BNCT: a brief overview

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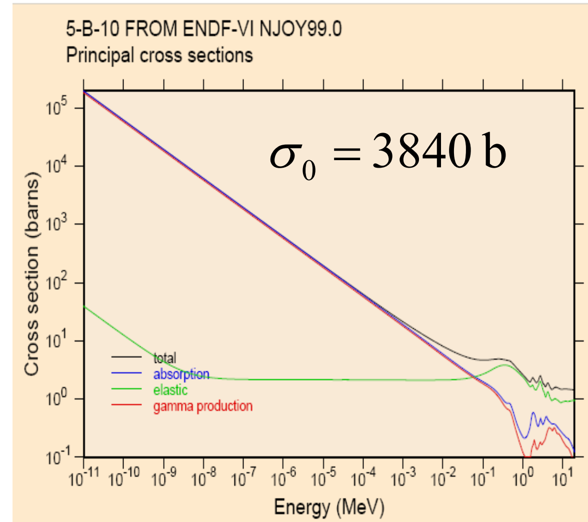
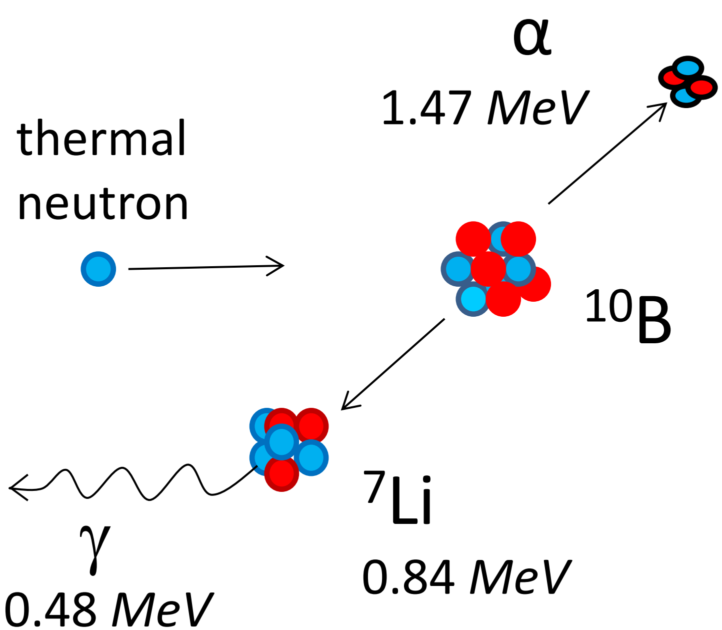
BNCT principle

$$Q_{value} = 2.79\, MeV$$

$$n + {}^{10}B \rightarrow \begin{cases} {}^{7}Li + \alpha + 2.79\,\text{MeV} & 6.1\% \\ \left({}^{7}Li\right)^{*} + \alpha + 2.31\,\text{MeV} & 93.9\% \end{cases}$$

$$\downarrow \rightarrow {}^{7}Li + \gamma\,(0.478\text{MeV})$$



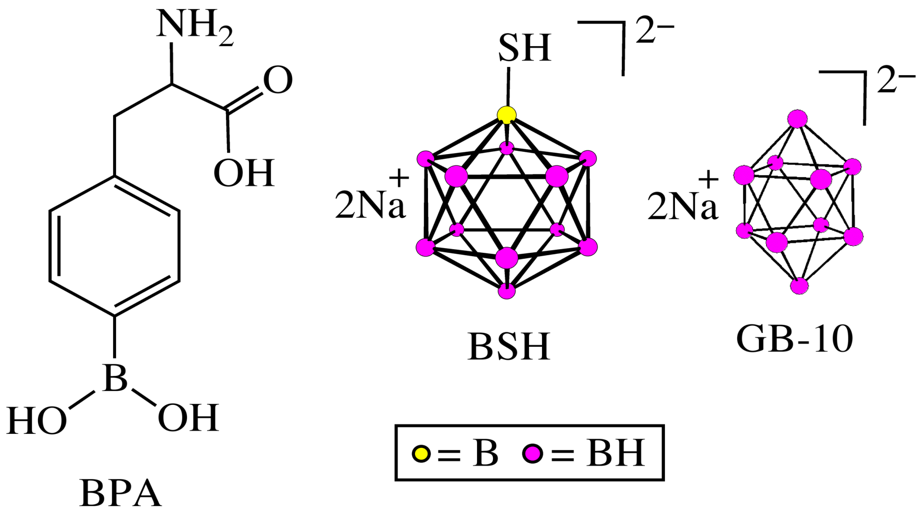


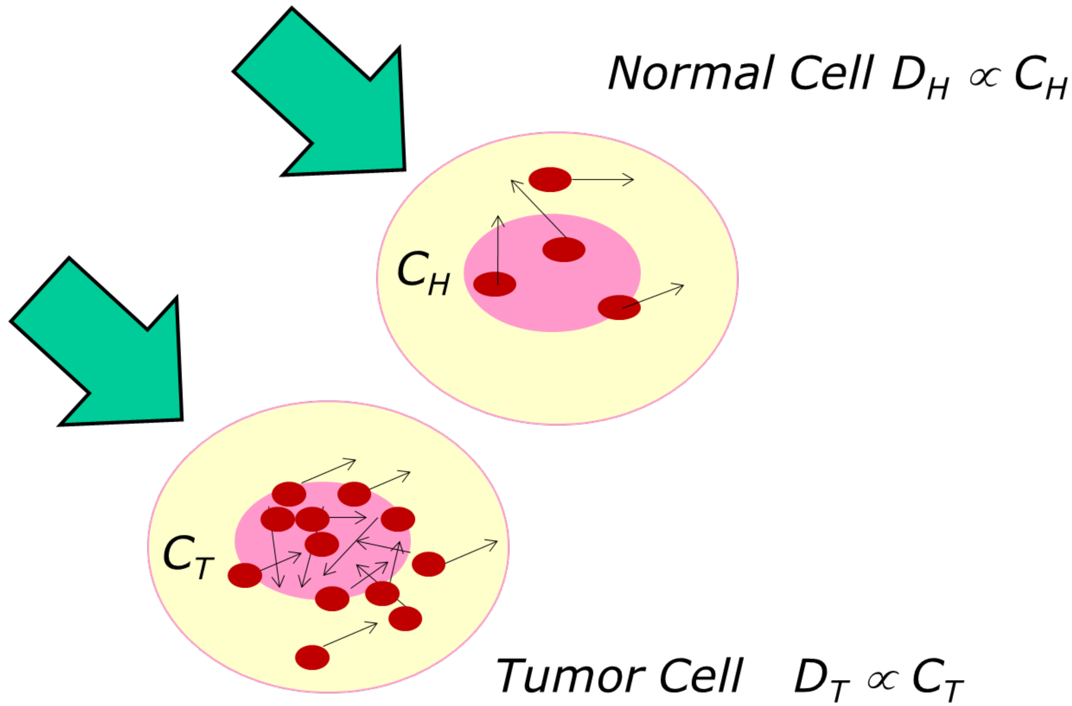
Range in tissues

$$R_{\alpha} \cong 8\,\mu m$$
$$R_{Li} \cong 5\,\mu m$$

shorter than
a cell diameter

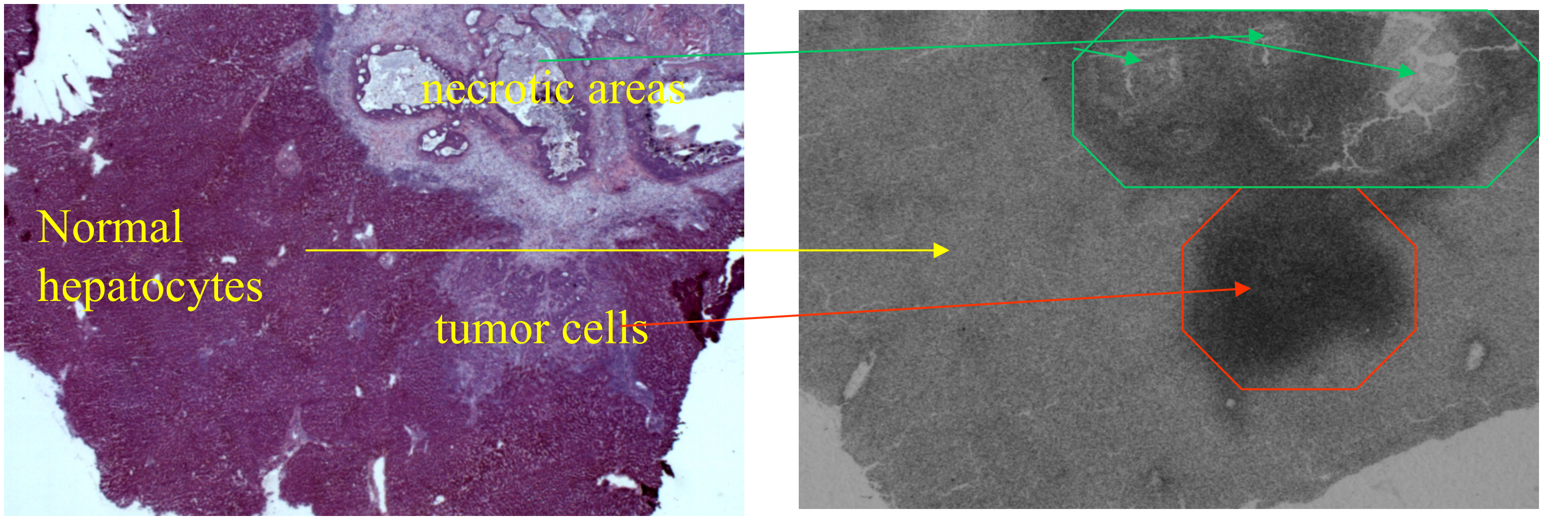
BNCT selectivity at cellular level





BNCT selectivity at cellular level

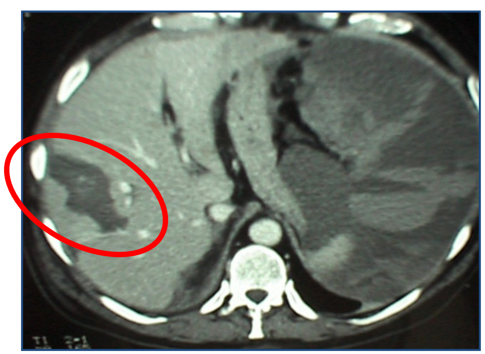
Some neutron autoradiography images of human liver with metastases



histological image

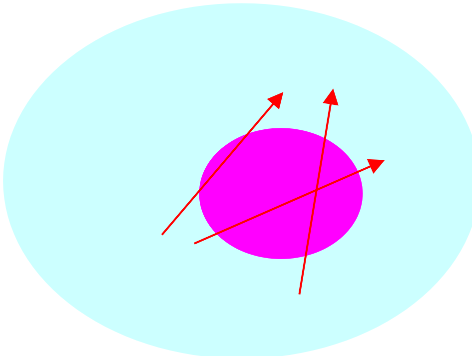
neutron autoradiography image

a big metastases distroyed after BNCT



S. Altieri et. al Applied Radiation and Isotopes 66 (2008) 1850– 1855

Boron concentration



from 2 to 6 tracks in the nucleus → a letal lesion in the cell

Tumour cells with boron

10^9 athoms of ^{10}B in a cell

$\Updownarrow$

$30\,\mu g\ ^{10}B / g$ of tissue

Boron concentration

$[\Psi_n]_{th} = 10^{12}\,cm^{-2}$

neutron fluence

2 - 3 (n, α) reactions in the cell with ^{10}B

number of reactions

BNCT absorbed dose ratio

$$[\Psi_n]_{th} = 10^{12} cm^{-2}$$

Tumour cells with boron

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

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

$$\frac{D_{Tumour}}{D_{Healthy}} \cong 4$$

Healthy cells without boron

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

$${}^{1}H(n,n')p$$

healthy cells with boron

$$\frac{C_T}{C_H} = 6 \Rightarrow \frac{D_T}{D_H} \cong 3.4$$

BNCT dose components

TABLE 7. THE FOUR PRINCIPAL DOSE COMPONENTS IN BNCT

Symbol	Common name(s)	Originating reactions
D_B	Boron dose	The $^{10}B(n,\alpha)^{7}Li$ reaction (Fig. 15);
D_N	Nitrogen dose Thermal neutron dose	Mainly the $^{14}N(n,p)^{14}C$ reaction yielding a recoiling ^{14}C nucleus and 583 keV protons
D_H (D_n, D_f)	Hydrogen dose Fast neutron dose Proton recoil dose	The (n,n′) moderation reaction occurs mainly with ^{1}H in the body. Energy is released by the recoiling protons produced by interaction with fast and epithermal neutrons.
D_γ	Photon dose	Prompt γ from radiative capture within the patient mainly from the $^{1}H(n,\gamma)^{2}H$ reaction and γ contamination of the incident radiation field.

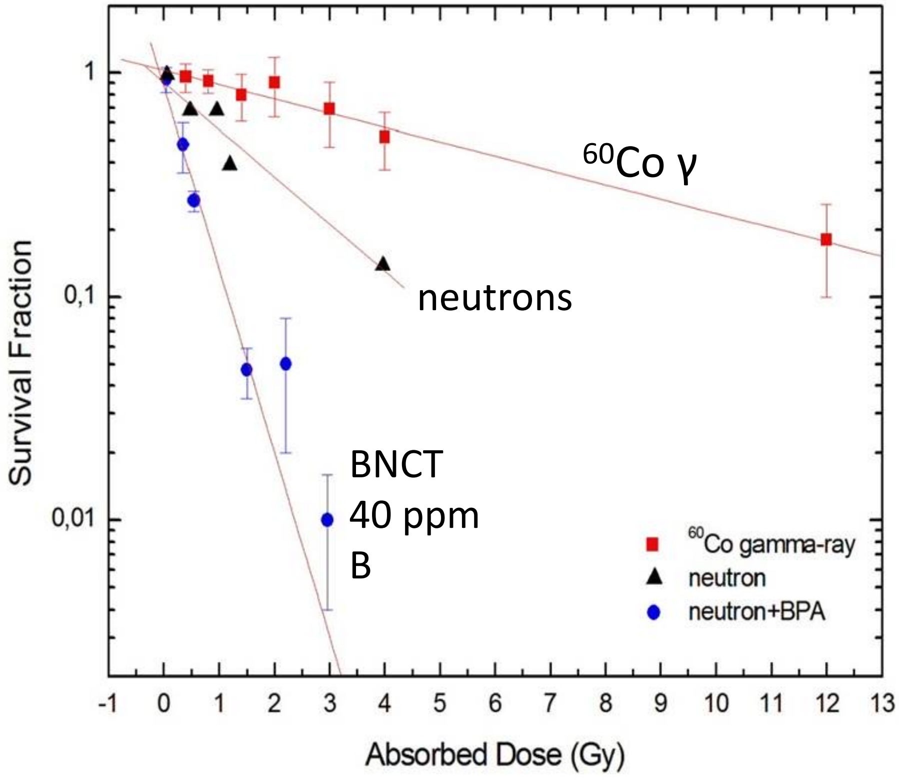
Note: In the literature, D_H has several notations, including D_n and D_f, where n = neutron and f = fast.

$$D_{tot} = D_B + D_N + D_H + D_\gamma$$

https://www-pub.iaea.org/MTCD/Publications/PDF/CRCP-BOR-002_web.pdf

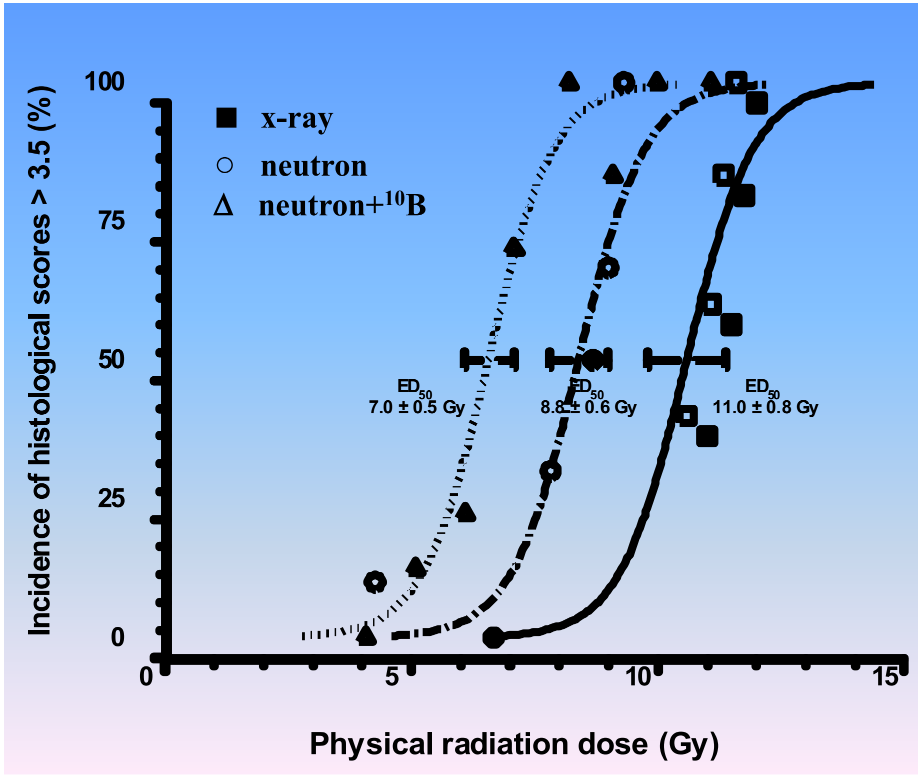
Photons Isoeffective dose

Survival curves of rat DHD cells



C.Ferrari et al. Rad Res 175 (2011)

Functional and histological changes in rat lung after irradiation



Kiger JL, et al. Radiat Res. 2008 Jul;170(1):60-9. doi: 10.1667/RR1266.1. PMID: 18582158.

Photons Isoeffective dose

Dose from

p, γ ← → α, Li

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

Radiation Biological Efficacy
RBE

Compound Biological Efficacy
CBE

Photons IsoEffective Dose Gy (IsoE)

$$D_{Gy\ (IsoE)} = w_1 D_B + w_2 D_N + w_3 D_H + w_4 D_\gamma$$

Tumour Control Probability

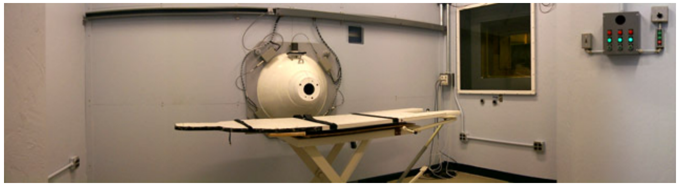
$$\mathrm{TCP}_{\mathrm{R}}(D_{\mathrm{IsoE}}) = \mathrm{TCP}_{\mathrm{BNCT}}(D_1, D_2, D_3, D_4)$$

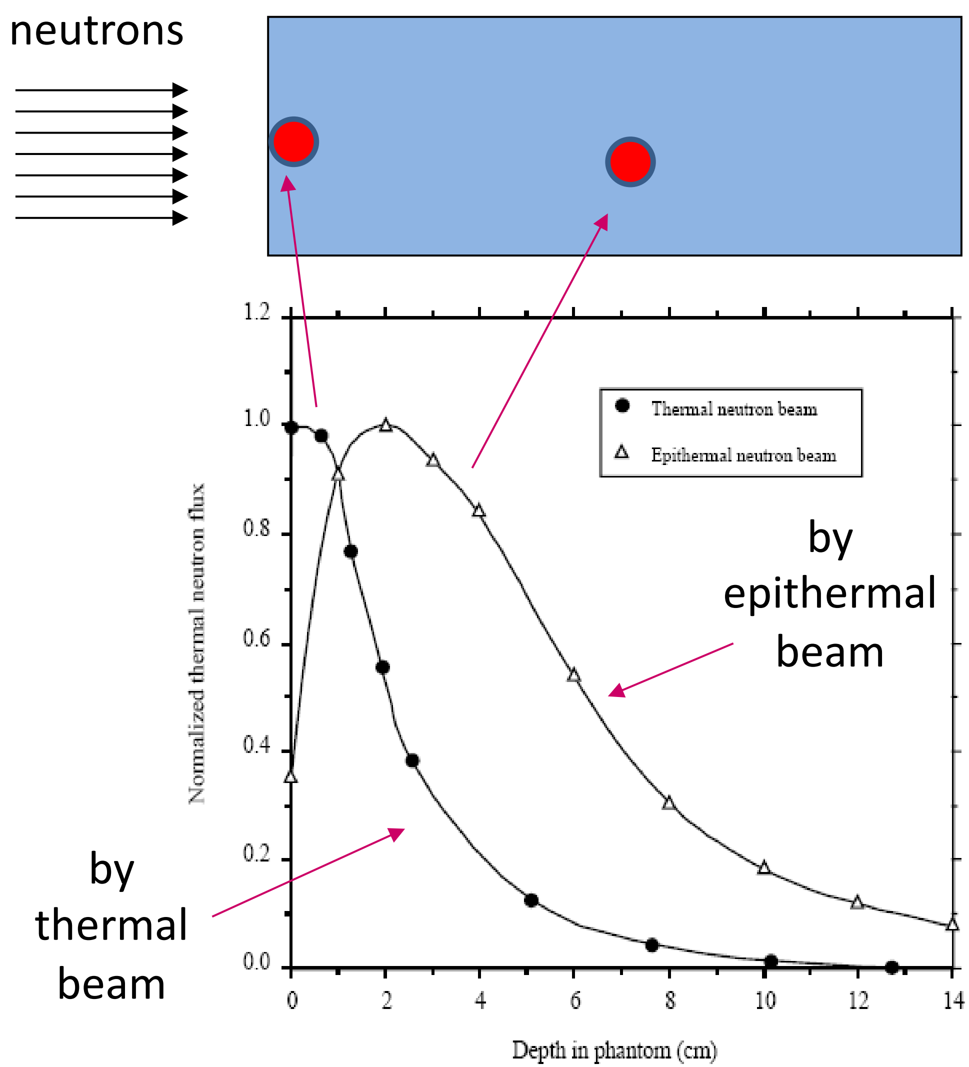
Normal Tissue ComplicationProbability

$$\mathrm{NTCP}_{\mathrm{R}}(D_{\mathrm{IsoE}}) = \mathrm{NTCP}_{\mathrm{BNCT}}(D_1, D_2, D_3, D_4)$$

González SJ, Santa Cruz GA. Radiat Res. 2012 Dec;178(6):609-21. doi: 10.1667/RR2944.1

Neutron beam: thermal or epithermal



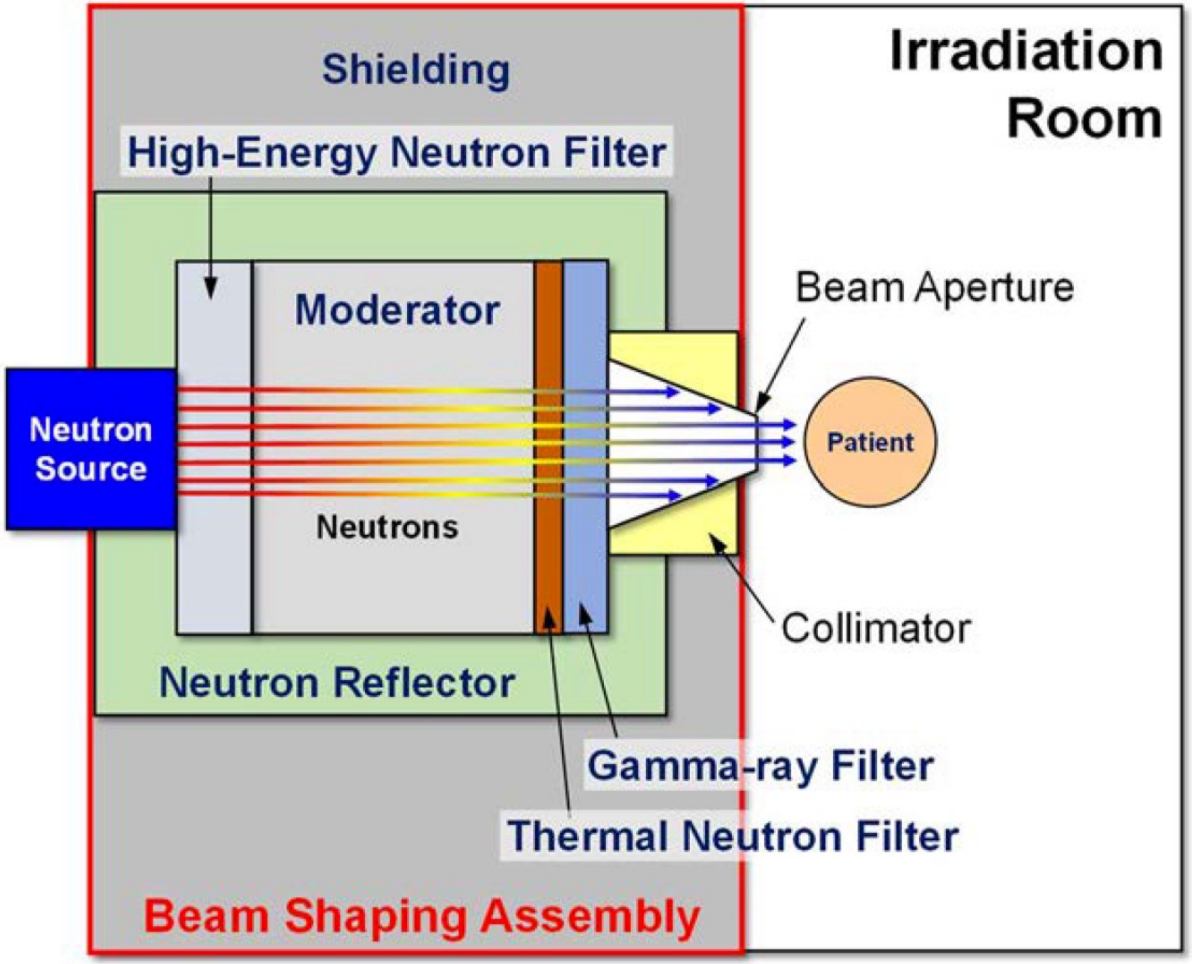


Thermal neutron distribution into the phantom

NEUTRON BEAM

THERMAL	EPITHERMAL
Shallow tumours	Deep seated tumours

Beam Shaping Assembly (BSA)



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BSA and neutron spectrum

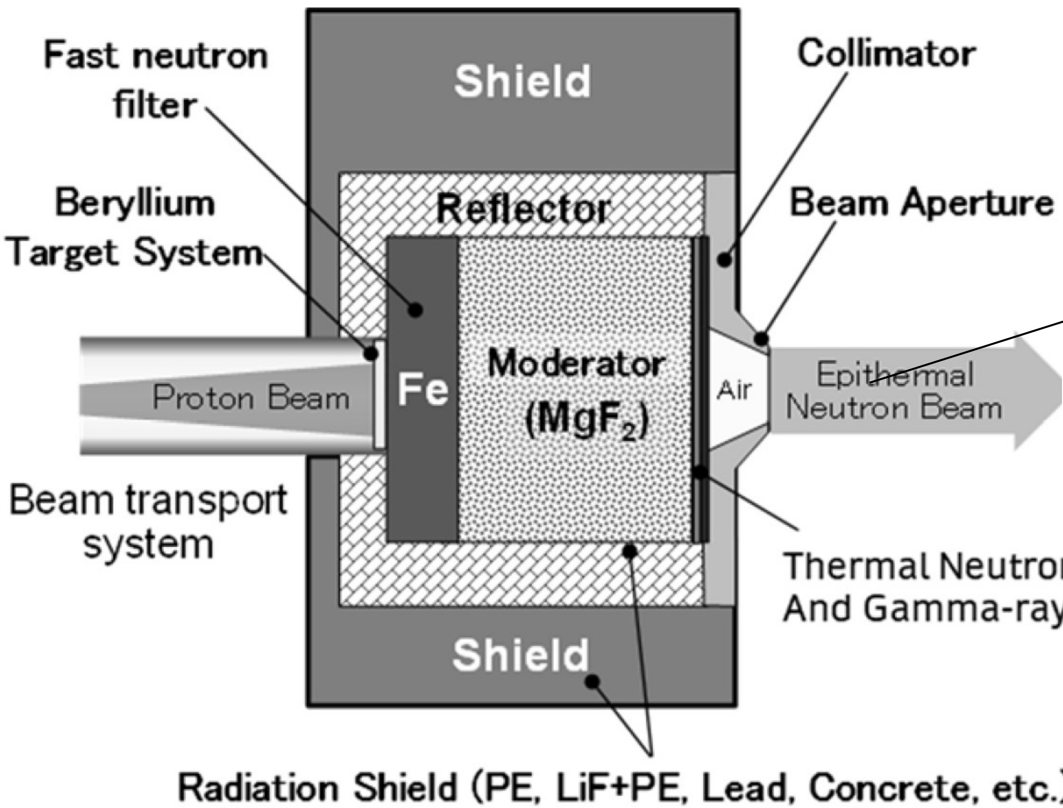


FIG.VIII-3. Schematic of the iBNCT001 BSA with the Be target system.

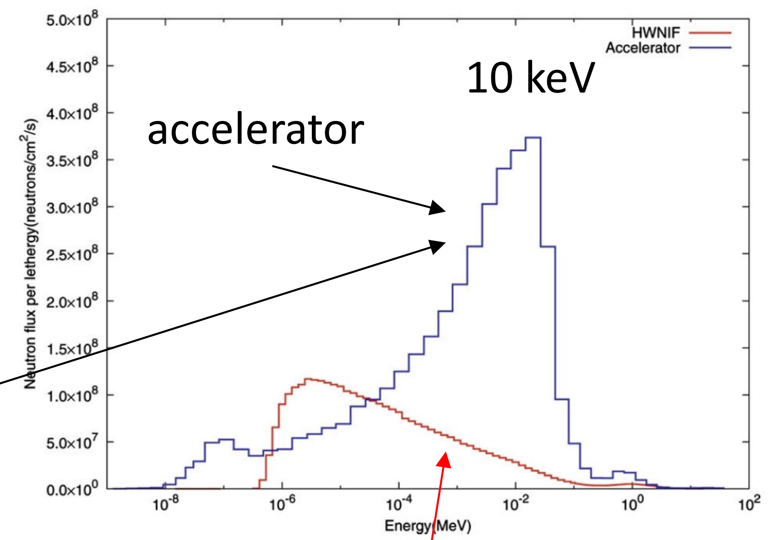


Fig. 2. Comparison of neutron spectrum between HWNIF and accelerator-based neutron source shaped with the BSA.

reactor

https://www-pub.iaea.org/MTCD/Publications/PDF/CRCP-BOR-002_web.pdf

Neutron beam characteristics

TABLE 6. REFERENCE NEUTRON BEAM QUALITY FACTORS

Beam quality component	Symbol or definition	Reference value
Therapeutic epithermal flux[a]	ϕ_{epi}	$\geq 5 \times 10^8$ cm$^{-2}\cdot$s^{-1} (e)
Thermal to epithermal flux ratio	ϕ_{th} / ϕ_{epi}	≤ 0.05
Beam directionality[b]	J / ϕ_{epi}	≥ 0.7
Fast neutron dose per unit epithermal fluence[c]	$D_H / \int\phi_{epi}(t)\cdot dt$	$\leq 7 \times 10^{-13}$ Gy$\cdot$cm^2
Gamma dose per unit epithermal fluence[c,d]	$D_\gamma / \int\phi_{epi}(t)\cdot dt$	$\leq 2 \times 10^{-13}$ Gy$\cdot$cm^2

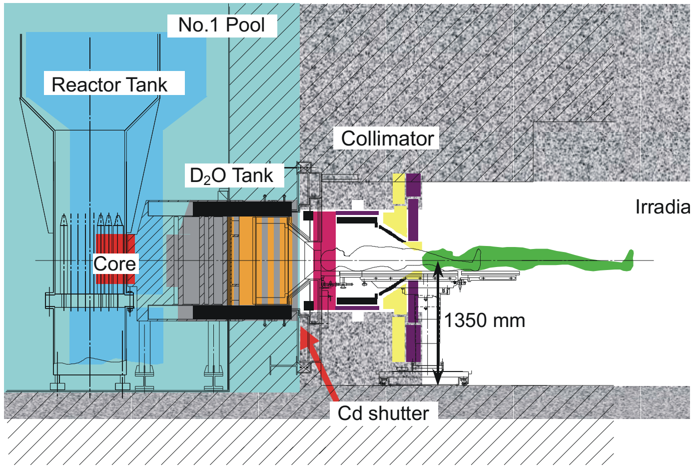
[a] ϕ_{epi} refers to the flux of epithermal neutrons in the energy range typically defined for BNCT (Table 1).
[b] Much lower values (e.g., 0.3) can be used for treatment of melanomas with more thermalized beams.
[c] These are doses per unit fluence of epithermal neutrons, where epithermal fluence is defined as $\int\phi_{epi}(t)\cdot dt$, in units of cm^{-2}.
[d] The range reported in reactor based BNCT facilities is 1–13 × 10^{-13} Gy$\cdot$cm^2.
[e] Ref. [78] reports $\int\phi_{epi}(t)\cdot dt = 5.3 \times 10^{11}$ cm^{-2} used clinically in t = 17 min, corresponding to $\phi_{epi} = 5.2 \times 10^8$ cm$^{-2}\cdot$s^{-1}.

https://www-pub.iaea.org/MTCD/Publications/PDF/CRCP-BOR-002_web.pdf

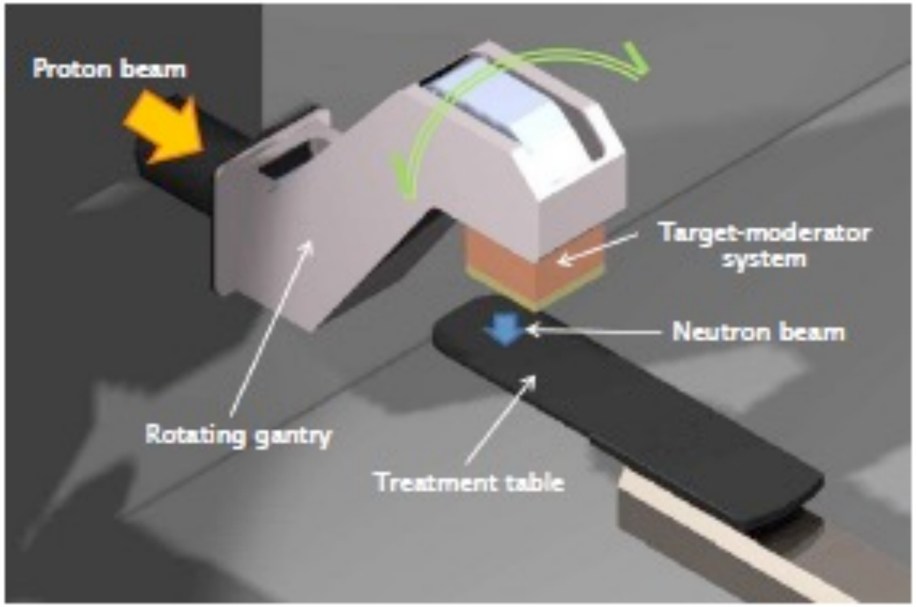
From reactors to accelerators

proton or deuteron accelerators

from nuclear reactors



to



Neutron produccing reactions

TABLE 2. LOW ENERGY NEUTRON PRODUCING REACTIONS

Reaction	E_{th} or Q (MeV)	E_p or E_d (MeV)	Total neutron yield (n/mA)	Percentage of neutrons with E_n < 1 MeV	$E_{n,max}$ (keV)	$E_{n,min}$ (keV)
ENDOENERGETIC REACTIONS						
$^7Li(p,n)^7Be$	1.880	1.89	6.3×10^9	100	67	0[c]
		2.30	5.8×10^{11}[a]	100	573	0[c]
		2.50	9.3×10^{11}[a]	100	787	0[c]
		2.80	1.4×10^{12}[b]	92	1100	0[c]
$^9Be(p,n)^9B$	2.057	2.50	3.9×10^{10}	100	574	0[d]
		4.00	1.0×10^{12}	50	2117	0[d]
		8.00	1.9×10^{13}	21[e]	6136	0[d]
$^9Be(p,xn)^9B$		30.0	1.34×10^{14}	9[f]	28147	214[f]
EXOENERGETIC REACTIONS						
$^9Be(d,n)^{10}B$	4.362	1.45[g]	1.6×10^{11}	69	5763[h]	225[i]
		1.50[j]	3.3×10^{11}	50	5815[h]	15[k]
$^{13}C(d,n)^{14}N$	5.237	1.50	1.9×10^{11}	70	6720[l]	59[m]
$^7Li(d,n)^8Be$	15.03	1.40	7.1×10^{11}	0	15765	12934[n]

Target properties

Thermal conductivity Melting point Gas permeability

Reaction	Target melting point (°C)	Target thermal conductivity (W/m-K)
^{7}Li(p,n)	181	85
^{9}Be(p,n)	1287	201
^{9}Be(d,n)	1287	201
^{13}C(d,n)	3550	230

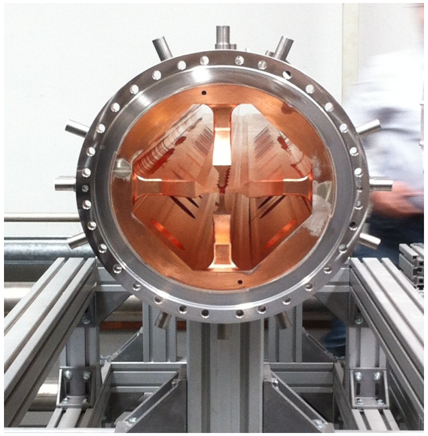
$10^9\ cm^{-2}s^{-1}$ ➡ $(\sim 10^{13}–10^{14}\ s^{-1})$ ➡ 10-20 mA

power on the target: kW/cm^2

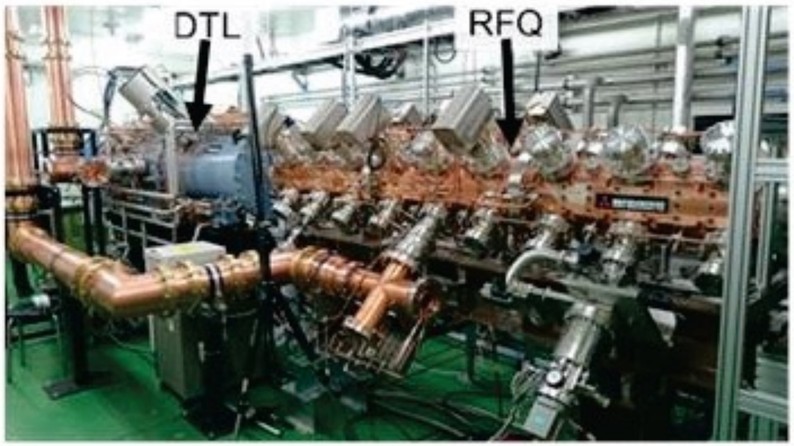
very efficient cooling required

Treatment Planning System for BNCT

INFN RFQ (Italy)



Kek (Japan)



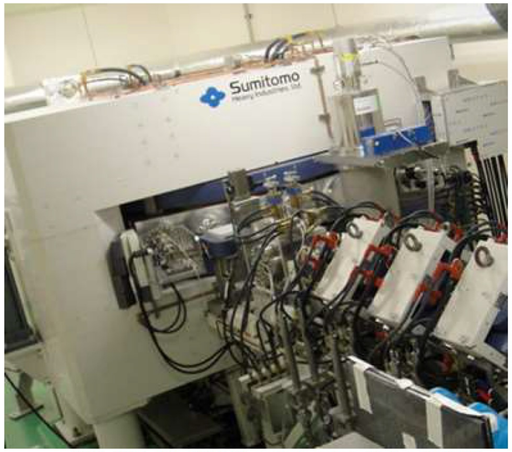
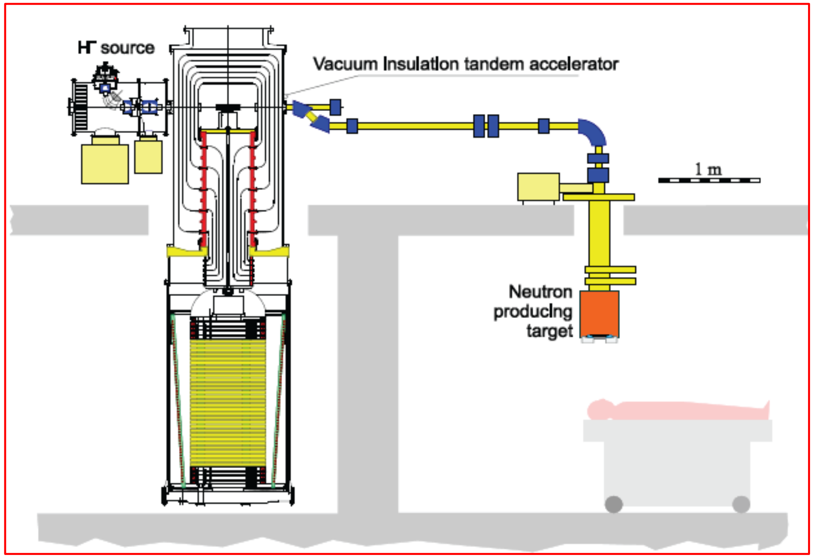


FIG. XI-1. The HM-30 cyclotron installed at KURNS.

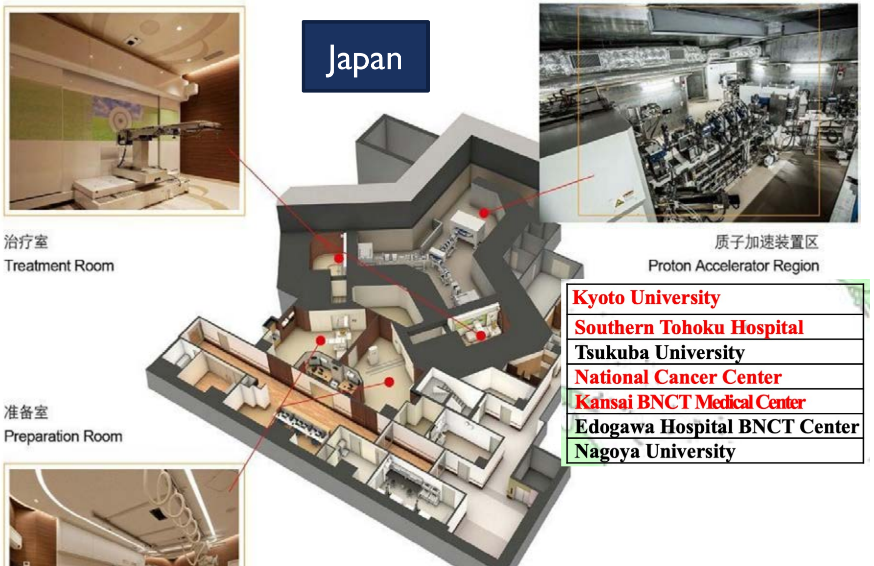
Sumitomo (Jpan)



TLS (USA)

AB-BNCT in the World

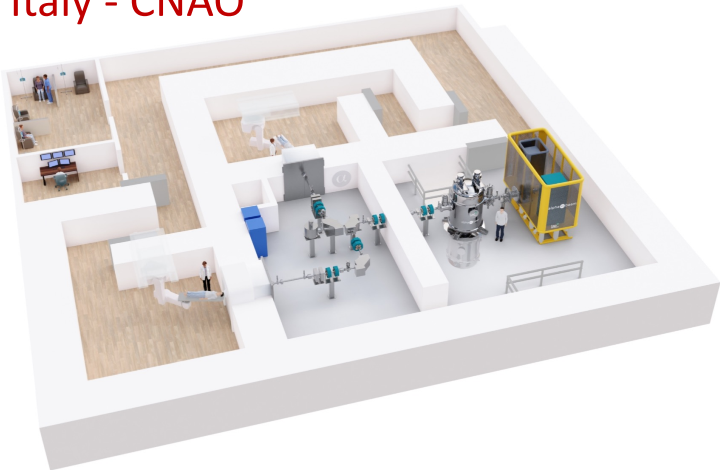
Japan



Finland

China

Italy - CNAO



Accelerators based BNCT facilities in the world

List of accelerator based BNCT facilities in the world

Facility name	Accelerator	Target	Incident particle, Produced neutron energy (MeV)	Designed current (mA)	Present status
Kyoto University	Cyclotron	Be	P: 30, N: < 28	1	Clinical trial has ended.
Southern Tohoku Hospital	Cyclotron	Be	P: 30, N: < 28	1	Treatment
Tsukuba University (iBNCT)	Linac	Be	P: 8, N: < 6	5	Physical meas.
National Cancer Center	RFQ Linac	Solid Li	P: 2.5, N: < 1	20	Clinical trial
Osaka Medical College (Kansai BNCT Medical Center)	Cyclotron	Be	P: 30, N: < 28	1	Commissioning
Edogawa Hospital BNCT Center	RFQ Linac	Solid Li	P: 2.5, N: < 1	20	Construction
Nagoya University	Electrostatic	Solid Li	P: 2.8, N: < 1	15	Commissioning
Shonan Kamakura General Hospital	Electrostatic	Solid Li	P:2.6, N: < 1	30	Construction
Budker Institute (Russia)	Electrostatic	Solid Li	P:2.0, N: < 1	10	Developing
Helsinki University Central Hospital (Finland)	Electrostatic	Solid Li	P:2.6, N: < 1	30	Commissioning Treatment (2021)
SARAF (Israel)	Linac	Liq-Li	P<4, N: < 1	20 (?)	Developing
CNEA (Argentina)	Electrostatic	Be, ^{13}C	P, d: 1.4, N: < 6	30	Constructing
Legnaro INFN (Italia)	Linac	Be	P<4, N: < 2	30	Developing
A-BNCT (Korea)	Linac	Be	P:10, N:<8	8	Commissioning
Xiamen BNCT Center (China)	Electrostatic	Solid Li	p:2.5, N:<1	10	Construction
D-BNCT01(China)	RFQ Linac	Solid Li	P:3.5, N<1.5	10	Construction

Y. Kiyanagi, Y. Sakurai, H. Kumada, H. Tanaka, AIP Conf. Proc. 2160, 050012 (2019).

CNAO (Italy)	**Electrostatic**	**Solid Li**	**P:2.5**	**10**	**Construction**

Treatment Planning Systems

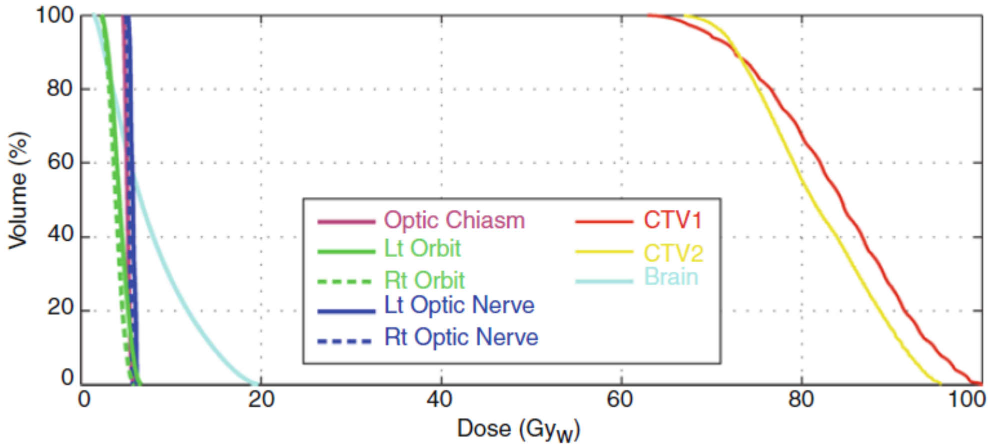


TABLE 23. TREATMENT PLANNING SYSTEMS DEVELOPED FOR BNCT

	TPS	Developers	MC code	User site
Research Reactors	NCTPlan	Harvard-MIT-CNEA	MCNP	MITR (MIT), RA-6 (CNEA)
	SERA	INEEL/MSU	seraMC	KUR (Kyoto) FiR 1 (Helsinki University Hospital) Studsvik (Sweden) Petten (Netherlands)
	JCDS	JAEA	MCNP/PHITS	JRR-4 (JAEA)
	THORplan	Tsing Hua Univ.	MCNP	THOR, Hsinchu City

Treatment Planning Systems

Accelerators	Tsukuba Plan	Univ. of Tsukuba	PHITS	iBNCT, University of Tsukuba Hospital
	Dose Cure Engine	SHI	PHITS	Southern Tohoku BNCT Research Center, Kansai BNCT Medical College
	NeuCure Dose Engine	RaySearch Laboratories in collaboration with SHI, NT, and TAE LS.	PHITS	Southern Tohoku BNCT Research Center, Kansai Medical BNCT Center
			A GEANT4 based dose engine by NT	Helsinki University Hospital, Shonan Kamakura General Hospital
			A dose engine by TAE LS	
	DM-BTPS	Dawon Medax	seraMC	DM-BNCT, Dawon Medax, Seoul
	NeuManta	Neuboron	COMPASS (dose engine) with support for PHITS and MCNP	Xiamen BNCT Center, Xiamen
	To be decided	CICS and NCC	PHITS	National Cancer Center, Tokyo

Note: SHI = Sumitomo Heavy Industries; NT = Neutron Therapeutics Inc; INEEL = Idaho National Engineering and Environmental Laboratory; JAEA = Japan Atomic Energy Agency; TAE LS = TAE Life Sciences; MSU = Montana State University; CNEA = Comisión Nacional de Energía Atómica, Argentina, CICS = Cancer Intelligence Care Systems, Inc.

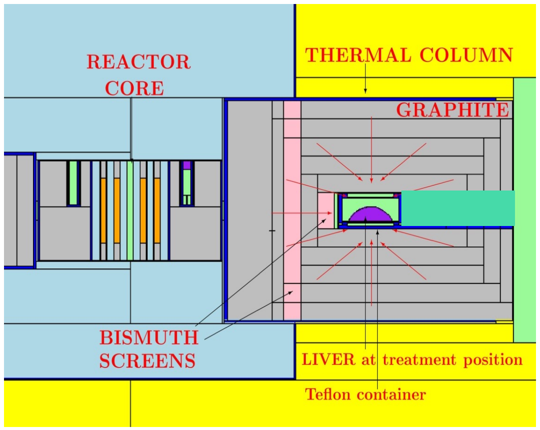
Clinical BNCT in the World

- **Japan (Tsukuba-Osaka-Kyoto)**:
  - Brain tumours (glioma, meningioma)
  - Recurrent Head and neck
  - Melanoma
  - A few cases of
    - lung tumours,
    - pleura,
    - liver …
- **Finland (Helsinki)**
  - Brain tumours
  - Head and neck
- **USA**
  - Brain tumours
- **Argentina (Bariloche)**
  - Skin Melanoma
- **Taiwan (Tsing Hua)**
  - Recurrent Head and n
- **Italy (Pavia)**
  - Liver metastases in the past
  - CNAO (under construction)

BNCT @ Triga reactor in Pavia

Disseminated liver metastases

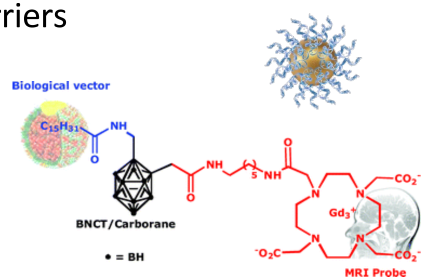
TAOrMINA project



A. Zonta, L. Roveda, S. Altieri Liver metastases in *Neutron Capture Therapy*, © Springer, 2012

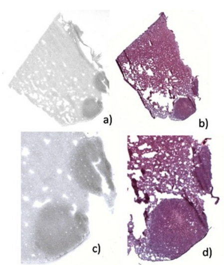
A. Zonta et al. ARI, 67, 7-8 S67-S75 JUL 2009

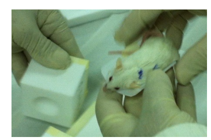
In vitro and in vivo research of new boron carriers

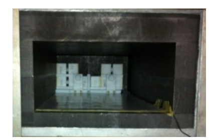


S. Geninatti-Crich et al., Chemistry -a European Journal, 17(30), 8479–8486, 2011

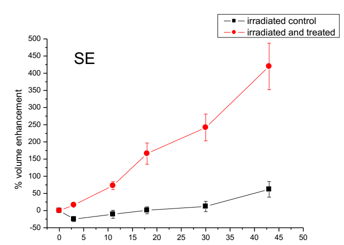
Neutron autoradiography







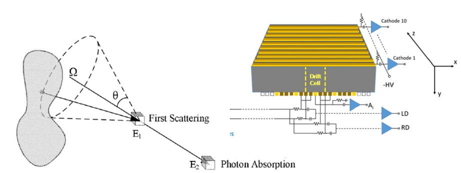
Tests of BNCT toxicity and effectiveness



S. Altieri et al. ARI 66 (2008) 1850 – 1855

S. Altieri et al., J.Med.Chem. 52 (2009)

In vivo boron dose imaging by SPECT and Compton camera based on CZT detectors



Cancers 2023, 15, 3582. doi.org/10.3390/cancers15143582

References

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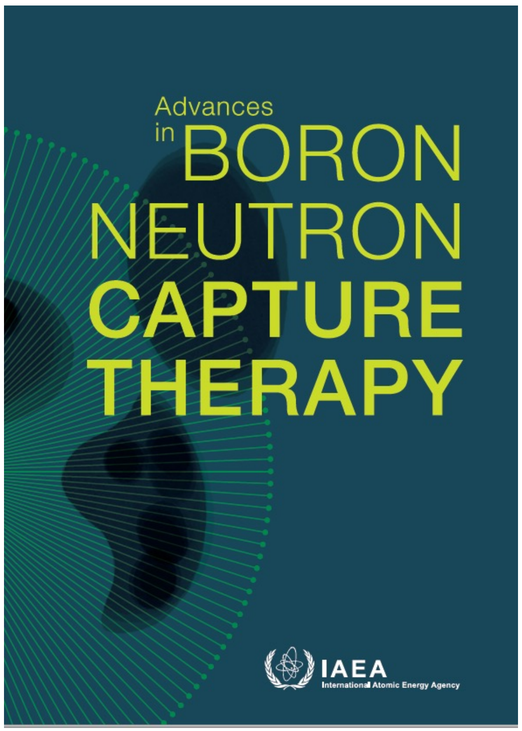

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Thank you

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