Development of an Inverse Optimization Package for Non-Uniform Dose Distribution Based on Spatially Inhomogeneous Radiosensitivity

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Introduction-Current Radiation Therapy

- Current std practice
  - Deliver a uniform radiation dose to tumor volume
  - Normal tissue sparing

- Problem with current std practice: inadequate dose to tumor
  - Limited by normal tissue--unsolvable
  - Ignore radiosensitivity inhomogeneity-solvable (IMRT can deliver nonuniform dose)

- How such treatment can be planned?
  Biological/functional images provide information to guide the design of non-uniform dose distributions
Inhomogeneous Radiosensitivities

Biological/functional images (e.g., PET, fMRI, SPECT) may provide information (anatomic, metabolic, biochemical, physiological and functional tumor and/or normal structures/tissue characteristics) to guide the treatment planning.

For example:

- **Brain case**
  - MRSI provides tumor metabolities
  - Perfusion-weighted MRI can be used to calculate relative cerebral blood volume (rCBV) which is an anatomic surrogate for tumor grade

- **PET: SUV** provides information about tumor proliferation rate
**EUD for Target w/ Inhomogeneous Radiosensitivities (1/2)**

Equal survival fractions with 3D dose and EUD

\[
\sum_{i=1}^{N} \omega_i S_i(D_i) = \sum_{i=1}^{N} \omega_i S_i(\text{EUD})
\]

with

\[
\omega_i = \frac{\rho_i V_i}{\sum_{j=1}^{N} \rho_j V_j}
\]

\[
S_i(D_i) = e^{-\alpha_i D_i - \beta_i D_i^2 / N_{Fx} + \gamma_i T}
\]
EUD for Target w/ Inhomogeneous Radiosensitivities (2/2)

Solution of EUD

\[ \sum_{i=1}^{N} \omega_i S_i(D_i) = \sum_{i=1}^{N} \omega_i [s_i(d)]^{EUD} \]

with

\[ s_i(d) = e^{-\alpha_i - \beta_i d + 1.4 \gamma_i / d} \]

- Regular analytic expression w/ homogeneous radiosensitivities
- Numeric solutions only w/ inhomogeneous radiosensitivities
- \( N_{Fx} = 20, \ d = 2 \text{ cGy} \)
- Used as objective function in our treatment planning
EUD for Normal Tissue

Definition: same NTCPs for 3D dose and EUD

\[
EUD = \left( \sum_{i=1}^{M} \nu_i D_i^{1/n} \right)^n
\]

- NTCP calculated w/ Lyman model
- \( \nu_i \) is the fraction volume
- \( n = 0.12 \) is used
Reconstruction of Radiosensitivities (1/3)

1. rCBV $\rightarrow$ tumor grade

Tumor angiogenesis: rCBV correlates tumor grade (Schmainda et al.)
Reconstruction of Radiosensitivities (2/3)

2. Tumor grade $\rightarrow$ radiosensitivities (Qi, Schultz, Li, et. al.)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>I/II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ (Gy$^{-1}$)</td>
<td>0.35 ± 0.07</td>
<td>0.11 ± 0.06</td>
<td>0.04 ± 0.03</td>
</tr>
<tr>
<td>$\alpha/\beta$ (Gy)</td>
<td>4.3 ± 5.0</td>
<td>5.8 ± 6.0</td>
<td>5.6 ± 4.8</td>
</tr>
</tbody>
</table>
Reconstruction of Radiosensitivities (3/3)

3. rCBV → radiosensitivities (step 1 combined with step 2)
Inverse Planning Algorithm

Mimic IMRT

- Calculation of 3D dose

\[ D_i = \sum_{\mu=1}^{N_B} w_{\mu} D_{\mu} \]

- Objective function
  - To maximize the target EUD
  - EUD is an implicit function of beamlet weights
  \[ \text{EUD} = f(\omega_1, \omega_2, \cdots, \omega_{N_B}) \]

- With constraints from organs at risk
Inverse Planning Package-DosePaint (1/2)

- A MATLAB package system

- Inputs
  - Beamlet doses from XiO: $D_{\mu i}$
  - Structure contours from XiO: to get voxels for involved structures
  - Fusion matrix of anatomical MRI to CT; rCBV data: to get $\alpha$ and $\alpha/\beta$ in each voxel
  - Select target and OARs
  - Add constraints

- Outputs
  - Optimized beamlet weights
Inverse Planning Package-DosePaint (2/2)
**Results**

The algorithm and the DosePaint package were tested

- With two brain tumor cases (referred as Case A and B)
- The OARs considered include left and right eyes, left and right optic nerves, optic chiasm, left or right inner ear, and the contra lateral white matter which was used as rCBV normalization structure.
- The anatomic MRI and rCBV data were employed, an MRI-CT fusion was applied to convert rCBV data to radiosensitivity parameter.
- An IMRT plan w/ uniform dose distribution was used for comparison.
Results-Inhomogeneous Radiosensitivities

(a) [Diagram showing inhomogeneous radiosensitivities for a patient and target]

(b) [Diagram showing inhomogeneous radiosensitivities for another patient and target]

Legend:
- patient
- target

α

α/β

Values:
- 0.05
- 0.1
- 0.15
- 0.2
- 0.25
- 0.3
- 0.5
- 1
- 1.5
- 2
- 2.5
- 3
- 3.5
- 4
- 4.5
- 5
- 5.5
Results-DVH and 2D Dose

![Graph showing DVH and 2D dose with various curves for different structures and dose levels.](image)
### Results - EUD

<table>
<thead>
<tr>
<th>Structure</th>
<th>EUD (Gy)</th>
<th>(D_{\text{min}}/D_{\text{mean}}/D_{\text{max}}) (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uniform dose plan</td>
<td>Non-uniform dose plan</td>
</tr>
<tr>
<td>target</td>
<td>68.2</td>
<td>80.8</td>
</tr>
<tr>
<td>WMT</td>
<td>37.2</td>
<td>34.8</td>
</tr>
<tr>
<td>L-Eye</td>
<td>3.4</td>
<td>2.5</td>
</tr>
<tr>
<td>L-Inner Ear</td>
<td>10.2</td>
<td>10.0</td>
</tr>
<tr>
<td>L-OpticNerve</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Optic Chiasm</td>
<td>6.3</td>
<td>6.2</td>
</tr>
<tr>
<td>R-Eye</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>R-Optic Nerve</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Unspecified tissue</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Results-$f_{EUD}$

An index to measure the biological effectiveness of a 3D dose distribution

- The more closer to unity, the better the plan

\[ f_{EUD} = \frac{1}{\sum_{i=1}^{n} \omega_i^{OAR} \cdot EUD_i^{OAR} + k \frac{\sum_{i=1}^{m} \omega_i^{Target} \cdot EUD_i^{Target}}{\sum_{i=1}^{m} \omega_i^{Target}}} \]

<table>
<thead>
<tr>
<th>Cases</th>
<th>Uniform dose plan</th>
<th>Non-uniform dose plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case A</td>
<td>0.380</td>
<td>0.433</td>
</tr>
<tr>
<td>Case B</td>
<td>0.445</td>
<td>0.467</td>
</tr>
</tbody>
</table>
Discussion (1/2)

1. Spatially homogeneous radiosensitivities
Discussion (2/2)

2. Spatially homogeneous radiosensitivities + Integral target dose constraint
Conclusions

- Compared with the uniform dose plan, the non-uniform dose plan is more effective
  - Substantial dose escalation can be achieved in low radiosensitive regions
  - Higher target EUD and lower OAR EUD
  - Larger $f_{\text{EUD}}$

- Uniform target dose distributions are not necessarily optimal
  - Uniform dose distribution is derived with optimized EUD plus integral target dose constraint
Acknowledgements

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- We wish to thank Dr. Kathleen Schmainda for providing the rCBV data.
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