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

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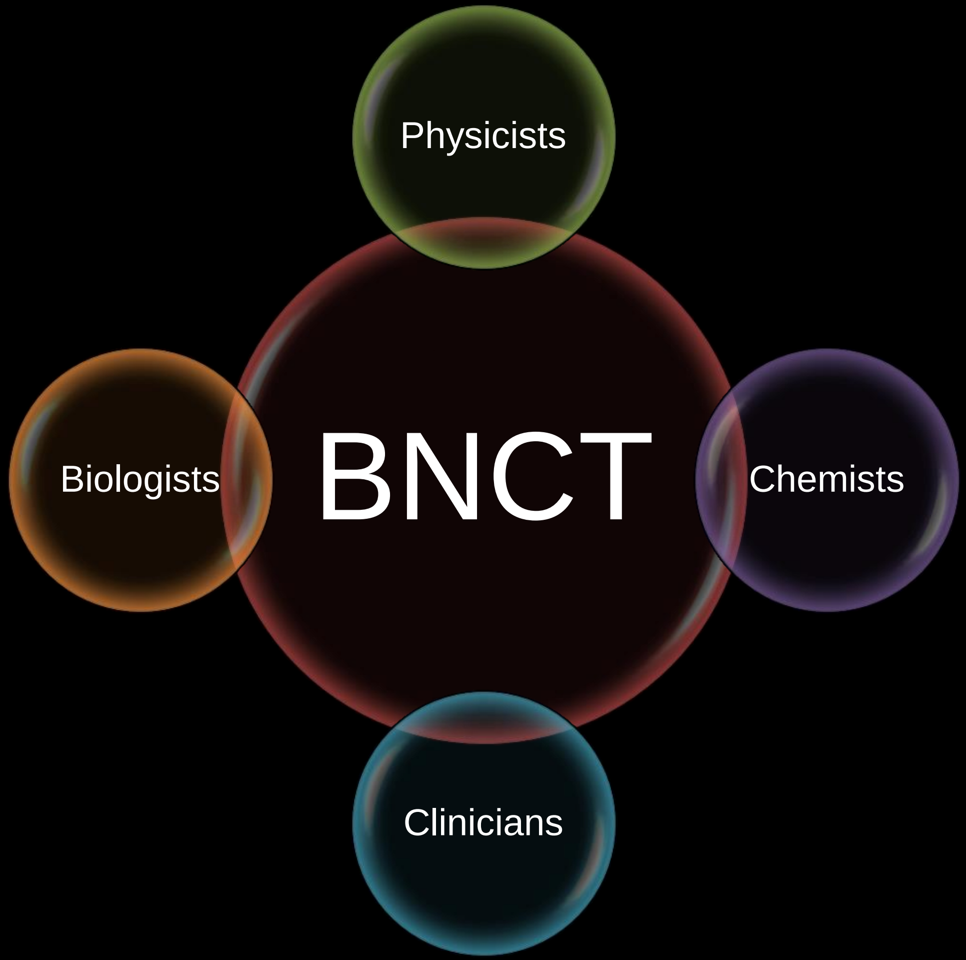
Multidisciplinary approach



Content

- Background
- Boron delivery agents
- Clinical dosimetry
- Treatment planning techniques
- Clinical trials (past and on going)
- Advantages and critical issues

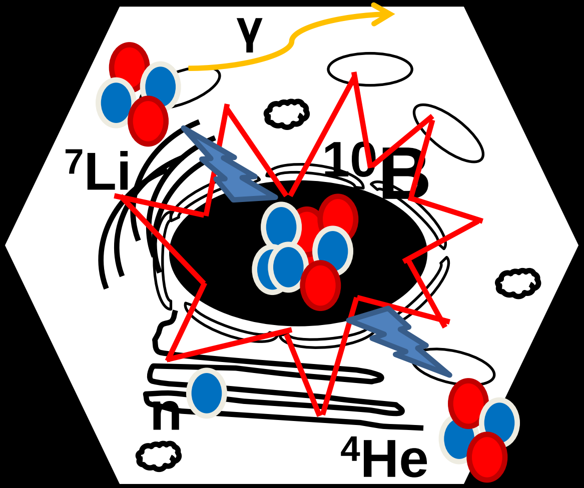
Background

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.



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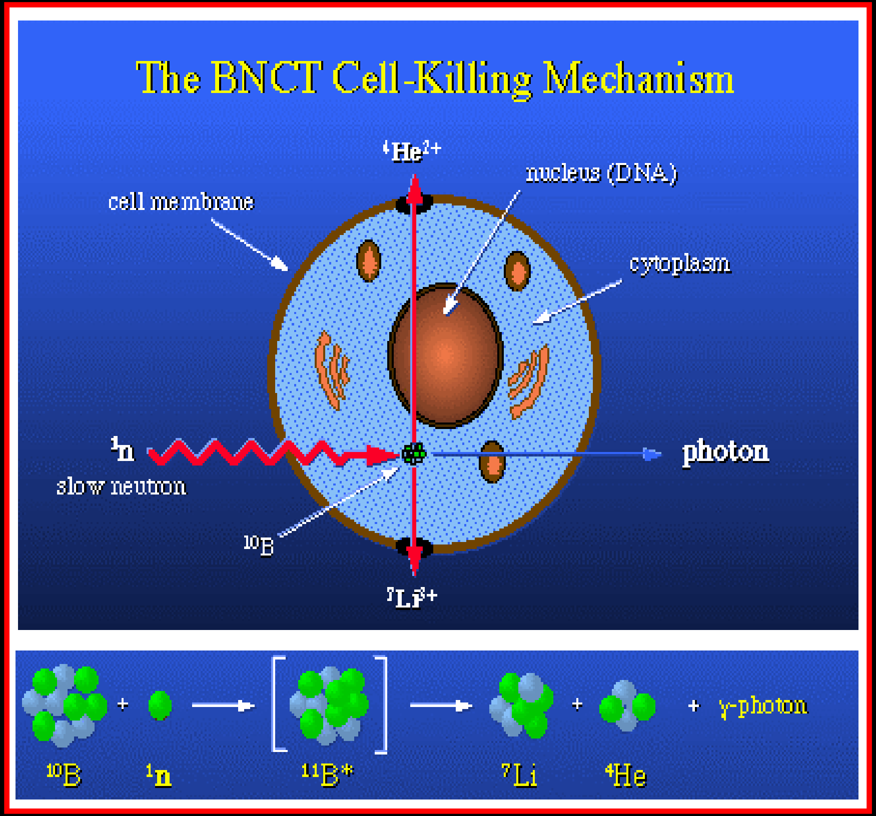
……superior than conventional RT

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

$$30\, ppm\ {}^{10}B$$

$${}^{10}B(n,\alpha)^{7}Li$$

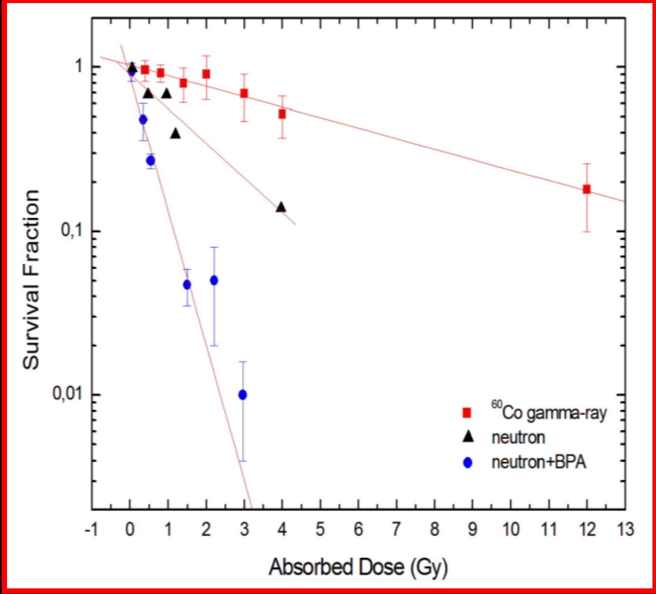
Health cells with boron

$${}^{14}N(n,p)^{14}C$$

$${}^{1}H(n,\gamma)^{2}H$$

$$\frac{D_{tumour}}{D_{health}} \cong 4$$

Inibition of cell proliferation



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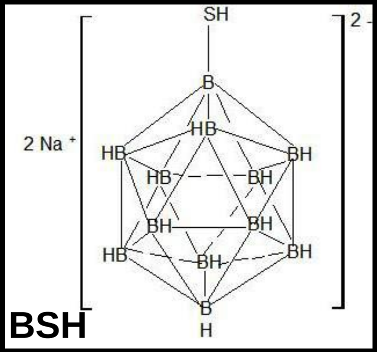
Boron delivery agent-characteristics

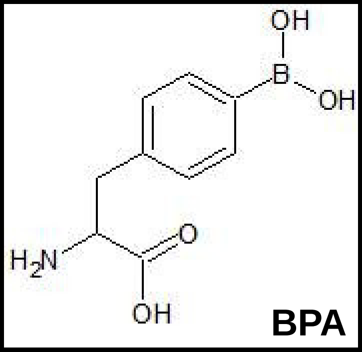
The most important requirements are:

- 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 →



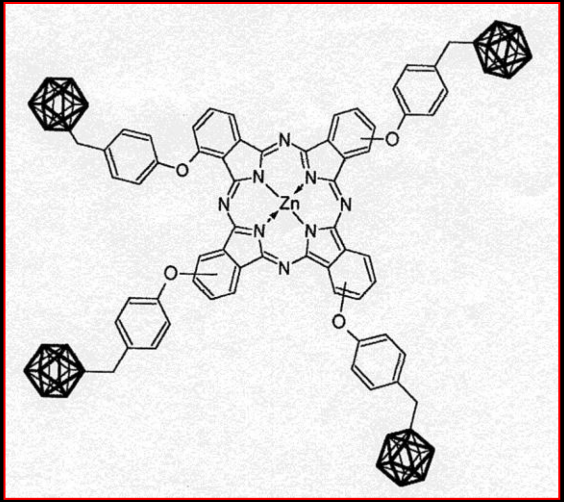


New molecules under investigation →

Boronated unnatural amino acids	**Carboranyl nucleosides**
Dodecaborate cluster lipids and cholesterol derivates	Boronated phorphyrins
Boron containing immunoliposomes and liposomes	Boronated EGF and anti-EGFR and VEGFR MoAbs
Boronated DNA intercalators	Boron-containing nanoparticles
Transferrin-polyethylene glycol liposomes	Carboranyl porphyrazines
Dodecahydo-closo-dodecaborate clusters	Boronated cyclic peptides and nitride nanotubes

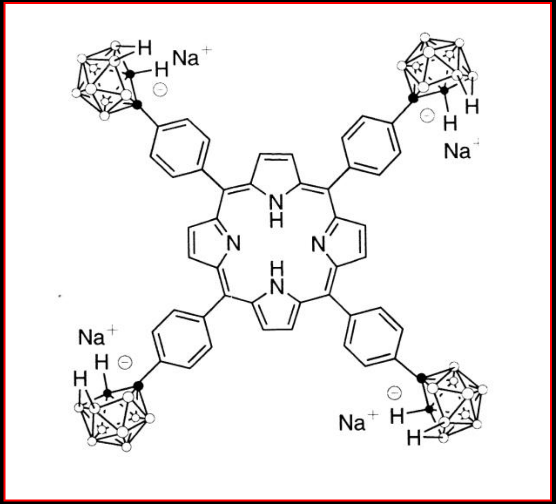
Boron delivery agents

Phtalocianine



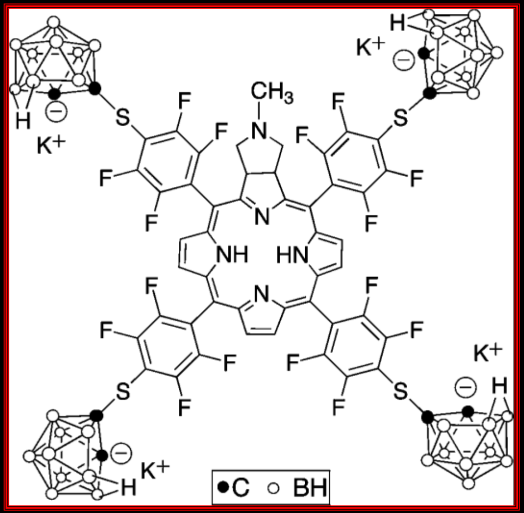
ZnB_4Pc

Phorphyrins



H_2TCP

Chlorine



TPFC

Department of Biology, University of Padua, Italy

Photochemical & Photobiological Sciences 5 (2006) 39-50

Journal of Photochemistry and Photobiology B: Biology 68 (2002) 123-132

Organic & Biomolecular Chemistry 6 (2008) 3732-3740

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Dosimetry of epithermal neutron beams

- Complicated by protons and fase neutron components →different biological effectiveness
- Multiplicative weighting factors → RBE

↓

Physicists

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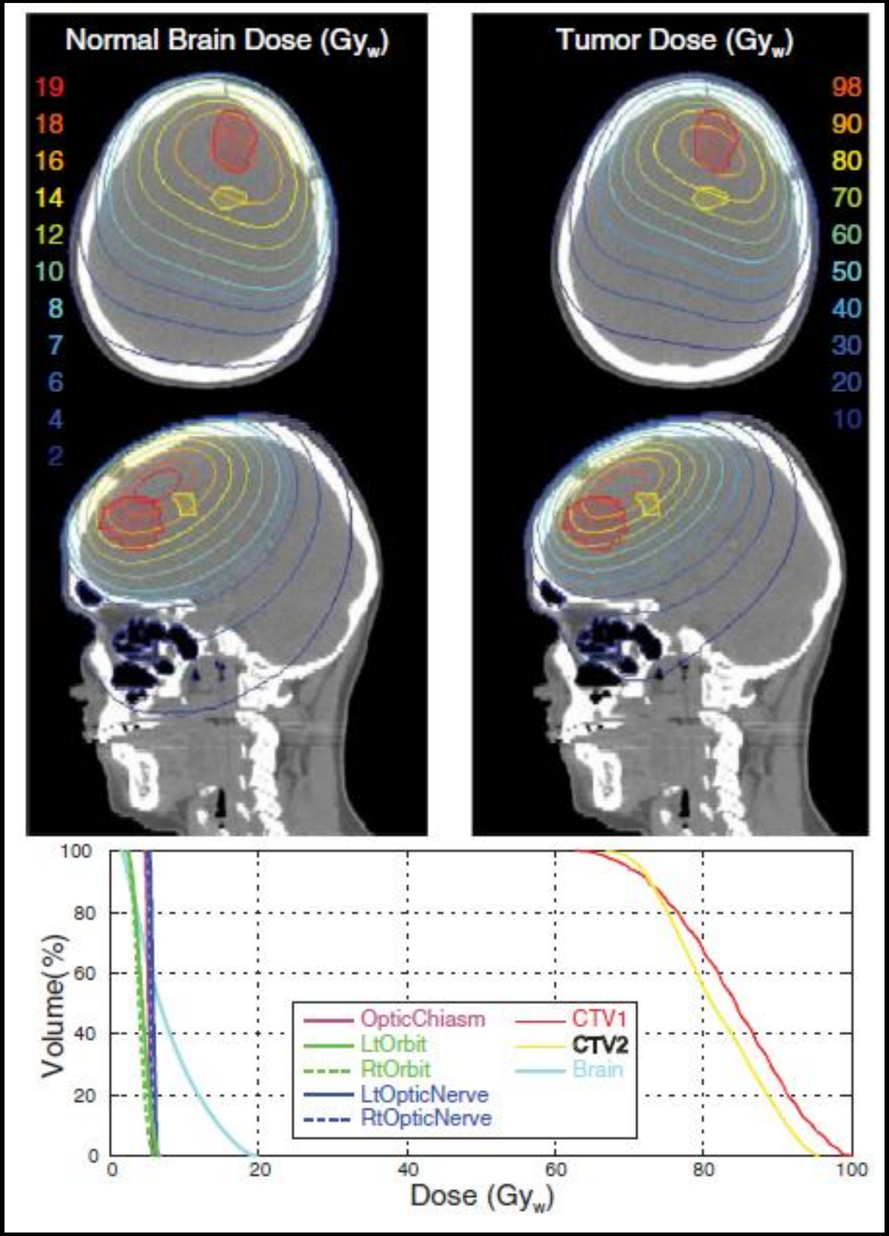
Treatment planning in a patient with GBM

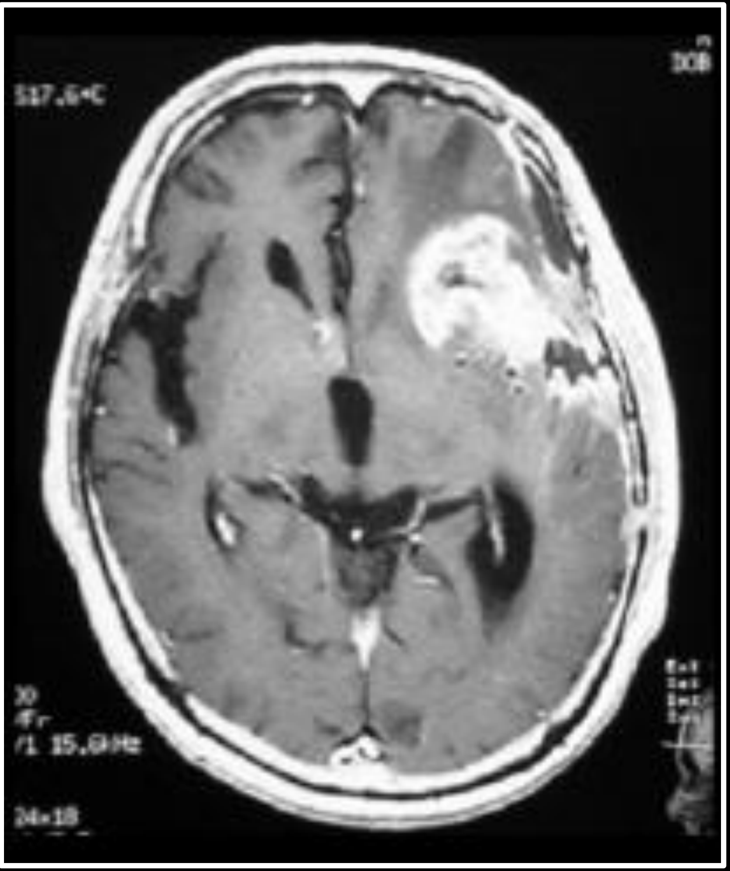


The prescription dose is a mean brain dose of 7.7 Gy.

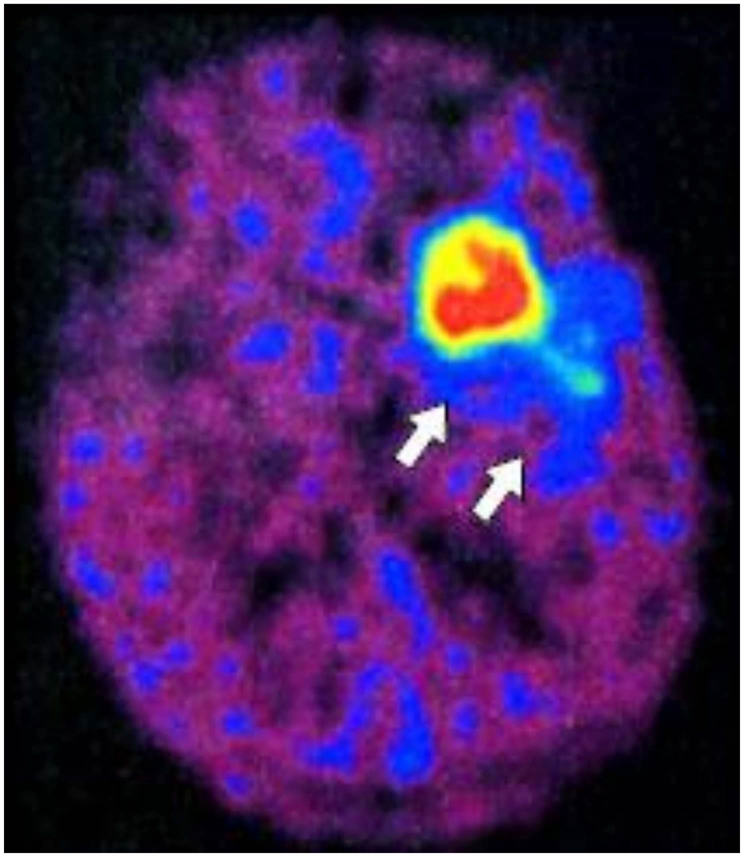
The integral dose volume histograms report dosimetry of interest including target volume and organs at risk.

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 ^{18}F-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, MD[1]

Fluorine-18-Labeled Fluoroboronophenylalanine PET in Patients with Glioma

Yoshio Imahori, Satoshi Ueda, Yoshio Ohmori, Tsukasa Kusuki, Koji Ono, Ryou Fujii and Tatsuo Ido

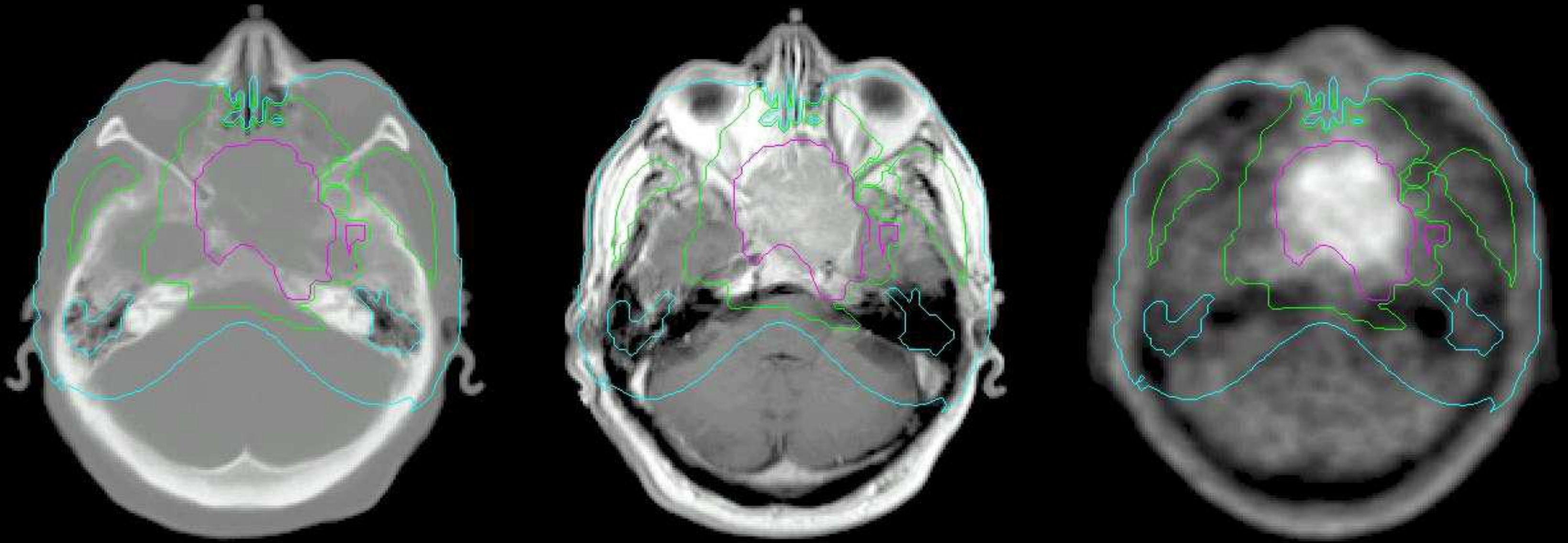
Positron emission tomography-based boron neutron capture therapy using boronophenylalanine for high-grade gliomas: part I.

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

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

George W. Kabalka, Gary T. Smith, Jonathan P. Dyke, William S. Reid, C.P. Desmond Longford, Tony G. Roberts, N. Kesavulu Reddy, Edward Buonocore and Karl F. Hübner

PET- guided BNCT planning



Gross tumour volume : 87 cm^3
Planning target volume : 233 cm^3

5888 *Vol. 9, 5888–5895, December 1, 2003* Clinical Cancer Research

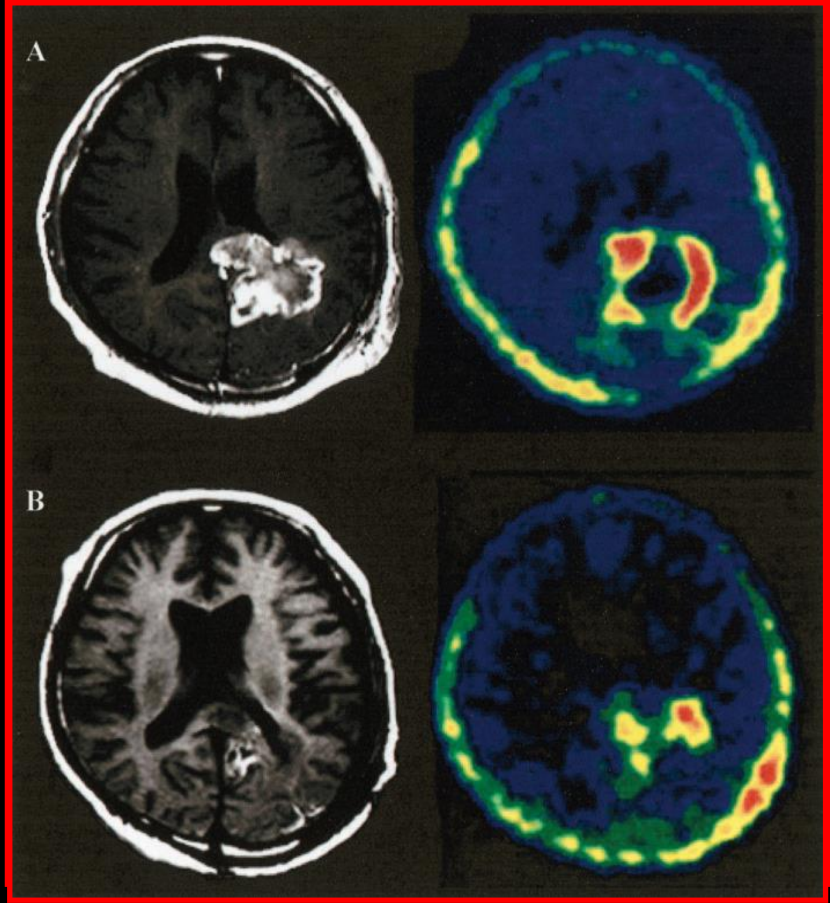
Prognostic and Therapeutic Indicator of Fluoroboronophenylalanine Positron Emission Tomography in Patients with Gliomas

Yoshinobu Takahashi, Yoshio Imahori, and Katsuyoshi Mineura

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, **K**1, 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.



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

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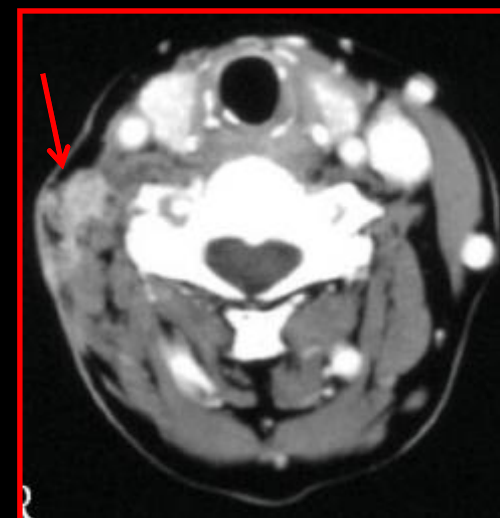
Boron Neutron Capture Therapy HEAD & NECK—DOI 10.1002/hed September 2006

A patients 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.



Before BNCT

After 12 mo. from BNCT

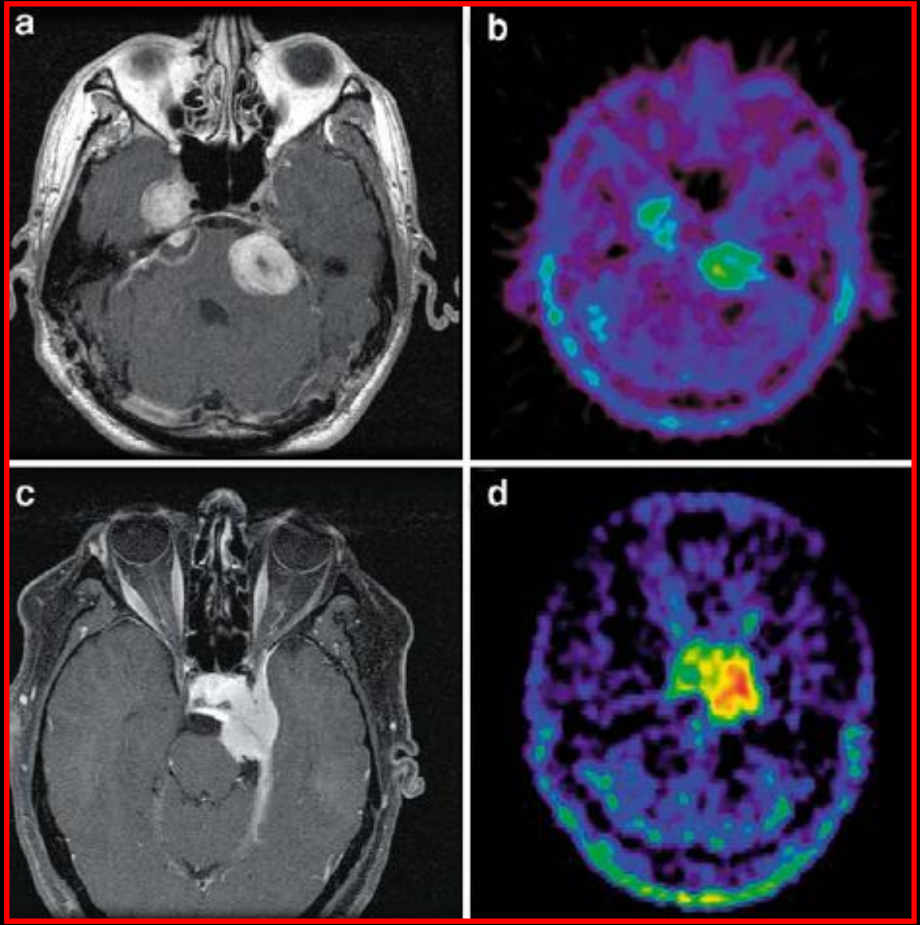
Uptake of 4-borono-2-[^{18}F]fluoro-L-phenylalanine in sporadic and neurofibromatosis 2-related schwannoma and meningioma studied with PET

European Journal of Nuclear Medicine and Molecular Imaging Vol. 34, No. 1, January 2007

Katja Havu-Aurén[1], Johanna Kiiski[1], Kaisa Lehtiö[1], Olli Eskola[1], Martti Kulvik[2], Ville Vuorinen[3], Vesa Oikonen[1], Jyrki Vähätalo[2], Juha Jääskeläinen[4], Heikki Minn[1, 5]

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.

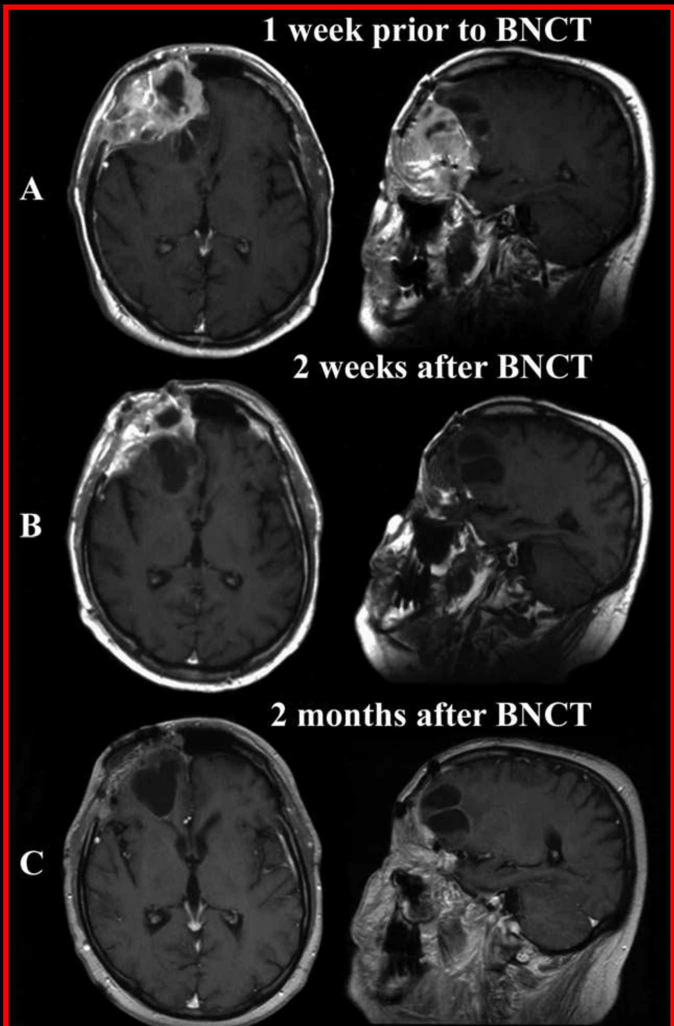
Conclusion: [18F]FBPA PET offers a viable means to evaluate BPA uptake in meningiomas and schwannomas in NF2. Meningiomas and schwannomas might respond to low-dose BNCT with BPA owing to their growth characteristics.



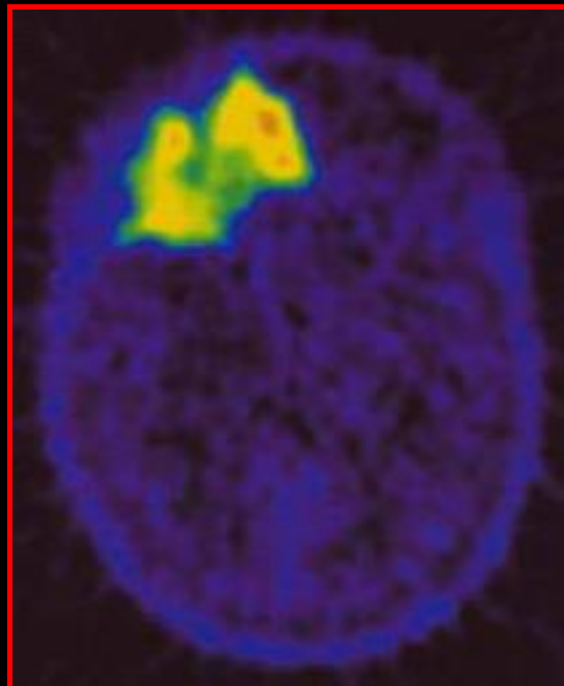
Undifferentiated sinonasal carcinoma may respond to single-fraction boron neutron capture therapy

Radiotherapy and Oncology 72 (2004) 83–85

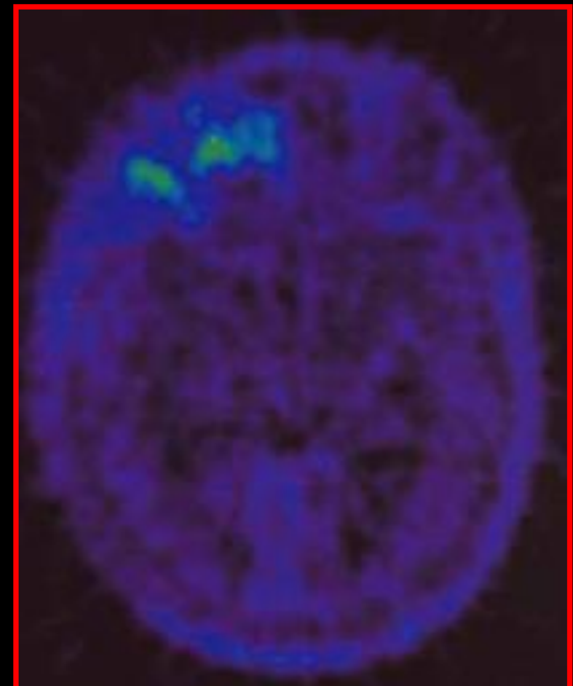
Mauri Kouri[a,1,*], Leena Kankaanranta[a,1], Tiina Seppälä[g,1], Leena Tervo[b], Merja Rasilainen[c], Heikki Minn[i], Olli Eskola[j], Jyrki Vähätalo[h], Anders Paetau[d], Sauli Savolainen[b,f,1], Iiro Auterinen[k], Juha Jääskeläinen[e], Heikki Joensuu[a,1]



Before BNCT



2-months after BNCT



Case: a 44-yr man with recurrent poorly differentiated sinonasal carcinoma

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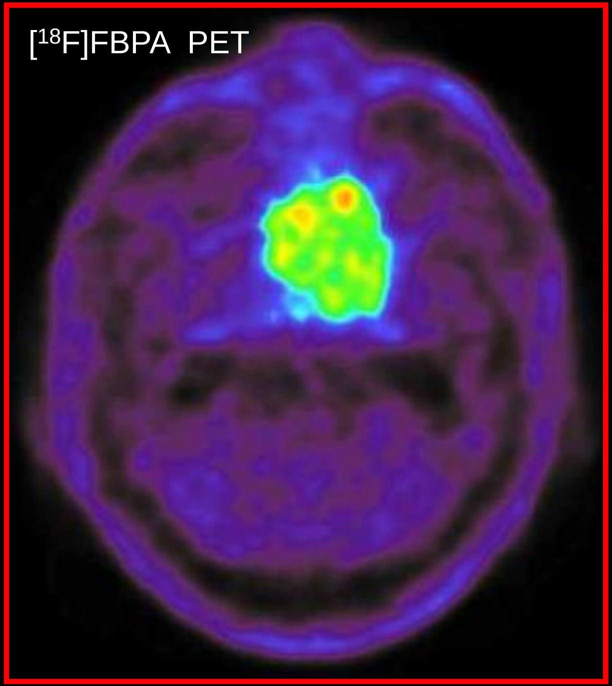
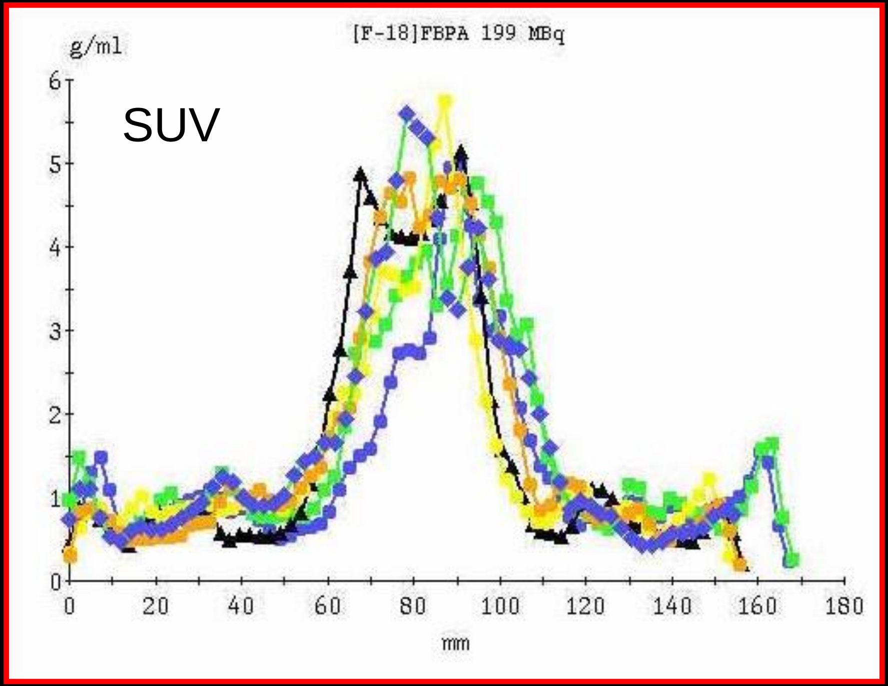
BNCT in locally recurred nasopharyngeal cancer



Nasopharyngeal cancer rT4N0



Scalp ◄ Brain ► ◄ Tumour ► ◄ Brain ► Scalp

Prerequisite for BNCT:

Uptake of [^{18}F]F-BPA 2.5 ≥ surrounding normal tissue

PLANNED FRACTIONATED BORON NEUTRON CAPTURE THERAPY USING EPITHERMAL NEUTRONS FOR A PATIENT WITH RECURRENT SQUAMOUS CELL CARCINOMA IN THE TEMPORAL BONE: A CASE REPORT

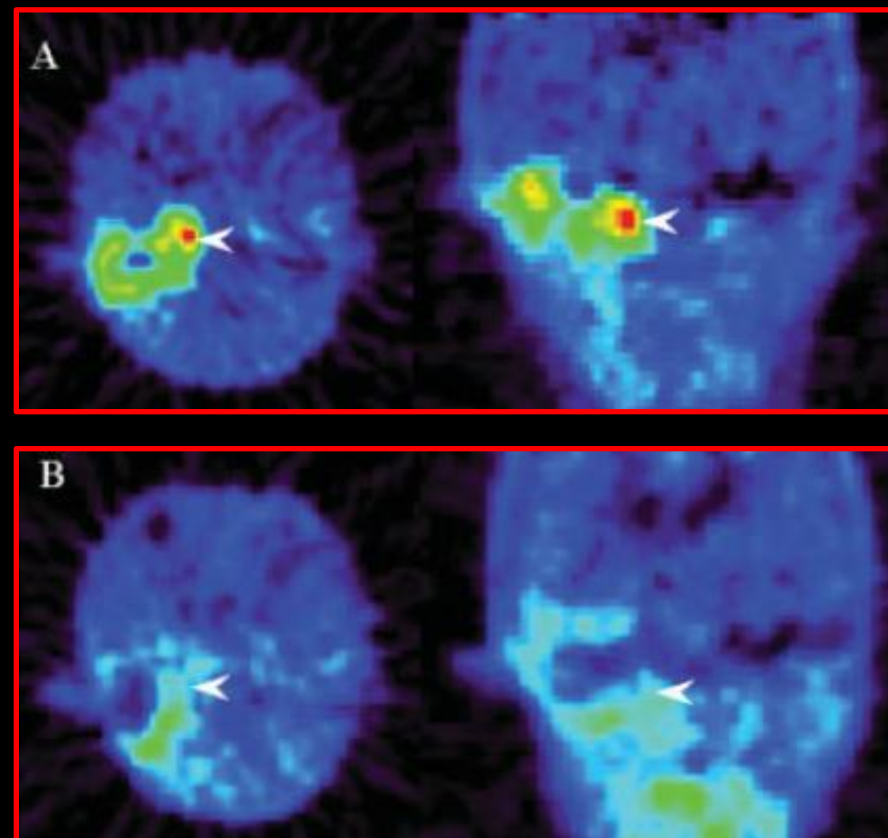
HEAD & NECK—DOI 10.1002/hed March 2009

Shin-Ichi Haginomori, MD,[1] Shin-Ichi Miyatake, MD,[2] Takaki Inui, MD,[1] Michitoshi Araki, MD,[1] Shinji Kawabata, MD,[2] Atsuko Takamaki, MD,[1] Koutetsu Lee, MD,[1] Hiroshi Takenaka, MD,[1] Toshihiko Kuroiwa, MD,[2] Yasuo Uesugi, MD,[3] Hiroaki Kumada, PhD,[4] Koji Ono, MD[5]

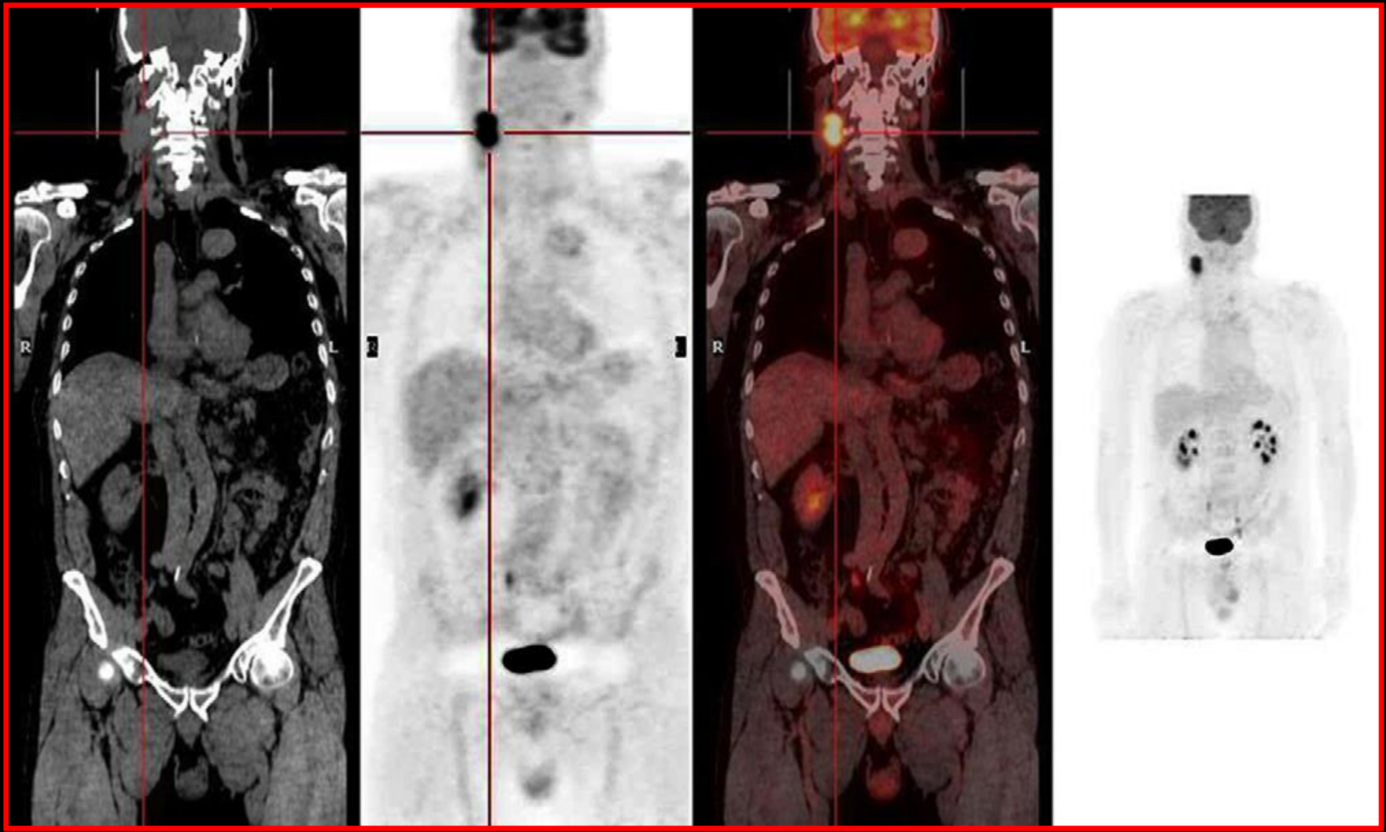
Squamous cell carcinoma in the temporal bone recurring after surgery, conventional radiotherapy, and chemotherapy, which was treated using planned fractionated BNCT

^{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



18F BPA PET/CT



A. Wittig et al. "Boron analysis and boron imaging in biological materials for Boron Neutron Capture Therapy (BNCT)" Critical Reviews in Oncology/Hematology 68 (2008) 66–90

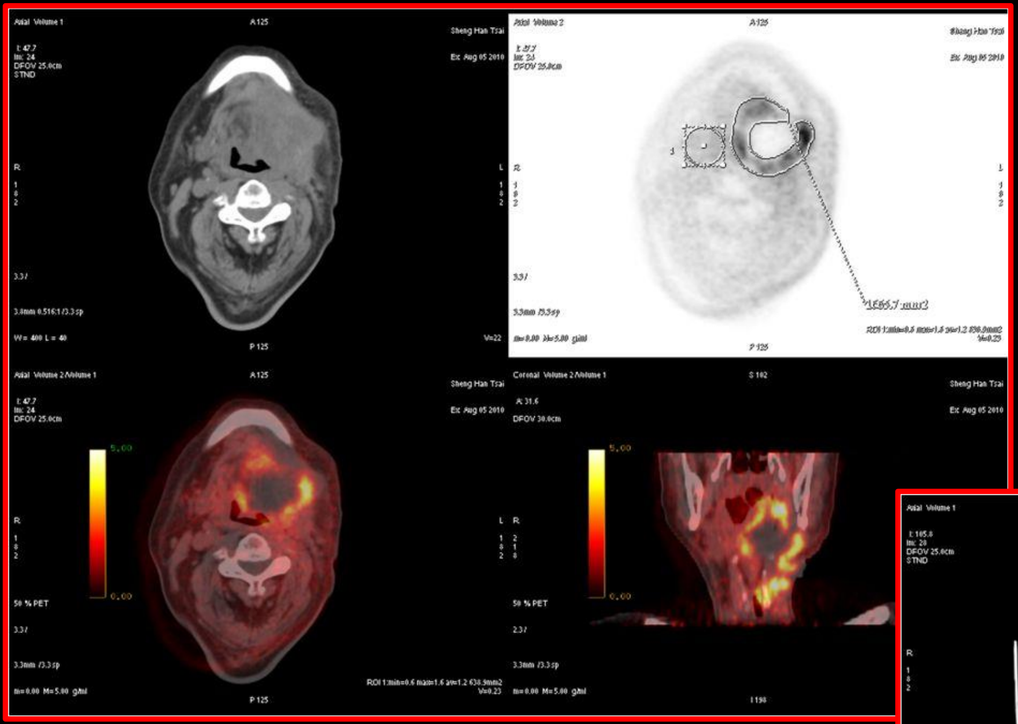
Pre and post-therapy 18F-BPA PET/CT

Pre-BNCT

Post- BNCT

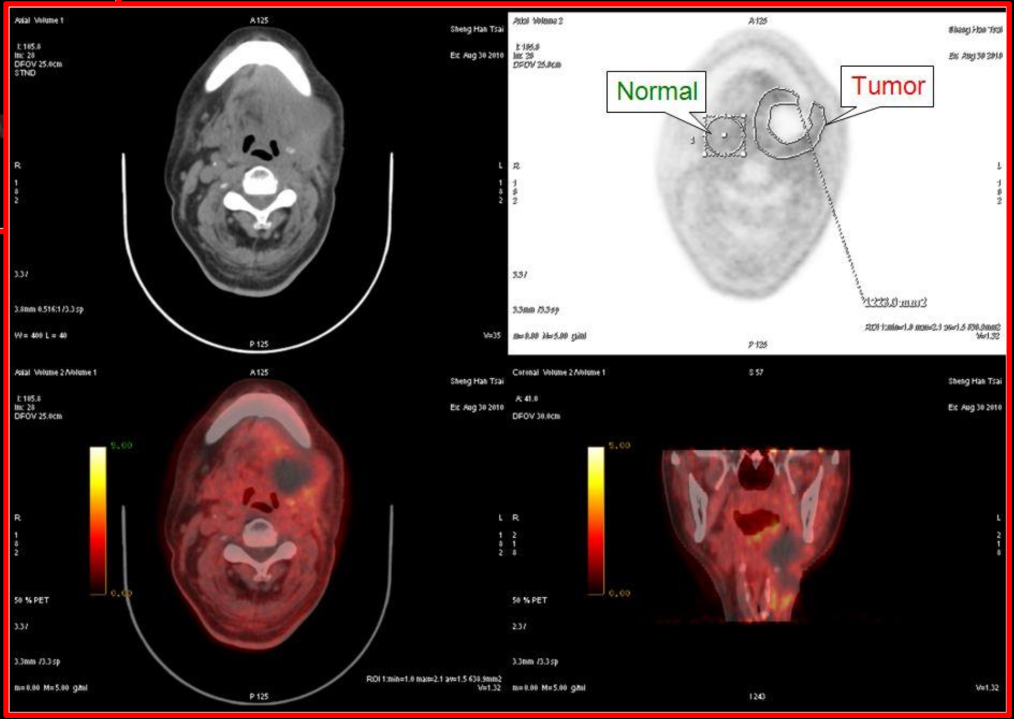
By Prof. Ling-Wei Wang, China

PET/CT in head-neck cancer



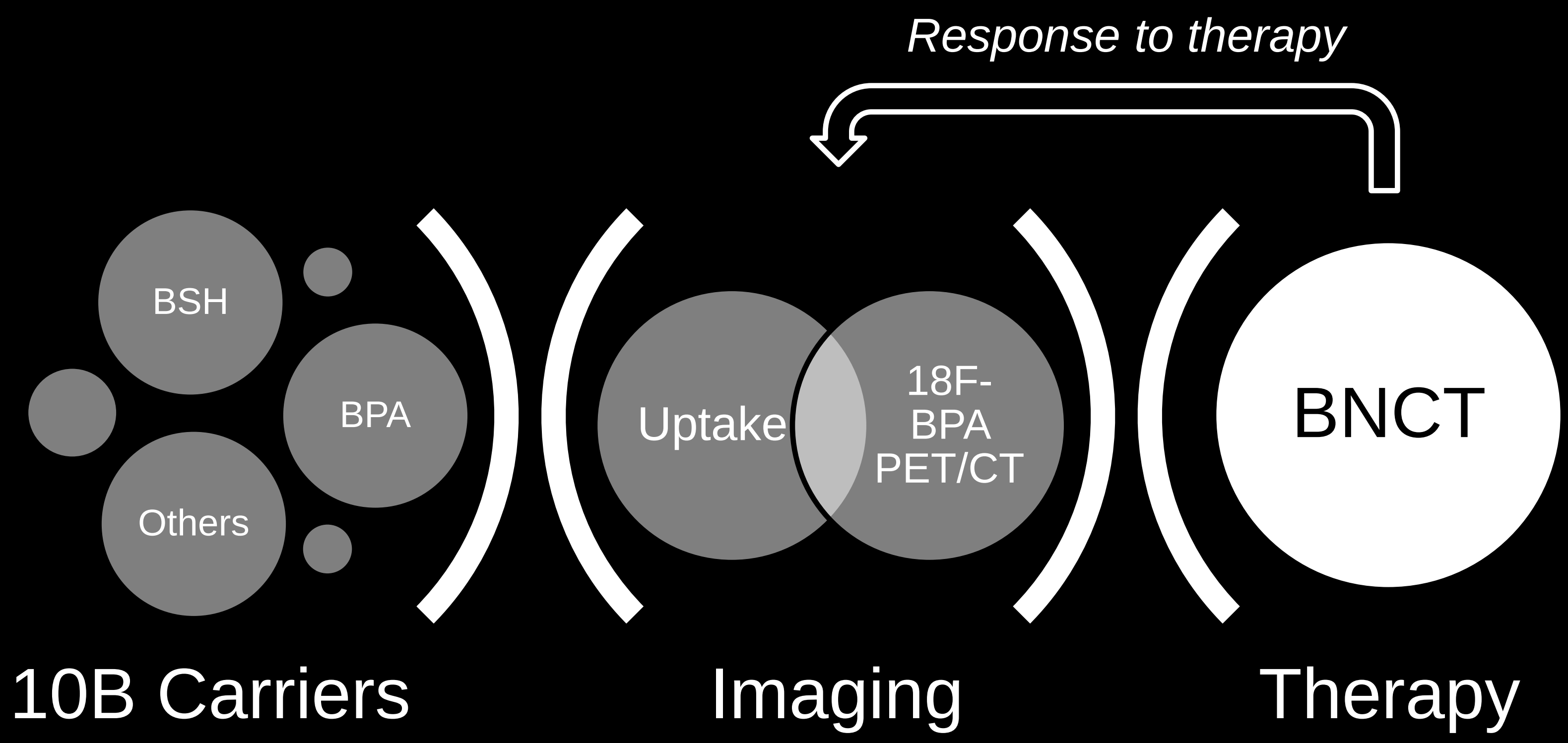
Pre-BNCT

Post- BNCT



By Prof. Ling-Wei Wang, China

BNCT - STEPs



Response to therapy
BSH
BPA
Others
Uptake
18F-
BPA
PET/CT
BNCT
10B Carriers
Imaging
Therapy

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…from a clinical point of view

Past		
Pathologies (country)	**N of pts**	**Phase**
GBM (USA)	53	I-II
GBM/MM (Germany)	26/4	I-II
GBM/AA/MRM/H&N (Japan)	83/7/7/124	I-II
GBM/AA/H&N (Finland)	50/2/31	I-II
GBM (Czech Republica)	34	I-II
GBM/MM (Sweden)	12/2	I-II
H&N (Taiwan)	10	I

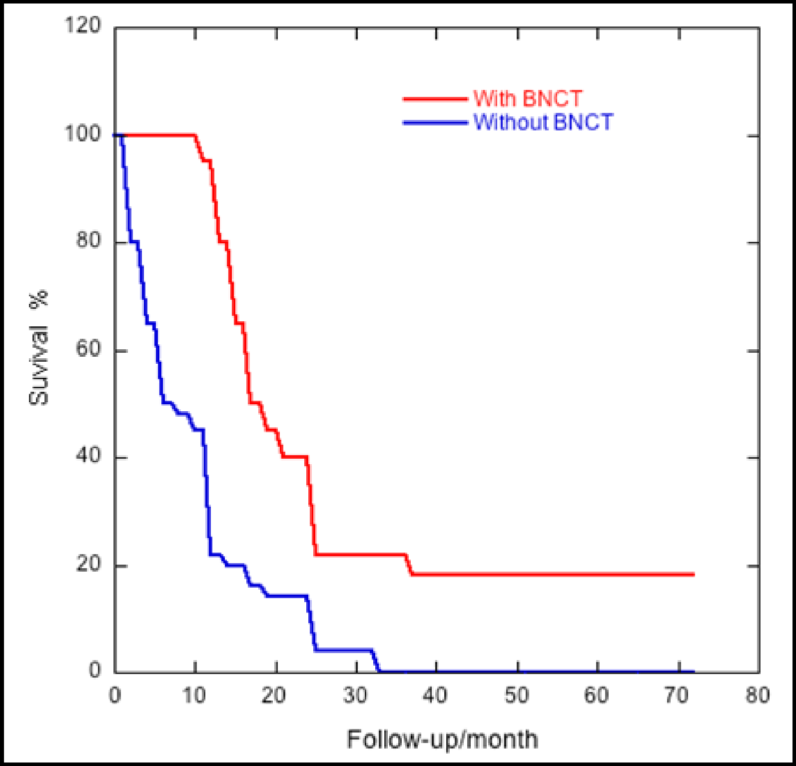
On going*		
Pathologies (Country)	**N of pts**	**Phase**
H&N (Taiwan)	27	I/II
H&N (Taiwan)	28	I/II
GBM (Japan)	45	II
Melanoma (Argentina)	15	I

GBM: glioblastoma multifome, MM: melanoma metastasis, AA: anaplastic astrocytoma, MRM: meningioma related malignancy; H&N: head and neck cancer

*by *clinicaltrial.gov*

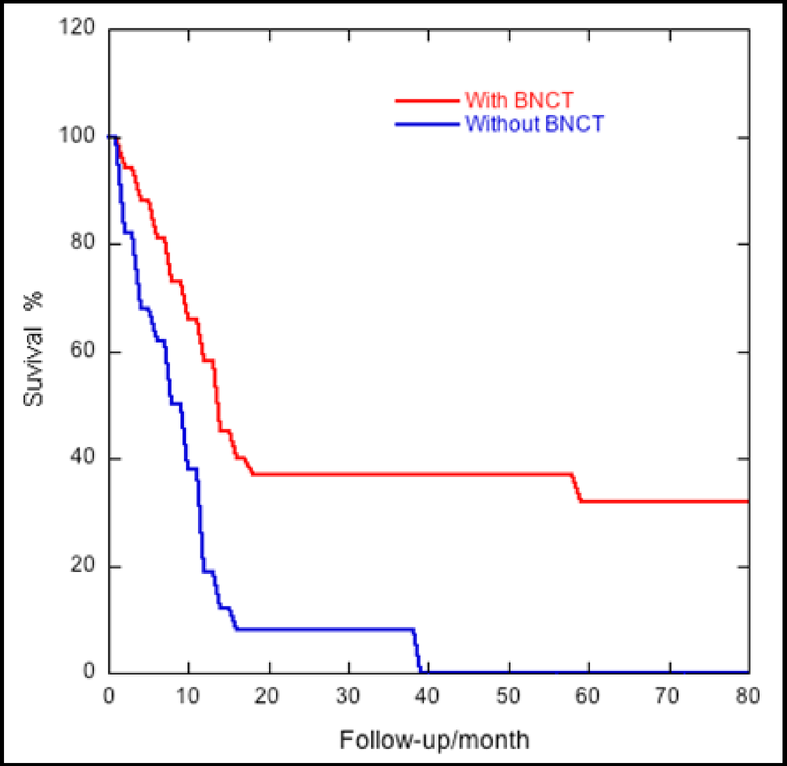
Improvement in survival rate

Glioblastoma multiforme



Kawabata et al. Appl Radiat Isot 2009; 67:S15-18

Recurrent head and neck cancer



Kato et al. Appl Radiat Isot 2009; 67:S37-42

Operative BNCT centres

CENTER	STATES	NEUTRON SOURCE	NEOPLASM	N° OF TREATED PATIENTS
Helsinki University Central Hospital, Helsinki, Finland	Europe	FIR-1, VTT Technical Reserch Centre, Espoo	GB and HN	50 GM 2 AA 31 HN
Faculty Hospital of Charles University, Prague, Czech Republic	Europe	LVR-15 Reactor, Nuclear Reserch Institute Rez	GB	5 GM
University of Tsukuba, Tsukuba City, Ibaraki	Japan	JRR-4, Japan Atomic Energy Agency, Tokai, Ibaraki	GB	20 GM 4 AA
University of Tokushima, Tokushima	Japan	JRR-4 (Kyoto University Research Reactor, Osaka)	GB	23
Osaka Medical College and Kyoto University Research Reactor, Kyoto University, Osaka and Kawasaki Medical School, Kurashiki	Japan	KURR	GB, HN, CM	30 GBM 3 AA 7 Men 124 HN
Taipei Veterans General Hospital, Taipei, Taiwan	Republic of China	THOR, National Tsing Hua University, Hsinchu, Taiwan	HN	10
Instituto de Oncología Angel H, Buenos Aires	Argentina	Bariloche Atomic Center	CM and AT	7CM 3 AT

Past…………………present

1950	Today
• Thermal neutron beams	• Thermal and Epithermal neutron beams
• Boronated agent (sodium tretraborate, sodium pentaborate, sodium decahydrodecaborate)	• Boronated agent (BPA and BSH)
• Intra-operative approach	• External irradiation (intra and extra-operative approach)
• No accurate dosimetric assessment	• Accurate microdometric assessment
• No BNCT planning	• MRI, PET and other device for BNCT planning
• Mostly brain cancer	• Many solid cancers (brain, melanoma, head and neck, liver, and so on)

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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