Imaging-guided BNCT applications: from physics to biology and medicine

Laura Evangelista MD, PhD
Oncological Institute of Veneto IOV – IRCCS, Padova, Italy

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Multidisciplinary approach

Physicists

Biologists

Clinicians

Chemists

BNCT
Content

- Background
- Boron delivery agents
- Clinical dosimetry
- Treatment planning techniques
- Clinical trials (past and on going)
- Advantages and critical issues
The critical requirements for a successful BNCT treatment are mainly:

(a) The boron-containing compound/material has to be delivered to the neoplastic tissue to realize a specific and selective tumor targeting, and

(b) The amount of 10B atoms concentrated inside/around the cancer cells must be sufficient for the therapeutic purpose.

If these rather stringent conditions are met, then irradiation of a given tissue or organ with therapeutic doses of thermal/epithermal neutrons can lead to a selective, complete ablation of malignant cells.
BNCT is a biologically-targeted radiotherapy, and contrary of the traditional radiotherapy, it can selectively hit the tumour cells, saving the surrounding normal tissue.
Tumoural cells with boron

\[ 30 \text{ ppm } ^{10}\text{B} \]

\[ ^{10}\text{B} (n,\alpha)^{7}\text{Li} \]

\[ \frac{D_{\text{tumour}}}{D_{\text{health}}} \approx 4 \]

Health cells with boron

\[ ^{14}\text{N} (n, p)^{14}\text{C} \]

\[ ^{1}\text{H} (n, \gamma)^{2}\text{H} \]
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Boron delivery agent-characteristics

The most important requirements are:

- Low toxicity
- Low uptake in normal tissue
- Tumour:normal tissue and tumour:blood ratio of ~ 3 and 2
- Tumour boron concentration of ~20 µg 10B per g of tumour
- Relatively rapid clearance from blood and normal tissue and persistence in tumour during neutron irradiation
Boron delivery agents

The most employed

New molecules under investigation

<table>
<thead>
<tr>
<th>Boronated unnatural amino acids</th>
<th>Carboranyl nucleosides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodecaborate cluster lipids and cholesterol derivates</td>
<td>Boronated phorphyrins</td>
</tr>
<tr>
<td>Boron containing immunoliposomes and liposomes</td>
<td>Boronated EGF and anti-EGFR and VEGFR MoAbs</td>
</tr>
<tr>
<td>Boronated DNA intercalators</td>
<td>Boron-containing nanoparticles</td>
</tr>
<tr>
<td>Transferrin-polyethylene glycol liposomes</td>
<td>Carboranyl porphyrazines</td>
</tr>
<tr>
<td>Dodecahydo-closo-dodecaborate clusters</td>
<td>Boronated cyclic peptides and nitride nanotubes</td>
</tr>
</tbody>
</table>
Boron delivery agents

ZnB₄Pc

H₂TCP

TPFC

Department of Biology, University of Padua, Italy

Organic & Biomolecular Chemistry 6 (2008) 3732-3740
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Dosimetry of epithermal neutron beams

- Complicated by protons and fased neutron components $\rightarrow$ different biological effectiveness
- Multiplicative weighting factors $\rightarrow$ RBE

Physics
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Treatment planning in a patient with GBM

The prescription dose is a mean brain dose of 7.7 Gy.

The integral dose volume histograms report dosimetry of interest including target volume and organs at risk.
Imaging-guided BCNT treatment

MRI - magnetic resonance imaging

PET - positron emission tomography
From BPA to 18F-BPA for PET imaging

FIRST CLINICAL CASE OF BORON NEUTRON CAPTURE THERAPY FOR HEAD AND NECK MALIGNANCIES USING 18F-BPA PET

Teruhito Aihara, MD,¹ Junichi Hiratsuka, MD,² Norimasa Morita, MD,² Masako Uno, MD,¹ Yoshinori Sakurai, PhD,³ Akira Maruhashi, PhD,³ Koji Ono, MD,³ Tamotsu Harada, MD¹

Fluorine-18-Labeled Fluoroboronophenylalanine PET in Patients with Glioma

Yoshio Imahori, Satoshi Ueda, Yoshio Ohmori, Tsukasa Kusuki, Koji Ono, Ryu Fujii and Tetuya Ida

Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I.

Y Imahori, S Ueda, Y Ohmori, et al.

Evaluation of Fluorine-18-BPA-Fructose for Boron Neutron Capture Treatment Planning

PET-guided BNCT planning

Gross tumour volume: 87 cm$^3$
Planning target volume: 233 cm$^3$
The prognostic significance of the metabolic values and ratios of $^{18}$F-$^{10}$B-BPA by PET in patients with gliomas.

**Experimental Design:** 22 patients underwent an $^{18}$F-$^{10}$B-BPA/PET study and were followed for at least 4 months thereafter. PET parameters, K1, k2, k3, and k4, were measured before treatment.

Data regarding the tumors, the contralateral normal region, and the uptake ratio of FBPA between the tumor and normal tissue 40 min after injection of the tracer were compared with survival rates after the PET treatment.
A patient with recurrent submandibular gland cancer underwent $^{18}$F-$^{10}$B-BPA PET before and after BNCT.

The tumor/normal tissue boron concentration ratio was 2.9.

The tumor was irradiated at the Kyoto University Research Reactor with epithermal neutrons 5 MW for 90 minutes.

Results. To date there has been continuous complete regression in the tumor and no acute and chronic complications for 1.5 years.
Dynamic uptake of [18F]FBPA in intracranial meningiomas (n=4) and schwannomas (n=6) of five sporadic and five NF2 patients. Tracer input function and cerebral blood volume were measured. [18F]FBPA uptake in tumour and brain was assessed with a three compartmental model and graphical analysis.

Conclusion: [18F]FBPA PET offers a viable means to evaluate BPA uptake in meningiomas and schwannomas in NF2. Meningiomas and schwannomas might respond to low-dose BNCT with BPA owing to their growth characteristics.
Undifferentiated sinonasal carcinoma may respond to single-fraction boron neutron capture therapy

**Case**: a 44-yr man with recurrent poorly differentiated sinonasal carcinoma
BNCT in locally recurred nasopharyngeal cancer

Prerequisite for BNCT:
Uptake of $[^{18}\text{F}]\text{F-BPA} \geq 2.5$ \(\geq\) surrounding normal tissue
Squamous cell carcinoma in the temporal bone recurring after surgery, conventional radiotherapy, and chemotherapy, which was treated using planned fractionated BNCT

$^{18}$F-BPA PET showed a high T/N ratio of 3.8 at the occipital condyle before the first BNCT of squamous cell carcinoma

$^{18}$F-BPA PET did not show high BPA accumulation in the temporal in the temporal bone at 6 months after the first BNCT
Pre and post-therapy 18F-BPA PET/CT

Pre-BNCT

Post-BNCT

By Prof. Ling-Wei Wang, China
PET/CT in head-neck cancer

Pre-BNCT

Post- BNCT

By Prof. Ling-Wei Wang, China
BNCT - STEP_s

10B Carriers

BSH

BPA

Others

Uptake

18F-BPA PET/CT

Response to therapy

Imaging

BNCT

Therapy
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...from a clinical point of view

<table>
<thead>
<tr>
<th>Pathologies (country)</th>
<th>N of pts</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM (USA)</td>
<td>53</td>
<td>I-II</td>
</tr>
<tr>
<td>GBM/MM (Germany)</td>
<td>26/4</td>
<td>I-II</td>
</tr>
<tr>
<td>GBM/AA/MMR/M/H&amp;N (Japan)</td>
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<td>I-II</td>
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<tr>
<td>GBM/AA/H&amp;M (Finland)</td>
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<td>I-II</td>
</tr>
<tr>
<td>GBM (Czech Republic)</td>
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<td>I-II</td>
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<tr>
<td>GBM/MM (Sweden)</td>
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<tr>
<td>H&amp;M (Taiwan)</td>
<td>10</td>
<td>I</td>
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</table>

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<thead>
<tr>
<th>Pathologies (Country)</th>
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<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;M (Taiwan)</td>
<td>27</td>
<td>I/II</td>
</tr>
<tr>
<td>H&amp;M (Taiwan)</td>
<td>28</td>
<td>I/II</td>
</tr>
<tr>
<td>GBM (Japan)</td>
<td>45</td>
<td>II</td>
</tr>
<tr>
<td>Melanoma (Argentina)</td>
<td>15</td>
<td>I</td>
</tr>
</tbody>
</table>


*by clinicaltrial.gov
Improvement in survival rate

**Glioblastoma multiforme**


**Recurrent head and neck cancer**

# Operative BNCT centres

<table>
<thead>
<tr>
<th>CENTER</th>
<th>STATES</th>
<th>NEUTRON SOURCE</th>
<th>NEOPLASM</th>
<th>Nº OF TREATED PATIENTS</th>
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</thead>
<tbody>
<tr>
<td>Helsinki University Central Hospital, Helsinki, Finland</td>
<td>Europe</td>
<td>FIR-1, VTT Technical Research Centre, Espoo</td>
<td>GB and HN</td>
<td>50 GM 2 AA 31 HN</td>
</tr>
<tr>
<td>Faculty Hospital of Charles University, Prague, Czech Republic</td>
<td>Europe</td>
<td>LVR-15 Reactor, Nuclear Research Institute Rez</td>
<td>GB</td>
<td>5 GM</td>
</tr>
<tr>
<td>University of Tsukuba, Tsukuba City, Ibaraki</td>
<td>Japan</td>
<td>JRR-4, Japan Atomic Energy Agency, Tokai, Ibaraki</td>
<td>GB</td>
<td>20 GM 4 AA</td>
</tr>
<tr>
<td>University of Tokushima, Tokushima</td>
<td>Japan</td>
<td>JRR-4 (Kyoto University Research Reactor, Osaka)</td>
<td>GB</td>
<td>23</td>
</tr>
<tr>
<td>Osaka Medical College and Kyoto University Research Reactor, Kyoto University, Osaka and Kawasaki Medical School, Kurashiki</td>
<td>Japan</td>
<td>KURR</td>
<td>GB, HN, CM</td>
<td>30 GBM 3 AA 7 Men 124 HN</td>
</tr>
<tr>
<td>Taipei Veterans General Hospital, Taipei, Taiwan</td>
<td>Republic of China</td>
<td>THOR, National Tsing Hua University, Hsinchu, Taiwan</td>
<td>HN</td>
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</tr>
<tr>
<td>Instituto de Oncologia Angel H, Buenos Aires</td>
<td>Argentina</td>
<td>Bariloche Atomic Center</td>
<td>CM and AT</td>
<td>7 CM 3 AT</td>
</tr>
</tbody>
</table>
### Past………………present

<table>
<thead>
<tr>
<th>1950</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thermal neutron beams</td>
<td>• Thermal and Epithermal neutron beams</td>
</tr>
<tr>
<td>• Boronated agent (sodium tretraborate, sodium pentaborate, sodium decahydrodecaaborate)</td>
<td>• Boronated agent (BPA and BSH)</td>
</tr>
<tr>
<td>• Intra-operative approach</td>
<td>• External irradiation (intra and extra-operative approach)</td>
</tr>
<tr>
<td>• No accurate dosimetric assessment</td>
<td>• Accurate microdometric assessment</td>
</tr>
<tr>
<td>• No BNCT planning</td>
<td>• MRI, PET and other device for BNCT planning</td>
</tr>
<tr>
<td>• Mostly brain cancer</td>
<td>• Many solid cancers (brain, melanoma, head and neck, liver, and so on)</td>
</tr>
</tbody>
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What are some advantages of BNCT?

1. To selectively deliver a high radiation dose to the tumor with a much lower dose to surrounding normal tissues

2. To more effectively target multicentric deposits of tumor than is possible with stereotactic radiosurgery of primary and metastatic brain tumor

3. To have a great local control, although it is usually employed in case of large disseminative disease.

4. To produce striking clinical responses

5. To increase the survival period in patients with gliomas if performed with specific protocol
Critical issues

1. The development of new low and high molecular weight boron agents and optimization of their delivery
2. To obtain approval for the clinical use
3. To compare and normalize dose descriptions between centers
4. The improvement of methods to determine the boron dose delivered to the residual tumor volume
5. To complete the neutron therapeutic approach with other treatments