Tossicità epatica

Marta Scorsetti, Milano
HEPATIC TOXICITY RESULTING FROM CANCER TREATMENT

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The terminology describing hepatic toxicity resulting from cancer treatment has been somewhat confusing. For instance, “radiation hepatitis” is often used to describe a lesion which, in the strict sense of the word, is not a “hepatitis,” for it lacks the characteristics of inflammation, such as exudate of various leukocytes. Therefore, in this article we will refer to hepatic injury produced chiefly by radiation as radiation-induced liver disease (RILD; usually subacute). This term will also be used to describe toxicity resulting from both moderate doses of chemotherapy and radiation in which the presentation resembles that of radiation injury alone. Hepatic injury that occurs in patients undergoing bone marrow transplantation can be distinguished clinically from RILD (see below), and will be called combined modality-induced liver disease (CMILD). As noted below, VOD occurs in both conditions.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Radiation-induced liver disease</th>
<th>Combined modality liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to presentation</td>
<td>2–16 weeks (typically 4–8 weeks)</td>
<td>1–4 weeks (typically 1–2 weeks)</td>
</tr>
<tr>
<td>after treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs/Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Ascites</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>+/−</td>
<td>++</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incr. bilirubin</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Incr. AST</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Incr. alkaline phosphatase</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Outcome</td>
<td>10–20% mortality</td>
<td>30–50% mortality</td>
</tr>
</tbody>
</table>
«Classic» RILD: anicteric hepatomegaly, ascites, elevated alkaline phosphatase, typically occurring between 2 weeks to 3 months after RT. Pathologically, there is occlusion and obliteration of the central veins of the hepatic lobules, retrograde congestion and secondary hepatocyte necrosis.

«Non-classic» RILD: elevated liver transaminases more than five times the upper limit of normal or CTCAE grade 4 levels in patients with baseline values more than 5 times the upper limit of normal, typically occurring between 1 week and 3 months after RT. The underlying pathology of non-classic RILD is unclear.
No therapy has been shown to prevent or to modify the natural course of the disease.

Treatment is mainly directed at control of symptoms. The drugs used for supportive care include diuretics for fluid retention, paracentesis for ascites, correction of coagulopathy, and steroids to reduce hepatic congestion.

Purpose: To identify risk factors relevant to radiation-induced liver disease (RILD) and to determine the hepatic tolerance to radiation.

Methods and Materials: The data of 109 primary liver carcinomas (PLC) treated with hypofractionated 3D-CRT were analyzed. Seventeen patients were diagnosed with RILD and 13 out of 17 died from it.

Results: The risk factors for RILD were late T stage, large gross tumor volume, presence of portal vein thrombosis, association with Child-Pugh Grade B cirrhosis, and acute hepatic toxicity.

Multivariate analyses demonstrated that the severity of hepatic cirrhosis was a unique independent predictor.
RADIATION-INDUCED LIVER DISEASE IN THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY FOR PRIMARY LIVER CARCINOMA: THE RISK FACTORS AND HEPATIC RADIATION TOLERANCE

Shi-Xiong Liang, M.D.,† Xiao-Dong Zhu, M.D.,† Zhi-Yong Xu, Ph.D.,†‡ Ji Zhu, M.D., M.S.,†‡ Jian-Dong Zhao, M.D.,* Hai-Jie Lu, M.D.,† Yun-Li Yang, M.D.,† Long Chen, M.D.,† An-Yu Wang, M.D.,† Xiao-Long Fu, M.D.,*‡ and Guo-Liang Jiang, M.D.,*‡

Table 1. Univariate analysis of clinical characteristics in correlation with RILD for 109 patients with primary liver carcinoma treated with 3D-CRT

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of cases</th>
<th>No. of RILD</th>
<th>%</th>
<th>$\chi^2$</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0.357</td>
<td>*</td>
</tr>
<tr>
<td>Male</td>
<td>99</td>
<td>17</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq55$</td>
<td>83</td>
<td>14</td>
<td>17</td>
<td>0.758</td>
<td>*</td>
</tr>
<tr>
<td>$&gt;55$</td>
<td>26</td>
<td>3</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCC-TNM stage</td>
<td></td>
<td></td>
<td></td>
<td>7.642</td>
<td>0.006</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>65</td>
<td>5</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4N0M0</td>
<td>44</td>
<td>12</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTV (cm$^3$)</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
<td>*</td>
</tr>
<tr>
<td>$&lt;125$</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125–1000</td>
<td>77</td>
<td>14</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt;1000$</td>
<td>11</td>
<td>3</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td></td>
<td></td>
<td></td>
<td>0.518</td>
<td>*</td>
</tr>
<tr>
<td>Negative</td>
<td>23</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>86</td>
<td>15</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVT</td>
<td></td>
<td></td>
<td></td>
<td>4.819</td>
<td>0.037*</td>
</tr>
<tr>
<td>Absent</td>
<td>81</td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>28</td>
<td>8</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh grade</td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>93</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>16</td>
<td>9</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE</td>
<td></td>
<td></td>
<td></td>
<td>5.677</td>
<td>0.017</td>
</tr>
<tr>
<td>Without</td>
<td>76</td>
<td>16</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>33</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Correlation between acute hepatic toxicity and RILD for 109 patients with primary liver carcinoma treated with 3D-CRT (Spearman test)

<table>
<thead>
<tr>
<th>Acute hepatic toxicity grade</th>
<th>No. of cases</th>
<th>No. of RILD</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>2 (3%)</td>
<td>0.407</td>
<td>0.000</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>11 (26%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>4 (57%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion: These data demonstrate that the liver exhibits a large volume effect for RILD, suggesting that the mean liver dose may be useful in ranking radiation plans. The inclusion of clinical factors, especially the diagnosis of primary hepatobiliary cancer vs. liver metastases, improves the estimation of NTCP over that obtained solely by the use of dose–volume data. These findings should facilitate the application of focal liver irradiation in future clinical trials.
Partial Volume Tolerance of the Liver to Radiation

Laura A. Dawson, MD*, and Randall K. Ten Haken, PhD†

The mean liver dose associated with a 5% risk of RILD for patients with metastatic and primary liver cancer are 37 Gy and 32 Gy, respectively, in 1.5 Gy per fraction, and 32 Gy and 28 Gy in 2 Gy per fraction, respectively.
• Liver obeys the **parallel architecture model of radiobiology**, so the risk of RILD is generally proportional to the **mean dose** of radiation delivered to normal liver tissue.

• It should be possible to safely treat small hepatic lesions with high doses of radiation by **using SBRT**, with adequate dose constraints for normal liver (minimum volume of 700mL should receive a total dose less than 15 Gy).
• **Stereotactic body radiation therapy (SBRT)** is an external beam radiation therapy method used to very precisely deliver a **high dose of radiation** to an extracranial target within the body, using either a single dose or a small number of fractions.

• Specialized treatment planning results in high target dose and **steep dose gradients** beyond the target.

• Maneuvers to either **limit or compensate for target movement** during treatment planning and delivery are often useful and may be required.
SBRT for liver lesion

SBRT 25Gy x 3; **10FFF**; DR 2400.

PTV1&PTV2: V95%=99.5%
Spinal cord: Max dose=17.3 Gy
Stomach: Max=21.0Gy, Mean=9.5 Gy
Liver: Mean=15.5 Gy, D15Gyfree=2811cc

1 isocentre, 3 arcs
Jaw tracking

MU:3216+3527+563
BOT: 174s(80+82+14s)
Patient treated with SBRT for local relapse after hepatic surgery for colorectal metastasis
SBRT 25Gy x 3; **10FFF**; DR 2400.

**PET before SBRT**

**PET after 6 months**

**PET –CT pre-treatment, CEA 72**

**PET –CT post-treatment, CEA 2.2**
SBRT for liver lesion

SBRT 25Gy x 3; 10FFF; DR 2400.

PET before SABR

PET after 6 months

RapidArc
1 isocentre
1 arc
Jaw tracking

MU:5103
BOT:130s
Liver SBRT: QUANTEC dose constraints

Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommendations for dose constraints during external beam radiation therapy (RT) to the liver.

<table>
<thead>
<tr>
<th></th>
<th>Liver metastases</th>
<th>Primary Liver cancer</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole liver RT</td>
<td>( \leq 30 \text{ Gy}, 2 \text{ Gy/F} )</td>
<td>( \leq 28 \text{ Gy}, 2 \text{ Gy/F} )</td>
<td>Whole organ prescription dose</td>
</tr>
<tr>
<td></td>
<td>( 21 \text{ Gy/7 F} )</td>
<td>( 21 \text{ Gy/7 F} )</td>
<td></td>
</tr>
<tr>
<td>Partial liver RT, conventional fractionation</td>
<td>( \leq 32 \text{ Gy} )</td>
<td>( \leq 28 \text{ Gy} )</td>
<td>Mean normal liver dose for tumor dose ( \leq 2 \text{ Gy/F} )</td>
</tr>
<tr>
<td>SBRT, 3–6 F</td>
<td>( &lt; 15 \text{ Gy/3F} )</td>
<td>( &lt; 13 \text{ Gy/3F} )</td>
<td>Mean normal liver dose</td>
</tr>
<tr>
<td></td>
<td>( &lt; 20 \text{ Gy/6 F} )</td>
<td>( &lt; 18 \text{ Gy/6F} )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CP B: ( &lt; 6 \text{ Gy/4-6F} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \text{At least } 700 \text{ cc normal liver } &lt; 15 \text{ Gy/3F} )</td>
<td>Critical volume model</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \text{At least } 800 \text{ cc normal liver } &lt; 18 \text{ Gy/3F} )</td>
<td>Only for Child-Pugh class A</td>
<td></td>
</tr>
</tbody>
</table>

\( ^{a} \) Normal liver refers to the total volume of liver minus the gross tumor volume.

Liver SBRT in 3 fractions: Humanitas Trial dose constraints

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>Dose-Volume Limits</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy liver (defined as total liver volume minus cumulative GTV)</td>
<td>&gt; 700 cc at &lt; 15 Gy in 3 F</td>
<td>The volume of healthy liver &gt; 1000 cc</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>&lt; 18 Gy in 3 F</td>
<td></td>
</tr>
<tr>
<td>Kidneys (R+L)</td>
<td>V15 Gy &lt; 35%</td>
<td></td>
</tr>
<tr>
<td>Stomach, duodenum, small intestine</td>
<td>&lt; 21 Gy in 3 F (also for minimum volumes)</td>
<td>Patients with GTV &lt; 8 mm from the heart, stomach, duodenum and small intestine to be excluded</td>
</tr>
<tr>
<td>Heart</td>
<td>&lt;30 Gy in 3 F</td>
<td></td>
</tr>
<tr>
<td>Rib</td>
<td>D30cm3 &lt;30Gy</td>
<td></td>
</tr>
</tbody>
</table>
Elegibility criteria for SBRT

- Adequate liver function, defined as:
  - total bilirubin < 2.5 mg/dL
  - albumin > 3 g/dL
  - serum levels of aspartate amynotransferase (AST) and alanine amynotransferase (ALT) less than 3 times the upper limit of normal

- Normal liver volume greater than 1000 cm³

- No active connective tissue disorders

- Karnofsky Performance Status 70

- No concurrent chemotherapy allowed
**Assessment of liver function**

### TABLE 3: Child-Pugh score

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2–3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8–3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>1–3</td>
<td>4–6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>I–II</td>
<td>III–IV</td>
</tr>
</tbody>
</table>

* Grade A = 5–6 points; grade B = 7–9 points; grade C = 10–15 points.

### Prospective trials studying SBRT in liver mets

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Design</th>
<th>No of patients</th>
<th>Tumor size</th>
<th>SABR dose</th>
<th>Toxicity</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scorsetti et al</td>
<td>Phase II (preliminary report)</td>
<td>61 (76 tumors)</td>
<td>1.8-143.4 cm² (mean 18.6 cm²)</td>
<td>75 Gy in 3 fractions</td>
<td>No case of RILD. Twenty-six percent had grade 2 transaminase increase (normalised in 3 mo). Grade 2 fatigue in 65% patients, one grade 3 chest wall pain which regressed within 1 yr. No dose-limiting toxicity 4 cases of Grade 2 late toxicity (2 GI, 2 soft tissue/rib) No serious toxicity</td>
<td>1-yr LC94, 22-mo LC 90.6%</td>
</tr>
<tr>
<td>Goodman et al</td>
<td>Phase I (HCC and liver mets)</td>
<td>26 (19 liver mets)</td>
<td>0.8-146.6 mL (median, 32.6 mL)</td>
<td>Dose escalation, 18-30 Gy (1 fr)</td>
<td>1-yr local failure, 3% 2-yr OS, 49% (mets only) Crude LC rate 74%</td>
<td></td>
</tr>
<tr>
<td>Ambrosino et al</td>
<td>Prospective cohort</td>
<td>27</td>
<td>20-165 mL (median, 69 mL)</td>
<td>25-60 Gy (3 fr)</td>
<td>No RILD, 10% Grade 3/4 acute toxicity No Grade 3/4 late toxicity No RILD, Late Grade ¾ &lt; 2%</td>
<td>Crude LC rate 74%</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Phase I - II</td>
<td>68</td>
<td>1.2-3090 mL (median, 75.9 mL)</td>
<td>Individualized dose, 27.7-60 Gy (6 fr)</td>
<td>1-yr LC, 71% Median survival, 17.6 mo</td>
<td></td>
</tr>
<tr>
<td>Rusthoven et al</td>
<td>Phase I - II</td>
<td>47</td>
<td>0.75-97.98 mL (median, 14.93 mL)</td>
<td>Dose escalation, 36-60 Gy (3 fr)</td>
<td>1-yr LC, 95% 2-yr LC, 92% Median survival, 20.5 mo 2-yr LC, 79% (by tumor) and 64% (by patient) 2-yr OS, 86% 2-yr OS, 62%</td>
<td></td>
</tr>
<tr>
<td>Hoyer et al</td>
<td>Phase II (CRC oligometas)</td>
<td>64 (44 liver mets)</td>
<td>1.8-8.8 cm (median, 3.5 cm)</td>
<td>45 Gy (3 fr)</td>
<td>One liver failure, two severe late GI Toxicities Two Grade 3 liver toxicities No significant toxicity reported</td>
<td>1-yr LC, 71% 18-mo LC, 67% 1-yr OS, 72%</td>
</tr>
<tr>
<td>Méndez Romero et al</td>
<td>Phase I - II (HCC and mets)</td>
<td>25 (17 liver mets)</td>
<td>1.1-322 mL (median, 22.2 mL)</td>
<td>30-37.5 Gy (3 fr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herfarth et al</td>
<td>Phase I - II</td>
<td>35</td>
<td>1.132 mL (median, 10 mL)</td>
<td>Dose escalation, 14-26 Gy (1 fr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SABR: Stereotactic ablative radiotherapy; RILD: Radiation induced liver disease; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; GI: Gastrointestinal; LC: Local control.

*Nair et al. World J Radiol 2014 February 28; 6(2): 18-25*
From 2005 to 2009, 60 patients with liver-confined HCC were treated with SBRT: 36 Child-Turcotte-Pugh Class A and 24 CTP Class B. The median number of fractions, dose per fraction, and total dose, was 3, 14 Gy, and 44 Gy, respectively, for those with CTP Class A cirrhosis and 5, 8 Gy, and 40 Gy, respectively, for those with CTP Class B. The median follow-up time was 27 months, and the median tumor diameter was 3.2 cm. The 2-year LC, PFS, and OS were 90%, 48%, and 67%, respectively, with median TTP of 47.8 months. Subsequently, 23 patients underwent transplant, with a median time to transplant of 7 months.

Although there was no relationship between toxicity and dose delivered to normal liver, there was an association between pretreatment CTP score and both the development of toxicity in any form (p = 0.035) and the occurrence of an increase of greater than one grade in hematologic/hepatic dysfunction (p = 0.008).
Prospective trials studying SBRT in liver mets

“Four patients, all with a CTP score > 8 and enrolled in the initial Phase I dose escalation study, developed progressive liver dysfunction either during treatment or shortly thereafter”

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1*</th>
<th>Patient 2</th>
<th>Patient 3*</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>69</td>
<td>72</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>KPS</td>
<td>70</td>
<td>70</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>CTP score</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Maximum tumor diameter (cm)</td>
<td>3.5</td>
<td>4.6</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>GTV (cc)</td>
<td>47</td>
<td>95</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Number of fractions</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Dose per fraction (Gy)</td>
<td>8</td>
<td>14</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Total dose (Gy)</td>
<td>24</td>
<td>42</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>Duration of SBRT (days)</td>
<td>6</td>
<td>17</td>
<td>41</td>
<td>8</td>
</tr>
<tr>
<td>Mean dose to uninvolved liver (Gy)</td>
<td>7.63</td>
<td>15.67</td>
<td>4.49</td>
<td>10.65</td>
</tr>
</tbody>
</table>

“Our findings do suggest, however, that SBRT may not be safe for patients with a CTP score ≥ 8”
Liver toxicity after SBRT in primary tumour and metastasis

Low Hepatic Toxicity in Primary and Metastatic Liver Cancers after Stereotactic Ablative Radiotherapy Using 3 Fractions

Sun Hyun Bae,1 Mi-Sook Kim,2
Won Il Jang,2 Chul Koo Cho,2
Hyung Jun Yoo,2 Kum Bae Kim,2
Chul Ju Han,3 Su Cheol Park,3
and Dong Han Lee4

78 patients with primary and metastatic liver cancers, who underwent SBRT in dose-escalation study with 33-57 Gy delivered in 3-4 fractionations between 2003 and 2008, and a phase II SABR study with 60 Gy delivered in 3 fractionations between 2008 and 2011.

Ten patients (13%) experienced hepatic toxicity ≥ grade 2. The clinical manifestations were hyperbilirubinemia, elevation of hepatic enzyme, hypoalbuminemia, ascites, and hepatic encephalopathy. Among these, 5 patients (6%) experienced the progression of CP class: from A to B in 4 patients; from A to C in 1 patient.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex/Age</th>
<th>Primary</th>
<th>Normal liver volume (mL)</th>
<th>PTV (mL)</th>
<th>$r_{V_{100}}$ (mL)</th>
<th>$r_{V_{150}}$ (mL)</th>
<th>Hepatic Toxicity*</th>
<th>CP score</th>
<th>Clinical manifestations of hepatic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/50</td>
<td>HCC</td>
<td>1,191</td>
<td>42</td>
<td>1,051</td>
<td>1025</td>
<td>1</td>
<td>5</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>2</td>
<td>M/70</td>
<td>CC</td>
<td>741</td>
<td>209</td>
<td>397</td>
<td>321</td>
<td>1</td>
<td>5</td>
<td>A/LP increased</td>
</tr>
<tr>
<td>3</td>
<td>M/59</td>
<td>HCC</td>
<td>1,108</td>
<td>34</td>
<td>1,004</td>
<td>985</td>
<td>1</td>
<td>6</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>4</td>
<td>M/49</td>
<td>HCC</td>
<td>1,187</td>
<td>118</td>
<td>866</td>
<td>807</td>
<td>0</td>
<td>6</td>
<td>Hyperbilirubinemia, Asites</td>
</tr>
<tr>
<td>5</td>
<td>M/73</td>
<td>HCC</td>
<td>914</td>
<td>65</td>
<td>757</td>
<td>731</td>
<td>1</td>
<td>6</td>
<td>Hyperbilirubinemia, Asites</td>
</tr>
<tr>
<td>6</td>
<td>F/62</td>
<td>HCC</td>
<td>889</td>
<td>38</td>
<td>766</td>
<td>729</td>
<td>1</td>
<td>10</td>
<td>Hyperbilirubinemia, Hepatic encephalopathy</td>
</tr>
<tr>
<td>7</td>
<td>M/61</td>
<td>HCC</td>
<td>842</td>
<td>188</td>
<td>700</td>
<td>677</td>
<td>1</td>
<td>6</td>
<td>Hyperbilirubinemia, Asites</td>
</tr>
<tr>
<td>8</td>
<td>F/69</td>
<td>HCC</td>
<td>717</td>
<td>62</td>
<td>590</td>
<td>556</td>
<td>0</td>
<td>6</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>9</td>
<td>F/66</td>
<td>HCC</td>
<td>1,104</td>
<td>86</td>
<td>880</td>
<td>838</td>
<td>1</td>
<td>7</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>10</td>
<td>F/67</td>
<td>HCC</td>
<td>724</td>
<td>18</td>
<td>626</td>
<td>594</td>
<td>1</td>
<td>7</td>
<td>Hyperbilirubinemia</td>
</tr>
</tbody>
</table>
Risk factors for liver toxicity

Low Hepatic Toxicity in Primary and Metastatic Liver Cancers after Stereotactic Ablative Radiotherapy Using 3 Fractions

Sun Hyun Bae,¹ Mi-Sook Kim,² Won Il Jang,² Chul Koo Cho,² Hyung Jun Yoo,² Kum Bae Kim,² Chul Ju Han,³ Su Cheol Park,³ and Dong Han Lee⁴

Predictors for hepatic toxicity: The baseline CP score, PTV, and normal liver volume were statistically significant clinical predictors. Dose-volumetric parameters of rV5Gy-rV35Gy were all statistically significant in univariate analysis, indicating a dependence of liver toxicity on the liver volume free from doses between 5 and 35 Gy. On multivariate logistic regression analysis including clinical and dosimetric variables, the baseline CP score (5 vs. 6-8) was the only significant predictor for hepatic toxicity ≥grade 2 (hazard ratio, 0.026; 95% confidence interval, 0.003-0.221, P=0.001).
## Experience with Liver SBRT

### Table 4. Hepatic toxicity from prospective studies using stereotactic ablative radiotherapy for primary and metastatic liver cancers, which had a good baseline liver function and satisfied their own liver dose constraints in all patients

<table>
<thead>
<tr>
<th>Study design/Author</th>
<th>Origin (No. of pts)</th>
<th>CP class</th>
<th>Median dose (range, Gy)/ fx’s</th>
<th>Liver dose constraints</th>
<th>Incidence of hepatic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I Schefter (26)</td>
<td>HCC (2) Liver mets (16)</td>
<td>*1</td>
<td>51 (36-60)/3</td>
<td>$r_{V_{15Gy}} \geq 700$ mL</td>
<td>No</td>
</tr>
<tr>
<td>Phase I/II Kavanagh (27)</td>
<td>Liver mets (36)</td>
<td>†2</td>
<td>60 (36-60)/3</td>
<td>$r_{V_{15Gy}} \geq 700$ mL</td>
<td>No</td>
</tr>
<tr>
<td>Phase I/II Rusthoven (28)</td>
<td>Liver mets (47)</td>
<td>*1</td>
<td>60 (36-60)/3</td>
<td>$r_{V_{15Gy}} \geq 700$ mL</td>
<td>No</td>
</tr>
<tr>
<td>Phase I Rule (29)</td>
<td>Liver mets (27)</td>
<td>A</td>
<td>50 (30,50,60)/5(3-5)</td>
<td>$r_{V_{15Gy}} \geq 700$ mL in 3 fx’s, $r_{V_{21Gy}} \geq 700$ mL in 5 fx’s</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 5. Hepatic toxicity from prospective or retrospective studies using stereotactic ablative radiotherapy for primary and metastatic liver cancers, which had patients with a Child-Pugh (CP) class of B and did not strictly satisfy their own liver dose constraints in all patients

<table>
<thead>
<tr>
<th>Study design/Author</th>
<th>Origin (No. of pts)</th>
<th>CP class</th>
<th>Median dose (range, Gy)/ fx’s</th>
<th>Liver dose constraints</th>
<th>Incidence of hepatic toxicity</th>
<th>Predictor for hepatic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I Cardenas (8)</td>
<td>HCC (17) A, B</td>
<td>36-48/3 in CP-A 40/5 in CP-B</td>
<td>$r_{V_{17Gy}} \geq 700$ mL</td>
<td>Grade 3: 12%</td>
<td>CP score</td>
<td></td>
</tr>
<tr>
<td>Retrospective Son (9)</td>
<td>HCC (36) A, B, C</td>
<td>36 (30-39)/3</td>
<td>$V_{20Gy}&lt;50%$</td>
<td>$\geq$ Grade 2; 33% CP class progression: 11%</td>
<td>$V_{15Gy}$ for $\geq$ grade 2 $V_{15Gy}$ for CP class progression</td>
<td></td>
</tr>
<tr>
<td>Phase I/II Andolino (10)</td>
<td>HCC (60) A, B</td>
<td>44 (30-48)/3 in CP-A 40 (24-48)/5 in CP-B</td>
<td>CP-A: D$<em>{max}$ $\leq$ 10 Gy + $r</em>{V_{15Gy}} \geq 500$ mL CP-B: D$<em>{max}$ $\leq$ 18 Gy + $r</em>{V_{15Gy}} \geq 500$ mL</td>
<td>CP score for toxicity $\geq$ 1 grade</td>
<td>CP score for toxicity $\geq$ 1 grade</td>
<td></td>
</tr>
<tr>
<td>Retrospective Bibault (11)</td>
<td>HCC (75) A, B</td>
<td>45 (24-45)/3</td>
<td>$r_{V_{17Gy}} &gt; 700$ mL $+V_{20Gy}&lt;50%$ $+V_{21Gy}&lt;33%$</td>
<td>Ascites: 7%</td>
<td>Normal liver volume</td>
<td></td>
</tr>
<tr>
<td>Retrospective Jung (12)</td>
<td>HCC (92) A, B</td>
<td>45 (30-60)/3-4</td>
<td>NS</td>
<td>$\geq$ Grade 2; 19%</td>
<td>CP class</td>
<td></td>
</tr>
<tr>
<td>Retrospective Janoray (13)</td>
<td>HCC (21) Liver mets (35)</td>
<td>A, B</td>
<td>45 or 60/3</td>
<td>$r_{V_{17Gy}} \geq 700$ mL $+V_{15Gy}&lt;33%$</td>
<td>Grade 3: 9%</td>
<td>CP class progression: 4%</td>
</tr>
<tr>
<td>Retrospective Sanuki (14)</td>
<td>HCC (180) A, B</td>
<td>40/5 in CP-A 35/5 in CP-B</td>
<td>$V_{20Gy}&lt;20%$</td>
<td>Grade 5: 4%</td>
<td>Transaminase ↑, CP score, and platelet count ↓ for grade 5</td>
<td></td>
</tr>
<tr>
<td>Current study HCC (61)</td>
<td>Others* (17) A, B</td>
<td>54 (36-60)/3</td>
<td>$r_{V_{17Gy}} \geq 700$ mL</td>
<td>$\geq$ Grade 2; 13%</td>
<td>CP score for $\geq$ grade 2</td>
<td></td>
</tr>
</tbody>
</table>
Stereotactic body radiation therapy for liver metastases

Marta Scorsetti, Elena Clerici, Tiziana Comito

Table 2 Selection criteria for SBRT

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Patients categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suitable</td>
</tr>
<tr>
<td>Lesion number</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td>1-3</td>
</tr>
<tr>
<td>Distance from OARs (mm)</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Liver function</td>
<td>Child A</td>
</tr>
<tr>
<td>Free liver volume (cc)</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiation therapy; OARs, organs at risk.
### Table 1: Summary of toxicities with abdominal stereotactic body radiotherapy (SBRT)

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Study</th>
<th>Disease</th>
<th>N</th>
<th>Dose (Gy)</th>
<th>Gy/Fx</th>
<th>Grade (%)</th>
<th>Toxicity 1 rate (%)</th>
<th>Toxicity 2 rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Andolino et al. (16) 2011</td>
<td>Class A HCC</td>
<td>36</td>
<td>44</td>
<td>14</td>
<td>35</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class B HCC</td>
<td>24</td>
<td>40</td>
<td>8</td>
<td>3</td>
<td>48</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Rusthoven et al. (15) 2009</td>
<td>Metastases</td>
<td>47</td>
<td>60</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Choi et al. (17) 2006</td>
<td>HCC</td>
<td>20</td>
<td>50</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Tse et al. (18) 2008</td>
<td>Class A HCC</td>
<td>41</td>
<td>36</td>
<td>6</td>
<td>24</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Kress et al. (19) 2012</td>
<td>Metastases</td>
<td>11</td>
<td>49.7</td>
<td>8.3</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Price et al. (20) 2012</td>
<td>Class A-C HCC</td>
<td>26</td>
<td>42</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

**Biliary**

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>N</th>
<th>Dose (Gy)</th>
<th>Gy/Fx</th>
<th>Toxicity 1 rate (%)</th>
<th>Toxicity 2 rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kopek et al. (21) 2010</td>
<td>Cholangiocarcinoma</td>
<td>27</td>
<td>45</td>
<td>15</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>Barney et al. (22) 2012</td>
<td>Cholangiocarcinoma</td>
<td>10</td>
<td>55</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Eriguchi et al. (23) 2013</td>
<td>HCC/Liver metastases</td>
<td>50</td>
<td>40</td>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Tarita O. Thomas et al., Journal of Gastrointestinal Oncology, Vol 5, No 3 June 2014
Published data on biliary toxicity after stereotactic body radiation therapy (SBRT) for liver tumors are scant. From among 297 SBRT-treated patients, we retrospectively analyzed 50 patients irradiated with >20 Gy to the central biliary system. Toxicity profiles were investigated by use of a dose-volume histogram analysis. Only 1 patient treated twice with SBRT metachronously experienced radiation-induced bile duct stenosis at the high-dose area >80 Gy. SBRT with 40 Gy/5 fractions for liver tumors adjacent to the central biliary system was feasible.
CONCLUSIONS

✔ SBRT is a safe and effective treatment.

✔ Risk factors for liver toxicity:
  ❖ Liver function
  ❖ Total Liver volume
  ❖ Presence of cirrhosis HCV- or HBV-related
  ❖ Respect strict dose contraints
  ❖ Concomitant chemotherapy
  ❖ Performance status and comorbidities