Neutron Radiotherapy: Past, Present, and Future Directions

Theodore L. Phillips Lecture -- 2014

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Overview

• Historical Background
• Clinical Data
• Fast Neutron Radiotherapy
• Boron Neutron Capture Therapy (BNCT)
• BNCT Boost for Fast Neutrons

Sir James Chadwick

Discovered neutron in 1932, Nobel Prize in 1935
Lawrence’s First Cyclotron (1932)

First Neutron Patient Treated in 1938

Evaluation of Past Experience with Fast Neutron Teletherapy and its Implications for Future Applications*

Why Does Radiotherapy Fail to Control Tumors?

- Inability to deliver a sufficiently high dose of radiation due to risk of damage to adjacent normal tissues
Neutron Radiotherapy

An example of biological targeting

Neutron Interaction with Tissue

NUCLEAR INTERACTIONS

- Neutron of reduced energy
- Recoil proton
- Proton

Radiobiological Rationale for High LET Radiotherapy

- Better able to kill hypoxic tumor cells
  - OER ~ 1.6 for fast neutrons
- Cells less able to repair radiation damage
  - Sublethal damage
  - Potentially lethal damage
- Less variation in radiosensitivity across cell cycle
Neutron RBE Data
Batterman 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>

Mapping of Physical Dose to Biological Dose

THERAPEUTIC GAIN FACTOR FOR FAST NEUTRONS

2,000 cGy neutrons

\[ \text{THERAPEUTIC GAIN} = 2.3 - 2.6 \]

\[ 3.0 - 3.5 \rightarrow 6,000 - 7,000 \text{ cGy} \]

\[ 8.0 \rightarrow 16,000 \text{ cGy} \]

Salivary Gland Protocol 80-01

STUDY DESIGN

NEUTRONS, 16.5, 17, 17.14, or 22 Gy, 12 fractions, 4 weeks

PHOTONS, 70 Gy in 7 weeks, or 55 Gy in 4 weeks

Inoperable, unresectable, or recurrent salivary gland carcinomas
Salivary Gland: Local Control

Salivary Gland: Survival

Example of Tumors Treated
UW Neutron Facility: Layout

UW Neutron Facility: Gantry

UW Neutron Facility: Multileaf Collimator

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)

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 conformality index 1.57 (range 1.3 - 3)
  - 61 historical control patients

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
Lacrimal Gland Adenoid Cystic Carcinoma

- 11 patients treated between 1988-2011
  - 3 patients with microscopic disease
  - 8 patients with gross residual tumor
- Actuarial Data (median f/u 6.2 years)
  - Median OS = 11.1 years
  - Median DFS = 6.3 years
  - 5-year LC = 80%

Treatment Sequellae

- 3 patients had severe vision impairment
- 2 patients required enucleation for “dry eye” syndrome

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
Operating Neutron Centers 2014

- University of Washington – Seattle, U.S.A.
- Tomsk Polytechnical University – Russia
- Technisch Universtat Munich – Germany
- iThemba Laboratories, Faure – South Africa
Boron Neutron Capture Therapy (BNCT)

**Binary System Therapy (Idealized)**
- Tumor specific targeting agent
  - Antibody
  - Small molecule
- Activate agent
  - Slow neutron beam
  - Little direct damage without targeting agent present

**NEUTRON CAPTURE THERAPY: BASIC IDEA**

\[ {}^{A}X_{p} + {}^{1}n_{0} \rightarrow {}^{A+1}_{p}X^{*} \rightarrow Y + Z + \text{Energy} \]

**THERMAL NEUTRON CROSS SECTIONS**

<table>
<thead>
<tr>
<th>ATOMIC SPECIES</th>
<th>CROSS SECTION (BARS)</th>
</tr>
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<tbody>
<tr>
<td>(^{10}\text{B})</td>
<td>3,838</td>
</tr>
<tr>
<td>(^{155,157}\text{Gd})</td>
<td>61,000 ; 254,000</td>
</tr>
<tr>
<td>(^{149}\text{Sm})</td>
<td>40,100</td>
</tr>
<tr>
<td>(^{235}\text{U})</td>
<td>681</td>
</tr>
<tr>
<td>(^{239}\text{Pu})</td>
<td>1,022</td>
</tr>
<tr>
<td>(^{1}\text{H})</td>
<td>0.332</td>
</tr>
<tr>
<td>(^{16}\text{O})</td>
<td>0.0018</td>
</tr>
<tr>
<td>(^{12}\text{C})</td>
<td>0.0035</td>
</tr>
<tr>
<td>(^{14}\text{N})</td>
<td>1.88</td>
</tr>
<tr>
<td>(^{35}\text{Cl})</td>
<td>43.7</td>
</tr>
</tbody>
</table>
**BORON - 10 CAPTURE REACTION**

\[
\begin{align*}
^{10}_5 B + {}^1 n &\rightarrow ^{11}_5 B^{*} &\text{2.79 MeV} \\
^{7}_3 Li + {}^4 He &\rightarrow ^{6}_3 Li + {}^4 He + \gamma &\text{6.3\%} \\
^{7}_3 Li + {}^4 He &\rightarrow ^{4}_2 He + \gamma &\text{93.7\%}
\end{align*}
\]

**NEUTRON CAPTURE THERAPY: HISTORICAL BACKGROUND**

- **1932**: Discovery of neutron (Chadwick)
- **1936**: NCT proposed (Locher)
- **1940**: In vitro measurements (Kruger) In vitro measurements (Zahl)
- **1950s**: Clinical trials
  - Brookhaven (Sweet et al)
  - MIT (Asbury et al)
  - Japan (Hatanaka et al)

**NEUTRON CAPTURE THERAPY: EARLY TRIALS FOR GLIOMAS**

**UNITED STATES**
- Borax used as carrier
  - high blood concentration
- Thermal neutron beam
  - poor penetration
- Intense capillary damage
Critical Review of Early Japanese BNCT Data

In collaboration with Alexander M. Spence

NEUTRON CAPTURE THERAPY: EARLY TRIALS FOR GLIOMAS

JAPAN

- BSH used as carrier
- Thermal neutron beam
  - poor penetration
  - craniotomy
- Poor documentation
  - 77 patients treated (1968-1985)
  - 10% ten year survival
  - 1 thirteen year survivor
  - 58% five year survival for tumors ≤ 6 cm deep

PURPOSE

- TO IDENTIFY A SUBSET OF PATIENTS FROM THE UNITED STATES WHO RECEIVED BNCT IN JAPAN
- TO PERFORM INDEPENDENT ANALYSIS OF TREATMENT OUTCOME COMPARED TO MATCHED SET OF PATIENTS TREATED CONVENTIONALLY

MATERIALS & METHODS

- Principal referral sources to Japanese treatment centers identified
- Japanese treating physicians contacted
- 14 patients from United States identified
  - Treated between 7/87 and 6/94
  - Permission to obtain pathology and medical records obtained for 13 patients
RESULTS

- CENTRAL PATHOLOGY REVIEW
  - 10 glioblastoma multiforme
  - 2 anaplastic astrocytoma
  - 1 CNS lymphoma

SURVIVAL BY PROGNOSTIC CLASS

BNCT RESULTS: ALL PATIENTS

BNCT RESULTS: GBM PATIENTS ONLY
What BNCT Dose is Required to Eradicate GBM?
Extrapolations from Fast Neutron Radiotherapy Data

**BNCT: SUMMARY OF FAILURE INFORMATION**

**AAF PATIENTS**
- One with long term local control -- died NED @ 80 months
- One with probable failure (low grade tumor vs. radiation effect)

**GBM PATIENTS**
- All patients dead -- median survival ~ 12 months
- All 10 patients with local failure
  - 7 cases histologically confirmed
  - Other 3 cases no tissue obtained

**Early Neuron Studies**
- Doses were set using photon tolerance doses and a constant RBE -- generally taken as 3
- High rate of complications -- particularly in CNS
  - High grade glioma studies -- clinical dose set to be 18 Gy-neutron

**GBM Post-Treatment Gross Specimen**
**GBM DOSE RESPONSE CURVE: BASIC APPROACH**

- **ANALYZE FAST NEUTRON TUMOR CONTROL DATA**
  - Neutrons alone
  - Mixed beam
  - Correct for RBE differences for various beams
- RBE(fast neutrons) : RBE(fission neutrons) \(\rightarrow 0.833\)
- **CORRECTION FOR SINGLE FRACTIONATION**
  - Hornsey *et al* (1981) \(\rightarrow 0.675\)
- RBE BROOKHAVEN FISSION SPECTRUM \(\rightarrow 3.2\)

**LOGISTIC REGRESSION ANALYSIS**

- **BASIC FUNCTIONAL FORM BASED ON EXPONENTIAL FORM FOR CELL SURVIVAL**

\[ P = \exp[ - \exp( a D + c) ] \]
Conclusions

• No compelling evidence that BNCT is a clinically-effective treatment for high grade gliomas of the brain.

• Early studies likely were operating in wrong region of parameter space to achieve tumor control.

Some Thoughts on Compounds for BNCT
Approximate Relative Target Values for Cell-Killing with BNCT

- Target Value 20 – Plasma membrane
- Target Value 50 – Cytoplasm
- Target Value 100 – Nucleus and DNA

- About one-billion ($10^8$) $^{10}$B-atoms are required per cancer cell for therapy ($\sim$ 30 micrograms of $^{10}$B per gram of tumor).
- The target value is related to the probability that a $^7$Li$^+3$ or $^4$He$^+2$ will encounter nuclear DNA or an essential component of the cell.
- About $10^{13}$ neutrons/cm$^2$ comprises the total neutron component required for one therapeutic session.

Compounds Currently Approved for Human Clinical Trials

- BSH ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$)
- BPA
- GB-10 ($\text{Na}_2\text{B}_{10}\text{H}_{10}$)

Tumors Types Treated

- High Grade Gliomas
- Melanoma
- Recurrent Meningomas
- Recurrent H&N Cancer
- Liver Metastases
Clinical BNCT Programs -- 2014

- Japan
  - KURRI
  - JRR-4
- Finland
  - FiR No. 1

BNCT Boost Enhancement of Fast Neutron Radiotherapy
Fast Neutron Radiotherapy Summary

- Neutron radiotherapy offers biological targeting advantages for salivary gland tumors that may outweigh physical dose targeting advantages of other technologies
- Neutron radiotherapy probably advantageous for certain other radioresistant tumors
  - Sarcoma
  - Melanoma
  - Anaplastic thyroid
BNCT Status Summary

- Primarily used in past for GBM and metastatic melanoma
- Newer indications: recurrent H&N, recurrent meningomas, liver tumors
- No proven advantage over conventional therapies
- Lack of compounds biggest hurdle
- Reactor beams satisfactory for proof of concept
  - If proven, then will need accelerator-based beams