Stereotactic Body Radiation Therapy III: Radiobiological Considerations

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LAST YEAR’S AGENDA

I. Molecular Radiobiology & Radiogenetic Therapy
II. The dose rate problem
III. Dose inhomogeneity & tumor control probability
IV. Target margin selection
V. Ongoing Formal Protocols
1. What happens inside and outside tumor and normal cells after SBRT?
2. What normal tissue radiation dose constraints should we use in SBRT?
3. What radiation doses should we try to give to tumors using SBRT?
Q1. What happens inside and outside tumor and normal cells after SBRT?

- **Intracellular signaling events**
  - Include repair signals and pro-proliferative signals
  - Can be mediated by cellular growth factor receptor events

- **DNA injury-mediated clonogenic cell death** (reproductive sterilization) and apoptotic death

- **Expression of messenger molecules, aka cytokines**

DNA injury-mediated clonogenic cell death (reproductive sterilization) and apoptotic death

- In tumor tissue, the more there is of both of these processes, the better
- In normal tissue, a different story (figures)

Expression of messenger molecules, aka cytokines

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>11</th>
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<tbody>
<tr>
<td>Apol/Fas</td>
<td>Leptin</td>
<td>Rantes</td>
<td>ICAMP-1</td>
<td>IL-2</td>
<td>IL-7</td>
<td>Positive</td>
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<tr>
<td>CTLA</td>
<td>MIP1α</td>
<td>TGFβ</td>
<td>VCAMP-1</td>
<td>IL-3</td>
<td>IL-8</td>
<td>Positive</td>
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<tr>
<td>Eotaxin</td>
<td>MIP1β</td>
<td>IFNγ</td>
<td>VEGF</td>
<td>IL-4</td>
<td>IL-10</td>
<td>Negative</td>
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<tr>
<td>GM-CSF</td>
<td>MIP4</td>
<td>TNFα</td>
<td>IL-1α</td>
<td>IL-5</td>
<td>IL-12(p40)</td>
<td>Negative</td>
<td></td>
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</tr>
<tr>
<td>EGF</td>
<td>MIP5</td>
<td>TNFRI</td>
<td>IL-1β</td>
<td>IL-6</td>
<td>IL-15</td>
<td>Positive</td>
<td></td>
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<tr>
<td>IP-10</td>
<td>MMP3</td>
<td>TNFRII</td>
<td>IL-1Rα</td>
<td>IL-6R</td>
<td>IL-17</td>
<td>Positive</td>
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</tbody>
</table>
Q2. What normal tissue radiation dose constraints should we use in SBRT?

• The lung
  – RTOG 0236 parameters
• The liver
  – Expected radiographic changes
  – The “critical volume” model
• The spine
RADIATION THERAPY ONCOLOGY GROUP (RTOG) 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

- PI: Robert Timmerman, MD
- Eligibility
  - Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 medically inoperable non-small cell lung cancer;
  - patients with T3 tumors chest wall primary tumors only
  - no patients with tumors of any T-stage in the zone of the proximal bronchial tree*.
- SBRT dose: 20 Gy x 3 fractions
“zone of the proximal bronchial tree” (figure)

Target dose homogeneity limits

Dose “isotropicity” limitation requiring falloff of approx 50% within 2 cm of PTV

V20 < 10%

Spinal cord, heart, esophagus, etc. limits
DRRs + Orthogonal XRays

FUSION

CERTAIN®

Colorado External Registration Thing And Instant Notifier
Liver Reactions on CT after SBRT

- **Type 1 reaction**: Hypodensity in portal-venous contrast phase, isodensity in the late contrast phase
- **Type 2 reaction**: Hypodensity in portal-venous contrast phase, hyperdensity in the late contrast phase
- **Type 3 reaction**: Isodensity / hyperdensity in portal-venous contrast phase, hyperdensity in the late contrast phase

Type 1, 6 weeks after SBRT

Type 2, 6 months after SBRT

Liver Dose Constraint in CU/Multi-institutional Phase II study of SBRT for liver lesions

- PI: Tracey Schefter, MD
- A modified “critical volume” model
  - Based upon observations that patients can generally tolerate complete surgical resection of 70-80% of the liver
  - Requirement: at least 700 cc of uninvolved liver must receive <15 Gy total over the 3 fractions
- More detail to be presented at ASTRO
Spinal SBRT,
aka Spine Radiosurgery when given in a single fraction

100% = 18 Gy

What radiation doses should we try to give to tumors using SBRT?

- Fowler, Tome, and Welsh’s analysis
- University of Colorado experience
<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Reference</th>
<th>BED Gy10</th>
<th>NTD, Gy 2-Gy Fractions</th>
<th>Estimated Progression-free Survival at 30 Mo. (Assuming No Hypoxia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional fractionation</td>
<td>—</td>
<td>(Fig. 1.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>60 Gy, 30 fractions</td>
<td>—</td>
<td>72</td>
<td>60</td>
<td>15%</td>
</tr>
<tr>
<td>70 Gy, 35 fractions</td>
<td>—</td>
<td>84</td>
<td>70</td>
<td>24%</td>
</tr>
<tr>
<td>SBRT</td>
<td>—</td>
<td>(Fig. 1.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>48 Gy, 4 fractions</td>
<td>(6)</td>
<td>106</td>
<td>63</td>
<td>34%</td>
</tr>
<tr>
<td>45 Gy, 3 fractions</td>
<td>(2)</td>
<td>113</td>
<td>94</td>
<td>95%</td>
</tr>
<tr>
<td>48 Gy, 3 fractions</td>
<td>(2)</td>
<td>125</td>
<td>104</td>
<td>99%</td>
</tr>
<tr>
<td>60 Gy, 5 fractions</td>
<td>(12)</td>
<td>132</td>
<td>110</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>60 Gy, 3 fractions</td>
<td>(3)</td>
<td>180</td>
<td>150</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>69 Gy, 3 fractions</td>
<td>(33)</td>
<td>228</td>
<td>190</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

BED, biologically equivalent dose; NTD, normalized total dose in 2-Gy fractions; SBRT, stereotactic body radiation therapy; NSCLC, non–small cell lung cancer; Tk, ; Td, ; LQ, linear–quadratic.

but if there is hypoxia in the tumor...

SBRT at the University of Colorado

- **Retrospective analysis cohort**
  - 93 patients, 114 tumors treated
    - Lung lesions 66
    - Liver lesions 38
    - Other sites 10
  - Tumor volume
    - median 11.2 cc (range, 0.1-185)

- **Prospective Trials Participants**
  - Phase I/II Lung SBRT trial
    - 15 patients
  - Phase I/II Liver SBRT trial
    - 15 patients
Methods of analysis: EUD and TCP

- Equivalent Uniform Dose (EUD)
- Tumor Control Probability (TCP)
- \( SF_2 \) estimated to be 0.4
- \( 10^7 \) clonogens/cc

EUD = \( 2Gy \frac{\ln\left(\frac{1}{V_{ref}} \sum_{i=1}^{N} V_i (SF_2)^{\frac{D_i}{2Gy}}\right)}{\ln(SF_2)} \)

\[
TCP = \prod BCP_j
\]

\[
BCP = \exp(-N \times SF)
\]
Results: retrospective cohort

- EUD alone not predictive of local control (upper graph)
- TCP estimate significantly correlated with freedom from progression
- Conclusion: – SIZE MATTERS
I promise you this:

3 x 10 Gy is not enough

F/u at 3, 7, 11 mos
Acknowledgements

• UCHSC Radiation Oncology Colleagues
  – Tracey Schefter, MD
  – Rebekah Zaemisch
  – Dan Gravdahl

• Clinical Trials Database construction and management
  – Peter Doyle, Principal Consultant, W.D. Ventures LLC
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  – Research Database Management Framework © 2004 Whitedragonfly Systems -