The rationale, clinical results and future development of boron neutron capture therapy (BNCT)

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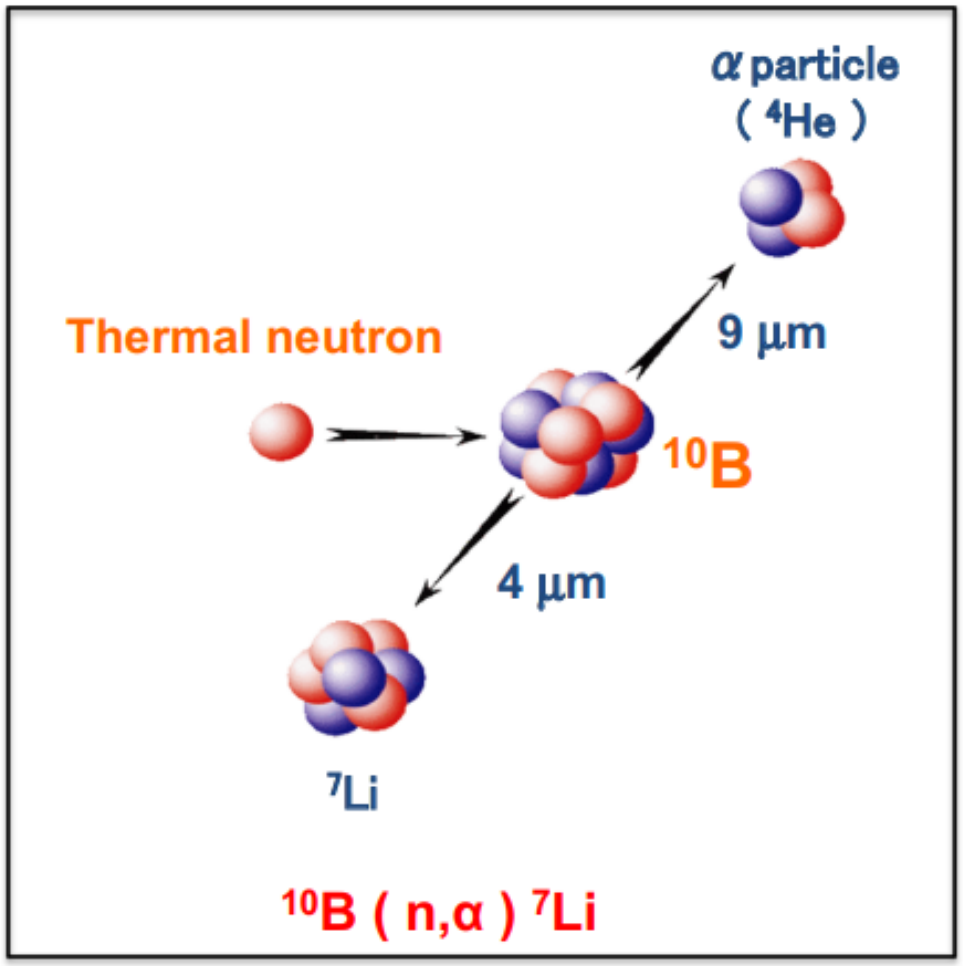
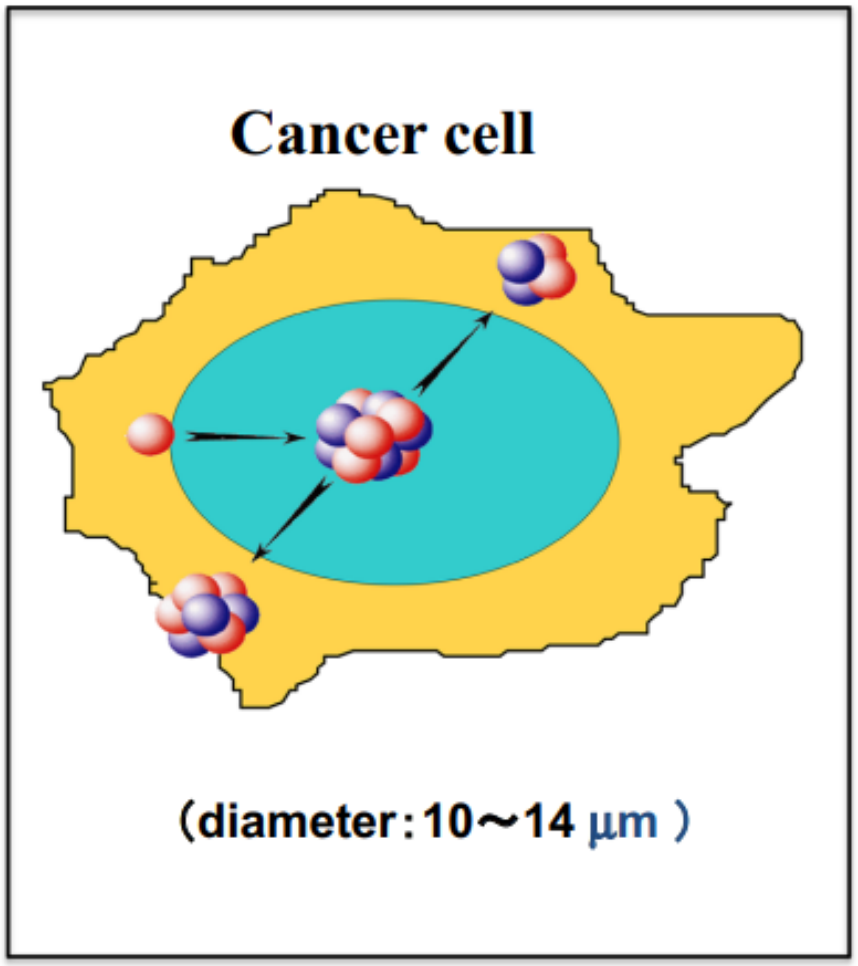
The principle of boron neutron capture therapy (BNCT)





Hiratsuka J et al. Cancer Commun 2018;38:38

Boron ^{10}B captures avidly neutrons

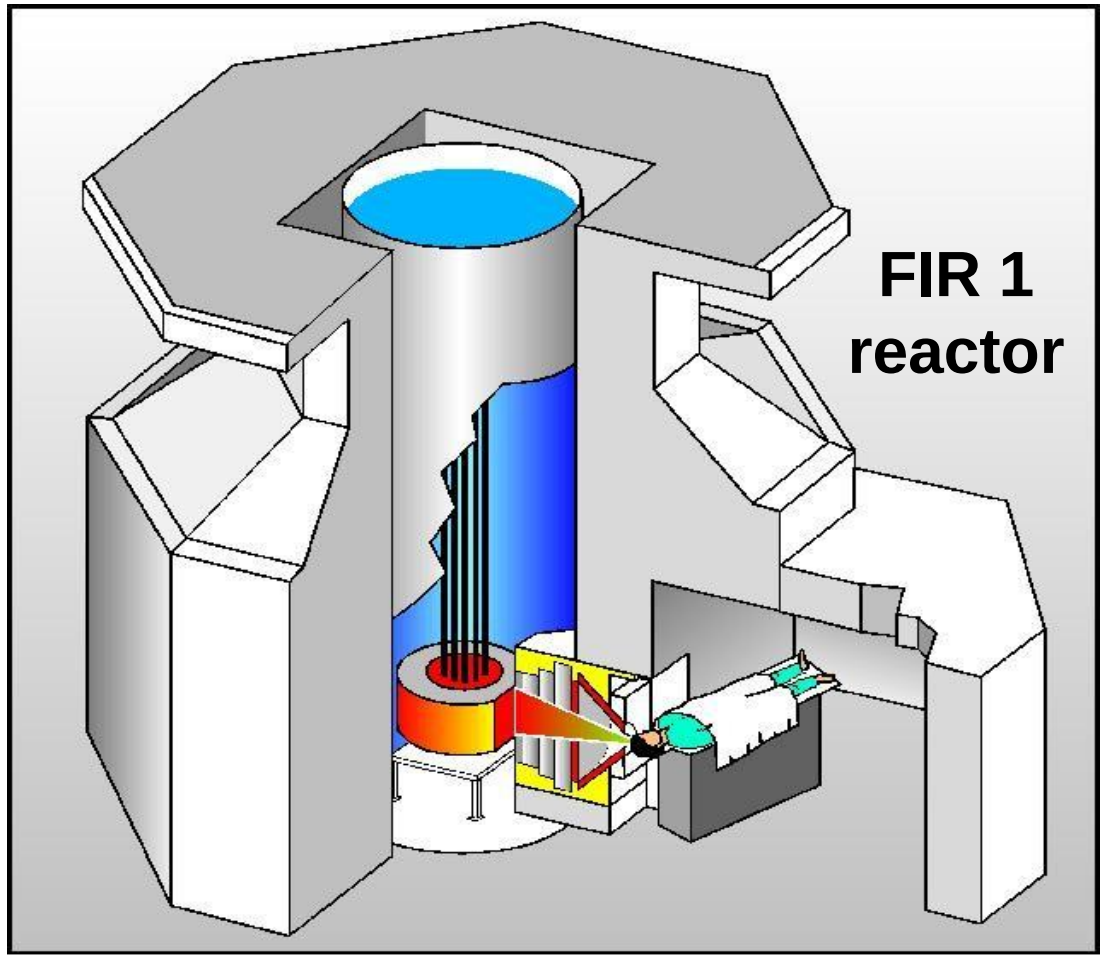
Boron metalloid

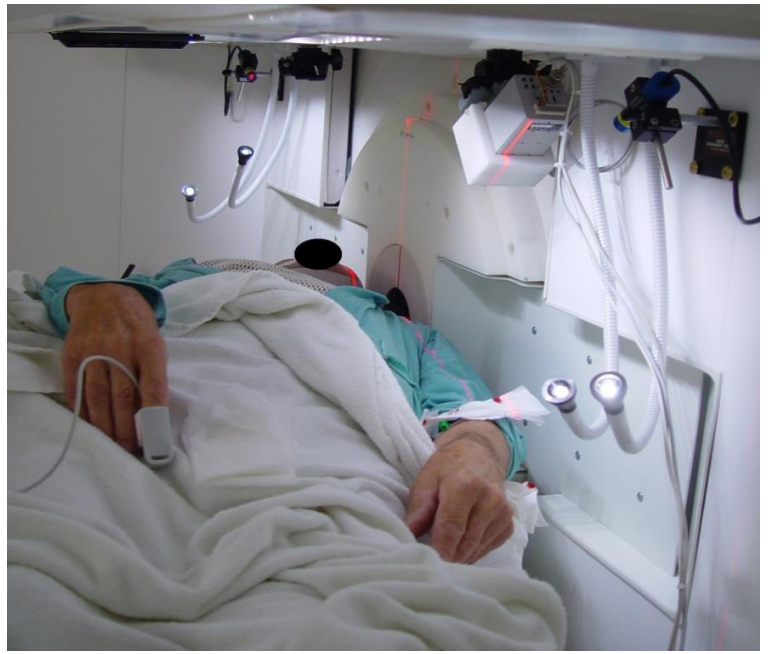
Boron ^{11}B (80%) and ^{10}B (20%) occur in the Earth crust in small quantities as oxidised compounds.

Neutron capture cross sections of common elements	
Element	**Cross section (Barns)**
Oxygen, ^{16}O	0.0002
Carbon, ^{12}C	0.0037
Hydrogen, ^{1}H	0.332
Sodium, ^{22}Na	0.536
Nitrogen, ^{14}N	1.75
Boron, ^{10}B	**3836**

^{10}B has a very large ”neutron capture cross section”

Our neutron source for BNCT in the past: the FIR1 nuclear reactor

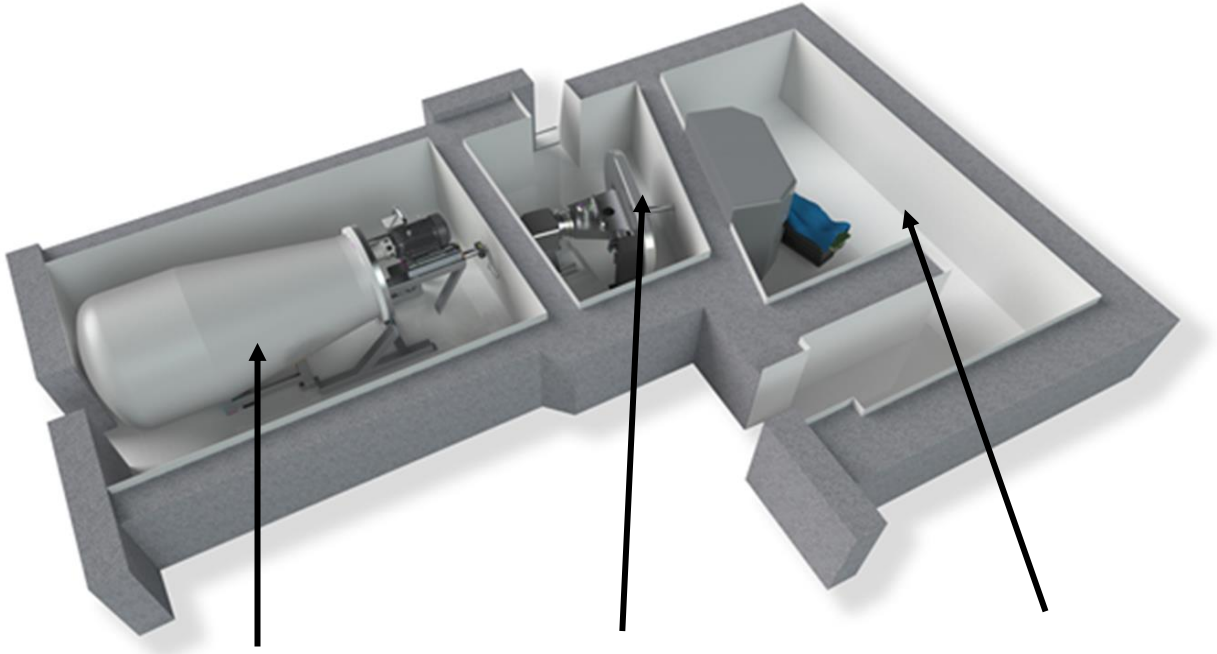




A patient being treated at FIR 1

- 249 patients were treated with BNCT at FIR1 in 1999-2012

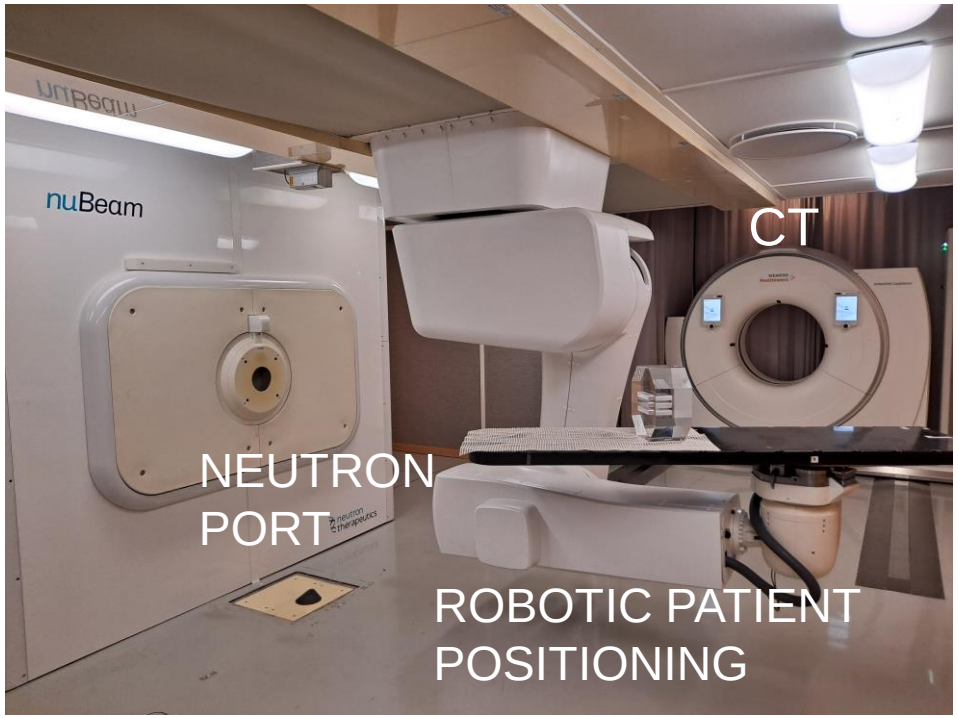
Modern neutron source: A proton accelerator linked with a proton to neutron converter



PROTON ACCELERATOR

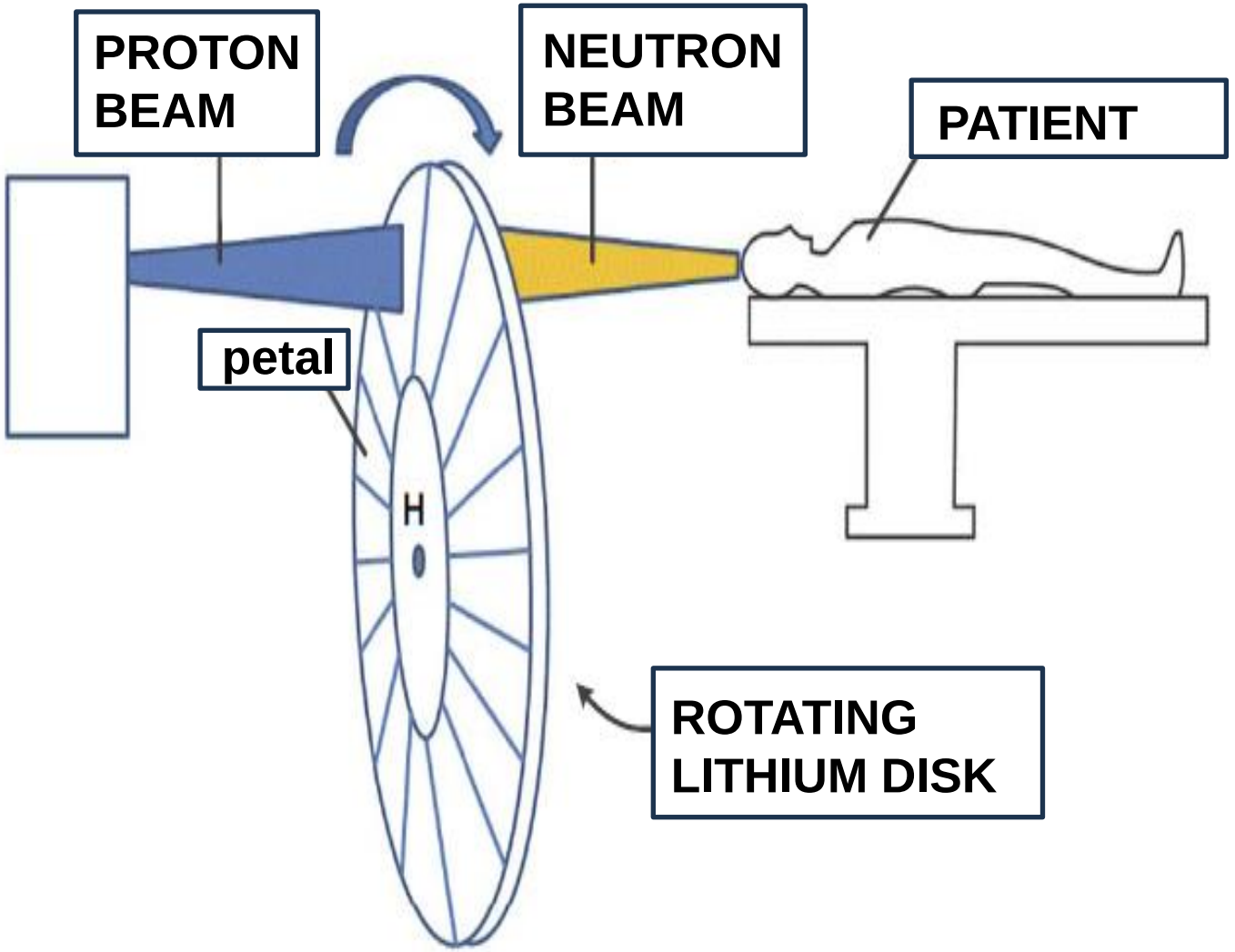
PROTON TO NEUTRON CONVERTER

TREATMENT ROOM



The NT neutron therapy system has not been approved by the FDA or the EMA

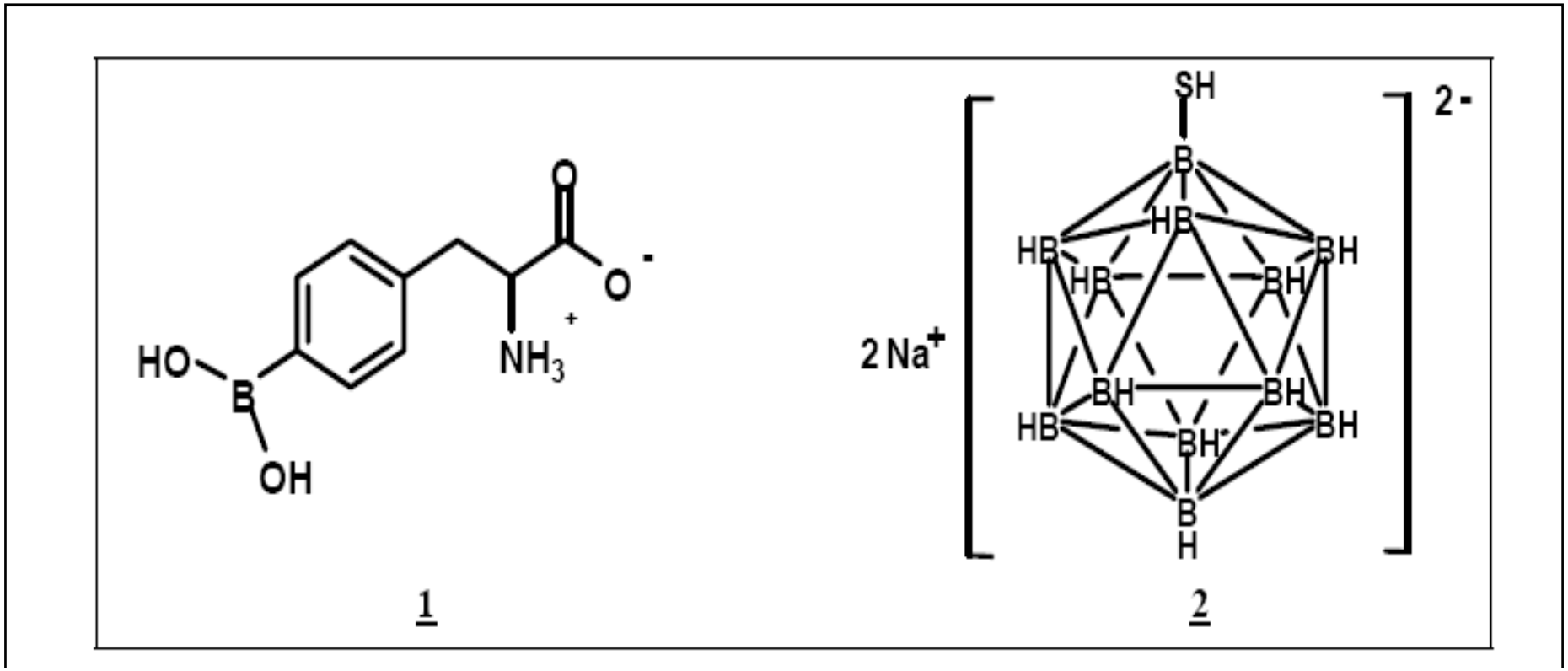
Proton to neutron converter



- When suitable energy (~2 MeV) protons hit a solid lithium disk neutrons are produced: $^{7}\mathrm{Li}+p\rightarrow{}^{7}\mathrm{Be}+n$
- The lithium disk is rotated and cooled to prevent lithium from melting (melts at 180ºC)

The NT neutron therapy system has not been approved by the FDA or the EMA.

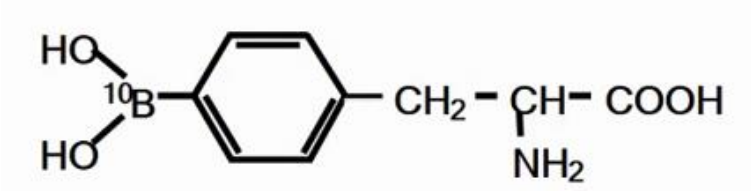
Boron delivery agents



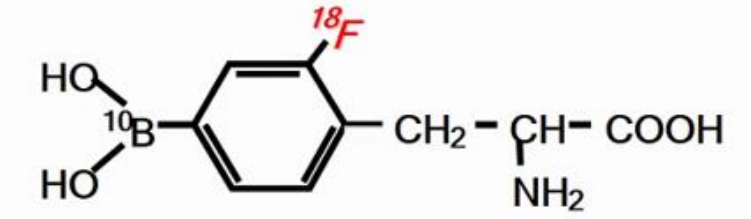
Boronophenylalanine (BPA)

BSH

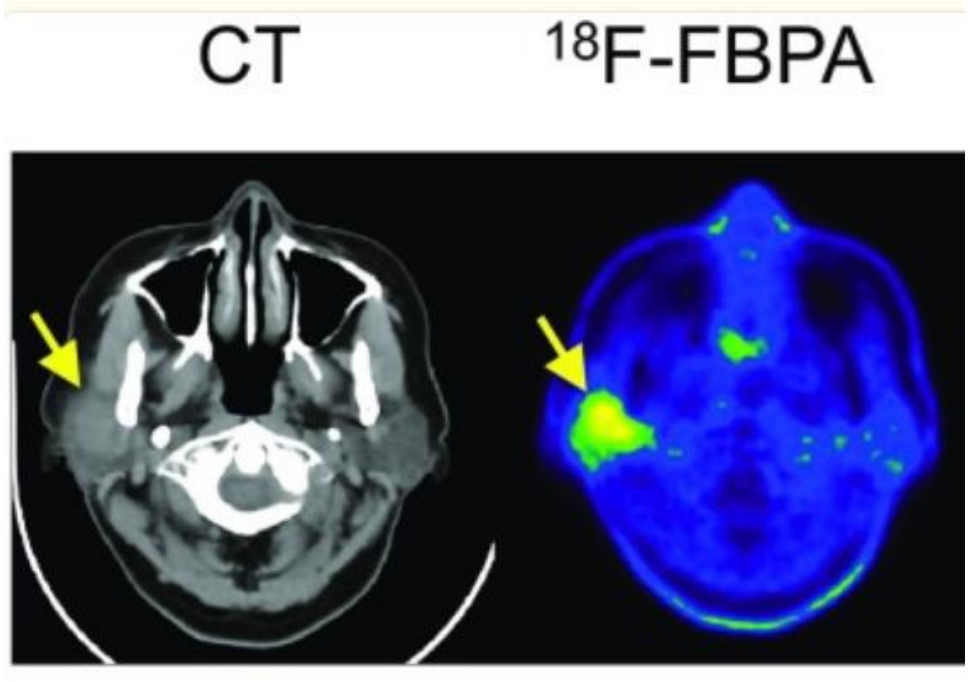
BPA tumor uptake can be measured using positron emission tomography (PET)



BPA



^{18}F-FBPA

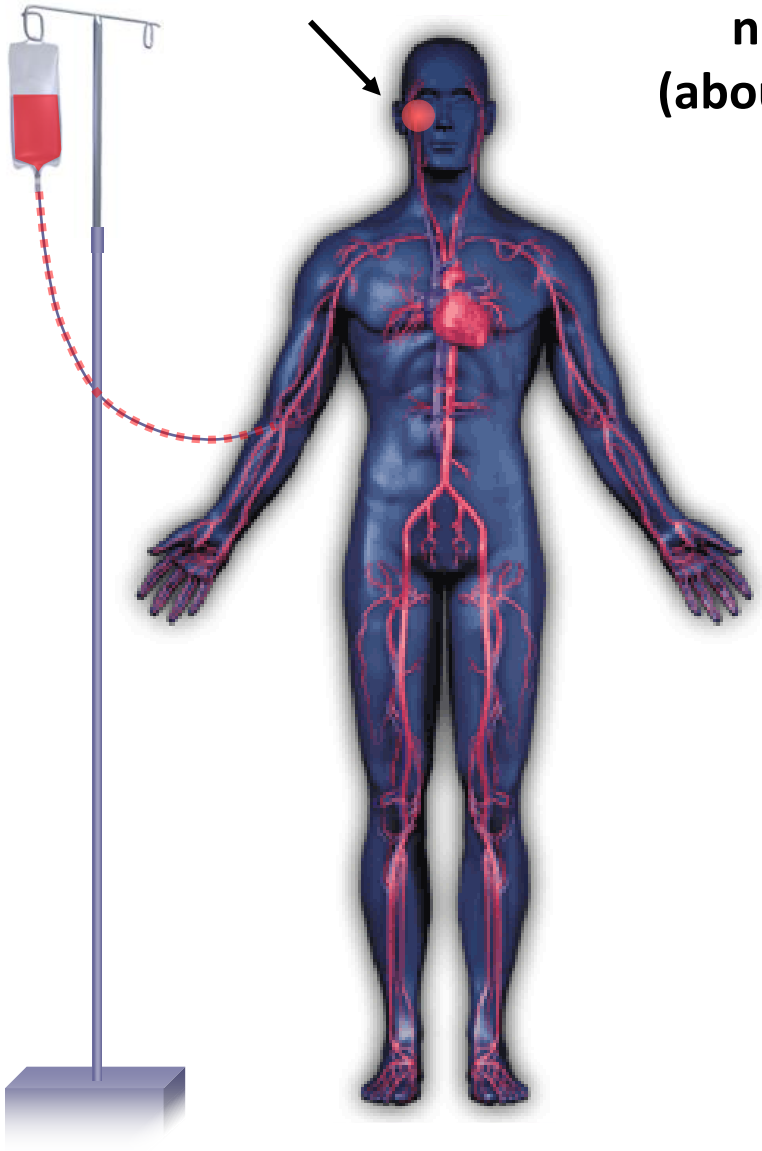


- Fluorine-18 labeled BPA can be imaged with PET
- In general, cancers accumulate ^{18}F-FBPA 3-4 times compared to normal tissues

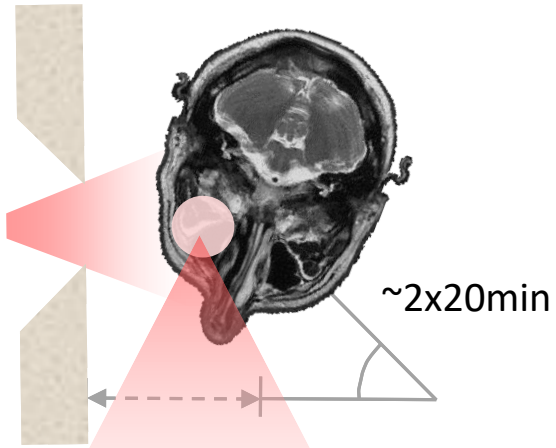
The BNCT procedure (often one time treatment)

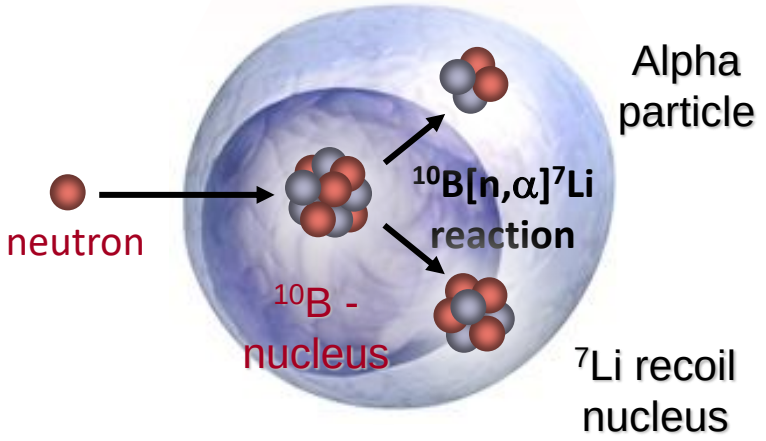
Boronophenyl alanine (BPA) infused over 2 hours into a peripheral vein

BPA accumulates in cancer tissue



Tumor irradiation with neutrons (about 40 mins)





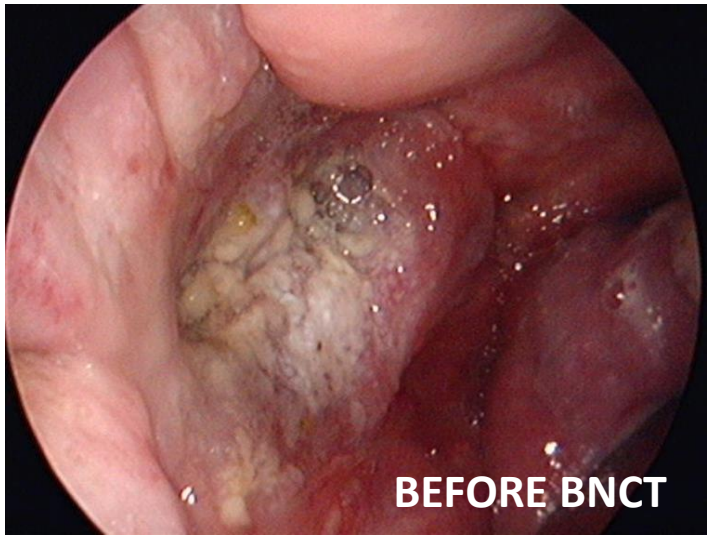
Boron neutron capture and fission, resulting in a large radiation dose to the tumor

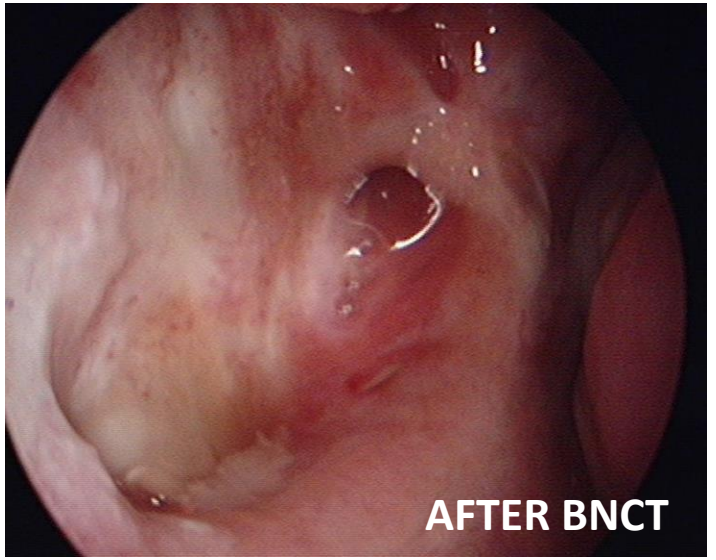
Clinical results

- Locally recurrent head and neck cancer
- Glioblastoma
- High grade meningioma
- Melanoma

Locally recurrent, inoperable head and neck cancer, a Phase I/II trial[1]

- 30 patients treated at the FIR 1 reactor facility; most received BNCT twice
- All had prior conventional radiotherapy in history (50 Gy to 98 Gy)
- 29 were evaluable for response
  - -22 (76%) responded
  - -6 (21%) had tumor stabilization for 5.1 to 20.3 months
  - -1 (3%) progressed





[1]Kankaanranta L et al. IJROBP 2012;82:e67-75; Trial ID NCT00114790

Response of locally recurrent or locally advanced head and neck cancer to BNCT: A summary

- Most patients had prior conventional radiotherapy in history
- Most were treated with BNCT only once

Study	No. of patients	Boron carrier	Response rate	Complete response rate
Kato et al. 2009	26	BSH+BPA or BPA	88%	48%
Kankaanranta et al. 2012	30	BPA	76%	45%
Aihara et al. 2014	20	BPA	90%	55%
Suzuki et al. 2014	62	BSH+BPA or BPA	58%	28%
Wang et al. 2016	17	BPA	71%	35%
Hirose & Sato 2024	47	BPA	74%	51%
Hirose et al. 2021	21	BPA	71%	24%
Sato et al. 2024	154	BPA	71%	46%
Total	377		**72% (267/370)**	**43% (158/370)**

Kato et al. Appl Radiat Isot 2009;67:S37-42; Kankaanranta et al. IJROBP 2012;82:e67-75; Aihara et al. Apl Radiat Isot 2014;88:12-5; Suzuki et al. J Radiat Res 2014:55:146-53; Wang et al. IJROBP 2016;95:396-403; Hirose et al. Radiother Oncol 2021;155:182-7; Hirose K, Sato M. IJROBP 2024 Apr 3; Sato et al. Cancers 2024;16:869.

BPA-based BNCT in the treatment of locally advanced or recurrent inoperable head and neck cancer: Japanese nationwide study

- The patients were treated BPA complexed with sorbitol (borofalan) in Japan between May 2020 and January 2022

Patients:
- No distant metastases.
- 93% had received prior conventional radiotherapy.
- 79% had prior systemic cancer therapy.

BNCT was given once.

Response	Squamous cell cancer (N=137) n (%)	Non-squamous cell cancer (N=17) n (%)
Overall response rate	99 (72%)	11 (65%)
Responses:		
Complete	63 (46)	8 (47)
Partial	36 (26)	3 (18)
Stable disease	31 (23)	5 (29)
Progression	6 (4)	0
Not evaluable	1 (1)	1 (6)

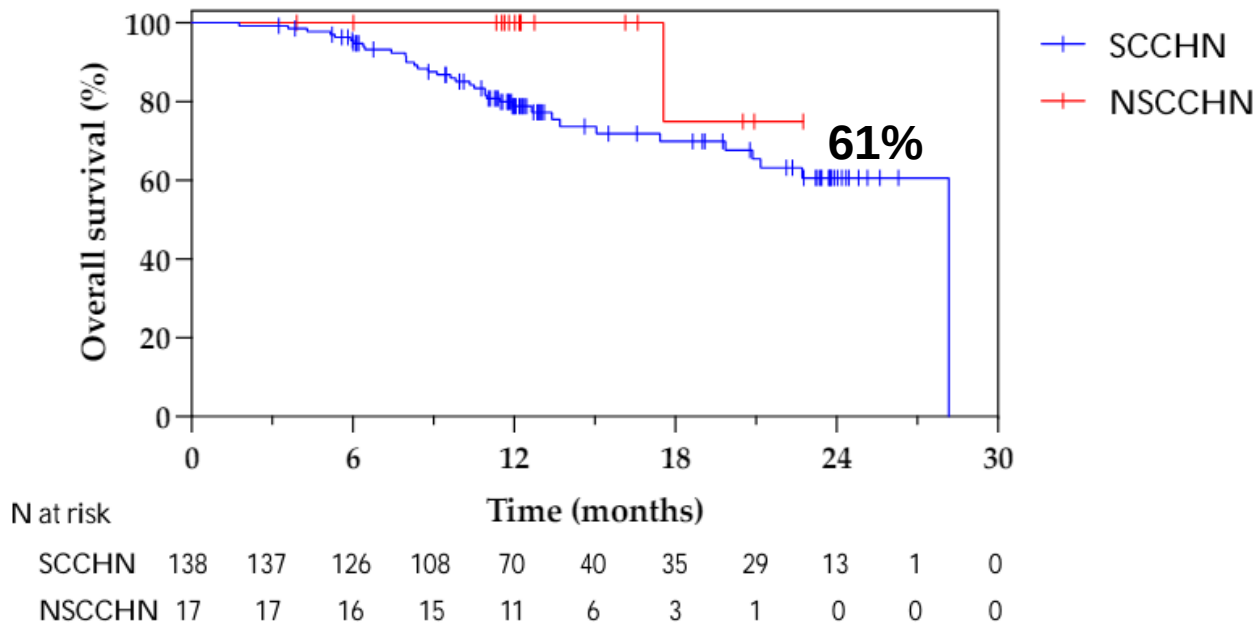
Sato M et al. Cancers 2024;16:869

Japanese nationwide study

2-year overall survival 61% in the squamous cell cancer group.

Safety

- BNCT was well tolerated. The most common acute adverse event was elevated serum amylase level.
- There were only few late severe (grade 3 or 4) adverse events, most common dysphagia was (2%).

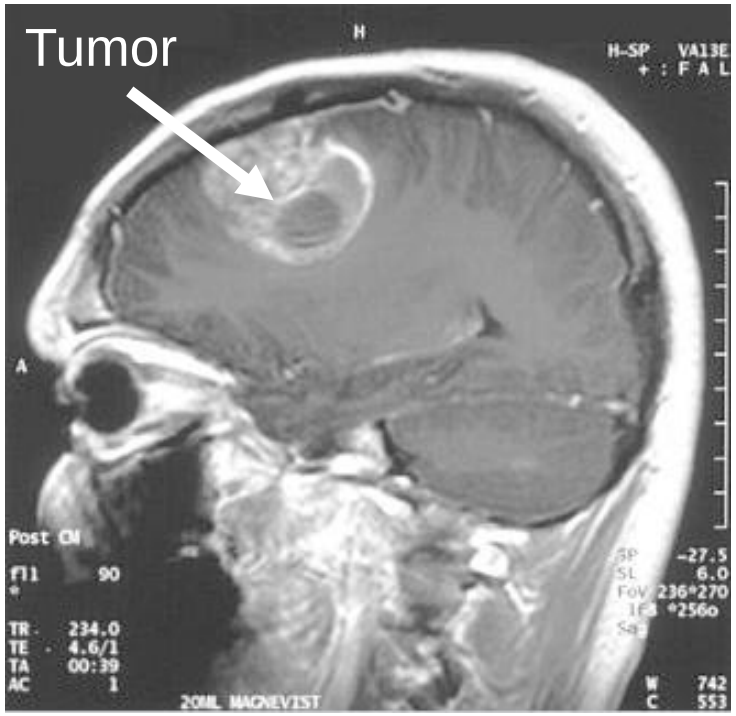


Acute TRAE ($N = 162$)	Grade 1 and 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hyperamylasemia *1	26 (16.1)	63 (38.9)	47 (29.0)
Stomatitis *2	66 (40.7)	17 (10.5)	0
Sialoadenitis *3	81 (50.0)	1 (0.6)	0
Alopecia	80 (49.4)	0	0
Decreased appetite *4	53 (32.7)	4 (2.5)	0
Nausea	48 (29.6)	2 (1.2)	0
Taste disorder	39 (24.1)	0	0

TRAE, treatment associated adverse event

Glioblastoma

- The most malignant brain tumor
- The median survival time after the diagnosis is 12-15 months
- Often treated with surgery, followed by radiotherapy plus chemotherapy (temozolomide)



- Glioblastoma was selected as the target tumor in the first BNCT trials

BNCT for newly diagnosed glioblastoma

Site	No. of patients	Carrier agent	Median survival (months)
Brookhaven, U.S.A.	53	BPA 250–330 mg/kg	12.8
MIT, U.S.A.	20	BPA 250–350 mg/kg	11.1
Studsvik, Sweden	30	BPA 900 mg/kg	17.7
FiR1, Finland	50	BPA 290–400 mg/kg	11.0
HFR, Netherlands	26	BSH 100 mg/kg	10.4 - 13.2

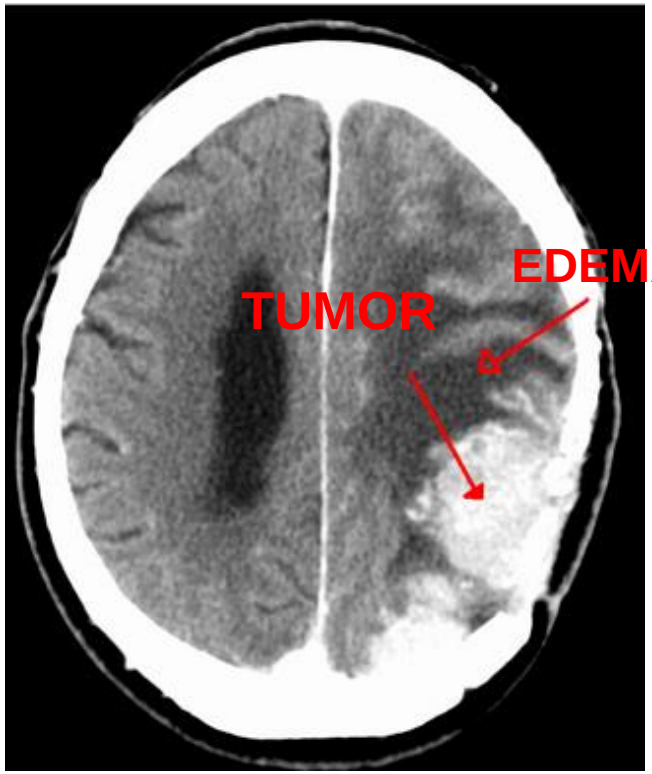
- These median survival times are no better than those achieved with the standard treatments
- Glioblastoma contains by definition necrotic areas, BPA uptake may thus be heterogeneous

Meningioma

- The most common tumor type of the central nervous system, arises from the meninges
- Usually slow-growing
- Patients are frequently observed, or treated with surgery or radiotherapy

High grade (anaplastic) meningiomas are aggessive tumors

- Rare (1-3% of meningiomas)
- Median survival time 1-3 years after detection
- May give rise to distant metastases

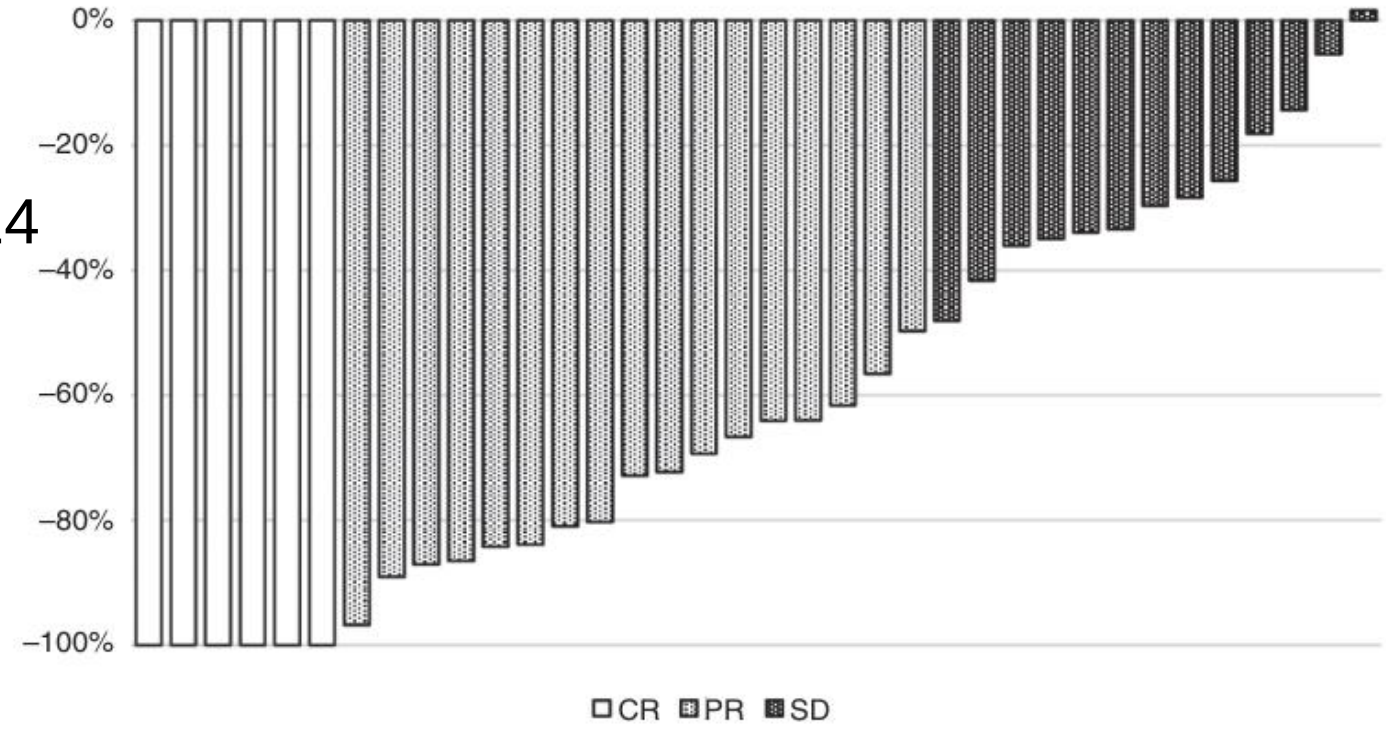


Recurrent meningioma after surgery with surrounding edema

BNCT for high grade meningioma

- Consecutive 44 tumors from Kansai BNCT Medical Center, Osaka
- All patients had prior surgery (median, 3); 91% had prior RT (median, 2 treatments)
- Tumors were large (mean volume 42 mL) and most (55%) grade 3

- All 36 tumors with follow-up MRI data available responded (64%) or stabilized (36%)
- Median PFS after BNCT was 14 months (with conventional RT, ~5 months)
- Only 22% had in-field recurrence
- 6 (14%) had grade 3 toxicity
- A randomized trial initiated

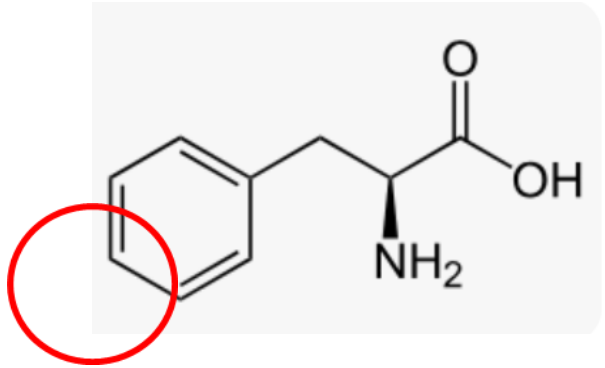


PFS, progression-free survival; RT, radiotherapy

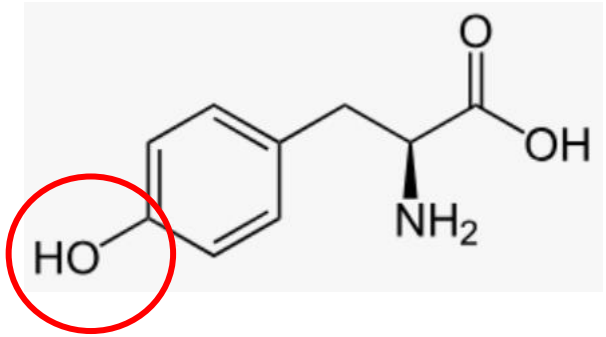
Takai et al. Neuro Oncol 2022;24:90-8

BNCT for melanoma

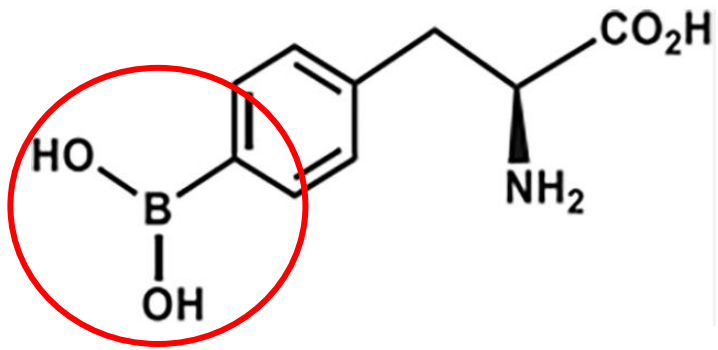
Phenylalanine



Tyrosine



Boronophenylalanine (BPA)

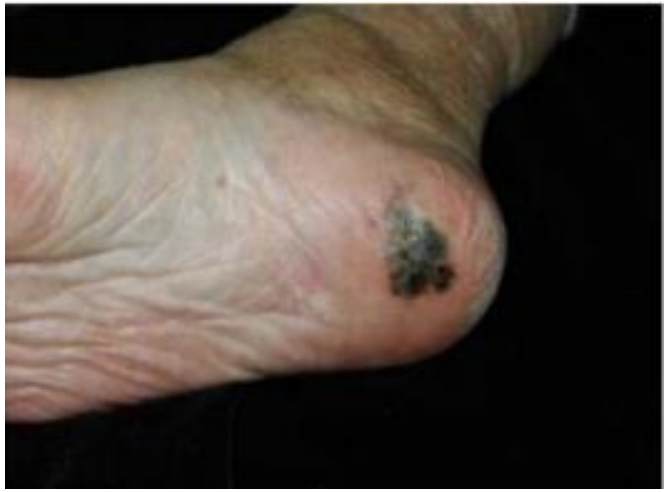


- Amino acid tyrosine is the starting point of melanin biosynthesis in human melanocytes
- Melanomas accumulate ^{18}F-FBPA more than non-melanomas in preclinical models[1]

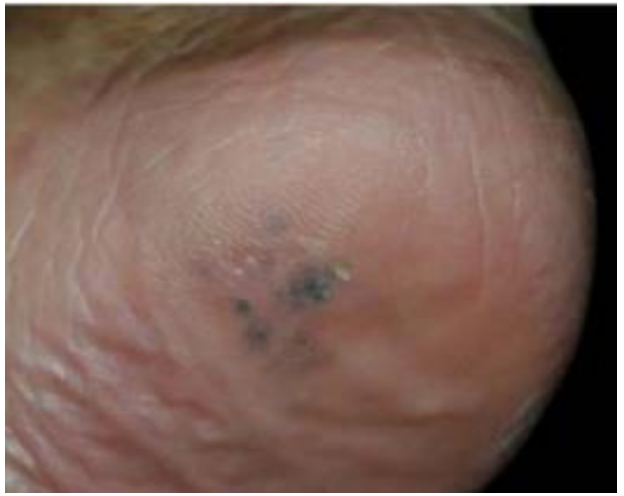
In the first larger series[2], 21/22 melanoma lesions responded; 16 completely

[1]Ishiwata K. Ann Nucl Med 2019;33:223-36; [2]Fukuda H et al. Australas Phys Eng Sci Med. 2003 Sep;26(3):97-103.

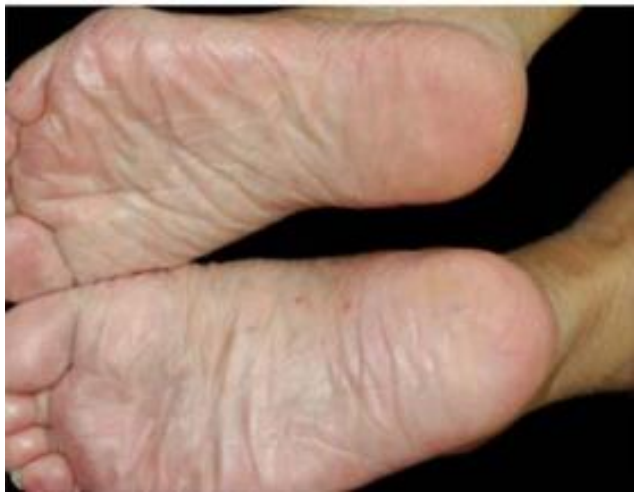
The Osaka series of skin melanomas treated with BNCT



Prior to BNCT



3 months afer BNCT



9 months after BNCT

- 8 patients with localized superficial melanoma of the sole or the face
- All patients responded to single BPA-based BNCT
- 6 had complete response; 2 partial response
- During a minimum follow-up time of 5.5 years only 1 lesion progressed
- No severe adverse events were recorded

Hiratsuka J et al. J Radiat Res 2020:61:945–51

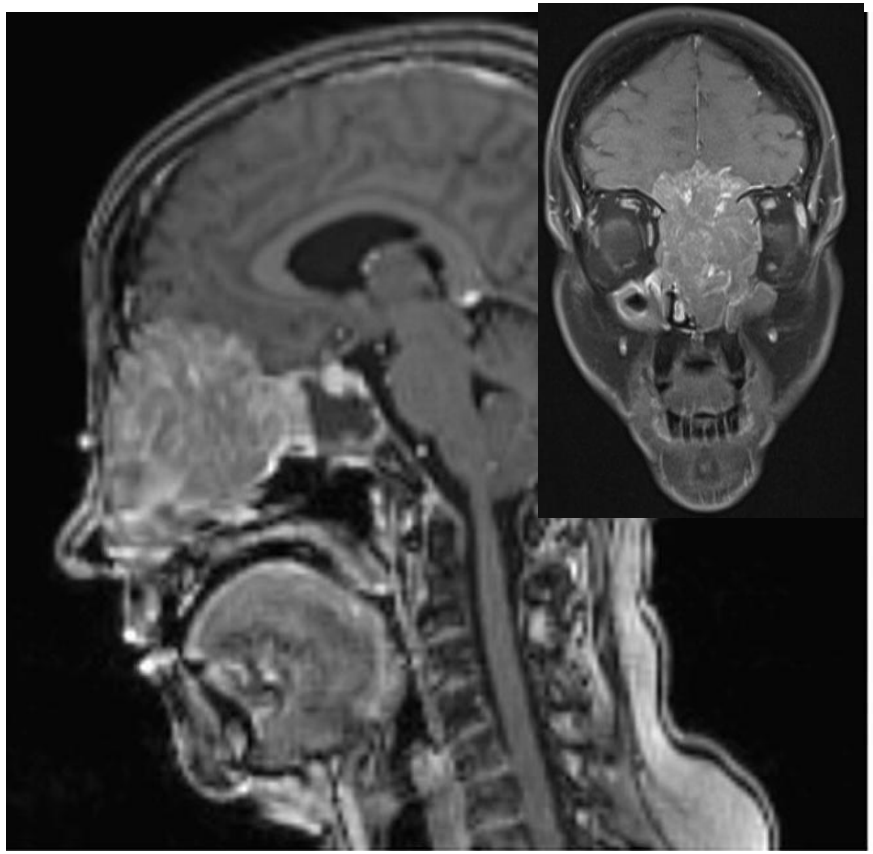
Potential indications for BPA-based BNCT

Tumor type	Comment
Head and neck cancer	Approved for locally recurrent H&N cancer after conventional RT in Japan since 2020
Glioblastoma	Combine with other therapies?
High grade meningioma	Promising early results
Primary/metastatic melanoma	Promising early results
Extramammary Paget's disease	Promising early results
Locally advanced/recurrent breast cancer	Under investigation
Some sarcomas	Under investigation
Other	Many tumor types unexplored

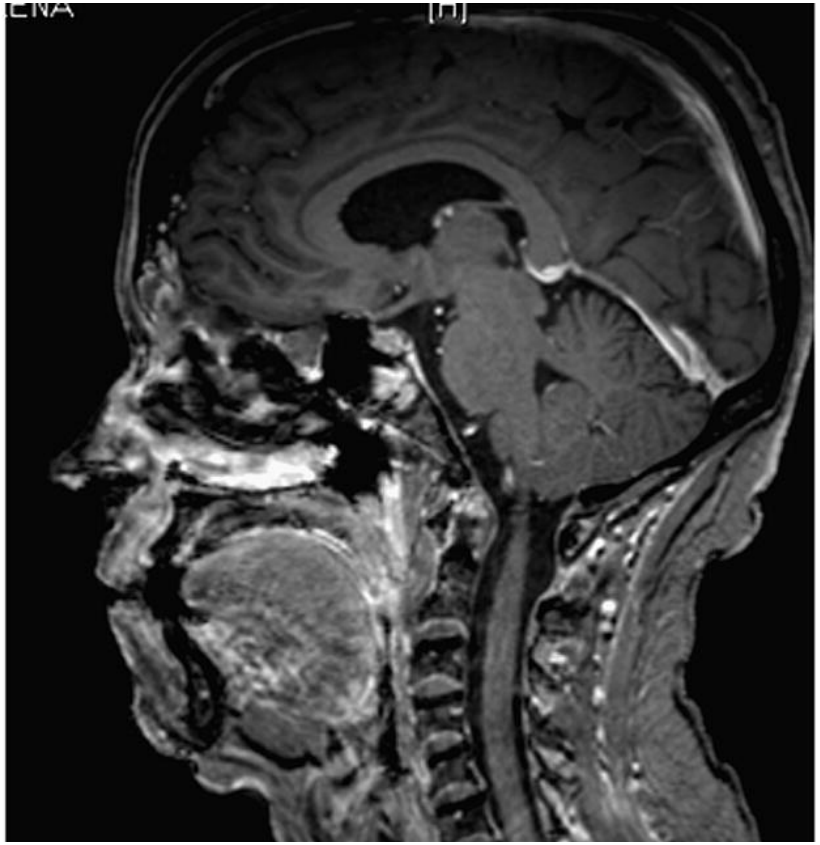
Future developments

Sequencing of BNCT with other cancer therapies

- Many tumors are heterogenous
- As usually one time treatment BNCT can be sequenced with
  - conventional radiation therapy
  - cancer chemotherapy and targeted anti-cancer agents
  - immunotherapy
- It may be best to administer BNCT early in the sequence when cancer cells are still metabolically active



Before treatment



Complete response

The patient was treated first with BNCT, and 4 weeks later with conventional radiotherapy plus weekly cetuximab and cisplatin

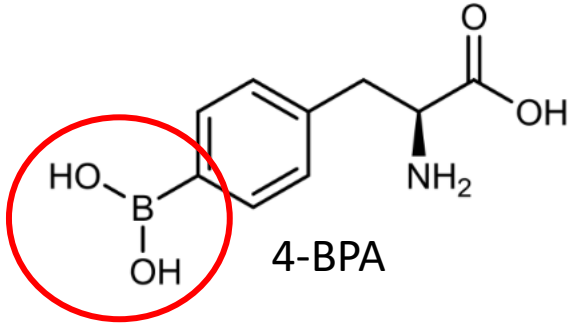
Kankaanranta et al. Radiother Oncol 2011;99:97-100

Novel boron delivery agents

BPA (4-BPA) is not an ideal boron delivery agent

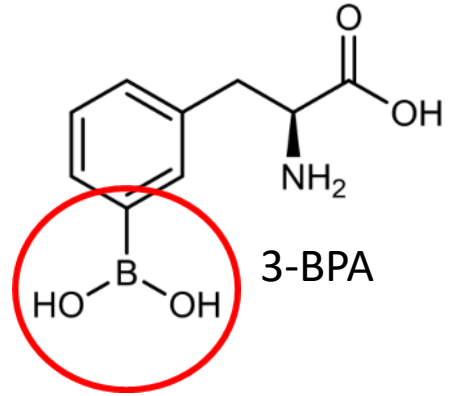
-short retention time in tumor

-complexed with fructose/sorbitol to increase water solubility



4-BPA

3-BPA has 10-100 times higher solubility[1]

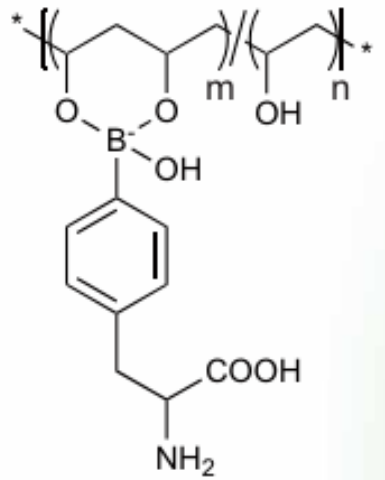


3-BPA

Polyvinyl alcohol-BPA (PVA-BPA)

-attains ~3x higher intracellular boron concentration than 4-BPA, has longer tumor retention time, and was more effective in a mouse tumor model[2]

PVA-BPA



Many novel boron delivery agents have been proposed

-fluorinated alphamethyl 3-BPA derivatives[4]; peptides, proteins, polyamines, carbohydrates, nucleosides, porphyrins, liposomes, monoclonal antibodies, and nanoparticles

[1]Kondo et al. Pharmaceuticals 2022;14:1106; [2]Nomoto et al. Sci Adv 2020;6:eaaz1722;
[3]Hirano et al. Bioorg Chem 2024;142;106940

Availability of clinical BNCT

Most BNCT centers are located in Asia

BNCT facilities are in planning or construction in Argentina, Belgium, China, France, Italy, Russia, South Korea, Spain, Taiwan, and the U.K.

Country	Center/location	Company	Accelerator type	Current status
Japan	Southern Tohoku BNCT Research Center, Fukushima	Sumitomo HI	Cyclotron	Patient treatments
Japan	Kansai BNCT Medical Center, Osaka	Sumitomo HI	Cyclotron	Patient treatments
Japan	University of Tsukuba	Own development	Linear	Clinical trial
Japan	National Cancer Center Hospital, Tokyo	CICS	Linear	Clinical trial
Japan	Edogawa hospital, Tokyo	CICS	Linear	Clinical trial
China	Xiamen Humanity Hospital	TAE	Electrostatic	Clinical trial
Finland	Helsinki University Hospital	Neutron Therapeutics	Electrostatic	Commissioning
Japan	Shonan Kamakura General Hosp., Kanagawa Prefecture	Neutron Therapeutics	Electrostatic	Commissioning
South Korea	Gachon University Gil Medical Center, Songdo	Dawson's	Linear	Commissioning
Taiwan	China Medical University Hsinchu Hosp., Zhubei City	Unknown	Cyclotron	Commissioning

Source: https://isnct.net/bnct-boron-neutron-capture-therapy/

Summary

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Availablity is currently very limited in the EU.