Non-uniform dose distributions in whole brain radiotherapy

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April 23, 2010

Under the supervision of:
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Outline

- **Background Information**
  - Whole brain radiotherapy and small cell lung cancer
  - Research question

- **Atlas of brain metastases**
  - Construction technique
  - Description of spatial biases found

- **Non-uniform dose prescriptions**
  - Modeling
  - Optimal dose distribution

- **Conclusion and future work**
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● Conclusion and future work
Whole Brain Radiotherapy

- Palliative treatment for Multiple Brain Metastases
  - 30 Gy in 10 fractions
  - Possible integrated or serial boost to metastases

- Prophylactic Cranial Irradiation (PCI) for small-cell lung cancer in complete remission
  - 25 Gy in 10 fractions
  - No boost is possible - we don’t know where micro-mets are!
Small Cell Lung Cancer

- For people with SCLC in complete remission, brain metastasis is a significant problem
  - 2 year survival is \(~40\%\) with current treatments \(^1\)
  - Incidence of brain metastases at 3 years \(~59\%\) without PCI \(^2\), \(~30\%\) with PCI \(^1\)
- A uniform dose is usually prescribed for PCI
  - There is interest in hippocampal sparing WBRT
    - Requires IMRT
    - Hippocampus believed to be a rare site for metastasis

Question

- Are there regional biases in the distribution of brain metastases?
- If so, can we take advantage of the biases when delivering PCI?
  - What is the consequence of sparing the hippocampus?
  - Could we boost high-risk regions?
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Atlas of Brain Metastases

- Distribution has been studied before but no 3D atlas has been created
  - Disease specific atlases will be created by mapping all brain metastases to a standard image set

## Atlas Brain Metastases

- 499 Brain Metastases from 163 patients were mapped to the ICBM template

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Number of Patients</th>
<th>Number of Metastases</th>
<th>Patients with a solitary lesion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>30</td>
<td>118</td>
<td>36.7</td>
</tr>
<tr>
<td>NSCLC</td>
<td>63</td>
<td>174</td>
<td>38.1</td>
</tr>
<tr>
<td>SCLC</td>
<td>22</td>
<td>53</td>
<td>45.5</td>
</tr>
<tr>
<td>Renal</td>
<td>11</td>
<td>43</td>
<td>45.5</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>8</td>
<td>38</td>
<td>62.5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>29</td>
<td>73</td>
<td>48.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>163</strong></td>
<td><strong>499</strong></td>
<td><strong>42.3</strong></td>
</tr>
</tbody>
</table>
Atlas Construction

- Step 1: Deform patient images to match the ICBM template image
Before deformation
Atlas construction

- Step 2: All metastases are collected in the ICBM template image
  - Can create disease specific atlases and one for all diseases combined
All diseases combined - Saturated at 7
All diseases combined - Saturated at 7
All diseases combined - Saturated at 7
Prevalence of Metastases in the Cerebellum

Metastases in the Cerebellum (%)

Primary Disease

All | Breast | Lung | NSCLC | SCLC | Renal | Gyn. | Melanoma

Graph showing the prevalence of metastases in the cerebellum for various primary diseases. The graph includes error bars indicating the variability in the data.
Estimated Prevalence of Metastases Near the Hippocampus

<table>
<thead>
<tr>
<th>Hippocampal Expansion</th>
<th>Metastases Near the Hippocampus (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H+5 mm</td>
<td>1.5 ± 1.0</td>
</tr>
<tr>
<td>H+10 mm</td>
<td>4.0 ± 1.5</td>
</tr>
<tr>
<td>H+15 mm</td>
<td>9.0 ± 2.0</td>
</tr>
</tbody>
</table>
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Radiobiological modeling

- How would non-uniform dose distributions affect the relative risk for brain metastases?
TCP Model for Non-Uniform Dose

- Model has to account for varying numbers of micro-metastases in the population
- Average dose is constrained

\[
TCP_{Pop}(\{d\}) = \sum_{N=1}^{N_{\text{max}}} \Pr(N) \left( \sum_{i=1}^{R} a_i TCP_1(d_i) \right)^N
\]

\[
\sum_{i=1}^{R} \nu_i d_i = D \\
TCP_1(d) = \frac{1}{1 + \left( \frac{TCD_{50}}{d} \right)^{4\gamma_{50}}}
\]
Dose Response for PCI in SCLC in Complete Remission

TCP Without Reseeding vs. Equivalent Dose in 2.5 Gy Fractions [Gy]

- Population TCP
- Individual metastasis TCP

Aupperin 1999
Le Pechoux 2009
Dose levels for Maximal TCP with most likely estimate for prevalences (no reseeding)
Predicted Change in RR with most likely estimate for prevalences (no reseeding)
Predicted Change in RR - upper 95% for prevalence in hippocampus, lower 95% for cerebellum (no reseeding)

Predicted Dose Response for Various Techniques

- Uniform dose with hipp. sparing
- Differential doses, hipp. sparing
- Uniform dose prescription

Change in RR vs. Average Dose outside of Hippocampus + 5 mm Region [Gy]
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Conclusion

- For our database, there is a higher risk for cerebellar metastasis in breast and lung cancer.
- The hippocampus region (5, 10, 15 mm expansion) is at lower risk when considering all diseases together.
- Hippocampal sparing may increase RR by up to 0.025 for standard fractionation.
- Redistribution of dose between cerebellum and elsewhere may lower RR by about 0.01.
Future Work

- Is there a cerebellar bias in recurrences after PCI for SCLC?
- Dose painting with multiple structures
  - This is feasible with current technology
  - How high can we push the TCP for constant integral dose?
- Inclusion of NTCP models
- TCP estimates based on physically deliverable dose distributions
Acknowledgements

Funding:
R01-CA118365
T32-CA09206-31

Committee members:
Dr. Kevin Kozak
Dr. Minesh Mehta
Dr. M. Elizabeth Meyerand
Dr. Bhudatt Paliwal
Dr. Bruce Thomadsen
Dr. Wolfgang Tomé

Dr. Vinai Gondi
Dr. Alonso Guitierrez
Dr. David Westerly

IT support:
Idarto Tan
Matt Schultz

Friends and family
student colleagues
Thank You