Uncertainty with Image-guided Radiotherapy in Lung Cancer

Joe Y. Chang, MD, PhD
Clinical Section Chief
Thoracic Radiation Oncology

Director
Stereotactic Ablative Radiotherapy Program
Lung Cancer

- No. 1 cancer killer
- 5 year overall survival: 15%
- Local control: < 50% with standard photon dose
- RT dose escalation improves LC but increases toxicity particularly when concurrent chemo is used
Improving RT conformality:

Radiation: Double edged sword

High dose: focuses on CA and avoids normal structures
Precise targeting
Uncertainty of target delineation
Gross Tumor Volume Uncertainty:

Lung parenchyma gross tumor: CT lung window
Mediastinal lymph nodes: Mediastinal window
Ideally with i.v. contrast
GTV Uncertainty: Tumor vs. collapsed lung

(Chang: Uncertainties in EBRT. Thorax, 575)
GTV: Involved vs. non-involved lymph nodes

Which SUV value should be used? 2.5? 40% SUVmax? Or ???
CTV margin uncertainty:

Cover 95% microscopic disease:
Adenocarcinoma: 8 mm; Squamous cell ca: 6 mm; Lymph node: 8 mm
Lymph node drainage in lung cancer: Should we TX LN prophylactically?
Exclusion of elective nodal irradiation in NSCLC

9% (1% isolated) elective nodal failure vs. 25% LF vs. 41% DM (Sulman and Chang et al: Rad Onc 4:5 2009)
PET/CT and IMRT in small cell lung ca

Exclusion of elective nodal irradiation: Among all failure
3% elective nodal failure 77% DM 26% LF

(Shirvani and Chang et al: Int I Rad Onc Bio Phy 2011 e-pub)
GTV after induction chemotherapy: Where is GTV and CTV?
PTV Uncertainty
Adaptive Radiotherapy (ART)

Tumor Motion:

- 10 mm: 10%
- 5 to 10 mm: 40%
- <5 mm: 50%


Uniformed Target volume

ITV
Gating
Breath-hold
Tracking

Adaptive Radiotherapy (ART)

IGTV: Path of gross tumor motion
Image-guided Radiation Therapy (IGRT)
From 2-D to 5-D
Conformal Radiotherapy

1. Location
2. Location
3. Location
Confirm location by imaging
Uncertainty of SBRT

Large beam numbers to achieve a sharp dose fall off
Stereotactic Body Radiation Therapy (SBRT)
Stereotactic Ablative Radiotherapy (SABR)

Local control >90% with ablative dose (BED>100 GY to PTV): 54 Gy in 3 Fx; 50 (48) Gy in 4 Fx; adaptive dose regimens

Loo, Chang, Dawson, Kavanagh, Koong, Senan and Timmerman: Practical Radiation Oncology Editorial 1:38, 2011

How to calculate the physics dose?

With or without heterogeneity correction

Which calculation algorithms?

Monte Carlo
Pencil beam
AAA
Pinnacle…….
LQ-model: limits of applicability

\[ \text{BED} = \text{TD}(1 + \frac{D}{a/b}) \]

Dose per fraction (Gy)

radiosensitivity (?)

Where the dose is prescribed?

90% I/S line

70% I/S line

PTV dose < 40 Gy with I/C Rx

GTV

PTV

I/C

Dose (cGy)

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 1000 2000 3000 4000 5000 6000 7000 8000

Absolute
7000.0 cGy
6000.0 cGy
5000.0 cGy
4800.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
Adapted radiation therapy during fractionations

Uncertainty in tumor position with respect to bony anatomy as seen from 3D bony alignment of a daily pre-treatment CT to a reference CT for a patient on SABR

(Chang: Uncertainties in EBRT. Thorax, 575)
Phase I/II SBRT in central/superior lesion: Defined as within 2 cm of brachial tree, mediastinal structures and brachial plexus


- **IGRT**: 4-D CT based, daily CT guided
- 50 Gy to PTV (GTV + 11 mm)
- Keep critical structures under normal tissue dose volume constraints proposed based on literature and BED calculation model
SBRT in centrally and superiorly located stage I or isolated recurrent NSCLC  

- **Local control:**
  - 100% at 2 years
- **Pneumonitis (>Grade 2):**
  - Stage I: 0%  Recurrent: 28.6%
- **Dermatitis and chest wall pain:** 11.1%
- **One case of brachial neuropathy**
Target and critical normal structure
Breath-hold provides 3 mm more distance between the ITV and OAR.

Abdominal Compression

Repeat Breath-holds

7 mm

10 mm
Before SBRT

29 months later

RT planning

Daily CT before SBRT

Brachial plexus

A.

B.

C.

Dose Volume Histogram

Brachial plexus

Total lung

Left lung

GTV

CTV

PTV

40 Gy

Uncertainty of normal tissue tolerance
Improves RT Conformality

1. Tumor target
2. Critical normal structures (Organ at risk, OAR)

(Chang and Cox: Seminar of Radiation Oncology, 20:171, 2010)
Propensity matched comparison of lobectomy and SABR (Chang et al: 2011 submitted)
Phase III Randomized study: Stereotactic Ablative Radiotherapy vs. Surgery (SARS) in operable stage I NSCLC

SABR

Lobectomy
SABR for Recurrent or Second Lung Cancers After Definitive Radiation for Intrathoracic Neoplasms

Kelly and Chang et al,
Int. J Rad Onco Biol Phy, 78:1387, 2010
Overall and Progression Free Survival

SABR in Field Local Control rate: 95%
Toxicity by Treatment Group

Out of field relapse

In-field relapse

Incidence (%)

- Out of field relapse
- In-field relapse

- Pneumonitis Grade 3
- Chest Wall Pain

* $p < 0.04$
** $p < 0.03$
Predicting radiation pneumonitis after SABR in recurrent Dz: Multivariate analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>p value</th>
<th>HR (95% CI)</th>
<th>Beta coefficient</th>
<th>Assigned score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG before SABR</td>
<td>0.008</td>
<td>10.49(1.83-60.13)</td>
<td>2.35</td>
<td>1</td>
</tr>
<tr>
<td>FEV1 before SABR</td>
<td>0.012</td>
<td>12.05(1.72-84.48)</td>
<td>2.49</td>
<td>1</td>
</tr>
<tr>
<td>V20(composite plan)</td>
<td>0.020</td>
<td>11.71(1.47-93.19)</td>
<td>2.46</td>
<td>1</td>
</tr>
<tr>
<td>Previous PTV location</td>
<td>0.024</td>
<td>10.92(1.37-87.11)</td>
<td>2.39</td>
<td>1</td>
</tr>
</tbody>
</table>
SPECT functional image guided SABR
Uncertainty of IMRT

- Low dose exposure due to more beam numbers
- Motion effect
- Efficiency

• Recommendations:
  - Image-guided motion management: IGRT
  - Use 5-7 beams or limited arcs
  - Avoid very small treatment field
  - High efficiency TX: VMAT

IMRT improves survival in stage III NSCLC treated with chemo/RT


- The combination of
  - IMRT
  - IGRT
  - 4DCT
- Increased
  - Local control
  - Overall Survival
- Decreased
  - Pneumonitis
IMRT reduces RT-Pneumonitis in NSCLC tx with concurrent Chemo/RT
Optimizing Radiotherapy: RTOG 0617

60 vs 74 Gy ± C225
PI: Bradley

STD dose vs High Dose

Tumor = 60 Gy* =

Tumor = 74 Gy =

*60 Gy to the PTV = 63 Gy to isocenter (9410 dose)

IMRT is allowed with motion < 1 cm; heterogeneity correction is required.
Not all GTVs are created equal
High SUV in PET predict for high local recurrence

Regions of interest contoured on fused PET/CT in Pinnacle treatment planning system. (Klopp and Chang et al: Int J Rad Onc Biol Phys 69:1409, 2007)
Volume and SUV to be predictors of recurrence.

Improve Biological Conformality
IMRT dose painting in high PET region

74 GY to SUV > 13.8

(Chang and Cox: Seminar of Radiation Oncology, 20:171, 2010)
Dose escalation to PTV is impossible for very extensive disease
Adaptive Radiation Therapy

Sim

Week 5
Uncertainty of Proton Therapy
Improving radiotherapy conformality in lung cancer
(Chang and Cox: Semin Rad Onc 20:171, 2010)
Non gate: Free breathing

Gating in 40~60% expiration phase

(Yoshikazu Tsunashima)
4-D CT-based proton treatment planning in patients with stage III NSCLC.

Chang et al: IGRT in lung cancer 2007
MDACC 2004-977
Phase I/II escalated/accelerated proton therapy in early stage NSCLC
(PI: Chang)

Eligibility:

Medically inoperable centrally located T1 or any location of T2 and selective T3N0M0 (chest all) (stage I-II)

Primary objectives:

Local control and toxicity

Proton Dose:

87.5 Gy with 2.5 Gy/F
Adaptive/ablative proton therapy in early stage NSCLC

(Chang et al: Int J Rad Onc Bio Phys 2011 Epub ahead of print))

28 pts enrolled.
Median F/U 16.3 months (range 5-36 months)

Toxicity:
No grade 4 or 5 toxicity, only grade 3 toxicity is dermatitis
Grade 2 pneumonitis: 11%
Grade 2 esophagitis: 6%

Tumor control:
Rates of local control: 89%
Regional lymph node failure 11%,
Distant metastasis 28%.
(Chang et al: Int J Rad Onc Bio Phys 2011)

A. Before treatment

B. After treatment

C.
(Chang et al: Int J Rad Onc Bio Phys 2011)

Pre-RT  Proton TX

A.

B. 3 months  6 months/Bx  9 months after chemo
Eligibility:
Inoperable extensive stage III NSCLC

Primary objectives:
Survival and toxicity

Proton Dose:
74 Gy with 2 Gy/F with concurrent Carb/Taxol
Phase 2 study of high dose proton/chemo therapy for stage III NSCLC
(Chang et al: Cancer 2011, Epub ahead of print)

Median F/U 19.7 months (range 6.1-44.4 months)

Median overall survival: 29.4 months.

Toxicity:

No grade 4 or 5 toxicity.

Grade 3 adverse effect:

Dermatitis (11.4%)

Esophagitis (11.4%)

Pneumonitis (2.3%)
## Failure Patterns After Concurrent Proton Beam Therapy and Chemotherapy

<table>
<thead>
<tr>
<th>Site of First Failure</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Distant</td>
<td>14 (31.8%)</td>
</tr>
<tr>
<td>Regional</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Local + distant</td>
<td>3 (6.8%)</td>
</tr>
<tr>
<td>Regional + distant</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Regional + local</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Distant + local + regional</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>

*Total local failure: 20%
Total DM: 43%*

(Chang et al: Cancer 2011, Epub ahead of print)
Tumor recurrence

PSPT with cold spot

Lei Dong
Joe Chang
Adapted proton therapy

(Chang et al: IGRT in lung cancer. 2008)

>400 lung cancer patients have been treated with adapted proton therapy
Adaptive Radiotherapy
(Gomez and Chang: J Oncology 2010)
CTV density change correlated with increased contra-lateral lung mean dose over 7 weeks of RT in proton but not IMRT

MGH and MDACC

NCI Program grant CA

(PI: Thomas Delaney and Radhe Mohan)

Optimizing proton therapy in cancers
IMPT improves normal tissue sparing and target coverage compared with PSPT in complicated anatomy

**IMPT vs. IMRT:**

Absolute improvement in lung: V5: 22%  V10: 13%

Individualized radical radiotherapy to dose of 74 Gy to 84 Gy


**IMRT**

**IMPT_MTD**
**IMPT improves OAR sparing**

(Register and Chang: Int J Rad Onc Bio Phy, 80:1015, 2011)
What you see may not be what you get.
PO1 randomized phase II clinical trial: Proton vs. IMRT

Eligibility:
Stage II/III NSCLC

Dose:
74 Gy with concurrent Carb/Taxol in both proton and IMRT

Primary objectives:
Grade 3 pneumonitis and local control

Patients randomized: >75 pts
PO1 randomized phase II clinical trial:  
**SBRT vs. SBPT**

Eligibility:
- Centrally located stage I NSCLC
- Isolated lung parenchyma recurrent NSCLC

Dose:
- 50 Gy in 4 FX

Primary objectives:
- Grade 3 lung and Esophageal toxicity
Summary

• Uncertainty is significant in lung cancer radiotherapy
• IGRT is crucial
• Cutting-edge technology improves clinical outcome by dose escalation/acceleration to target while minimizing dose to critical structures
• More research is needed
Thank you

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