Individualized dosimetry treatment planning for liver irradiation

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Outline

- Introduction
- Materials
- Methods
- Results
- Conclusions
Introduction

- Availability of IG-IMRT/gating for liver targets invites alternative or more effective RT strategies.

- Various prescribed doses and dose rates are being used clinically (e.g., 61.5 Gy 1.5 Gy/fx, 53.6 Gy 4.88 Gy/fx) for RT liver tumor treatment.

- New hypofractionation regimens (RTOG 0438) were initiated: 10 fractions @3.5 Gy/fx, 4.0 Gy/fx, 4.5 Gy/fx and 5.0 Gy/fx.

- Allow to evaluate fractionation schemes and design individualized treatment plans
Flow of an individualized treatment plan

- DVH for normal liver and tumor
- Fractionation scheme
- NTCP and NTCP limit
- Maximum tolerable Dose (MTD)
- BED and expected survival rate
- Update the plan with MTD as the new prescription dose

Gating, IGRT, Tumor tracking etc

Need reliable radiobiological parameters
Gating vs non-gating plan
normal tissue sparing and tumor dose escalation

Mean dose to normal liver is reduced by 15% with gating
## Dose fractionation scheme vs outcomes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient no.</th>
<th>Median prescribed dose</th>
<th>Fraction scheme (Gy/fx)</th>
<th>Treatment time (day)</th>
<th>Median survival rate (month)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. X. Liang etc</td>
<td>128</td>
<td>53.6</td>
<td>4.88</td>
<td>28</td>
<td>20</td>
<td>Cancer Vol103, 218 (2005)</td>
</tr>
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<td>J. Seong etc.</td>
<td>51</td>
<td>45</td>
<td>1.8</td>
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<td>9</td>
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<td>J. Seong etc.</td>
<td>24</td>
<td>32.5</td>
<td>1.8</td>
<td>25</td>
<td>13</td>
<td></td>
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</table>
Survival rate and tumor cell proliferation

(1) Death probability of a liver cancer patient with $K$ tumor cell in the tumor is given by

$$P = \begin{cases} 
1 & K > K_{cr} \\
0 & K < K_{cr} 
\end{cases}$$

(2) Assume that the distribution of $K_{cr}$ among patient population follows a Gaussian distribution.

$$S(D, \tau) = 1 - \frac{1}{\sqrt{2\pi}\sigma_{cr}} \int_{-\infty}^{K} e^{-\frac{(K_{cr}^-K_{cr}^0)^2}{2\sigma_{cr}^2}} dK_{cr}$$

(3) We used the following equation to describe time dependence $\tau$ of tumor cells from beginning of radiation treatment to time

$$K = K_0 e^{-\left[\alpha \left(1+\frac{d}{\alpha / \beta}\right)D - \gamma \tau - (\gamma (\tau - T))^\delta\right]}$$

where $\gamma = \ln 2 / T_b$.

Gompertzian tumor growth model
Fitting results

\[ K_0 = 1244 \pm 16 \]
\[ \alpha = 0.010 \pm 0.002 \text{ (Gy}^{-1}\text{)} \]
\[ \alpha/\beta = 14 \pm 2.0 \text{ (Gy)} \]
\[ T_b = 110 \pm 7 \text{ days} \]
\[ K_{50} = 2625 \pm 55 \]
\[ \sigma = 924 \pm 71 \]
\[ \delta = 0.20 \pm 0.01 \]

\[ \text{error} = p_i \sqrt{\frac{1 - p_i}{N_i}} \]

Euro. J. of Surg. Oncol
Survival rate at different time

\[ \text{BED} = \left(1 + \frac{d}{\alpha / \beta}\right) \cdot D - \gamma T / \alpha \]
Lyman model and fractionation scheme

\[
NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx
\]

\[
t = (D - TD_{50}(\nu)) / m \cdot TD_{50}(\nu)
\]

\[
TD_{50}(\nu) = TD_{50}(1) \cdot \nu^{-n}
\]

\[
\nu = V_{\text{eff}} = \sum_i \nu_i \left( \frac{D_i}{D_{\text{max}}} \right)^{1/n}
\]

\[
D_i(d_{\text{ref}}) = \frac{(\alpha / \beta + d)}{(\alpha / \beta + d_{\text{ref}})} \cdot D_i(d)
\]

Two sets of Lyman model parameters were used for the calculations of NTCP:

Parameter set 1: (1.5 Gy/fx)
Dawson LA etc)
TD50=40.5 Gy, m=0.28 and n=1.1

Parameter set 2: (4.6 Gy/fx)
Liang SX etc)
TD50=39.8 Gy, m=0.12 and n=0.97

For normal liver \( \alpha/\beta = 2 \text{ Gy} \)
## Dose escalation based on NTCP

Lyman model parameters: $n=0.97, m=0.12, TD50(1)=39.8 \text{ Gy}$

<table>
<thead>
<tr>
<th>RT regimen for 3 liver patients</th>
<th>Mean dose (Gy) and calculated NTCP</th>
<th>BED (Gy) and expected 1 year survival rate</th>
<th>Escalated prescription dose (Gy) for NTCP&lt;10%</th>
<th>BED (Gy) and expected 1 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.05 GyX22 5fx/week</td>
<td>20.3, 0.04%</td>
<td>32, 44%</td>
<td>64</td>
<td>45.5, 55%</td>
</tr>
<tr>
<td>1.8Gyx30 5fx/week</td>
<td>22.0, 0.05%</td>
<td>34, 40%</td>
<td>75</td>
<td>48, 58%</td>
</tr>
<tr>
<td>1.8Gyx25 5fx/week</td>
<td>22.3, 0.06%</td>
<td>29, 37%</td>
<td>62</td>
<td>40, 50%</td>
</tr>
</tbody>
</table>
NTCP are calculated using parameters of Set 1 with exception of 2 and 3 Gy per fraction of which NTCP are calculated using parameters of Set 2. The dose/fx, marked by *, are those recommended in RTDG 038. Other regimens produce nearly the same BED for tumor as that for the proven dose fractionation regimen (1.5 Gy/fx and 10 fractions/wk).

<table>
<thead>
<tr>
<th>dose/fx (Gy)</th>
<th>fraction /wk</th>
<th>fraction</th>
<th>Pres. Dose (Gy)</th>
<th>Treatment time (day)</th>
<th>BED for tumor (Gy)</th>
<th>Veff(%)=30-35 NTCP (%)</th>
<th>Veff(%)=35-40 NTCP(%)</th>
<th>MTD(10% NTCP at Veff=40%) (Gy)</th>
<th>SR(1y) (%) at MTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>5</td>
<td>33</td>
<td>66</td>
<td>45</td>
<td>47.1</td>
<td>0.0-0.4</td>
<td>0.4-3.3</td>
<td>71.8</td>
<td>61</td>
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<tr>
<td>3</td>
<td>3</td>
<td>21</td>
<td>63</td>
<td>47</td>
<td>46.9</td>
<td>0.7-6.5</td>
<td>6.5-28</td>
<td>57.4</td>
<td>52</td>
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<td>3.5*</td>
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<td>10</td>
<td>35</td>
<td>12</td>
<td>36.2</td>
<td>0.2-0.3</td>
<td>0.3-0.4</td>
<td>84.9</td>
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<tr>
<td>4</td>
<td>3</td>
<td>13</td>
<td>52</td>
<td>29</td>
<td>48.6</td>
<td>0.7-1.2</td>
<td>1.2-2.1</td>
<td>77.9</td>
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<tr>
<td>4*</td>
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<td>40</td>
<td>12</td>
<td>43.9</td>
<td>0.3-0.5</td>
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<td>0.6-1.0</td>
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<tr>
<td>5*</td>
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<td>12</td>
<td>60.3</td>
<td>1.0-1.8</td>
<td>1.8-3.2</td>
<td>66.7</td>
<td>81</td>
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<tr>
<td>5</td>
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<tr>
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<tr>
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<td>19</td>
<td>1</td>
<td>44.2</td>
<td>1.6-3.0</td>
<td>3.0-5.3</td>
<td>22</td>
<td>58</td>
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</table>
Conclusions

- A plausible set of radiobiological parameters has been obtained based on clinical RT data for primary liver tumor: $\alpha=0.01$ (Gy$^{-1}$), $\alpha/\beta=14$ (Gy) and $T_b=110$ day.

- These parameters may be used to evaluate different fractionation schemes and to design new individualized treatment strategies for liver tumor.

- Regimens with dose per fraction between 3.5 to 5 Gy may lead to improved one-year survival rates (around 80%).