Role of Radiation Therapy

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Topics

• How radiotherapy works (4Rs)
• Role of Radiation Therapy
• Hippocampus
• Meningioma
Radiotherapy

• What is it?
  – Ionizing RT
  – DNA strand breaks
  – Cell death
Fractionation

• Why do we fractionate?

Historical Background

• Early experiments:
  – Ram Testis (as tumor equivalent)
  – Sterilization (as cure)
  – Skin damage
• Fractionation of the radiation dose produces better tumor control for a given level of normal tissue toxicity than a single large dose
Why fractionation works - 4 R’s

• Repair
• Reassortment
• Repopulation
• Reoxygenation

Cellular Radiosensitivity

- Studied through radiation-induced cell death (loss of reproductive integrity)
- Useful in assessing the relative biologic impact of various types of radiation and exposure conditions
- Cellular inability to form colonies as a function of radiation exposure → cell survival curves
- Three parameters defining response to radiation: n, $D_0$, and $D_{00}$
Repair

- Sublethal damage is repaired
  - Increase in survival that is observed if a given radiation dose is split into two fractions separated by a time interval

Reassortment

- RT kills sensitive cells, mostly M & G2
- After RT, most survivors are in S phases
- Progression of cells through the cycle after sensitive cells are killed
- Return to a more even cell age distribution within the cycle
Repopulation - Accelerated

• After RT, cells will grow back
• Treatment with any cytotoxic agent can trigger the surviving cells to divide FASTER than before – ACCELERATED REPOPULATION

Reoxygenation

• After RT and cell killing, hypoxic areas become more oxygenated
Normal Tissue vs. Tumor

- Spares normal tissues
  - Repair (only for acute effects)
  - Repopulation (if time sufficiently long)
- Increases damage to tumor
  - Reoxygenation
  - Reassortment

CNS Tumors with a Role for Radiotherapy

- Low grade astrocytoma
- Anaplastic astrocytoma
- GBM
- Low grade oligo
- Anaplastic oligo
- Mixed gliomas
- Ependymoma
- PNET
- CNS lymphoma
- Meningioma
- Schwannoma
- Craniopharyngioma
- Pituitary tumors
- CNS germ cell tumors
- Pilocytic astrocytoma
- Ganglioglioma
- Hemangioblastoma
- Hemangiopericytoma
- Sarcoma
- Choroid plexus carcinoma
Roles of Radiotherapy

• Post-op adjunct to:
  – decrease local failure
  – delay progression/relapse
  – prolong survival, eg GBM, AA
• Primary curative therapy:
  – PNET, Germ Cell Tumors, Pilocytic astrocytoma
• To halt tumor growth:
  – Meningioma, Schwannoma
• To alter endocrine function
• To palliate

Radiotherapy Improves Survival

<table>
<thead>
<tr>
<th>Disease</th>
<th>Survival (no XRT)</th>
<th>Survival (with XRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNET</td>
<td>&lt; 10%</td>
<td>50-70%</td>
</tr>
<tr>
<td>CNS Germinoma</td>
<td>&lt; 5%</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>10 yr: 37%</td>
<td>10 yr: 77%</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>MS: 18 wks</td>
<td>MS: 42 wks</td>
</tr>
</tbody>
</table>
## Radiotherapy Improves Local Control

*Craniopharyngioma as a case-study: 34 literature reports*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TR</th>
<th>STR</th>
<th>STR/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-YR SURV</td>
<td>81%</td>
<td>53%</td>
<td>89%</td>
</tr>
<tr>
<td>10-YR SURV</td>
<td>69%</td>
<td>37%</td>
<td>77%</td>
</tr>
<tr>
<td>RECURRENCE</td>
<td>29%</td>
<td>73%</td>
<td>17%</td>
</tr>
</tbody>
</table>

## Radiotherapy Diminishes Local Failure

*Meningioma as a case-study: Literature reports*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TR</th>
<th>STR</th>
<th>STR/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-YR PROGR</td>
<td>5%</td>
<td>37%</td>
<td>11%</td>
</tr>
<tr>
<td>10-YR PROGR</td>
<td>10%</td>
<td>55%</td>
<td>23%</td>
</tr>
<tr>
<td>15-YR PROGR</td>
<td>32%</td>
<td>91%</td>
<td></td>
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</table>
The Impact of Radiation Dose

Medulloblastoma as a case-study: Literature reports

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>&lt;50 Gy</th>
<th>&gt;50 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harisiadis</td>
<td>1977</td>
<td>24%</td>
<td>48%</td>
</tr>
<tr>
<td>Cumberlin</td>
<td>1979</td>
<td>17%</td>
<td>86%</td>
</tr>
<tr>
<td>Berry</td>
<td>1981</td>
<td>42%</td>
<td>78%</td>
</tr>
<tr>
<td>Silverman</td>
<td>1982</td>
<td>38%</td>
<td>80%</td>
</tr>
<tr>
<td>Kopelson</td>
<td>1983</td>
<td>50%</td>
<td>78%</td>
</tr>
<tr>
<td>CCG</td>
<td>1987</td>
<td>33%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Decreasing posterior fossa dose increases relapses

The Impact of Radiation Dose

Medulloblastoma as a case-study: Clinical Trials

- 2-ve Ph III trials
- 3 yr isolated neuraxis failure: 2/44 vs. 11/45.
- SIOP II: 4 arms; 35 vs. 25 Gy CSI +/- pre-RT chemo
- 5 yr RFS= 75 vs. 42% for chemo RT arms
**GBM: Dose Escalation**

1. Dose escalation matters
2. Focal boost volumes can be identified
3. RT can be focally delivered

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**The Role of the Hippocampus**

- Many patients exhibit learning/memory deficits with no pathologic changes, especially when the RT field involves the temporal lobes.
- Recent work has shown that hippocampus-dependent learning and memory are strongly influenced by the activity of neural stem cells and their proliferative progeny.
- The hippocampal granule cell layer undergoes continuous renewal and restructuring by the addition of new neurons.
- Radiation at low doses affects the highly proliferative progenitors. A single low dose to the cranium of a mature rat is sufficient to ablate hippocampal neurogenesis.

Hippocampus Avoidance Hypothesis

- The hippocampus plays a significant role in RT induced dementia
- Doses as low as 2 Gy cause significant toxicity to the hippocampus
- Conformal avoidance of the hippocampus may help reduce neurocognitive deficits

Hippocampus Delineation
Hippocampus Avoidance with IMRT

- Second most frequent primary brain tumor
- Options for management
  - Conservative approach
  - Surgery
  - Radiotherapy
    - Fractionated External Beam (~ 30 fractions)
    - Stereotactic Radiosurgery (single fraction)
    - Stereotactic Radiotherapy (2-5 fractions)

Radiotherapy for Meningiomas
Radiotherapy for Meningiomas

- Indications for RT
  - Subtotally resected tumors
  - Unresectable/hard-to-resect locations
  - Atypical/Anaplastic histologies
- Fractionated external beam
  - Low daily dose reduces risk of toxicity to normal structures within or adjacent to target volume
Radiotherapy for Meningiomas

- External Beam Results
  - Univ Florida
  - 101 patients with skull-based meningiomas
    - 40 recurrent after surgery
      - Excellent local control


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Radiotherapy for Meningiomas

- UCSF
  - 140 patient series, older era
  - Local control reviewed as function of year

Radiotherapy for Meningiomas

- What about SRS/Gamma Knife?
- Univ Pittsburgh
- 1045 cases!
- Exclusions
  - Diameter > 3.5 cm
  - Mass effect
  - Optic sheath with vision
  - Atypical imaging without histology


Radiotherapy for Meningiomas

Intracranial Tumor Control By WHO Grade

Conclusions

• Radiotherapy has an important role to play