Particle Beam Therapy for Lung Cancer

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Learning Objectives

- Indication of Current Particle Beam Therapy (PBT) for Lung Cancer
- Treatment Planning and Beam Delivery
  - CT scan
  - GTV, CTV, PTV of Stage I Non-Small Cell Lung Cancer
  - Gating & 4DCT
- Outcomes
- Adverse Events
Indications of Particle Therapy

- Early stage non-small cell lung cancer (NSCLC)
  - T1-3N0M0
  - Node negative should be confirmed by FDG-PET
- Locally advanced NSCLC
  - Should be treated in clinical trial basis
    - Concurrent use of cytotoxic agent and/or molecular-targeted agent, but adequate regimen has not been determined yet
    - Optimal dose-fractionation has not been determined yet
- Limited stage small cell lung cancer
  - Should be treated in clinical trial basis
    - The reasons are the same with locally advanced NSCLC
- Lymph node(s) recurrence after surgery
  - Patient & physicians preference
Stage I (T1-2N0M0) NSCLC

- Operable patients, but refusal of surgery
  - Operable possibility with standard lobectomy
    - Expected post-operative $\text{FEV}_{1.0} \geq 800$ ml
    - $\text{PaO}_2 \geq 65$ torr (room air)
    - No cardiac insufficiency
    - No uncontrollable arrhythmia
    - No uncontrollable diabetes mellitus

- Medically inoperable patients
  - $\text{FEV}_{1.0} \geq 800$ ml
Preparation (Fixation)

- Vacuum cushion
Preparation (CT scanning)

- Respiratory-gated CT
  - Acquired on exhalation phase (same with respiratory-gating (RG) at irradiation)
  - Slice thickness of 3-5 mm
  - Whole lung scanned in order to obtain DVH
- X-ray fluoroscopy
  - Check respiratory movement
- 4D-CT
  - Maximum intensity projection (MIP) lesion should be covered as a GTV without using RG
Treatment Planning 1 (GTV)

- GTV (red circle) should be delineated on lung field imaging CT slices
Treatment Planning 2 (CTV)

- CTV (blue circle) is expanded from GTV + 8 mm in all directions
Why 8 mm Margin for CTV

- CTV = GTV + 8 mm in all directions

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**EVALUATION OF MICROSCOPIC TUMOR EXTENSION IN NON–SMALL-CELL LUNG CANCER FOR THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY PLANNING**

**CLINICAL INVESTIGATION**

Lung

PURPOSE: One of the most difficult steps of the three-dimensional conformal radiotherapy (3D-CRT) is to define the clinical target volume (CTV) according to the degree of local microscopic extension (ME). In this study, we tried to quantify this ME in non–small-cell lung cancer (NSCLC).

Material and Methods: Seventy NSCLC surgical resection specimens for which the border between tumor and adjacent lung parenchyma were examined on routine sections. This border was identified with the naked eye, outlined with a marker pen, and the value of the local ME outside of this border was measured with an eyepiece micrometer. The pattern of histologic spread was also determined.

Results: A total of 354 slides were examined, corresponding to 176 slides for adenocarcinoma (ADC) and 178 slides for squamous cell carcinoma (SCC). The mean value of ME was 2.69 mm for ADC and 1.48 mm for SCC (p < 0.01). The 15% value was 2.89 mm for ADC and 2.05 mm for SCC. The 95% value was 3.48 mm for ADC and 2.47 mm for SCC. The most frequent pattern observed was followed by lymphatic invasion for ADC and interstitial extension for SCC.

Conclusion: The ME was different between ADC and SCC. The usual CTV margin of 5 mm appears inadequate to cover the ME for either group, and it must be increased to 8 mm and 6 mm for ADC and SCC, respectively, to cover 95% of the ME. This approach is obviously integrated into the overall 3D-CRT procedure and with other margins. © 2000 Elsevier Science Inc.
Treatment Planning 3 (PTV)

- PTV (yellow circle) is expanded from CTV + 5 mm in respiratory movement + 3 mm for set-up error
- Then modification will be done by physician
4D-CT (sample)
Why 5 mm Margin in Respiratory Gating

- We analyzed targeting accuracy of respiratory-gated proton beam irradiation for 15 HCC patients

Strain Gauge

Respiratory & Gating Signal

Optical devices also available

PTCOG47, Ogino, NCC, Kashiwa
Optical Device (Laser Sensor)
Respiratory-Gating System

Inhalation  Exhalation

Respiratory Signal

Beam On

Beam Off

Gating Signal
Digital Radiographies for Movement Analysis

Markers in HCC patient (DR image)

Digital Radiographies for Movement Analysis

Markers

Respiratory signal

Gating signal

Ruler

PTCOG47, Ogino, NCC, Kashiwa
Example Time Course of Markers’ Displacement

1, 2, 3, 4, 5, 6, 7, 8, 9
Averaged Cumulative Target Displacement (Cranial-Caudal Direction)
PTV (yellow circle) = CTV + 5 mm in respiratory movement + 3 mm for set-up error

Copy & paste method, but automatically done by our RTP system
Individualized Margin for Respiratory Movement
Add distal margin of 3 mm WEL to ensure dose to PTV – taking into account for uncertainties of the range and treatment planning.

Distal margin = 3 mm water equivalent path length (WEL)

90-95% dose level
We prefer 2 ports, but usually 2-4 ports are used.

- Bronchus
- Esophagus
- Spinal Cord

Proton beam does not stop in lung tissue.

Take into account for the difference between CT couch with treatment couch.
opposing rectangular 4 portal

DVH of the lung

Miyamoto T, NIRS
Treatment Planning 7 (DVH)

- V20 never exceeds 20%
Collimator & Bolus

- Smearing of bolus is necessary to ensure dose to the target

Smearing diameter = 15 mm
Dose-Fractionation

- Protons
  - 80 GyE / 20 fr / 4 w (Japanese standard)
  - → 66 GyE / 10 fr / 2 w

- Carbons (NIRS)
  - 72 GyE / 9 fr / 3 w
  - → 52.8 GyE / 4 fr / 1 w for stage IA,
    60 GyE / 4 fr / 1 w for stage IB
  - → Single fraction (dose-escalating study)

Note: this dose-fractionation should be applied for peripheral type cancer
Fig. 1. Response-dose curve for NSCLC patient survival at 30 months constructed using the parameters reported by Martel et al. (16): D-50 = 84.5 Gy and slope γ-50 = 1.5. The LQ parameters assumed for NSCLC tumors are α/β = 10 Gy, α = 0.35 ln/Gy, Tk = 28 days, and Tp = 3 days (See text). The difference between the BEDs calculated with and without proliferation (3rd and 4th lines of x axis legend) illustrates the loss of tumor effect due to repopulation.
<table>
<thead>
<tr>
<th>Location</th>
<th>Fraction 1</th>
<th>Fraction 2</th>
<th>Fraction 3</th>
<th>Total Dose</th>
<th>BED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loma Linda</td>
<td>5.1 Gy</td>
<td>6.0 Gy</td>
<td></td>
<td>51 Gy</td>
<td>77.0 Gy</td>
</tr>
<tr>
<td>Japan</td>
<td>4.0 Gy</td>
<td>6.6 Gy</td>
<td></td>
<td>80 Gy</td>
<td>112.0 Gy</td>
</tr>
<tr>
<td>SRT (Japan)</td>
<td>12 Gy</td>
<td></td>
<td></td>
<td>48 Gy</td>
<td>105.6 Gy</td>
</tr>
<tr>
<td>3D-CRT (RTOG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93-11</td>
<td>2.15 Gy</td>
<td>2.15 Gy</td>
<td></td>
<td>83.8 Gy</td>
<td>101.8 Gy</td>
</tr>
<tr>
<td>0117</td>
<td>2.4 Gy</td>
<td>2.65 Gy</td>
<td></td>
<td>84 Gy</td>
<td>104.2 Gy</td>
</tr>
</tbody>
</table>
Irradiation

- Passive scattering with respiratory-gating is a safe, reliable, and easy way.
Respiratory-Gated Irradiation

- End exhalation phase is used
- Irradiation duration might be 2-5 times longer
- All ports should be irradiated in each fraction
Proton Therapy for NSCLC

- **Loma Linda U. MC** (Bush DA, Chest 2004;126:1198-)
  - Stage I NSCLC  68 pts
  - 51, 60 GyE/10 fr./2 w
  - 3y LC 74%, 3y OAS 72%  (Median FU 30 m)

- **NCC, Kashiwa** (Nihei K, IJROBP 2006;65:107-)
  - Stage I NSCLC  37 pts (T1/T2 : 17/20)
  - 70-94 GyE (Median 80 GyE)/20 fr./4-5 w
  - 2y LC 80%,  2y OAS 84%  (Median FU 24 m)

- **Tsukuba U.** (Hata M, IJROBP 2007;68:786-)
  - Stage I NSCLC  21 pts (T1/T2 : 11/10)
  - 50, 60 Gy/10 fr./2 w
  - 2y cause specific survival 86%, 2y OAS 74%  (Median FU 25 m)
Carbon-ion Therapy for NSCLC

- NIRS, Carbon ion (Miyamoto T, IJROBP 2007;67:750-)
  - Stage I NSCLC  51 pts  (T1/T2 : 30/21)
  - 72 GyE/9 fr./3 w
  - 5y LC 95%,  5y OAS 50%  (Median FU 59 m)
### Outcomes of Stage I NSCLC

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Treatment</th>
<th>Detail of Tx.</th>
<th>N</th>
<th>T1/T2</th>
<th>3y OS</th>
<th>5y OS</th>
<th>3y LC</th>
<th>5y LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mountain/1997</td>
<td>Surgery</td>
<td>Surgery</td>
<td>1876</td>
<td>T1(687) T2(1189)</td>
<td>T1:71% T2:46%</td>
<td>T1:61% T2:38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rens/2000</td>
<td>Surgery</td>
<td>Surgery</td>
<td>1201</td>
<td>T1(404) T2(797)</td>
<td>T1:76% T2:59%</td>
<td>T1:63% T2:46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krol/1996</td>
<td>X</td>
<td>60Gy/20fr-65Gy/26fr</td>
<td>108</td>
<td>T1(51) T2(57)</td>
<td>31%</td>
<td>15%</td>
<td>71%</td>
<td>66%</td>
</tr>
<tr>
<td>Morita/1997</td>
<td>X</td>
<td>64.7Gy(55-74) 2-3Gy/fr</td>
<td>149</td>
<td>T1(60) T2(89)</td>
<td>34%</td>
<td>22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uematsu/2001</td>
<td>X-SRT</td>
<td>50-60Gy/5-10fr/1-2w</td>
<td>50</td>
<td>T1(24) T2(26)</td>
<td>66%</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley/2003</td>
<td>X-SRT</td>
<td>70Gy(60-84)/1.8-2Gy/fr</td>
<td>56</td>
<td>T1(31) T2(25)</td>
<td>34%</td>
<td>63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shioyama/2003</td>
<td>Proton</td>
<td>76Gy(49-93) 3Gy(2-6)/fr</td>
<td>51</td>
<td>Stagel(28)</td>
<td>T1:70% T2:16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bush/2004</td>
<td>Proton</td>
<td>51Gy/10fr 60 Gy/10fr</td>
<td>68</td>
<td>T1(29) T2(39)</td>
<td>72%</td>
<td>74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ogino/2007</td>
<td>Proton</td>
<td>70-94Gy/20fr</td>
<td>61</td>
<td>T1(33) T2(28)</td>
<td>87%</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyamoto/2003</td>
<td>Carbon</td>
<td>59.4-95.4Gy/18fr 68.4-79.2Gy/9fr</td>
<td>81</td>
<td>T1(41) T2(40)</td>
<td>42% T1:64% T2:22%</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acute Adverse Events

- Grade 2 or greater toxicities (mostly Grade 2)
  - Pneumonitis: < 5%
  - Dermatitis: < 5%
  - Esophagitis: = 0%
Late Adverse Events

- Grade 2 or greater toxicities
  - Pneumonitis, pleural effusion: 0-8%
  - Chest pain: <5%
  - Rib fracture: 5% (NCC experience)
    - Aged female patients
    - Tumor close to the chest wall
Pneumonitis Gr. 1: 80 GyE, 2 portals

Before PBT 1 m 6 m 1 y

2 y
Pneumonitis Gr. 2: 94 GyE, 2 portals
Before PBT

11/8 (1 m)

11/20

12/10

Pneumonitis Gr. 3: 88 GyE, 2 portals
Protocols for Locally Advanced NSCLC

- NCC, Kashiwa: Phase I/II
  - Stage IIIA/IIIB
  - Concurrent Chemo + Proton
    - Chemo: CDDP (80mg/m², d1)+ VNR (20mg/m², d1,8), q4w
    - Proton: 66-70-74 GyE, 2 GyE/fr

- MDACC: Phase II
  - Stage IIIA/IIIB
  - Concurrent Chemo + Proton
    - Chemo: TAX(50mg/m²)+CBDCA(AUC 2mg/min/ml), weekly
    - Proton: 74 GyE, 2 GyE/fr
PBT Conclusions

- Respiratory gating and 4D-CT are convenient tools for the treatment of lung cancer
- The loco-regional progression-free and overall survival rates may be comparable to those of surgery in stage I patients
- Clinical trials for locally advanced NSCLC and limited-stage SCLC should be conducted at many institutions
- To evaluate the efficacy of PBT, prospective studies are mandatory