Neutron Radiotherapy for Adenoid Cystic Carcinomas

An Example of Biological Targeting

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METHODS OF IMPROVING TUMOR CONTROL

Conformal
Intraoperative
Brachytherapy
Stereotactic

DOSE DISTRIBUTION

Proton beam
α – particle

TUMOR BIOLOGY

Heavy ion beam
π – meson

BNCT

Neutron beam

Hyperthermia
Chemo / rads
Hypoxic sensitizers
Bio Response Mod
Neutron Interaction with Tissue

NUCLEAR INTERACTIONS

n (neutron of reduced energy)

p+ (recoil proton)

e- (electron)

neutron of reduced energy
Mapping of Physical Dose to Biological Dose
Salivary Gland Tumors

• Salivary gland tumors of early interest to neutron radiotherapy investigators
  – Suboptimal control rates with standard radiotherapy -- 25% when gross tumor present
  – Relatively superficial location made it feasible to treat with early neutron beams which were poorly penetrating

• Radiobiological data shows highest RBE for salivary gland tumors
  – High expected therapeutic gain factor
## Neutron RBE Data

Battermann *et al* - 1981

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>SINGLE FX</th>
<th>MULTIPLE FXS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoidcystic Ca</td>
<td>5.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Colon/Rectum</td>
<td>2.5-5.7</td>
<td>4.5-5.2</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>3.0-4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Bone sarcoma</td>
<td>2.5-4.6</td>
<td>-----</td>
</tr>
<tr>
<td>Bladder (transitional)</td>
<td>4.1</td>
<td>-----</td>
</tr>
<tr>
<td>Lung (scc)</td>
<td>3.5-3.8</td>
<td>-----</td>
</tr>
<tr>
<td>FOM (scc)</td>
<td>3.0</td>
<td>-----</td>
</tr>
</tbody>
</table>
THERAPEUTIC GAIN FACTOR FOR FAST NEUTRONS

2,000 cGy neutrons -> 3.0 - 3.5 -> 6,000 - 7,000 cGy

8.0 -> 16,000 cGy

THERAPEUTIC GAIN = 2.3 - 2.6
University of Washington Fast Neutron Radiotherapy Facility

• Operational in September, 1984
• Approximately 2800 patients treated to date
• Currently emphasize treatment of patients with advanced salivary gland tumors
• Approximately 100 patients per year
UW Neutron Facility: Layout
UW Neutron Facility: Gantry
UW Neutron Facility: Multileaf Collimator
Lateral Projection
Salivary Gland
Tumor and Nodes
AP Projection
Salivary Gland Tumor and Nodes
Treatment of Locally Advanced Adenoid Cystic Carcinoma of the Head and Neck Region with Neutron Radiotherapy
Patient Characteristics

- 151 patients with gross residual tumors after surgery or unresectable disease
  - 62% minor salivary glands
  - 29% major salivary glands
  - 11% tracheal-bronchial tree, lacrimal gland
- Size
  - GT 4 cm 56%
  - LT 4 cm 44%
  - Median F/U 32 months (3-142)
Overall and Cause-Specific Survival

![Graph showing overall and cause-specific survival probabilities over time. The x-axis represents time in months, and the y-axis represents probability. The graph illustrates the decrease in survival probability over time, distinguishing between overall survival and cause-specific survival.](image-url)
Cause Specific Survival

Multivariate

size \( p = .74 \)
surgery \( p = .11 \)
presenting status \( p = .06 \)
lymph node status \( p = .001 \)
BOS \( p < .0001 \)
Local-Regional Control

Multivariate

Size $p = .12$
surgery $p = .02$
BOS $p = .005$
Development of Distant Metastases

![Graph showing the probability of development of distant metastases over time. The graph compares two groups based on lymph node status: Lymph node - and Lymph node +. The x-axis represents time in months, ranging from 0 to 135, and the y-axis represents probability, ranging from 0 to 0.6. The graph indicates a higher probability of metastasis in the Lymph node + group compared to the Lymph node - group.](image-url)
Findings

• Local control rate of 59% for whole group (5 year actuarial)
  • 73% if LT4 and BOS negative

• Cause specific survival rate of 77% overall
  • BOS involvement and LN involvement are poor prognostic factors
Findings

- Almost 50% of all patients develop distant metastases
  - BOS involvement and LN positive patients develop metastases sooner
- Acceptable long term toxicity
  - 9% grade 3 - 4
Adenoid Cystic Carcinoma
Patient
Adenoid Cystic Carcinoma
Patient (1 year later)
Consequences of Skull Base Disease

• Increased RBE for CNS structures requires neutron dose limited to 12 Gy-neutron
  – Approximately 54 Gy-equivalent for CNS structures
  – Approximately 96 Gy-equivalent for tumor
• Reduced local control rate at 5 years
  – 70% without skull base disease (198 patients)
  – 19% with skull base disease (61 patients)
Adenoid Cystic Carcinoma at Skull Base
Actuarial Local/Regional Control Curves
Gamma Knife Radiosurgery Boost to Underdosed Region

• Treat superior aspect of tumor at skull base
• 12 Gy in single fraction @ 50% isodose line
• Limit dose to optic nerve to 6-8 Gy
• Comparative data
  – 34 patients with Gamma Knife boost
    • Median treated volume 18.3 cm³ (range 5.9 - 53.9)
    • Median conformity index 1.57 (range 1.3 - 3)
  – 61 historical control patients
Gamma Knife Boost for Adenoid Cystic Carcinoma at the Skull Base
Actuarial Local/Regional Control Curves

\[ p = 0.039 \]
Results

• Complications
  – RTOG/EORTC grade 3-4 similar
  – One potential grade 5 in Gamma Knife boost
    • Infectious process at skull base but no tumor on autopsy
• Recurrence pattern
  – Four failures to date
    • 2 within Gamma Knife boost region
    • 1 within neutron field
    • 1 outside neutron field
• Asymptomatic T2 signal changes in white matter in about 25% of patients
Post Neutron RT & GK Scans
Summary and Conclusions

• Fast neutron radiotherapy is highly effective in the treatment of salivary gland tumors
  – Basic radiobiology & clinical data
• Increased RBE for damage to CNS structures limits physical dose in certain situations -- e.g., tumor extension to skull base
  – 12 Gy-neutron --> ~ 96 Gy-equivalent to tumor
    • Insufficient for control
    • Addition of Gamma Knife boost improves control
      – Significance of white matter changes under investigation
• Data indicates that biologically-effective doses in range of 110-120 Gy-equivalent are required
• Skull base adenoid cystic carcinomas are possible indication for C-ion therapy