportion surviving
  - Time (months)
  - Cox: p=0.07 HR=0.61 (0.36, 1.04)
  - Log-rank: p=0.008 HR=0.44 (0.23, 0.82)

- **BR21 FISH +**
  - Proportion surviving
  - Time (months)
  - Cox: p=0.42 HR=1.16 (0.81, 1.64)
  - Log-rank: p=0.59 HR=0.85 (0.48, 1.51)
Concurrent Chemoradiotherapy → Consolidation Docetaxel in Unresectable Stage IIIB NSCLC: SWOG 9504

Unresectable stage IIIB NSCLC

Cisplatin (50 mg/m² on days 1, 8, 29, 36) + Etoposide (50 mg/m² on days 1-5, 29-33) + Radiotherapy (61 Gy chest [1.8-2.0 Gy/d]) starting on day 1

Docetaxel (75-100 mg/m²) q3w for 3 cycles

MS 26mo 5yrS 29%

Gandara et al. 2006, Clin Lung Ca; 8;116.

Is maintenance therapy required after consolidation docetaxel?

Gefitinib maintenance in inoperable IIIA/ IIIB NSCLC SWOG 0023

Cisplatin
50 mg/2 d 1,8,29,36
Etoposide
50mg/m2 d1-5, 29-33
XRT
1.8-2 Gy/d 61 Gy

DOCETAXEL
75 mg/m² x 3 cycles

PLACEBO
GEFITINIB
500 mg/day 250 mg/day

RANDOMIZE

1st Endpoint: Overall Survival; 2nd Endpoint: PFS, toxicity and correlative

Kelly et al. ASCO, 2007, Abstr# 7513.
**Abstract # 7513**

**Overall Survival**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gefitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>47%</td>
<td>71%</td>
</tr>
<tr>
<td>Dead</td>
<td>54%</td>
<td>71%</td>
</tr>
<tr>
<td>Cancer</td>
<td>61%</td>
<td>43%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Other Causes</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*P = .01*

**Median FU time:** 27 months

**Gefitinib**

- N = 118
- Median in Months: 1 YR = 23, 2 YR = 35
- OS = 73%, 46%

**Placebo**

- N = 125
- Median in Months: 1 YR = 20, 2 YR = 30
- OS = 81%, 59%

**Is even consolidation docetaxel required?**

Unresectable stage IIIb NSCLC

MS 26mo 5yrS 29%


**Concurrent chemo/RT with or without consolidation docetaxel**

Unresectable stage IIIA/B NSCLC

- Cisplatin (50 mg/m² on days 1, 8, 29, 36) + Etoposide (50 mg/m² on days 1-5, 29-33) + Radiotherapy (61 Gy chest [1.8-2.0 Gy/d]) starting on day 1
- Docetaxel (75-100 mg/m²) q3w for 3 cycles
- Observation

Docetaxel (75-100 mg/m²) q3w for 3 cycles

N=73

- N=74

1° Endpoint: Overall Survival

Hanna et al, Proc ASCO 2007, Abstr# 7512
Unresectable stage III NSCLC

- **Concurrent chemoradiotherapy**
- Is superior to sequential chemo-radiotherapy
- Should be offered to eligible candidates.

- **Consolidation or maintenance therapy**
  - Does not improve OS
  - Associated with increased toxicity
  - Should not be routinely used

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**Abstract # 7512**

**Overall Survival**

- Observation: 3yr S 27.6%
- Docetaxel: 3yr S 27.2%
- P-value: 0.940

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**Staging – Proposed changes**

<table>
<thead>
<tr>
<th>6th Edition T/M and Descriptor</th>
<th>Proposed T/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (≤ 2 cm)</td>
<td>T1a</td>
</tr>
<tr>
<td>T1 (2 – 3 cm)</td>
<td>T1b</td>
</tr>
<tr>
<td>T2 (≤ 5 cm)</td>
<td>T2a</td>
</tr>
<tr>
<td>T2 (5 – 7 cm)</td>
<td>T2b</td>
</tr>
<tr>
<td>T2 (&gt; 7 cm)</td>
<td>T3</td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T3</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td>T3</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td>T4</td>
</tr>
<tr>
<td>T4 (pleural dissemination)</td>
<td>M1a</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>M1a</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1b</td>
</tr>
</tbody>
</table>