Photon versus Proton Therapy: Have we reached the limit?

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Stephen M. Hahn
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Effect of underdosage and overdosage

![Graph showing the effect of tumor dose on tumor control and late normal tissue damage](image)

Challenges in Radiation Therapy

1. Cost & Value
2. Beam Uncertainties
   -Protons scatter differently (charged particle) – very sensitive to tissue inhomogeneity
   -Range Uncertainty
   -Affects beam directions & introduces uncertainty about delivered dose
   -Accentuate the issues related to random & systematic set up errors
3. Conformality
4. Motion & Imaging

Beam Uncertainties - Range Uncertainty

- Range uncertainty has several treatment planning & clinical implications
- Limits field arrangements and beam weighting
  -Fields where the distal edge is at the interface of a critical structure (cord, optic nerve)
  -May limit the amount of dose delivered by any given field
- Affects the margin placed at the distal edge of the beam
- Measurement of range is likely to be important in hypofractionated regimens
Dose Conformality and Protons

- Protons administered with double scattering (DS) technologies, in particular, do not provide the level of dose conformality* that modern x-ray technologies do
- For many clinical situations, the high dose regions in normal tissue are higher & certainly no better than x-rays
- PBS (SFUD) and IMPT typically provide greater dose conformality compared to DS protons and perhaps modern x-ray technologies but motion is a more significant issue


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Early Stage Disease: Stereotactic Body Radiation Therapy

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Hypofractionated Protons for Stage I NSCLC

- PT treatment plans were generated using single-, two-, and three-field passively scattered and actively scanned proton beams. Calculated dose characteristics were compared.
- Comparable planning target volume (PTV) median minimum and maximum doses were observed between PT and SBRT plans. Higher median maximum doses 2 cm from the PTV were observed for PT, but higher median PTV doses were observed for SBRT.
- The total lung mean and V5 doses were significantly lower with actively scanned PT. The lung V13 and V20 were comparable. The dose to normal tissues was lower with PT except to skin and ribs.
- Passively scattered plans, compared with actively scanned plans, typically demonstrated higher doses to the PTV, lung, and organs at risk.

Macdonald OK et al. IJROBP 2009

Prostate Cancer: The Evolution of Radiotherapy

Are Protons Better than IMRT?

### Efficacy & Toxicity of IMRT and PBT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IMRT</th>
<th>PBT</th>
<th>FU (yrs)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>&gt;80-90%</td>
<td>&gt;80-90%</td>
<td>5</td>
<td>Limited</td>
</tr>
<tr>
<td>DSS8</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>5</td>
<td>Limited</td>
</tr>
<tr>
<td>FF85</td>
<td>74-96%</td>
<td>69-95%</td>
<td>3.0-6</td>
<td>Limited</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Acute vs. Late</th>
<th>IMRT (Pooled Rate 95 CI)</th>
<th>PBT (Pooled Rate 95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Acute</td>
<td>18.4 (8.3, 28.5)</td>
<td>0*</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>6.6 (3.9, 9.4)</td>
<td>16.7 (1.6, 31.8)</td>
</tr>
<tr>
<td>GU</td>
<td>Acute</td>
<td>30.0 (13.2, 46.7)</td>
<td>40.1*</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>13.4 (7.5, 19.2)</td>
<td>5.5 (4.6, 6.5)</td>
</tr>
<tr>
<td>ED</td>
<td>Acute</td>
<td>48-49**</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

**2 studies *1 study

**Are Protons Better?**

Although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment. J Natl Cancer Inst 2013;105:25–32

**Study Schema**

- Follow: Months 1, 3, 6, 9, 12, 18, 24
- Primary Endpoint: Decline in function in 0.5 ml (SPRC)
- Secondary Outcomes: Urinary and erectile function, HRQOL, and QoL
- Direct and Indirect Costs, Adverse events, Satisfaction, Radiation endpoints
Liao – P01 Randomized Phase II NSCLC Trial

A Bayesian Randomized Trial of IMRT vs. 3D-PSPT for Locally Advanced NSCLC

Analyses ongoing – two manuscripts in preparation

Adapted from Liao's ASCO Slides

Hypothesis

• Proton therapy will
  – Reduce irradiated lung volume, hence reduce radiation pneumonitis (RP)
  – Achieve same local control (LC) for the same prescribed biologically effective radiation dose (RBE = 1.1)

Lung and Heart V5-V80

Lung V5 – V80

Heart V5 – V80

Note: Analysis carried out using the Wilcoxon rank-sum test (also known as Mann-Whitney Two-Sample Statistics)
Radiation Pneumonitis

<table>
<thead>
<tr>
<th>RP Grade</th>
<th>IMRT</th>
<th>3DPT</th>
<th>Total</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=92</td>
<td>N=57</td>
<td>N=149</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>65</td>
<td>36</td>
<td>101</td>
<td>0.36</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>11</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Gr 0-2</td>
<td>86</td>
<td>51</td>
<td>137</td>
<td>0.54</td>
</tr>
<tr>
<td>Gr 3-5</td>
<td>6 (6.5%)</td>
<td>12 (8.1%)</td>
<td>18 (10.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Median Time to RP: All = 4.3 month, IMRT = 4.5 month, 3DPT = 4.0 month (p=0.15)

Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p-value</th>
<th>95%CI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>1.03</td>
<td>0.012</td>
<td>1.01</td>
</tr>
<tr>
<td>RT Time</td>
<td>&gt;=74</td>
<td>0.62</td>
<td>0.036</td>
<td>0.39</td>
</tr>
<tr>
<td>GTV</td>
<td>Continuous</td>
<td>1.002</td>
<td>0.02</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Conclusions

- Considerably fewer events occurred in both arms compared what was expected based on statistical considerations in the trial design
  - No statistically significant difference in RP or Local Failure when IMRT and 3DPT plans were required to meet identical normal tissue dose constraints and target prescription dose
- Patient enrolled after 9/27/2011 did better – learning curve and improving in techniques, but differential greater for protons
An Example of 3D Isodose Comparison for 3DPT vs. IMRT Plans: High dose volume for PSPT > for IMRT

Understanding Factors Affecting Outcomes (Toxicities and Recurrences) for the Randomized Lung Trial

- Trial design – Requirement of the same normal tissue dose constraints and same prescription in both arms
- Greater vulnerability of proton dose distributions to intra-fractional motion and inter-fractional anatomy changes
- Larger penumbra and large spot sizes → larger higher dose volume outside the target
- State of the art of proton dose calculation algorithms
- Assumption of RBE = 1.1
- Technological state of the art insufficiently advanced (PSPT used, not IMPT; image guidance; …)
- Planning experience and expertise still evolving and lags behind IMRT

RTOG 1308

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage IIIB NSCLC

| SCHEMA | Both Arms: | Consolidation chemotherapy x 2 is allowed
|--------|-----------|----------------------------------|
| Stage  | RTOG 1308 | Chemotherapy
| GTV Volume | Ann 1: Photon dose—Higher achievable dose between 60-75 Gy (RBE), once daily plus platinum-based doublet chemotherapy |
| Histology | Ann 2: Proton dose—Higher achievable dose between 60-75 Gy (RBE), once daily plus platinum-based doublet chemotherapy |
| Neoadjuvant Chemotherapy | 1. No | 
| | 2. Yes |
Symptom burden less with IMPT after treatment than IMRT based on patient reported outcomes


MDACC case-Matched analysis IMPT vs IMRT

- Patients with OP cancer, 50% p16+
- Using a preplanned analysis, feeding tube 3 months post RT or grade 3 weight loss (>20%)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>During RT</th>
<th>3-Months post RT</th>
<th>1 year post RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-tube presence</td>
<td>IMPT (%)</td>
<td>IMRT (%)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>Weight loss &gt;20% compared to baseline</td>
<td>4 (5.6)</td>
<td>2 (1.7)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

| Combined G-tube OR with weight loss >20% | 5 (10.4) | 2 (1.7) | 0.03 | 1 (0.1-8.1) | 0.10 | 0.05 |

Source: Blanchard et al. Radiotherapy and Oncology 2016 (in press)

Potential Benefit for OPC IMPT vs IMRT

A randomized controlled trial

Eligibility
1) Stage III-IV oropharyngeal cancer
2) Squamous cell carcinoma
3) ECOG <=2
4) Target volume delineation

IMPT (75 GyRBE) (Chemotherapy (locally advanced disease))

IMRT (70 Gy) (Chemotherapy (locally advanced disease))

Frank, PI: Trial Activated at MD Anderson – Sept 2013
Esophagus is surrounded by critical normal tissues (heart & lungs).

How do we deliver tumoricidal dose and also reduce exposure to the surrounding organs?

Physical characteristics of PBT have the potential to further reduce toxicities while delivering an effective dose to the tumor.

Length of hospitalization comparing radiation modalities:

<table>
<thead>
<tr>
<th>Radiation Modality</th>
<th>Mean Length of Hospital Stay (days)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D (N=208)</td>
<td>9.9 days (8.7-10.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IMRT (N=164)</td>
<td>11.6 days (10.6-12.7)</td>
<td></td>
</tr>
<tr>
<td>PBT (N=72)</td>
<td>13.2 days (11.1-14.4)</td>
<td></td>
</tr>
</tbody>
</table>

Wang et al., IJROBP 2013

Lin SH et al., ASTRO 2015

MD Anderson Cancer Center

Value Proposition- H&N

Cumulative Cost of Care During Radiation Therapy

Value = \sum \text{Outcomes} - \sum \text{Costs}

Equivalent at 21 Fxs

Number of patient treatments

Thaker N et al. Oncology Payers 2014
**Mean Radiation Dose to Normal Organs**

**Protons vs Photons**

<table>
<thead>
<tr>
<th>3D-CRT</th>
<th>IMRT</th>
<th>VMAT</th>
<th>PROTONS (PASSIVE)</th>
<th>PROTONS (IMPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUNG – 1747</td>
<td>LUNG – 1324</td>
<td>LUNG – 1103</td>
<td>LUNG – 966</td>
<td>LUNG – 775</td>
</tr>
<tr>
<td>HEART – 2833</td>
<td>HEART – 1933</td>
<td>HEART – 2200</td>
<td>HEART – 1301</td>
<td>HEART – 943</td>
</tr>
</tbody>
</table>

**Key Question:** Does reducing the *unnecessary* exposure of the heart and lungs to radiation using proton beam improve clinical outcomes?

ClinicalTrials.gov: NCT01512589

**MDACC 2011-1036**

**Phase IIB Randomized Trial of Proton Beam Therapy (PBT) versus Intensity Modulated Radiation Therapy (IMRT) for the treatment of Esophageal Cancer (U19)**

PI: Steven H. Lin, M.D., Ph.D. (MDACC)

Co-PI: Theodore S. Hong, M.D. (MGH)

Statisticians: Peter Thall, Ph.D., Brian Hobbs, Ph.D.

Research Nursing: Denise Erdman, RN

Activated 4/30/2012

**Phase IIB Randomized Trial of PBT vs IMRT for Esophageal Cancer (MDA 2011-1036)**

Activated 4/30/12

79 patients registered and randomized

Target = 180

Treated = 62

**Protons’ (N=39)**

- Treated (N=26)
- Insurance denial (N=11)
- Wanted IMRT (N=2)
- No clinical trial insurance coverage (N=2)

**IMRT (N=40)**

- Treated (N=36)
- Wanted Protons (N=2)
- No clinical trial insurance coverage (N=2)

* Passive Scattering Proton (36 of 39)
Eligibility:
1) Stage II-III esophageal adenocarcinoma (SCCA)
2) Potentially resectable or unresectable
3) ECOG ≤1
4) Baseline PROs

Treatment Break: 28 days

Follow-up period

Conclusions

- Do the physical advantages of protons translate into clinical benefit? – an unanswered question
- Despite the dosimetric advantages of proton therapy, studies have yet to show a clinical benefit to proton therapy compared to IMRT.
- There are NO level 1 data published to support the use of protons over photons
- Such data are being generated – NSCLC, esophageal cancer, breast cancer, prostate cancer, OP cancer
- Encouraging early results in esophageal and OP cancers

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Ignacio Wistuba, PhD, MD

Bioinformatics

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