Reirradiation with Proton Therapy

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Disclosures

- Consulting for Glaxo Smith Kline
- DSMC for Cellectar
Rationale for Reirradiation

- Reirradiation may offer patients and physicians hope in cases where few other options exist surgically or systemically.

- However, it raises a lot of unanswered questions:
  - Which is a greater threat to critical organs at risk? Tumor or repeat radiation therapy (RT)?
  - What is the actual risk when critical tissues reach high cumulative radiation doses?
  - Do any tissues ever forget radiation dose?
  - Are recurrent tumors more resistant to RT?
  - Are radiation-induced tumors more resistant?
We are Hesitant to Reirradiate

Fig. 1. Poll of radiation oncologists’ (ROs) opinions for case scenarios of patients referred for reirradiation (Re-RT). Abbreviations: CNS = central nervous system; H&N = head and neck; NSCL = non–small-cell lung cancer; gyne = gynecologic; GIT = gastrointestinal; GU = genitourinary.

Joseph IJROBP 2008
And Here’s Why…

- Patients are complicated, planning is complicated, it takes a lot of work
- Toxicity concerns usually dominate, especially concern for late toxicity
- Liability is high, success rates are thought to be low, uncertainty is great
- Saying “No” is usually the easiest course
Can Technology Help with Reirradiation?

- **Early Detection:**
  - Advanced imaging and biomarkers may help detect localized recurrences
  - Better systemics may increase importance of local therapy

- **Target Definition:**
  - Advanced imaging (PET/CT, MRI)
  - Fusion with planning CT scans

- **Surgery:**
  - Debulking, spacers

- **Conformality:**
  - Brachytherapy, IMRT, SBRT, Proton therapy
Target Definition
# Options for Reirradiation

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>SBRT</th>
<th>Brachytherapy</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformality</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Integral Dose</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Fractionation</td>
<td>Std/Hyper</td>
<td>Hypo</td>
<td>HDR/LDR</td>
<td>Standard</td>
</tr>
<tr>
<td>Applicability</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Target Motion Sensitivity</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Cost</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>
Rationale for Proton Reirradiation

- Proton radiotherapy well suited to the problem of reirradiation
  - Highly spatially conformal radiation
  - No exit dose may allow for complete sparing of structures that have been “maxed out” by prior radiation
  - Reported success with uveal melanoma (Marucci et al. IJROBP 2006 Mar 15;64(4):1018-22)
Multi-institutional Trial of Proton Radiotherapy for Reirradiation of Recurrent Tumors

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³CDH Proton Center, Warrenville, IL

June 6, 2013
Primary and Secondary Objectives

**Primary Objective:**
- Establish **feasibility** and **acute toxicity** of proton reirradiation
- Infeasible if >10% of patients are unable to:
  - Have a dosimetrically satisfactory treatment plan devised to have 95% of the target volume covered by 95% of the prescribed dose
  - Tolerate 15% of treatments using proton radiotherapy
  - Complete all treatments within 10 days of estimated date of treatment completion or treatment break > 5 days

**Secondary Objectives:**
- Assess late complications
- Compare the dose distribution of proton plan and photon plan generated for comparison
- Monitor the rates of local control, overall and disease specific survival
What is a “safe“ spinal cord dose? Traditionally 45-50 Gy

Recent studies show low risk of myelopathy if:

• >6 month interval between courses
• each course is of modest dose (<BED 98 Gy$_2$)
• total dose is limited to BED <135.5 Gy$_2$

• Nieder et al. IJROBP 2005 Mar 1;61(3):851-5, Nieder et al. IJROBP 2006 66:

Table 2. Risk score for development of radiation myelopathy

<table>
<thead>
<tr>
<th>Cumulative BED (Gy$_2$) Interval &lt;6 mo One BED course ≥102 Gy$_2$</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
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<tr>
<td>120.1-130</td>
<td>1</td>
</tr>
<tr>
<td>130.1-140</td>
<td>2</td>
</tr>
<tr>
<td>140.1-150</td>
<td>3</td>
</tr>
<tr>
<td>150.1-160</td>
<td>4</td>
</tr>
<tr>
<td>160.1-170</td>
<td>5</td>
</tr>
<tr>
<td>170.1-180</td>
<td>6</td>
</tr>
<tr>
<td>180.1-190</td>
<td>7</td>
</tr>
<tr>
<td>190.1-200</td>
<td>8</td>
</tr>
<tr>
<td>&gt;200</td>
<td>9</td>
</tr>
</tbody>
</table>

X (4.5)
X (4.5)

Table 3. Risk groups for development of radiation myelopathy

<table>
<thead>
<tr>
<th>Group</th>
<th>Score</th>
<th>Myelopathy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>≤3</td>
<td>0/24 (0)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>4-6</td>
<td>2/6 (33)</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;6</td>
<td>9/10 (90)</td>
</tr>
</tbody>
</table>

Abbreviation: BED = biologically effective dose.
Methods

- 3/2010-12/2012
- **Inclusion Criteria**
  - Histologically-confirmed, non-CNS solid malignancies
  - Previously radiated and have a tumor recurrence in or near prior radiation fields
  - KPS $\geq$ 60, life expectancy $\geq$ 3 months
  - Age $\geq$ 18
- **Exclusion Criteria**
  - Prior radiation treatment < 3 months from planned start of re-irradiation
- Toxicity scored according to NCI-CTCAE version 4
- **Primary endpoints:**
  - Feasibility
  - Acute toxicity (occurring $\leq$ 90 days from PRT start)
    - Unlikely, possibly, probably, or definitely related to RT
Stratification: Ten Cohorts

- **Feasibility Phase**
  First 12 patients in each cohort
  Waiting period to assess for feasibility, including acute toxicity (90 days from start of RT)

- **Registration Phase**
## Stratification of First 90 Patients

<table>
<thead>
<tr>
<th>Site/Volume</th>
<th>Number of Patients</th>
<th>Diagnoses</th>
</tr>
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<tbody>
<tr>
<td><strong>Head and Neck</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>Head and Neck (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoma (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chordoma (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast (1)</td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>Thorax</strong></td>
<td>32</td>
<td>NSCLC (14)</td>
</tr>
<tr>
<td>Low</td>
<td>20</td>
<td>Esophagus (8)</td>
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<tr>
<td></td>
<td></td>
<td>SCLC (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sarcoma (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hodgkin’s Disease (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thymus (1)</td>
</tr>
<tr>
<td>High</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td>16</td>
<td>Pancreas (9)</td>
</tr>
<tr>
<td>Low</td>
<td>12</td>
<td>Sarcoma (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCC (1)</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td></td>
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<tr>
<td><strong>Pelvis</strong></td>
<td>25</td>
<td>Rectal (10)</td>
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<tr>
<td>Low</td>
<td>12</td>
<td>Sarcoma (7)</td>
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<tr>
<td></td>
<td></td>
<td>Anal (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervical (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder (1)</td>
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<tr>
<td>High</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td></td>
<td>Sarcoma (4)</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Acute Toxicity

- Grade 3 toxicity (20/90):
  - Neutropenia

- Grade 4 toxicity (8/90):
  - Neutropenia

- Grade 5 toxicity (3/90):
  - Neutropenia, pneumonia (1)
  - Hemoptysis (1)
  - Anorexia (1)
Non Small Cell Lung Cancer: Sample Case

- 72 yo M cT4N2M0, Stage IIIIB NSCLC who completed chemoradiation and one year later developed a left endobronchial lesion obstructing the left upper lobe
  - Additionally EBUS confirmed a 4L lymph node to be positive for SCC.

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Thoracic Reirradiation: NSCLC

✧ **Std Fractionation with Photons**
- 11 Studies (1982-2009)
- Palliative > Definitive
- OS: 1yr 9% – 59% s\(\frac{\text{yr}}{\text{s}}\) (50Gy)
- Toxicity: G2-3 Pneumonitis 5-21%
- G2-3 Esophagitis 4-21%


✧ **Std Fractionation with Protons (MDACC)**
- 33 patients at 11 months median follow-up.
- 1 year overall survival of 47%
- 21% rate grade 3 or higher pulmonary toxicity

NSCLC: Patient and Tumor Characteristics

- 25 pts with recurrent NSCLC in or near their prior thoracic RT identified at 3 proton therapy centers:
  - University of Pennsylvania
  - Procure Proton Therapy Center, Oklahoma City
  - CDH Proton Center, Warrenville, IL

- Low volume (LV, clinical target volume [CTV] 250 cc) : 17/25

- Pts were deemed infeasible if unable to tolerate 15% of proton radiotherapy (PRT) fractions or complete all treatments in <10 days of estimated end date and without a break > 5 days.

<table>
<thead>
<tr>
<th>Patient and Tumor Characteristics.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>67 (47-89)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>22 (88)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Center</td>
<td></td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Procure Proton Therapy Center</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ECOG Performance Status at presentation, n (%)</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>18 (72)</td>
</tr>
<tr>
<td>2</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Stage at original diagnosis (AJCC 7th edition), n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (12)</td>
</tr>
<tr>
<td>II</td>
<td>3 (12)</td>
</tr>
<tr>
<td>III</td>
<td>13 (52)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

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In the HV cohort, there were 2 deaths possibly related to PRT:
1) hemoptysis at 3240 cGy in subject with an endobronchial tumor who presented with hemoptysis prior to starting PRT
2) neutropenic fever the week after end of PRT
Revised HV Thoracic Protocol

- **Inclusion Criteria**
  - KPS of ≥ 70
  - Life expectancy ≥ 6 months with treatment

- **Exclusion Criteria**
  - ANC < 1500/mm³ or platelet count < 100,000/mm³ if receiving concurrent chemotherapy
  - Pleural effusions > 5mm
  - Active pneumonia within 1 mo
  - History of ≥ grade 3 radiation-induced pneumonitis (severe, limiting self care ADL, requiring oxygen)
  - Weight loss > 10% within 6 months prior to starting PRT directly related to tumor and not directly related local esophageal symptoms (e.g. dysphagia, odynophagia)

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Esophageal cancer reirradiation

Managing isolated locoregional recurrences
MDACC: CMT for Esophageal Cancer

- 518 pts with esophageal adenocarcinoma treated with trimodality therapy, median FU 29.3 mo
- 27 (5% had isolated local-regional failure)
  - 12 had salvage chemoRT, 5 survived over 2 years
  - 4 had salvage surgery, 3 survived over 2 years

Kaplan-Meier survival plot from diagnosis of locoregional failure for 27 patients.

Sudo K et al J Clin Oncol. 2013 Dec 1;31(34):4306-10.
Recurrent Esophageal Cancer

- Salvage surgery only in selected patients
- Brachytherapy is limited to superficial targets
- Chemo alone is not considered curative (but tends to be the de facto standard of care in many clinics)
Proton reirradiation of locally recurrent esophageal cancer

- 10 pts (6/2011-8/2013) with locally recurrent esophageal ca after prior RT
  - 8 intraluminal and 2 paratracheal nodal recurrences.
  - 8 adenocarcinoma, 2 SCC; 7 concurrent chemotherapy

- median follow-up
  - 7.9 months (1-23) from the start of retreatment
  - 15 months (2.4-27.8) from the development of local recurrence.
  - median interval between radiation courses 31.4 mos (12-105)

- Toxicity: Grade 2 (30%), 3 (30%), and 4 (40%)
  - Grade 4 toxicities:
    - 1 esophagopleural fistula/respiratory failure
    - 3 were neutropenia toxicities
  - 1 late grade 3 dysphagia, required PEG tube

- Outcomes:
  - 3 pts developed metastatic disease at a median of 28 mos
  - 3 pts developed in-field locoregional recurrence at a median of 13 mos
  - 5 pts died after a median of 13 mos
  - 8 presented with symptoms: 4 had complete resolution, 2 decreased, 1 stable

Berman, Fernades et al
ASCO GI 2014
Rectal cancer reirradiation

Can local control be reclaimed?
Proton Reirradiation: Rectal Subgroup

Dosimetric Benefits: Rectal Reirradiation

PRT

IMRT

Plan Sum of PRT and Prior 2 Courses

small bowel average DVH (n=7)
Skin Dose in Recurrent Rectal Cancer

DS

IMRT

Proton

PBS

IMRT
Biology is King, Selection is Queen, Technical maneuvers are the Prince and Princess.

Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, but usually to no long term avail.

- Blake Cady, MD
**Recurrent Pancreas Cancer**

- **Toxicity:**
  - 9 pts had Grade 2 and 1 had only Grade 1 non-hematologic acute toxicity
  - No Grade 2 or higher non-hematologic late RT-related toxicities

- **Endpoints:**
  - 5 pts developed mets at a median of 7.4 months (4.8-13.2) after starting RT
    - 1 of whom died at 5.3 months
  - 8 pts were controlled locally within the retreated fields
    - 1 pt developed progressive regional (paraaortic) disease inferior to the fields while on treatment and was stopped early at 45 Gy.
    - 1 pt developed a regional metastasis (porta hepatis) outside of the retreated volume
  - Overall, 90% alive and 80% locally controlled median 8.2 months after reirradiation

- **UPDATE:** 10/12 have died, 9/12 with known metastatic progression, median f/u 10.4 months
  - 4/12 are “long term survivors” (22.5, 35.5, 19.5, 12.1 months from ReRT)
  - 1 viscous perforation

Plastaras et al. ASCO GI 2013
Grade 5 Toxicity: Bowel Perforation

- 59 M with a history of pancreatic head adenoca, Whipple in 7/2012, T3N1 with PNI/LVI with invasion of lesser omentum. 3 cycles Gem, then chemo/PRT to 50.4 Gy EOT 2/2013. Adjuvant Gem, restaging showed local recurrence. FOLFOX, restaging showed local progression, CA19-9 878. Re-irradiation with PRT alone, 50 Gy in 2.5 Gy/fx, EOT 10/2013
Grade 5 Toxicity: Bowel Perforation

- Developed worsened ascites on treatment, GOO shortly after RT
- CA19-9 increased to 928
- Metallic stent placed across gastrojejunostomy
- MRI abdomen showed thickened omentum, suspicious for carcinomatosis
- CA19-9 increased to 2062
- Developed worsened abdominal pain, free air discovered
- Died just over 1 month after re-irradiation
Reirradiation: Conclusions

- Re-irradiation with proton therapy can help solve some difficult clinical problems
  - PBS may be even more helpful in select cases
- Feasibility for individual cohorts will be determined to help guide future selection criteria
- Late toxicities may be tough to recognize and manage
- Additional risk with stents?
Reirradiation: Future Directions

- Disease-specific protocols, refined selection criteria
- Biomarkers of radiation resistance correlated with reirradiation response
- Dose-volume histogram models for normal tissue tolerance
- Identification of biomarkers that predict normal tissue sensitivity