Advances in Stereotactic Body Radiation Therapy for Primary and Metastatic Cancer

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I do not intend to discuss an off-label use of a product during this activity.
Financial Disclosure(s)

• I **have not had** any relevant financial relations during the past 12 months to disclose
However...

• I am a radiation oncologist.
Objectives

• Describe the basic principles of SBRT/SABR

• Discuss clinical indications of SBRT for primary tumors

• Discuss clinical indications of SBRT for metastatic tumors
Basic Principles of Radiation Therapy
Types of Radiation

• Non-ionizing radiation
  – Ultrasound
  – Microwaves

• Ionizing radiation
  – X-rays (photons)
    • From orbital electron transitions
    • Higher energy used for radiation therapy, lower energy used for diagnostic radiology
  – Gamma rays
    • From radioactive decay of high energy nucleus
  – Electrons
How Does Radiation Work?

- Photons enter the human body – penetration, absorption or scatter
How Does Radiation Work?

X-rays interact with water → radiolysis → free radicals → binds to and damages DNA → mitotic catastrophe → cell death
Where Does Radiation Come From?

- **Linear accelerator**
  - External Beam Radiotherapy (EBRT)

- **Decay of Radioactive Isotope**
  - Brachytherapy, Gamma Knife
Simulation

- Position patient, design immobilization, CT scan

  - Alpha-cradle:
    - Foam ingredients mixed $\rightarrow$ exothermic reaction $\rightarrow$ foam rises to conform to patient

  - Aqua-plast:
    - Plastic "mesh" heated until soft $\rightarrow$ shaped to conform while warm $\rightarrow$ cools to rigid form
Target-Volume Delineation

- **GTV**: Gross Tumor Volume
  - Visible disease (by any means!)

- **CTV**: Clinical Target Volume
  - GTV + margin for clinical uncertainty/microscopic spread

- **PTV**: Planning Target Volume
  - CTV + margin for physical uncertainties (e.g. positioning, respiratory motion)

- Image “fusion” with PET or MRI can help
Image Guidance (IGRT)

- PTV margins depend on how much you trust your daily setup.
- Daily imaging is used to confirm that the positioning of patient and/or tumor is the same as it was at the time of simulation.
- Can shift patient based on bony anatomy (X-rays) or soft tissue anatomy (CT, MRI, or US) or implanted fiducial markers.

Fiducial markers in prostate visualized and aligned
Dose-Fractionation

• A total dose is delivered in a series of daily **fractions**.
  – NOT cycles!

• The effectiveness of a regimen depends on both the total dose & dose/fraction.
  – 60Gy is not always “better” than 20Gy!

• **Conventional fractionation:**
  – Typically 1.8-3.0Gy/day for 25-45 fx{s}
Stereotactic Radiosurgery
A Fundamentally Different Radiation Delivery Approach

• Deliver high dose/fraction (1-5 fractions) to a well-defined, small-medium sized target volume.

• Mechanism of action may be different
  – more ablative (i.e. SABR)

• Highly conformal, rapid dose falloff

• Secure immobilization and excellent image guidance is crucial for precise targeting
  – Account for organ motion

• Brain: SRS, SRT

• Body: SBRT, SABR
  – A “Gamma knife-like” treatment...in the body
Gamma Knife

• Stereotaxis: Realization of tumor position via the use of coordinates derived from external surrogate markers (head frame)
SBRT

- No rigid frame, no coordinate system
  - Reproducible positioning of body frame on table

- Reproducible positioning of patient within frame
- Reproducible positioning of target within patient

- “Stereotactic” = precise positioning
What SBRT Is Not

• Not simple or low tech

• Not a prophylactic treatment
  – Used for gross disease

• Not a biologically elegant treatment

• Not a “forgiving” treatment
  – An experienced team and systematic approach to QA, staff training, and credentialing is essential for safety.
“Radiation Offers New Cures, and Ways to Do Harm”

“As Technology Surges, Radiation Safeguards Lag”

“Radiation Therapy’s Harmful Side”

“A Pinpoint Beam Strays Invisibly, Harming Instead of Healing”

January, 2010
December, 2010
Characterizing Tumor Motion

- **4DCT**: Infrared camera tracks the motion of a reflective marker, measuring respiratory patterns and excursion
  - CT scan is correlated with respiratory trace
  - Respiratory trace divided into 10% “phase” bins

Infrared camera

Reflective respiration monitor
Like Sports Photography

- Oversampling: Capture the states or "phases" between inhale and exhale.
4DCT

https://www.youtube.com/watch?v=DfijRBvaG7o
Accounting For Tumor Motion

- Tumors at the base move more than tumors at the apex
Strategies of RT Delivery to Account for Respiratory Motion

- **Conventional (ITV-based)**
  - Contour and treat full tumor ROM

- **Accelerator beam gating**
  - Patient breathes normally; beam only on while patient is in a certain phase of the respiratory cycle

- **Active breathing control**
  - Patient holds breath in a certain position; beam only on in that phase of the respiratory cycle

- **Dynamic tumor tracking**
  - Patient breathes normally; tumor is tracked; beam always on and moves with tumor
SBRT for Definitive Treatment of Primary Tumors
Early Stage NSCLC

- 80M smoker with h/o T2DM, CAD, pacemaker, p/w T1N0 RUL AdenoCA
  - Referred to thoracic surgeon
  - FEV1 36% predicted

- He is considered medically inoperable
Treatment Options?

– Best Supportive Care
  • MS ~ 1 year, 5Y-OS ~ 10%
  • Majority die of lung cancer despite other comorbidities
    – 5Y-OS for severe COPD is ~40%

– Conventionally fractionated RT (+/- chemo)
  • 5Y-LC ~65%, 5Y-OS 15-30%

– RFA
  • 5Y-LC 25-50%, 5Y-OS 15-30%
  • PTX ~ 25% (chest tube required in ~10%)

– SBRT
  • >90% 5Y-LC, 5Y-OS 30-60%
RTOG 0236

- Multicenter phase II study (n=55)
- T1-2N0M0 NSCLC (<5 cm), medically inoperable, peripheral
- Treated with **60 Gy in 3 fractions** (over 1.5-2 weeks)
- 5Y-LC 93%, 5Y-lobar control 80%, 31% distant failure
- 5Y-DFS 26%, 5Y-OS 40%
- Toxicity: Grade 3 in 13%, Grade 4 in 4%, Grade 5 in 0%
Adjust Dose Based on Location

- **Dutch VU Series (Senthi, 2012)**
  - 676 pts, T1-2, risk-adapted SBRT (ideal location 20x3, very peripheral 12x5, central 7.5x8)
  - 3Y-LC **90%**, 3Y-OS 53%, MS 41mo, 66% of relapses were distant mets
    - Among operable patients, 3Y-OS 85%
  - **Acute Toxicity:** fatigue ~30%, chest wall pain ~10%, nausea ~10%, cough/dyspnea 5%
  - **Late Toxicity:** G3 pneumonitis 3%, rib fracture 2%, chronic pain ~2%

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**Table 2. Commonly Used Doses for SABR**

<table>
<thead>
<tr>
<th>Total Dose</th>
<th># Fractions</th>
<th>Example Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34 Gy</td>
<td>1</td>
<td>Peripheral, small (&lt;2 cm) tumors, esp. &gt;1 cm from chest wall</td>
</tr>
<tr>
<td>45-60 Gy</td>
<td>3</td>
<td>Peripheral tumors and &gt;1 cm from chest wall</td>
</tr>
<tr>
<td>48-50 Gy</td>
<td>4</td>
<td>Central or peripheral tumors &lt;4.5 cm, especially &lt;1 cm from chest wall</td>
</tr>
<tr>
<td>50-55 Gy</td>
<td>5</td>
<td>Central or peripheral tumors, especially &lt;1 cm from chest wall</td>
</tr>
<tr>
<td>60-70 Gy</td>
<td>8-10</td>
<td>Central tumors</td>
</tr>
</tbody>
</table>
Lung SBRT Treatment Planning

6 weeks                     3 months                 2 years
Hepatocellular Carcinoma - Challenges

- Two diseases - cancer and cirrhosis
- The normal liver is relatively radiosensitive
  - Cirrhotic liver is more fragile
- Many sensitive normal tissues in abdominal cavity
Hepatocellular Carcinoma

- An alternative to RFA or TACE, or when these therapies have failed.

- Used most often for 1-3 tumors (cumulative size <6cm), >800cc normal liver, Child A

- 2Y-LC 60-90% (OS variable)
Hepatocellular Carcinoma – Early Stage

- Japanese Series (Sanuki, 2013)
  - 185 HCC patients, single lesion (≤ 5cm, 84% T1)
    - Unfeasible or difficult surgery or ablation, or refusal
    - Child A (40Gy, n=137) or B (35Gy, n=48) in 5 fractions.
  
  - 3Y-LC 91%, 3Y-OS 70%.
  - 13% had acute ≥ G3 toxicity
  - 10% had worsening of Child score by two points (all but 3 recovered)
    - G5 liver failure occurred in two Child B patients

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Hepatocellular Carcinoma – Advanced Stage

- Princess Margaret Hospital (Bujold 2013)
  - Prospective, 102 pts, Child A
  - Tumor thrombus in 55%, prior therapies in 52%, multifocality in 61%, median sum of tumor diameter 10cm (BIG!)
  - Dose Rx driven by liver effective volume and proximity to GI structures
    - Median 36Gy (range 24-54Gy) in 6fx over 2 weeks

- Results:
  - 1Y-LC in 87%, Med-PFS 5.4mo, MS 17mo, 1Y-OS 56%
  - Most recurrences outside the RT field
- Toxicity ≥ grade 3 was seen in 30%
  - Child score progression by 2 or more points in 30% within 3mo (some reversible)
  - 7 deaths, possibly treatment related (most with MLD >18Gy)
**RTOG 1112**

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma

**SCHEMA (8/26/14)**

<table>
<thead>
<tr>
<th>Registration</th>
<th>Stratify</th>
<th>Randomize</th>
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</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td>hepatitis B or B and C vs. C vs. other</td>
<td><strong>Arm 1</strong></td>
</tr>
<tr>
<td></td>
<td>North American site vs. Non-North American site</td>
<td>Daily sorafenib</td>
</tr>
<tr>
<td></td>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td><strong>Arm 2</strong></td>
</tr>
<tr>
<td></td>
<td>SBRT alone (27.5 Gy – 50 Gy in 5 fractions)</td>
<td>Followed by Sorafenib alone daily</td>
</tr>
</tbody>
</table>
WVU Prospective Trial

- Unresectable HCC > 3cm, ≤ Child A cirrhosis
  - If TACE candidate → TACE → SBRT vs. RFA
  - If non-TACE candidate → SBRT vs. Y90
Prostate Cancer

• Rationale:
  – Generally slow growing → theoretically more responsive to larger doses per fraction.
  – Dose escalation has been found to have a biochemical DFS benefit for all risk groups.

<table>
<thead>
<tr>
<th>Author (Institution)</th>
<th>Sample Size (Risk Group)</th>
<th>Median FU (Months)</th>
<th>Regimen</th>
<th>Grade 2+ Toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madsen (VMMC)</td>
<td>40 (Low)</td>
<td>41</td>
<td>33.5 Gy/6.7 Gy</td>
<td>GU: 20, GI: 7.5</td>
</tr>
<tr>
<td>King (Stanford)</td>
<td>67 (Low to low-intermediate)</td>
<td>32</td>
<td>36.25 Gy/7.25 Gy</td>
<td>GU: 8.5, GI: 2</td>
</tr>
<tr>
<td>Friedland (Naples)</td>
<td>112 (Low &gt; intermediate &gt; high)</td>
<td>24</td>
<td>35 Gy/7 Gy</td>
<td>&lt;10, &gt;95</td>
</tr>
<tr>
<td>Katz (Winthrop)</td>
<td>304 (Low &gt; intermediate &gt; high)</td>
<td>30</td>
<td>35 Gy/7 Gy</td>
<td>&lt;10, &gt;95</td>
</tr>
<tr>
<td>McBride (multicenter)</td>
<td>45 (Low)</td>
<td>44.5</td>
<td>37.5 Gy/7.5 Gy</td>
<td>GU: 19, GI: 12</td>
</tr>
<tr>
<td>McBride (multicenter)</td>
<td>45 (60% intermediate, 40% low)</td>
<td>18</td>
<td>47.5 Gy/9.5 Gy</td>
<td>GU: 31, GI: 18</td>
</tr>
<tr>
<td>McBride (multicenter)</td>
<td>45 (60% intermediate, 40% low)</td>
<td>12</td>
<td>50 Gy/10 Gy</td>
<td>GI: 100</td>
</tr>
</tbody>
</table>

• Better form of dose escalation that brachytherapy?
Pancreatic Cancer

• The only curative treatment is surgery, however, < 25% of patients are amenable to surgery at diagnosis

• Most unresectable non-metastatic patients receive chemo-RT, but local progression rates are high (~50%)
  – Often causes pain or obstructive symptoms that negatively affect quality of life (QoL)
Pancreatic Cancer SBRT

- SBRT is considered experimental for pancreatic cancer.
- May be particularly valuable for patients with “borderline” resectable disease and those with locally recurrent disease after chemo-RT

Outcomes: 1Y LC 57-100%, 5-15% ≥ grade 3 toxicity (bowel and stomach)
Renal Cell Carcinoma

- “Radioresistant” tumor → requires high doses

- Limited data, but SBRT may have a role in patients with medically unresectable tumors, particularly those > 3cm (worse outcomes with RFA).
Renal Cell Carcinoma

- 55F with locally recurrent papillary RCC.
- Considered inoperable due to probable IVC invasion
- Plan: 9 Gy x 5 fractions with active breathing control
WVU Prospective Trial

• Patient Population:
  – Medically inoperable renal parenchymal RCC or renal pelvis TCC limited to the kidney with an intact capsule.
  – Patients with metastatic RCC who would be a candidate for cytoreductive nephrectomy but are not a surgical candidate.
  – No size limit

• Treatment = 5 fraction SBRT (40-60Gy)
  – Give maximum dose that is able to achieve all normal tissue constraints
SBRT for Treatment of Metastases
Rationale #1: Symptom Palliation

• Palliation of symptomatic lesions
  – Brain Metastases
  • Subject for another talk
  – Bone Metastases

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Excluded</th>
<th>Randomized</th>
<th>Med f/u</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch Trial 1999</td>
<td>1171</td>
<td>C-spine &amp; cord compression</td>
<td>8/1 vs. 24/6</td>
<td>4mo</td>
<td>No difference in pain relief (=70%), No difference in time to response (=3 wks) No difference in acute toxicity. Retreatment: 25% for 8/1 vs. 7% for 24/6 8/1 had 2x more subsequent pathologic fracture</td>
</tr>
<tr>
<td>British Trial 1999</td>
<td>765</td>
<td></td>
<td>8/1 vs. 30/5 vs. 30/10</td>
<td>12mo</td>
<td>No difference in pain relief (=78%) No difference in time to response (&lt;1mo) No difference in analgesic use Retreatment: 23% for 8/1 vs. 10% for others No difference pathological fractures</td>
</tr>
<tr>
<td>RTOG 97-14 Hartsell 2005</td>
<td>898</td>
<td>cord compression skull, hands, &amp; feet</td>
<td>8/1 vs. 30/10</td>
<td>3mo</td>
<td>No difference in pain relief or the use of narcotics Retreatment: 18% for 8/1 vs. 9% for 30/10 - Single men were less likely than married men to seek retreatment (no difference in women) Acute Toxicity: 10% with 8/1 vs. 17% with 30/10 (SS) No difference pathological fractures</td>
</tr>
<tr>
<td>Howell 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochrane MetaAnalysis 2004</td>
<td>11 trials 3435 pts</td>
<td>Single vs. Multi-fraction</td>
<td></td>
<td></td>
<td>No difference in pain response (60%) No difference in complete response (33%) Retreatment: 21% with 8/1 vs. 7% Pathological fracture: 3% with 8/1 vs. 1.5%</td>
</tr>
</tbody>
</table>

• However, radioresistant histologies have worse outcomes!
Spine SBRT

• Pain improvement in ~ 85-95% of patients.

• Relief is more rapid (days – weeks), and more durable (90% LC).

• Allows for retreatment of previously irradiated areas.
Figure 6. Schematic depiction of the neurologic, oncologic, mechanical, and systemic (NOMS) decision framework. Abbreviations: cEBRT, conventional external beam radiation; SRS, stereotactic radiosurgery.
Spine SBRT

- Requires only 3mm between PTV & spinal cord.
CT/MRI Treatment Planning

• Localize cord within the canal using:
  – MR fusion (T2 & T1 post)
  – Alternative: CT myelogram prior to planning CT
Rationale #2: Improving Survival

- Oligometastastic ≠ diffusely metastatic
  - Survival benefit from metastatectomy has been demonstrated for several types of cancer (colorectal, sarcoma, renal)

- SBRT is a reasonable option in patients who refuse surgery or are medically inoperable.
  - Healthy liver and lung are much less fragile than in primary HCC or NSCLC, so can treat to higher doses → 3Y-LC ~ 90%
SBRT for liver metastasis

- 66M with sigmoid colon cancer s/p partial colectomy (pT3N1 with a positive circumferential resection margin).
- Received FOLFOX chemotherapy
- Progressed in 2 lung nodules → metastatectomy
- Progressed in presacral tumor bed and single liver nodule. Refused surgery.
SBRT for lung metastases

- 87M with pT3N1 penile urethral cancer (2006). He has 2 lung nodules since 2011 which began growing more rapidly in the past year. No other evidence of disease.
SBRT for Diffuse Metastases?

- U Colorado (Rusthoven 2009):
  - Assessed patterns of failure to 1\textsuperscript{st} line chemo for Stage IV NSCLC
  - Median-TTP 3.9mo
    - 64\% progression in only existing sites of mets
    - 9\% progression in only new sites
    - 27\% progression in both existing and new sites
  - Conclusion: Chemo fails relatively soon after initiation, and typically in pre-existing sites. Suggests benefit of SBRT to multiple metastases.
SBRT for Diffuse Metastases?

• UT Southwestern/U Colorado (JCO, 2015):
  – Single arm phase II study
  – 24 pts with Stage IV NSCLC who failed 1st line Pt-based chemo, with ≤ 6 sites of extracranial disease
  – Tx = Erlotinib + SBRT to all sites of disease.
    • Unselected for EGFR mutation
  – **M-PFS 14.7mo**, and MS 20.4mo (substantially better than historical standards, M-PFS 2.3mo)
  – Patterns of failure:
    • Most patients progressed in new distant sites
  – Two G3 toxicities were radiation related.
NRG BR-001

A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

SCHEMA

Patients with metastatic breast, adenocarcinoma of the prostate or non-small cell lung cancer with ≤ 4 metastases; all metastases not resected must be amenable to SBRT
See Section 3.0 for details

REGISTER

SBRT (in 3 or 5 fractions) to all existing metastases in 1-3 weeks
See Table 6-1 in Section 6.1 for dose levels and Table 13-1 in Section 13.3 for Dose Limiting Toxicities (DLTs)
Summary

- Advances in imaging and physics have allowed for development of SBRT

- A growing body of literature related to SBRT enables us to deliver it safely to a variety of tumor sites.

- SBRT provides highly effective treatment for both primary and metastatic tumors.

- Randomized trials comparing SBRT to other local modalities are needed to further its use in patients.
Thank You!