Lung Cancer: Part II

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Pre-Treatment Evaluation

• From the Evaluation thus far:
  – Assign a cTNM status
  – Classify as to Stage
  – Suggest a treatment approach

• And answer the first question:
  – Is this tumor resectable?

• Now is the patient operable
Barriers to surgical resection

Perspective on Staging

Physiologic

Anatomic

Poor lung function, co-morbidity etc.,

Healthy Normal PFT

Locally advanced disease, metastatic disease, CAD, COPD, etc.,

T1

T2

T3

T4

N0

N1

N2

N3
Question 1

Which of the following parameters is most likely to eliminate a patient from consideration of surgery for an otherwise resectable lung cancer:

A. He is 83 years old
B. His post operative predicted DLCO is 38% predicted
C. His FEV1 is 1 liter
D. He has had an MI with stents placed 8 months ago
Short Term Risk

• Low Risk Patient
  – FEV1 > 2L (or > 60% of predicted)
  – DLCO > 60% of predicted
  – MVV > 50% of predicted
  – ppoFEV1 > 40% of predicted
  – ppoDLCO > 40% predicted
  – Absence of heart disease (Goldman index)
Short Term Risk

• High Risk Patient
  – PCO2 > 45
  – PO2 < 50
  – ppoFEV1 < 35% of predicted
  – PPO DLCO < 35% predicted
  – Age > 80
  – Poor exercise performance
Short Term Risk

- Age is not an independent risk factor
- Physiologic age might be
- Chronologic age alone should not preclude surgery
Short Term Risk

- Hypoxemia and Hypercapnia
  - Not absolute contraindications
- Lower ppoFEV1 are at higher risk
  - Risk is relative
- Exercise tolerance is predictive
  - Self-reporting
  - Timed walk test (6 and 12 minute)
  - Ability to climb stairs
Short Term Risk

• **Ballpark risk of surgery is:**
  
  – 3.0-5.0 % for lobectomy
  
  – 6.0-10% for pneumonectomy
  
  – 1.5 % for lesser resections
Quantitative Ventilation/Perfusion Scanning

• Post-op function may be estimated

• Percent function is measured
  – Right vs Left

• ppoFEV1 and ppoDLCO is obtained by multiplying pre-op value by the percent lung that will remain after surgery
Algorithmic Approach

- Cardiac Evaluation
  - All should have an EKG
  - If History, Physical, or EKG are abnl, go to full cardiology evaluation
  - If normal, go to Lung Evaluation
Algorithmic Approach

• Lung Evaluation - Spirometry
  – Proceed with surgery
    ▪ If pBD FEV1 > 1.5 L (for planned lobectomy)
    ▪ If >2.0 L (for planned pneumonectomy)
  – If not, order full study with ABG and calculate ppoFEV1 and ppoDLCO
    ▪ Perfusion (V/Q) method for pneumonectomy
    ▪ Can use segmental method for lobectomy
Algorithmic Approach

- Calculate ppoFEV1 and ppoDLCO
  - If %ppoFEV1 and %ppoDLCO are > 40%, proceed with surgery
  - If %ppoFEV1 < 30% or %ppoFEV1 x %ppoDLCO < 1650, consider non-op
  - If either is < 40%, order cardiopulmonary exercise testing
Algorithmic Approach

• Exercise Testing
  – If VO2max > 20 ml/kg/min
    ▪ Proceed with surgery
  – If VO2max < 10 ml/kg/min
    ▪ Consider non-operative treatment or less extensive resection (wedge, segment)
  – Between 10 and 20 ml/kg/min
    ▪ It’s a judgment call
Treatment
Treatment of Extensive SCLC

• **Standard tx is Cis-platin and VP-16 (etoposide)**
  – Carboplatin plus VP-16 may be less toxic
  – Cis-platin plus irinotecan (CPT-11) is an option

• **Two cycles for induction then re-assess**
  – Two (to maybe 4) more cycles for consolidation
  – No benefit to more than 6 cycles
Treatment of Extensive SCLC

- Initial response rate of 60 – 85%
  - Complete response in 20 – 30%
- Median survival is 6 – 12 months
  - Remember 2 – 4 months without tx
- Two year survival = 20%
- Five year survival < 5%
Treatment of Limited SCLC

- Identical chemotherapy, but

- Add XRT (45 Gy)
  - Concurrent is better than sequential (1st or 2nd)
    - But more toxic
  - Hyperfractionation may be slightly better
    - 1.5 Gy bid versus 1.8 Gy qd
  - Accelerated fractionation may be better
    - Over three weeks

- Survival benefit with adding XRT to chemo
  - 5% at 3 years; 5 to 7% at 2 years
Treatment of Limited SCLC

• Initial response rates of 65 – 90%
  – Complete response in 45 – 75%

• Median survival of 16 – 24 months
  ▪ 40 – 50% 2 year survival

• In some studies, up to 20% are cured
Small Cell Lung Cancer

• PCI is indicated in pts achieving a PR/CR
• Not only a slight survival benefit
  ▪ 3 year survival improves from 15% to 21%
  ▪ 5% improvement in median survival
• But, more importantly, a “quality of life” benefit
  ▪ 60% chance of developing CNS mets within 2-3 yrs
  ▪ Decreases chance of CNS mets by 50%
Non-small Cell Lung Cancer

- Stage IA, IB, IIA, IIB = Surgery
  - Lobe with node sampling/dissection (VATS is preferred approach)
    - 3 or more nodal stations at least
    - Pneumonectomy may be necessary
    - Sleeve over pneumonectomy, if possible
  - Lesser resections (e.g. wedge, segmentectomy) may be appropriate in pts with marginal function
Non-small Cell Lung Cancer

- Stage IA, IB, IIA, IIB = Surgery
  - 5 year survival is not 100%
  - Actually 56%-90% depending on stage
  - Therefore, relapse is common

- In 2/3rds, relapse occurs distally and 1/3 locally
  - This is the rationale behind adjuvant therapy
Adjuvant Chemotherapy

- LACE group pooled the results of 5 trials with 4,584 patients
  - Median follow-up of 5.2 years

- Overall HR of death was 0.89 for chemo
  - Absolute 5 year survival benefit of 5.4%
Question 2

Adjuvant chemotherapy should be offered to patients following resection for lung cancer for all of the following stages except:

A. Stage IA
B. Stage IIA
C. Stage IIB
D. Stage IIIA
Adjuvant Chemotherapy

- Benefit varied with Stage
  - Stage IA = HR of 1.4
  - Stage IB = HR of 0.93
  - Stage II = HR of 0.83
  - Stage III = HR of 0.83

- Did not vary with choice of 2\textsuperscript{nd} agent
  - Vinorelbine, Etoposide, Vinca alkaloids, others

- Adjuvant chemo should be offered for stage 2 and resected stage 3
Non-small Cell Lung Cancer

- **Follow-up and Surveillance**
  - H&P plus imaging with CT every 6 months for 2 years then yearly until 5 yrs. If still eligible for screening then LDCT as appropriate for age and smoking hx

- **Second primaries are common**
  - Treatment is no different from initial though outcome is poorer
Non-small Cell Lung Cancer

- Those who are not candidates for surgery may be considered for other forms of therapy

- Standard XRT with curative intent is a distant 2nd to surgery in Stage I disease
  - 15 – 35% cure

- SBRT or SABR is treatment of choice for non-operative stage 1 patients.
Stereotactic Body Radiotherapy

Stereotactic body radiation therapy (SBRT) is a noninvasive cancer treatment in which numerous small, highly focused, and accurate radiation beams are used to deliver potent doses in 1 to 5 treatments to tumor targets in extracranial sites.
Stereotactic radiotherapy (SBRT)

High-precision image-guided RT characterized by:
- Accurate target definition
- Reproducible patient/tumor positioning
- Multiple non-coplanar RT beam
- Arc therapies

Features of SBRT delivery
- Steep dose-gradients
- Hypofractionation (3-8 sessions)
- High biological effective dose
97% three year local control rate.

Timmerman, R. et al. JAMA 2010;303:1070-1076.
Neoadjuvant Therapy

- **Stage IIIA**
  - 2 large randomized trials have found no survival benefit in patients given several cycles of chemo prior to surgery
    - Idea being that such therapy may result in tumor shrinkage and eradication of micrometastases
      - Thus enabling complete resection
  - Practice guidelines suggest there that standard of care remains concurrent chemoradiotherapy.
  - If considered outside clinical trial should be presented at tumor board
Adjuvant Tx Options for Resected IIIA Non-small Cell Lung Cancer

- Unsuspected Stage IIIA discovered at the time of surgery
  - Recent study of 7465 patients found that post-op XRT improved survival in patients with involved N2 nodes but not N1 or N0
  - Adjuvant XRT should be considered after adjuvant chemotherapy with IIIA disease
Non-small Cell Lung Cancer

• **Stage IIIB**
  – For good performance status
    ▪ Concurrent chemo and XRT is best
    ▪ Sequential may be better tolerated
  – For poor performance status
    ▪ XRT only
Pancoast (Sup Sulcus) Tumor

- Tumors in the apex of the lung that may invade contiguous structures
  - May cause local pain
  - May involve brachial plexus with pain down the medial aspect of the arm – MRI useful here

- Horner’s syndrome with involvement of the sympathetic chain and stellate ganglion
  - Unilateral enopthalmos, ptosis, meiosis, ipsilateral anhydrosis
Pancoast (Sup Sulcus) Tumor

- **Treatment**
  - If possible, En bloc resection
  - If resectable, good results with better results with pre-op chemorads with a 5 yr survival of 54%
  - If not completely resectable or have N2 involvement, concurrent chemo/rads
Non-small Cell Lung Cancer

- Stage IV (not curable)
  - For good performance status (ECOG0/1)
    - Chemotherapy provides a survival benefit
      - Median survival improves by 4 mos
      - Doubling of 1 yr survival
    - Quality of life benefit
    - Cost-effective therapy
Non-small Cell Lung Cancer

• Stage IV
  – For ECOG 2
    ▪ Single drug or Platinum doublet
  – For ECOG 3 or 4
    ▪ “Best supportive care”
Non-small Cell Lung Cancer

- **Stage IV**
- Cis-platin, vinblastine, vinorelbine, paclitaxel, docetaxel, carboplatin, topotecan, and gemcitabine are active
  - Two drug combinations are more effective
    - 2 month increase in median survival with the addition of bevacizumab in selected patients
      - Non-squamous, no brain mets, no hemoptysis
    - Another found a 1.2 month advantage with cetuximab
Non-small Cell Lung Cancer

- Duration of treatment
  - For responders
    - 4 - 6 cycles for responders then observe
    - Recently approved, in non-squamous cell, maintenance pemetrexed until progression
      - OS 15.5 mos versus 10.3 months
    - Recently reported, maintenance erlotinib
      - PFS of 22 weeks versus 16 weeks
  - For progressive disease
    - 2nd line chemotherapy
Non-small Cell Lung Cancer

- Stage IV
- Virtually all patients will recur
  - With good PS, consider 2nd line therapy
    - Docetaxel (8.8% respond; improves by 2 mo)
    - Pemetrexed (9.1% respond); ? Less toxicity
    - Erlotinib (small 2 month survival benefit)

- No benefit from doublet tx in 2nd line
Systemic Therapy

• Many have concluded that the treatment of Stage IV NSCLC has reached a plateau
  – Little can be expected of new cytotoxic agents or new combinations of existing drugs

• New approaches are needed
  – Targeted Therapy
  – Personalized Therapy
Targeted Therapy

- Directed at specific cell-signaling and regulatory pathways that are altered in the neoplastic cell.

- Opposed to a non-specific generalized attack on cell proliferation
  - So-called “cytotoxics”
Precision Medicine: Oncology

- Tailoring treatment to the individual’s tumor molecular characteristics
  - Depends on availability of molecular profiling tests
  - Specific targetable mutations

Lung Cancer Mutation Consortium in Lung Adenocarcinoma

- 1,007 (91%) Patients Tested for Mutation
  - 733 (66%) tested for all 10 genes
  - 60% female; median age 63
  - 34% NS; 58% former smokers

- Driver Mutation Found in 64% (n=466)
  - Two or more mutations in 3% (n=24)

Lung Cancer Mutation Consortium: Incidence of Drive Mutations

- KRAS: 25%
- EGFR (sensitizing): 17%
- ALK: 8%
- EGFR (other): 4%
- Mutation in >1 gene: 3%
- HER2: 3%
- No oncogenic driver detected: 36%
- MEK1: <1%
- NRAS: 1%
- MET: 1%
- PIK3CA: 1%
- BRAF: 2%
Lung Cancer Mutation Consortium in Lung Adenocarcinoma

- 938 Had Follow-up Data
  - 260 with driver mutation and Rx with a targeted agent: MST 3.5 years
  - 318 driver mutation and no Rx with targeted agent: MST 2.4 years
  - 3
  - 60 with no driver mutation: MST 2.1 years
MOLECULAR PATHOGENESIS

• Epithelial Growth Factor Receptor (EGFR)
  – Overexpressed in many cancers
    ▪ In up to 17% of lung cancers in North America
  – Binding of EGF to the cell surface receptor triggers intracellular signaling events through at least 3 major pathways (Akt, MAPK, and STAT)
In tumor cells, the EGFR-TK signal is inappropriately turned on by various mechanisms inside or outside the cell.

EGFR-TK enzyme activity drives uncontrolled tumor growth.

- Proliferation
- Invasion
- Angiogenesis
- Metastasis
- Inhibition of apoptosis
Turning Off the EGFR-TK Signal Inside the Cell

- Small Molecule EGFR-TK Inhibitors; such as gefitinib and erlotinib

Adapted with permission from Ritter CA, Arteaga CL. Semin Oncol. 2003;30(suppl 1):3-11.
MOLECULAR PATHOGENESIS

- EGFR
  - EGFR-TKI’s have minimal effect in most lung cancers
    - Dramatic effect in others
    - Clinical factors that predict response:
      - Adeno, never smokers, females, East Asian heritage
Five Year Survival in EGFR Mutant Lung Adenocarcinoma Treated with TKIs

- 137 patients with metastatic adenocarcinoma
  - PFS was 12.1 months
  - Overall median survival of 30.9 months

- Five year survival of 14.6%
  - 95% CI of 9.7-21.9%

- No dose limiting events at 28d
- Response rate of 84% similar at each dose level
- Side effects: diarrhea, nausea, rash, decreased appetite

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<thead>
<tr>
<th></th>
<th>Objective RR</th>
<th>Disease CR</th>
<th>Median PFS</th>
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<tbody>
<tr>
<td>T790M-positive</td>
<td>61%</td>
<td>95%</td>
<td>9.6 months</td>
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<tr>
<td>T790M-negative</td>
<td>21%</td>
<td>61%</td>
<td>2.8 months</td>
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Figure 3. Progression-free Survival According to Status with Respec to EGFR T790M.
Alectinib Phase I/II as frontline therapy in ALK positive NSCLC

- Alectinib 300mg BID PO for NSCLC after progression on chemotherapy
  - All were ALK inhibitor naïve
- 25 of 46 phase II patients were still on Rx
  - 3 year PFS was 62%
  - 3 year OS was 78%
- 14 pts had brain mets at baseline and 6 remain on study without CNS or systemic progression

Tamura T et al. J Clin Oncol pub online March 15, 2017
Cancer Immunotherapy

- Cancer cells have mutations that make them recognizable by the immune system

- However, cancer cells can evade the immune surveillance by expressing proteins such as PD-L1

- Inhibiting the PD-L1/PD-1 interaction can restore anti-tumor T-cell activity, potentially leading to long-lasting responses
Chemotherapy, patients with squamous-cell carcinoma of the lung have few treatment options

**Objective:** Phase 3 study to evaluate efficacy and safety of Novolumab compared with docitaxel
Figure 1. Kaplan–Meier Curves for Overall Survival.

<table>
<thead>
<tr>
<th></th>
<th>Median OS Mo (95% CI)</th>
<th>1-Yr OS % of pts (95% CI)</th>
<th>No of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N=135)</td>
<td>9.2 (7.3-13.3)</td>
<td>42 (34-50)</td>
<td>86</td>
</tr>
<tr>
<td>Docetaxel (N=137)</td>
<td>6.0 (5.1 -7.3)</td>
<td>24 (17-31)</td>
<td>113</td>
</tr>
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Pembrolizumab and Long Term Survival in Stage IV NSCLC

- **KEYNOTE** trials with pembrolizumab in second or greater line therapy
  - Evaluated with long term survival models
  - Estimated survival beyond 5 years at 21% and 25% in two trials
  - With docetaxel long term survival 5%

Hellman MD et al ASCO-SITC Clin Immuno-Oncology symposium abst #77, 2017
History of Therapy in Advanced NSCLC: FDA Approval Dates

- Not approved
- First-line
- Second-line
- Third-line
- Maintenance
- ALK positive
- EGFR Positive

Dates:
- Docetaxel 2002
- Gefitinib 2003
- Nab-Paclitaxel w/Carbo 2012
- Erlotinib 2013
- Afatinib 2013
- Ceritinib 2014
- Ramucirumab w/docetaxel 2014
- Gefitinib 2015
- Nivolumab 2015
- Pembrolizumab 2015
- Osimertinib 2015

Medians:
- OS (max) ~ 2-4
- ~ 6
- ~ 8-10
- 12+

Therapies:
- Cisplatin 1978
- Carboplatin 1989
- Vinorelbine 1994
- Docetaxel 1999
- Paclitaxel Gemcitabine 1998
- Bevacizumab 2006
- Pemetrexed 2008/2009
- Crizotinib 2011
- Erlotinib 2010
- Gefitinib 2015


BSC Single-agent platinum Doublets Bevacizumab + PC Mutation-directed Therapy

Standard therapies

Histology-directed therapy

Note: *Label does not include NSCLC-specific indication.
BSC = best supportive care; PC = paclitaxel/carboplatin; OS = overall survival.
Overview of NSCLC Treatment

Stage I
- Surgery (Radiation if inoperable)

Stage II
- Surgery With Adjuvant Chemotherapy

Stage III
- Radiation With Chemotherapy

Stage IV or Recurrent Disease
- Chemotherapy
- Targeted Therapy
- Immunotherapy