Radiation Dose-Volume Effects for Liver SBRT

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Introduction

- Stereotactic Body Radiation Therapy for liver cancer
  - highly effective in providing LC in selected patients with small hepatic malignancies
  - dose response with increasing doses yielding higher LC rates
  - risk to the adjacent OARs and, when selecting doses, there are trade-offs between LC and OARs complications
  - Various dosing and fractionation schemes with a wide range of toxicity end-points have been reported
Objective

- Review/analyze the data reported in the literature for normal tissue dose-volume effects in liver SBRT
- Derive normal tissue complication probability models
- Recommend dose/volume limits

Radiological Changes Post SBRT

- 34 patients with mets; 96 follow-up non-contrast CTs
- Presc. dose 52 Gy [39 – 60] in 3-5 fractions
- 1-8 follow-up CTs [median, 2 per patient] [range, 0.7-36 mos., median, 8 mos.]
- Dose mapped to follow-up using rigid registration
- In each time bin and in each 5 Gy dose region, mean HU change was computed
Liver Normal Tissue Dose-Response Curve

Liver Radiological Changes

- Hypodense radiation reaction is the result of acute changes: edema and variable amounts of fatty infiltration
- Chronic changes may appear iso- or hyperdense, the result of the lack of fatty replacement

Herfarth Classification of Liver Reactions on CT after SBRT

<table>
<thead>
<tr>
<th></th>
<th>Portal venous phase</th>
<th>Late contrast phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Hypodensity</td>
<td>Isodensity</td>
</tr>
<tr>
<td>Type II</td>
<td>Hypodensity</td>
<td>Hyperdensity</td>
</tr>
<tr>
<td>Type III</td>
<td>Iso/hyperdensity</td>
<td>Hyperdensity</td>
</tr>
</tbody>
</table>
Liver Normal Tissue Reaction after SBRT

Type 1, 6 weeks after SBRT

Type 2, 6 months after SBRT

Courtesy of T. Schefter

Liver Normal Tissue Reaction after SBRT

Tolerance of adjacent intestinal mucosa is an important dose-limiting issue

30 Gy in 3 fractions given here; progressed to ulceration but eventually healed in approx 3 mos

Courtesy of B. Kavanagh

Literature Review

• 12 studies contained both dose/volume and toxicity data from 541 patients with HCC, HNC, and/or liver mets
• Median dose: 40 Gy (range, 18-60 Gy) in 1-6 fractions
• 3 end points chosen for pooled dose-response analysis
  - G3+ liver enzyme elevation as a function of MLD
  - G2+ general GI toxicity as a function of RX or PTV dose
  - G3+ general GI toxicity as a function of RX or PTV dose
• RX/PTV doses were selected because doses to specific OARs were not available in many instances.
### Dose-Response Modeling

- Modeling was performed using a probit model with maximum likelihood (ML) parameter fitting.
- The ML method determined the probit model parameters that best fit the binomial (toxicity/no-toxicity) data.
- The input data were the reported toxicity rates and corresponding dose metrics reported in each study.
- The average toxicity rate was then binned into binary outcomes to facilitate probit model estimation with ML parameter fitting.

#### Grade 3+ liver enzyme toxicity vs. MLD

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>#Events/ #Patients</th>
<th>D_{50} Gy (95% CI)</th>
<th>Y_{50} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ liver enzyme</td>
<td>17/288</td>
<td>40.8 (25.5 - 46.3)</td>
<td>0.95 (0.58 - 1.44)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Grade 3+ Liver Enzyme Toxicity</th>
<th>GI Toxicity Rate</th>
<th>Total Dose Range (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barney 2012</td>
<td>IHC</td>
<td>28</td>
<td>17/288</td>
<td>40.8</td>
</tr>
<tr>
<td>Hwang 2012</td>
<td>IHC</td>
<td>43</td>
<td>13/43</td>
<td>30.0</td>
</tr>
<tr>
<td>Kang 2012</td>
<td>HCC</td>
<td>41</td>
<td>10/41</td>
<td>24.0</td>
</tr>
<tr>
<td>Lee 2010</td>
<td>IHC</td>
<td>28</td>
<td>9/28</td>
<td>30.0</td>
</tr>
<tr>
<td>Andolino 2011</td>
<td>primary HCC</td>
<td>56</td>
<td>18/56</td>
<td>20.0</td>
</tr>
<tr>
<td>Bujold 2013</td>
<td>HCC</td>
<td>102</td>
<td>11/102</td>
<td>30.0</td>
</tr>
<tr>
<td>Son 2010</td>
<td>primary HCC</td>
<td>36</td>
<td>11/36</td>
<td>20.0</td>
</tr>
</tbody>
</table>
Grade 2+ general GI toxicity vs. RX/PTV dose

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>#Events/#Patients</th>
<th>D_{50} Gy (95% CI)</th>
<th>Y_{95} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2+ GI</td>
<td>99/278</td>
<td>48.0 (43.6 - 65.9)</td>
<td>0.83 (0.37 - 1.31)</td>
</tr>
</tbody>
</table>

Grade 3+ general GI toxicity vs. RX/PTV dose

<table>
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<tr>
<th>Endpoint</th>
<th>#Events/#Patients</th>
<th>D_{50} Gy (95% CI)</th>
<th>Y_{95} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ GI</td>
<td>25/399</td>
<td>87.1 (61.1 - 134.4)</td>
<td>1.22 (0.78 - 1.68)</td>
</tr>
</tbody>
</table>

- D10 & D20 values were 50.6 Gy & 63.1 Gy
- D50 of 87.1 Gy can be attributed to low rates of G3+ GI toxicity

Recommended Dose Limits

- QUANTEC recommendations remain reasonable
  - Primary: MLD 13 Gy (3 fx) & 18 Gy (6 fx)
  - Mets: MLD 15 Gy (3 fx) & 20 Gy (6 fx)
- Why
  - acceptable grade 3 liver enzyme toxicity risk \( \rightarrow < 20\% \)
  - Liver planning objective \( \geq 700\)cc to \( \leq 15\)Gy
    - \( \rightarrow \) low G3+ GI toxicity: 7.6% (9/118)
HCC data from Son et al (IJROBP) suggest sparing ≥ 800cc to ≤ 18Gy in 3 fractions

abrupt increase of Child-Pugh class progression with a steep curve

RILD CT/Pathology correlation: evidence that partial volumes can be treated safely

- No cases of classic or non-classic RILD (clinical)
- We evaluated several cases who underwent surgery after SBRT in order to evaluate pathology associated with imaging changes
- CT obtained preoperatively 6 weeks after SBRT
- The treated area shows underlying pathologic findings c/w veno-occlusive disease

Olsen et al, IJROBP 73(5) 2009

SBRT results in focal classic RILD that isn’t clinically manifest (c/w critical volume model)

Normal liver, same patient, outside zone of reaction

Type I reaction: lobular disarray, sinusoidal congestion, pigment accumulation in hepatocytes, some macrophages

Courtesy of T. Schefter
Special Situations
• Toxicity profile of patients with metastatic disease is different from patients with primary tumors.
• Patients with metastatic liver disease tolerate RT more than patients with primary liver tumors.
  – Not enough data to model each patient cohort separately.
• GI toxicity should be a function of the dose delivered to the individual GI organs.
  – In the absence of dosimetric data for each GI organ, RX or PTV doses were used.

Factors Beyond Dose/Volume Affecting Liver and GI Toxicities
• Pre-treatment Child-Pugh status
• Pre-existing GI conditions
• Increasing tumor size and pre-treatment systemic therapies
• Patients with primary tumors are more likely to develop RT-induced liver injury than patients with metastatic lesions

Future Studies
• Explicit studies of the toxicity differences between patients with liver mets, HCC, and IHC.
• Dose-response analysis could be improved if studies report on the achieved dose-volume metrics utilized for treatment planning.
• Minimum standards for reporting treatment outcomes should include relevant clinical and dosimetric data.
• Many journals allow for the inclusion of supplemental data that can be used to include detailed DVH data and additional dosimetric details.
Conclusions

• Not all publications reported on the "actual" delivered doses.
• HCC data suggest the total liver volume receiving <18 Gy should be > 800 cc to spare hepatic function.
• QUANTEC recommendations for MLD should be followed.
• Many studies that used ≥700cc ≤ 15 Gy in planning reported < 8% G3+ GI toxicity risk.
• RX or PTV mean dose of 50 Gy in 3-6 fractions would result in G3+ general GI toxicity risk of < 10%.

Thank You