Adjuvant Radiation Therapy for Incompletely Resected/Recurrent Non Small Cell Lung Cancer

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Treatment Modalities-NSCLC

- Surgery with or without adjuvant chemotherapy or radiation
- Definitive radiation
  - SBRT for early stage
  - Standard fractionation if larger/node positive tumors
- Definitive chemo radiation for unresectable disease

- 30-55% develop recurrence and die of their disease after curative surgery.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>High CEA, lymphatic permeation, and pleural invasion</td>
<td>High CEA level, lymphatic permeation, pleural invasion and, peri-operative transfusion were proven to be independent factors for overall recurrence</td>
</tr>
<tr>
<td>Histological differentiation, vessel invasion, and visceral pleural invasion</td>
<td>Histological differentiation, vessel invasion, and visceral pleural invasion in stage I and Adenoca histology and visceral pleural invasion in stage IIINo and stage IIIN1 were shown to be independent significant risk factors for recurrence</td>
</tr>
<tr>
<td>Intratumoral vascular invasion and nodal involvement</td>
<td>Intratumoral vascular invasion and nodal involvement significantly influenced recurrence five years after complete resection</td>
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<tr>
<td>Intratumoral blood vessel invasion</td>
<td>Independent prognostic factor in poor DF</td>
</tr>
<tr>
<td>SUV</td>
<td>Patients with high max SUV and LVI were more likely to have recurrence</td>
</tr>
<tr>
<td>Number of LNs</td>
<td>Systematic sampling and complete MLNs dissection were associated with improved survival in comparison to random LNs sampling</td>
</tr>
<tr>
<td>PS, and symptoms at recurrence, liver recurrence, stage IIB or worse, and multiple recurrences</td>
<td>Strongly associated with post-recurrence survival</td>
</tr>
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</table>
**Molecular parameters**


<table>
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<tr>
<th>Parameter</th>
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<tbody>
<tr>
<td>KRAS and Ki-67</td>
<td>Excellent prognostic marker to predict the postoperative recurrence of stage I AD</td>
</tr>
<tr>
<td>Ki-67</td>
<td>Ki-67 expression was independently associated with an increased risk of poor DFS</td>
</tr>
<tr>
<td>MIB-1 and Bcl-2</td>
<td>The mitosis count and MIB-1 expression significantly correlated with recurrence and Bcl-2 tumors had a poor outcome</td>
</tr>
<tr>
<td>p16 and CDH1</td>
<td>Methylation of the promoter regions of p16 and CDH13 in both tumor and MLNs were associated with recurrence for patients with stage I NSCLC</td>
</tr>
<tr>
<td>MACC</td>
<td>MACC1 gene amplification may be a useful marker for predicting postoperative recurrence</td>
</tr>
<tr>
<td>EGFR mutations</td>
<td>Activating mutations within the EGFR TK domain can be used to predict the risk of recurrence in curatively resected pulmonary AD</td>
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</table>

**Molecular parameters (cont’d)**


<table>
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<tbody>
<tr>
<td>CXCR7</td>
<td></td>
</tr>
<tr>
<td>TS</td>
<td></td>
</tr>
<tr>
<td>CK 19</td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td></td>
</tr>
<tr>
<td>micro RNA expression profiles</td>
<td></td>
</tr>
<tr>
<td>IGF1R</td>
<td></td>
</tr>
<tr>
<td>EMT</td>
<td></td>
</tr>
<tr>
<td>micro RNA</td>
<td></td>
</tr>
<tr>
<td>... and many others</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant treatment options

- Chemo alone: patients with high systemic risk
- Radiation alone: patients with high loco regional risk
- Chemotherapy and radiation

- 20-40% still have local failure after complete resection and adjuvant chemotherapy.
- There is new interest in PORT (post operative radiation therapy)

PORT trials – Olden days

- Controversial results for completely resected patients without N2 disease
- PORT vs. Observation trials
  - From 1960-70's
  - Pre CT or PET based treatment
  - Cobalt-60 or orthovoltage (5 yr survival: 8% with Co 60 vs. 30% with modern xrt)
  - Treated larger volumes to account for breathing, organ motion, set up uncertainties: Tumor + up to 2.5 cm
  - Unconventional fractionations (>2 Gy/day)
  - Dose ranged from 50-50 Gy
  - Cord Dose limitation (45 Gy) due to 2D planning which has to block cord -> mediastinal underdosing
Radiation treatment planning

**NOW:** *new and improved*

- CT / PET based planning
- 4D CT
- Patient set up technique
- Respiratory gating
- Treatment planning advances
- Cone beam CT on treatment machine to localize tumor prior to each fraction
- Smaller treatment margins

Patient set up /Immobilization techniques

Medical Intelligence BodyFIX
Real-Time Position Management (RPM) System

Reflective marker
Box placed on abdomen for CINE-mode CT

Infrared camera system monitors box motion during CT

RPM System Breathing Trace

Inspiration: 1.8 sec.
Expiration: 2.5 sec.
Breathing Period: 4.4 sec.

Increase Treatment Time by ×4.6 (22% Duty Cycle)
4D CT

- 4D CT to delineate treatment volume
- MIP (maximum intensity projections) created
- Fused with diagnostic CT
- Volume delineated (clips, OP note, post op CT)
- Add margin for set up uncertainties, organ motion, etc.
  - Smaller margins due to better imaging techniques
  - 0.5-1 cm margins with 4D CT
- Dose: 5400-6000 cGy in 30 fractions
Radiation volume / Dose

- Use previous imaging, operative note
- Include positive nodal stations at surgery
- Level IV and Level VII
  - Risk of nodal involvement
    - 48% around the trachea
    - 41% in the subcarinal region
- Ipsilateral hilum
- 54 – 60 Gy

Modern Results

- Better outcome with better radiation techniques
- Benefit for PORT even for Stage I completely resected patients.
  - Italian study
PORT for Stage I resected patients

- Not routinely recommended

- However ...
  - *Italian Study by Trodella et al, 2002*
    - Prospective phase III randomized study
    - Pathologically stage I (T1/T2 No) patients, after lobectomy and hilar/mediastinal lymphadenectomy
    - PORT vs. Observation
    - 51 received PORT and 53 observation

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*Italian Study by Trodella et al, 2002 (cont’d)*

- All pts with CT planned treatment plan
- Linear accelerators used
- Volume: bronchial stump and ipsilateral hilum
- Dose: 50.4 Gy (1.8 Gy/fx) to bronchial stump and ipsilateral hilum
- CT based treatment planning
- Follow up: mean 63 months
RESULTS: @ 5 years

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<tr>
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<th>Observation</th>
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<tbody>
<tr>
<td>Recurrence</td>
<td>1 (2.2%) p=nsig</td>
<td>12 (23%)</td>
</tr>
<tr>
<td>DFS (no detrimental effect)</td>
<td>71% (p=0.03)</td>
<td>60%</td>
</tr>
<tr>
<td>OS (no detrimental effect)</td>
<td>67% (p=0.046)</td>
<td>58%</td>
</tr>
<tr>
<td>Lung function changes</td>
<td>No difference</td>
<td></td>
</tr>
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Post Operative Radiation Therapy (PORT)

- Stage I and II
  - If positive margins (microscopic or gross)
  - Pleural invasion
  - Chest wall invasion
PORT indication for Stage III

- N2 disease
- Positive margins (macroscopic or gross)
- Patients with proven N2 disease after induction chemotherapy followed by surgery (high risk of recurrence 20-60%)
- ANITA trial sub group analysis (Int. J. Radiation oncology, biol, phys 2008)
  - Benefit for PORT in N2 patients

ANITA: p N2 patients

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Observation +PORT</th>
<th>chemotherapy</th>
<th>Chemo +PORT</th>
</tr>
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<tbody>
<tr>
<td>5 yr OS</td>
<td>17 %</td>
<td>21%</td>
<td>34%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Median survival</td>
<td>12.7 months</td>
<td>22.7 months</td>
<td>23.8 months</td>
<td>47 months</td>
</tr>
</tbody>
</table>
Case: HW

- 84 year old female with abnormal CXR
- Left upper lobectomy and mediastinal sampling
- Path: 3.5 cm poorly diff. adeno carcinoma
- Visceral pleural invasion
- Mediastinal node (V) positive at surgery
- Refused chemotherapy
- Has pace maker on left chest wall

PET Scan: HW

Pace maker
Post op CT: HW

Case: HW

Pace maker moved
Radiation Dosimetry: HW

Treatment fields: HW

AP  LPO
Case: HH

- 66 year old male with Adenocarcinoma of the right upper lobe
- Right upper lobectomy and mediastinal sampling
- Pathology 1.8 cm, grade 2 adenocarcinoma, negative mediastinum
- Positive right chest wall margin at final path and invasion into visceral pleura
Plan HH

Plan HH
Case: DH

- 64 year old female
- History of squamous cell ca of larynx s/p supraglottic laryngectomy in 2009
- History wedge resection of left lower lobe in Aug 2004 for 1.5 cm, grade 2, adeno ca with visceral pleural involvement.
- Now with mediastinal lymphadenopathy
- EBUS: adeno ca
SS: 46 year old male

- Early 2011 with CXR: RUL consolidation
- 4/12/2011: Right upper lobectomy/completion pneumonectomy and mediastinal lymph node sampling
- Pathology:
  - 2 cm Squamous cell carcinoma,
  - Station 4R positive
  - Final staging: T2 N2 Mo or stage IIIA.
- CT chest on 05/12/11: a new mediastinal lymphadenopathy
- Chemo/ radiation 41.4 Gy then off cord to 12 Gy, boost to GTV

PET scan 5/19/2011
Pt SS (2011) Still alive

Summary:
- PORT: New and improved
- Better tumor localization, radiation delivery, patient positioning and verification methods
- PORT revisited?
Thank you!