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I hope this is where we are with SBRT...
[insert gratuitous puppy photos here]


Educational Objectives

1. To present the operational definition of SBRT

2. To present the clinical rationale for the application of SBRT in the most commonly used indications

3. To review reported clinical outcomes data for SBRT, with discussion of the practical radiobiological ramifications
SBRT is a treatment that couples a high degree of anatomic targeting accuracy and reproducibility with very high doses of extremely precise, externally generated, ionizing radiation, thereby maximizing the cell-killing effect on the target(s) while minimizing radiation-related injury in adjacent normal tissues.

**ASTRO SBRT Policy**

**Definition, continued**

- “stereotactic” implies target localization relative to 3-D coordinates
  - e.g., a body frame with external reference markers, implanted fiducial markers that can be visualized with KV x-rays, and CT imaging-based systems

- All SBRT is performed with IGRT of some kind
  - To minimize breathing-related or other intra-treatment tumor motion, some form of motion control or “gating” may be used

- SBRT may be fractionated (up to 5 fractions)
  - Each fraction requires an identical degree of precision, localization and image guidance
  - A course of treatment >5 fractions is not considered SBRT

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**ASTRO SBRT Policy**

**Definition, continued: the fuzzy parts...**

- The border/overlap with cranial SRS
  - Base of skull region
  - Nasopharynx
  - Paranasal sinuses
  - Note: SRS can be up to 5 fractions, also

- Is there a minimum dose for SBRT?

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**Stereotactic Body Radiation Therapy: Part 1. Clinical and Biological Findings**

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Spectrum of potential indications for SBRT

- Intensified treatment to a primary cancer
  - Stage I lung cancer
  - Best studied to date
  - Primary HCC
  - Pancreas cancer
  - Prostate cancer
  - Favorable due to low alpha/beta ratio
- Treatment of selected spinal/paraspinal lesions
- Palliation for challenging sites of recurrence
  - Retroperitoneal
  - Previously irradiated volumes
- Adjuvant systemic cytoreductive therapy
  - “Radical” treatment for isolated liver, lung, and other mets

Why SBRT for medically inoperable early stage NSCLC?

- Conventional RT results generally underwhelming
  - 50+% local failure
  - 30% or less 3-5 yr disease-specific survival
- SBRT might allow higher doses
  - Careful delivery technique
  - Biologically more potent...

So why do we think SBRT is biologically more potent?

...and a quick caveat, before we overestimate...

Note:
MODELS LOOK GOOD ON PARISIAN RUNWAYS, BUT THIS BATTLE IS RADIATION versus CANCER AND NOT RALPH LAUREN versus CALVIN KLEIN!
Prospective Trials of SBRT for Stage I NSCLC

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>SBRT dose and fractionation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indiana University</td>
<td>4</td>
<td>24.66 Gy/3 fractions</td>
<td>Phase I study; maximum tolerated dose (MTD) not reached for T1 lesions; MTD 66 Gy for T2 lesions</td>
</tr>
<tr>
<td>Technical University, Munich</td>
<td>7</td>
<td>30 Gy/1 fraction</td>
<td>1 yr local control 98%</td>
</tr>
<tr>
<td>University of Marburg, Beijing</td>
<td>4</td>
<td>45 Gy/5 fractions</td>
<td>1 yr local control 95%</td>
</tr>
<tr>
<td>Air Force General Hospital, Beijing</td>
<td>4</td>
<td>30 Gy/1 fraction</td>
<td>1 yr local control 94%</td>
</tr>
<tr>
<td>Technical University, Munich</td>
<td>4</td>
<td>33.75 Gy/3.5 fractions</td>
<td>2 yr local control 88%</td>
</tr>
<tr>
<td>Radiation Therapy Oncology Group (RTOG) 0236</td>
<td>50</td>
<td>60 Gy/3 fractions</td>
<td>1 yr local control 98%</td>
</tr>
</tbody>
</table>

Example case: T1N0 medically inoperable lung cancer
- 62-year-old male, h/o emphysema, on 3-5 L/min supplemental O₂
  - 70 pack-yr smoker
- CT in 2003 revealed LUL lesion (T)
  - Repeat CT 3 mos later showed enlargement of the soft tissue nodula, up to 1.5 x 2 cm
- Biopsy: adenocarcinoma
- FEV1 0.9 L (28% of predicted)

Treatment: 60 Gy/3 fractions

Characteristic radiographic findings
- Baseline
- 4 mos, CR
- 8 mos, soft tissue window
- 12 mos, lung window
- 18 mos, NED
Summary of forthcoming RTOG trials of SBRT for lung cancer

- **RTOG 0618 (R Timmerman):**
  - SBRT for Medically Operable NSCLC
  - Still a potential inhomogeneity correction snag
- **RTOG 0624/NCTG (B Kavanagh, PI)?**
  - SBRT (60 Gy/3) vs another fractionation schedule?
- **RTOG 0633 (A Bejzak, PI):**
  - SBRT for Pulmonary lesions near the proximal bronchial tree
- **RTOG 06xx (V Stieber, PI):**
  - SBRT for Pulmonary Metastases

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Selected spinal SBRT reports

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Dose</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henry Ford Hospital</td>
<td>40</td>
<td>10-16 Gy</td>
<td>Pilot study, SBRT as boost</td>
</tr>
<tr>
<td>(Ryu, 2004)</td>
<td></td>
<td>Single fn</td>
<td>Good palliation reported</td>
</tr>
<tr>
<td>MD Anderson (Chang, 2004)</td>
<td>10</td>
<td>30 Gy/5</td>
<td>10 Gy point dose max to cont</td>
</tr>
<tr>
<td>MSHCC (Yamada, 2004)</td>
<td>16</td>
<td>Variable</td>
<td>Custom body frame used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT-on-rails setup for verification</td>
<td></td>
</tr>
<tr>
<td>Georgetown U (Deen, 2005)</td>
<td>51</td>
<td>Variable</td>
<td>Avg 8.5 Gy x 3.6 fnm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant pain reduction observed</td>
<td></td>
</tr>
<tr>
<td>Stanford (Dodd, 2006)</td>
<td>51</td>
<td>18-30 Gy</td>
<td>Benign tumors treated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 fnm</td>
<td>1 case of toxicity noted</td>
</tr>
</tbody>
</table>


- Cord drawn 6mm above and below target
- Major constraint: no more than 10% of cord receives dose above 10 Gy
- Only 1 observed cord complication among 177 pts
Note: patient was heavily pre- and post-treated with chemotherapy.
Symptoms included RLE weakness, resolved with steroids.

From Ryu et al., continued

Note: patient was heavily pre- and post-treated with chemotherapy.
Symptoms included RLE weakness, resolved with steroids.

Spinal SBRT for benign tumors: Stanford experience

Note: 1 case of “posterior column dysfunction” after 24 Gy/3 fractions
1.7 cc of cord received prescription dose

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Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer
JCO, October, 2006
What is The Effect of Novel Molecular Targeted Agents on Normal Lung Parenchyma after SBRT to Pulmonary Malignancies?

- There is interest in combining SBRT with systemic agents, especially some of the newer agents targeting growth factor receptors, VEGF, and other non-DNA targets.
- In a recent trial combining cranial SRS and an EGFR tyrosine kinase inhibitor for recurrent glioma, we saw a pronounced effect on normal brain.
- Therefore, we hypothesized that the combination of SBRT and similar molecular agents would lead to an exaggerated normal lung tissue response.

Methods: Case-Control Cohorts

- From a database of > 200 patients treated with SBRT, we identified patients who fit the following criteria:
  - primary or secondary lung tumor(s) treated with SBRT
  - 45-60 Gy in 3 fractions
  - the administration of a molecular targeted agent (TA) during or within 8 months after SBRT
- Matched cohort
  - Histology (if unavailable, gender and age +/- 5yrs)
  - Contemporaneous SBRT +/- 1 yr
  - no TAs given prior to repeat CT scan 6-10 mos post-SBRT

Methods: study endpoint

- Volume of post-SBRT dense fibrosis (DF)
  - Treatment planning software used to quantify
  - post-treatment CT imaging 6-10 months after SBRT and at least 2 months after the initiation of the TA was fused with the pre-SBRT planning study
- Volume of DF volume was analyzed for correlation with dosimetric parameters
  - PTV
  - V15, V30, V50
Dense fibrosis (DF) definition: Hounsfield level and window settings

- Range: -1000 to 500
  - Too fuzzy

- Range: -300 to 200
  - Good compromise

- Range: -50 to 50
  - Too fragmented

DF only scored if within the 15 Gy isodose volume

Note: it is assumed that a combination of active fibrosis and segmental or sub-segmental retraction is ongoing, thus rendering perfect image fusions impossible

Results: Matched patient cohorts

<table>
<thead>
<tr>
<th>No TA</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>5 NSCLC</td>
<td>2 1H+N</td>
</tr>
<tr>
<td>1 Melanoma</td>
<td>1 Breast</td>
</tr>
<tr>
<td>1 melanoma + TA</td>
<td></td>
</tr>
<tr>
<td><strong>Med. ages, yrs (range)</strong></td>
<td>53 (31-74)</td>
</tr>
<tr>
<td><strong>Agents given post-SBRT</strong></td>
<td>gefitinib (n=4)</td>
</tr>
<tr>
<td></td>
<td>cetuximab (n=2)</td>
</tr>
<tr>
<td></td>
<td>bevacizumab (n=2)</td>
</tr>
<tr>
<td></td>
<td>erlotinib (n=1)</td>
</tr>
<tr>
<td></td>
<td>sorafenib (n=1)</td>
</tr>
<tr>
<td></td>
<td>imatinib (n=1)</td>
</tr>
<tr>
<td></td>
<td>STA 4783 (n=1)</td>
</tr>
</tbody>
</table>

Results: DVH comparisons

<table>
<thead>
<tr>
<th>PTV</th>
<th>No TA Mean, cc +/- SEM</th>
<th>+TA Mean, cc +/- SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT1</td>
<td>65 +/- 18</td>
<td>56 +/- 7</td>
<td>NS</td>
</tr>
<tr>
<td>V15</td>
<td>421 +/- 76</td>
<td>448 +/- 72</td>
<td>NS</td>
</tr>
<tr>
<td>V90</td>
<td>173 +/- 41</td>
<td>185 +/- 33</td>
<td>NS</td>
</tr>
<tr>
<td>V50</td>
<td>73 +/- 16</td>
<td>68 +/- 9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Results: paired post-SBRT dense fibrosis (DF) comparisons

<table>
<thead>
<tr>
<th></th>
<th>No TA Mean, cc +/- SEM</th>
<th>+TA Mean, cc +/- SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
<td>5.5 +/- 1.7</td>
<td>10.5 +/- 9.6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Note p = 0.04 if outlier removed

PTV and V50 as predictors of V50

- Ratio of DF to PTV or V50 significantly different, TA v no TA
- “soft” linear correlation

Sample comparison studies

- Upper panel:
  - Pre- v post-SBRT, no TA
- Lower panel:
  - Pre- v post-SBRT, + TA
- Note—fibrosis not always in “obvious” location

Conclusions

- The volume of dense fibrosis generated by lung SBRT is predicted by the PTV and V50
  - no obvious direct clinical sequelae
  - Maybe a model for the study of agents that retard post-radiotherapy fibrosis?
- The use of molecular targeted agents following lung SBRT is associated with a greater volume of dense fibrosis
  - The interpretation of local control in studies involving this combination should take this phenomenon into account
Strategies for setting normal liver dose constraints

- NTCP-based
  - Eg. PMH experience, Dawson et al

- Critical volume model
  - At least 700 cc normal liver received < 15 Gy cumulative

Liver Reactions on CT after SBRT: Herfarth classification

- Type 1 reaction:
  - Hypodensity in portal-venous
  - Isodensity in the late contrast

- Type 2 reaction:
  - Hypodensity in portal-venous
  - Hyperdensity in the late contrast

- Type 3 reaction:
  - Isodensity / hyperdensity in portal-venous

Sample case: metastatic nasopharyngeal cancer

- 71F T1N2cM0 nasopharynx ca
  - cisplatin and 70 Gy

- 8 mos later, neck recurrence
  - salvage dissection and brachytherapy

- 9 mos later, bx-proven liver met
  - weekly gemcitabine and cisplatin
  - Transient minor response

- 6 mos later, Phase I SBRT study
Histologic analysis of early liver SBRT effects

- Case study:
  - Pre-op chemoRT for rectal cancer
  - SBRT for solitary liver met
  - At time of APR, resection of treated liver and new, previously unknown other liver met

Herfarth Type I reaction, in vivo, continued

Herfarth Type I in vivo, continued

Normal liver, same patient, outside zone of reaction

Type I reaction: lobular disarray, congestion, pigment accumulation in hepatocytes, some macrophages
Fibrosis, residual degenerating tumor cells

Also common: transient normal liver volume reduction

Liver V30 and Mean dose versus percent volume change

Suggestion: Predominantly parallel architecture
Scheffer et al, ASTRO 2007

Thanks for your attention!