Image-Guided Proton Therapy in Non-small Cell Lung Cancer (NSCLC)

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Objectives:

1. Introduce proton therapy in NSCLC

2. Discuss impact and management of intra- and inter- fraction tumor motion and anatomy change in proton treatment planning and delivery

3. Review undergoing proton therapy clinical trials in NSCLC

4. Discuss proposed clinical studies
Lung Cancer Basic Factors

• No. 1 cancer killer
• 161,840 patients will die in 2008
  – Higher than prostate, breast, colon/rectum, pancreas cancers combined
• 1 patient dies every 3 min in US
• Overall 5 year survival 15%
• Local control: about <50% with standard photon dose (60 to 66 Gy)

• Changes are needed!
Proton Therapy in lung cancer: Improves therapeutic ratio and allows dose escalation/acceleration.
Spread Out Bragg Peak (SOBP)
Proton delivery:

1. Passive Scattering Proton Therapy (PSPT)

Movie.7

Rotating Modulating Wheel

Movie.8

Second Scatter

Spread Out Bragg Peak (SOBP)

Compensator

Collimator

Target

(Yoshikazu Tsunashima)
Proton Delivery:

2. Spot scanning (Intensity-modulated proton therapy, IMPT)

Cumulative dose

Spot position

Movie.9

Movie.10 (Yoshikazu Tsunashima)
PSPT:
Reduce normal tissue dose compared with 3-DCRT and IMRT

10-20% absolute improvement in lung V5 and V10
33-61% absolute improvement in non-target integral dose

PSPT:
Dose escalation of PSPT in NSCLC:

87.5 CGE in stage I
74 CGE in stage III
DVH showed: spares more normal tissues compared with 3-DCRT or IMRT using 60 Gy

IMPT:
Reduces the normal tissue dose compared with IMRT in stage IIIB NSCLC

13-22% absolute improvement in lung V5 and V10
(Chang et al: PTCOG 47, poster 39)
**IMPT:**
Improves normal tissue sparing compared with PSPT and allows further dose escalation

5-10% absolute improvement in lung V5 and V10
(Chang et al: PTCOG 47, poster 39)
Lung cancer moves

50%: move 0.5 to 1 cm
10%: move > 1 cm

IGTV: Path of gross tumor motion

Proton radiotherapy margins for motion and other uncertainty

Aperture Margin 10 mm alone (50-90% proton penumbra)

Border smoothing margin 10 mm

Smearing margin:

\[
Smearing\ margin = \sqrt{(IM + SM)^2 + [0.03 \times (distal\ CTV\ depth + compensator\ thickness)]^2}
\]

DM = 0.035 XCTV distal depth + 3 mm

PM = 0.035 X CTV proximal depth + 3 mm

Intra-fraction tumor motion:
4-D CT planning guarantees delivery of prescribed dose and spare more normal tissue
**4D Proton Plans**

**Non gating**
Free breathing
0~10 % phase
GTV from MIP

**Gating**
40~60% expiration phase
GTV from MIP_{40-60}

(Yoshikazu Tsunashima)
Non gate: Free breathing

Gating in 40~60% expiration phase

(Yoshikazu Tsunashima)
4-D CT-based simulation: individualized ITV approach

Lung cancer moves

“Average” CT

MIP motion envelope
4-D CT-based proton planning: ITV approach

MIP density replaces IGTV in average CT data base for compensator design and dose calculation achieved the best overall target coverage and critical structure sparing.
4-D CT-based ITV approach proton treatment planning

PET

MIP density replaces IGTV in average CT data set

Isodose distribution in average CT

Chang et al: IGRT in lung cancer 2007
Respiratory gated proton therapy
(Chang et al, PTCOG 2006)

6% absolute improvement in lung V5, V10 and V20

Stage I NSCLC

Stage III NSCLC
Inter-fraction tumor motion and anatomy changes: A typical case

CTV density change correlated with increased contra-lateral lung mean dose over 7 weeks of RT in proton but not IMRT

Inter-fraction anatomy/motion change
A extreme case

CTV coverage drops from 99% to 92.3% with proton but not in IMRT

Adapted proton therapy

Initial plan

87.5 CGE in T2N0M0 NSCLC

Initial plan recalculated based on CT after 5 wks TX

Re-plan based on CT after 5 wks TX
Adapted proton therapy

Dashed line: Initial plan
Solid line: Initial plan recalculated based on CT taken after 5-weeks of proton therapy
Dot-dashed line: re-plan
A. Simulation

B. 3 weeks later

C. Adapted plan

Adapted proton radiotherapy

74 CGE with Carb/Taxol in Stage III NSCLC

Chang et al: IGRT in lung cancer 2007
Proton therapy clinical studies in NSCLC


Total of 5 published series (n=215), mainly stage I NSCLC. No concurrent chemo

1. Dose: range 45 to 94 CGE in 7 to 32 Fx

2. Issues:
   - Wide range of disease stage
   - Tumor motion: no 4-D CT
   - Wide range of dose and fractionation
   - Dose may not be adequate in some studies

3. Toxicities appear reduced.
   - Data in stage Ia with BED > 100 CGE comparable to surgery
1. Phase II escalated/accelerated proton radiotherapy for medically inoperable centrally located T1N0M0 or any location of T2N0M0 and selective T3N0M0 (chest all) (stage I-II) NSCLC

87.5 CGE with 2.5 CGE/F
15/23 pts enrolled.

Dermatitis: grade III: 15%
Pneumonitis Grade II: 6.7%, no grade III
No esophagitis

2. Phase II concurrent proton and chemotherapy in inoperable stage III NSCLC

74 CGE with 2 CGE/F
32/56 pts enrolled:

Acute esophagitis: grade II: 25%, grade III: 6%
Dermatitis: grade III: 9%
Pneumonitis Grade II: 19%, no grade III
Proton therapy (87.5 CGE) in central stage I NSCLC

A. Before Proton
B. After Proton

C. Before Proton
D. After Proton

E. Diagram showing treatment plan and dose distribution.
Stage IIIA NSCLC treated with 74 CGE proton and chemotherapy

Before proton RT

6 months after
Stage IIIB NSCLC treated with 74 CGE proton and chemotherapy

Before proton therapy

One year After therapy

CT

PET
Proposed phase II adaptively randomized clinical trials to compare proton to photon therapy (MDACC and MGH)

1. Proton therapy (87.5 CGE with 2.5 CGE/F) vs photon therapy (84 Gy with 2.15 Gy/F) in centrally located T1 or T2 stage I NSCLC
2. Proton therapy (74 CGE with 2 CGE/F) vs photon IMRT therapy (74 Gy with 2 Gy/F) with concurrent chemotherapy in stage III NSCLC

Proposed phase I clinical trials to escalate/accelerate proton therapy:

1. IMPT simultaneous integrated boost (SIB) dose escalation to IGTV with concurrent chemotherapy in stage II/III NSCLC
2. Hypofractionated stereotactic body proton therapy in centrally located T1 or T2 stage I NSCLC
Conclusions:

• Proton therapy may reduce toxicity and allow for dose escalation/acceleration in NSCLC

• 4-D based treatment planning is crucial and adapted treatment is indicated in selective patients

• Further optimizing proton therapy and clinical trials are needed.
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