Compact accelerator based epithermal neutron source and its application for cancer therapy

OMPU Osaka Medical and Pharmaceutical University

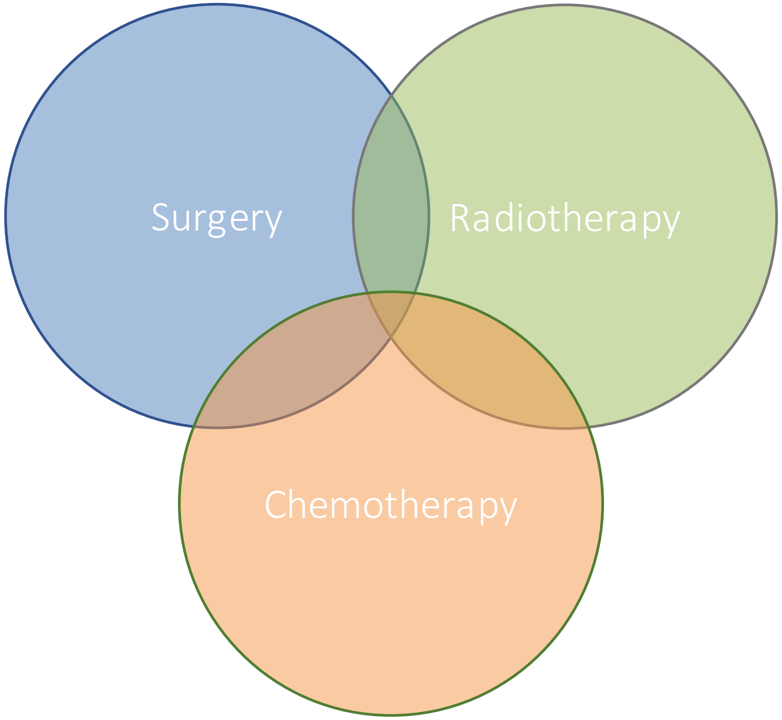
Naonori Hu[1,2]
Assistant professor | Medical Physicist

1. Kansai BNCT Medical Center, Osaka Medical and Pharmaceutical University
2. Institute for Integrated Radiation and Nuclear Science, Kyoto University

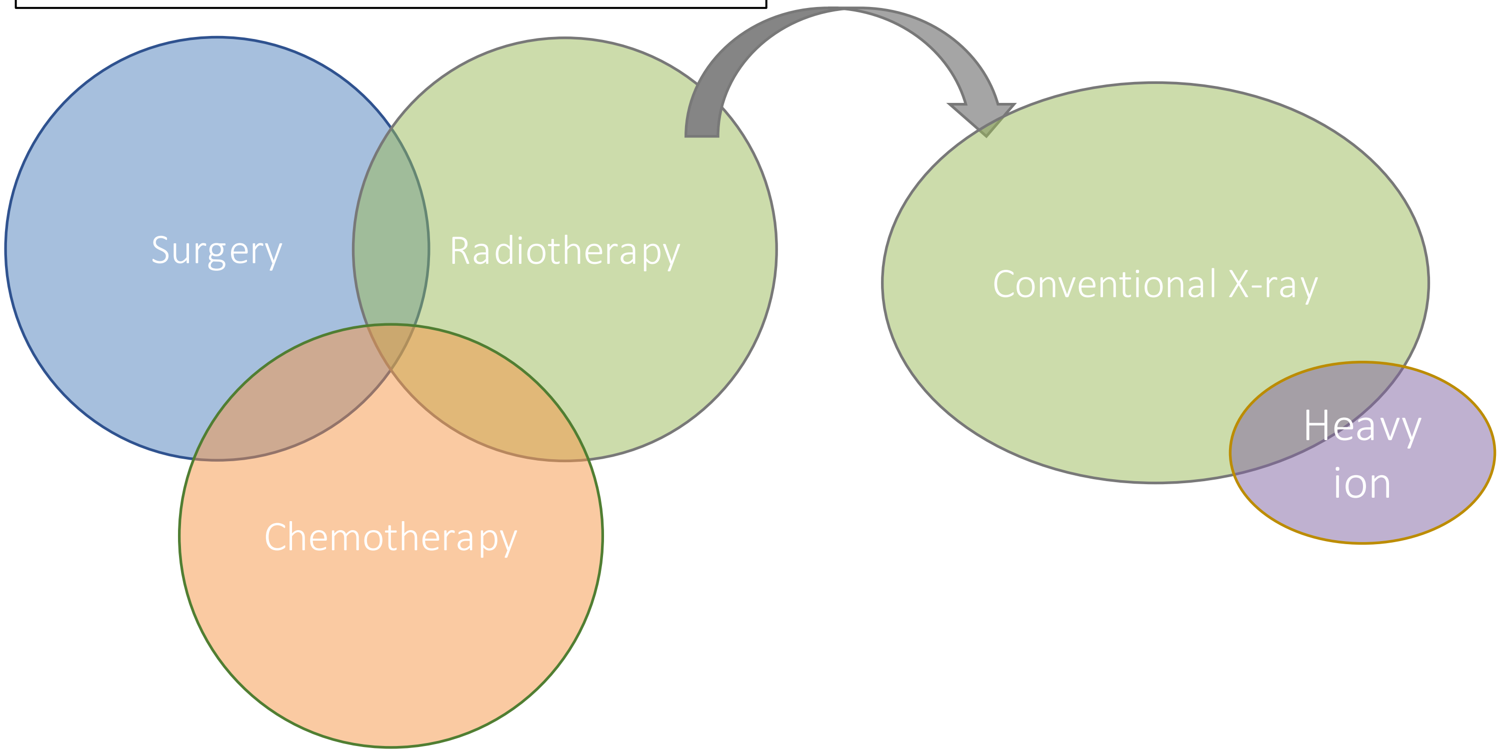
Content

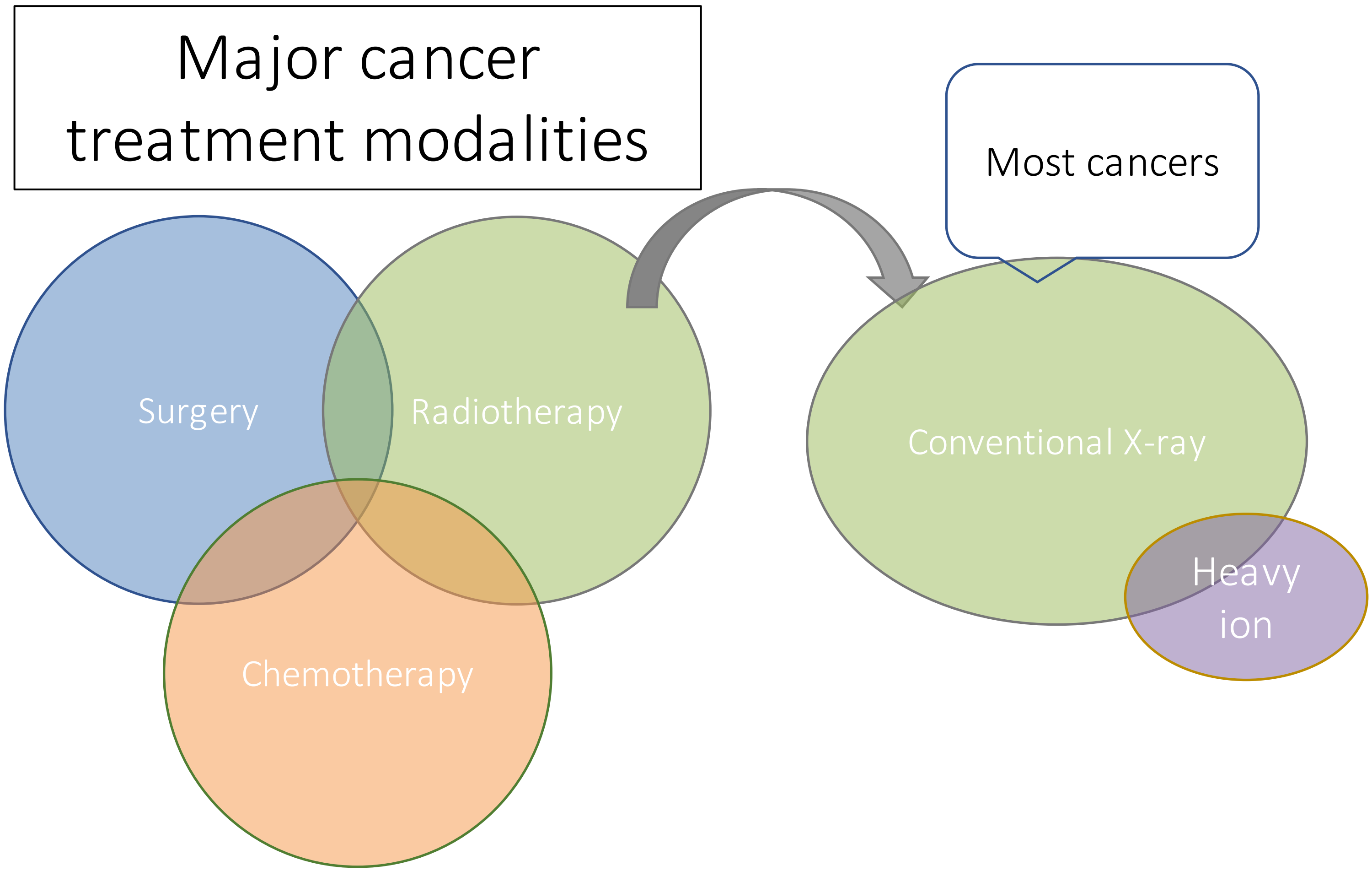
Principle of Boron Neutron Capture Therapy

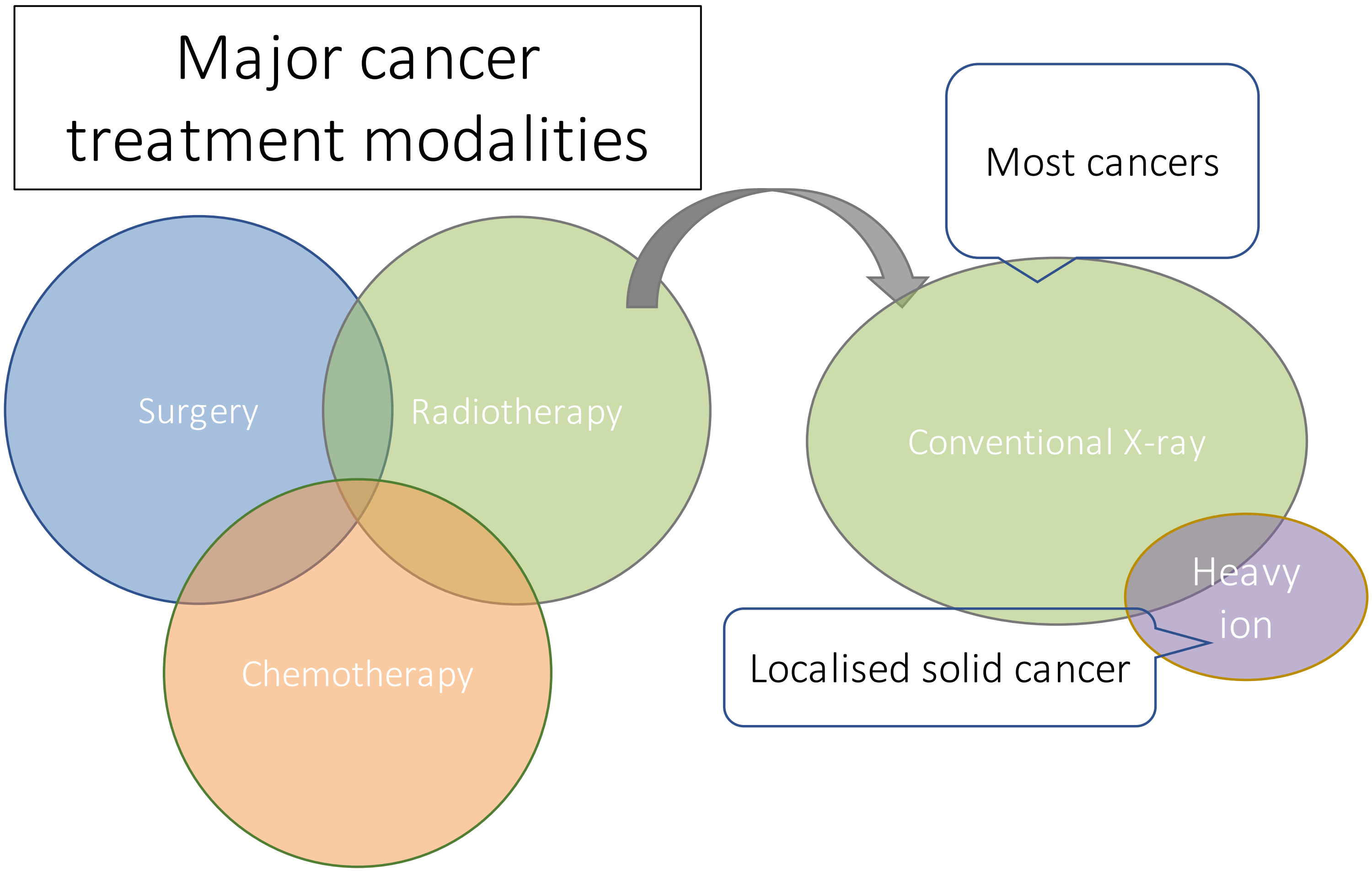
Major cancer treatment modalities



Major cancer treatment modalities




Major cancer treatment modalities
Most cancers
Surgery
Radiotherapy
Chemotherapy
Conventional X-ray
Heavy ion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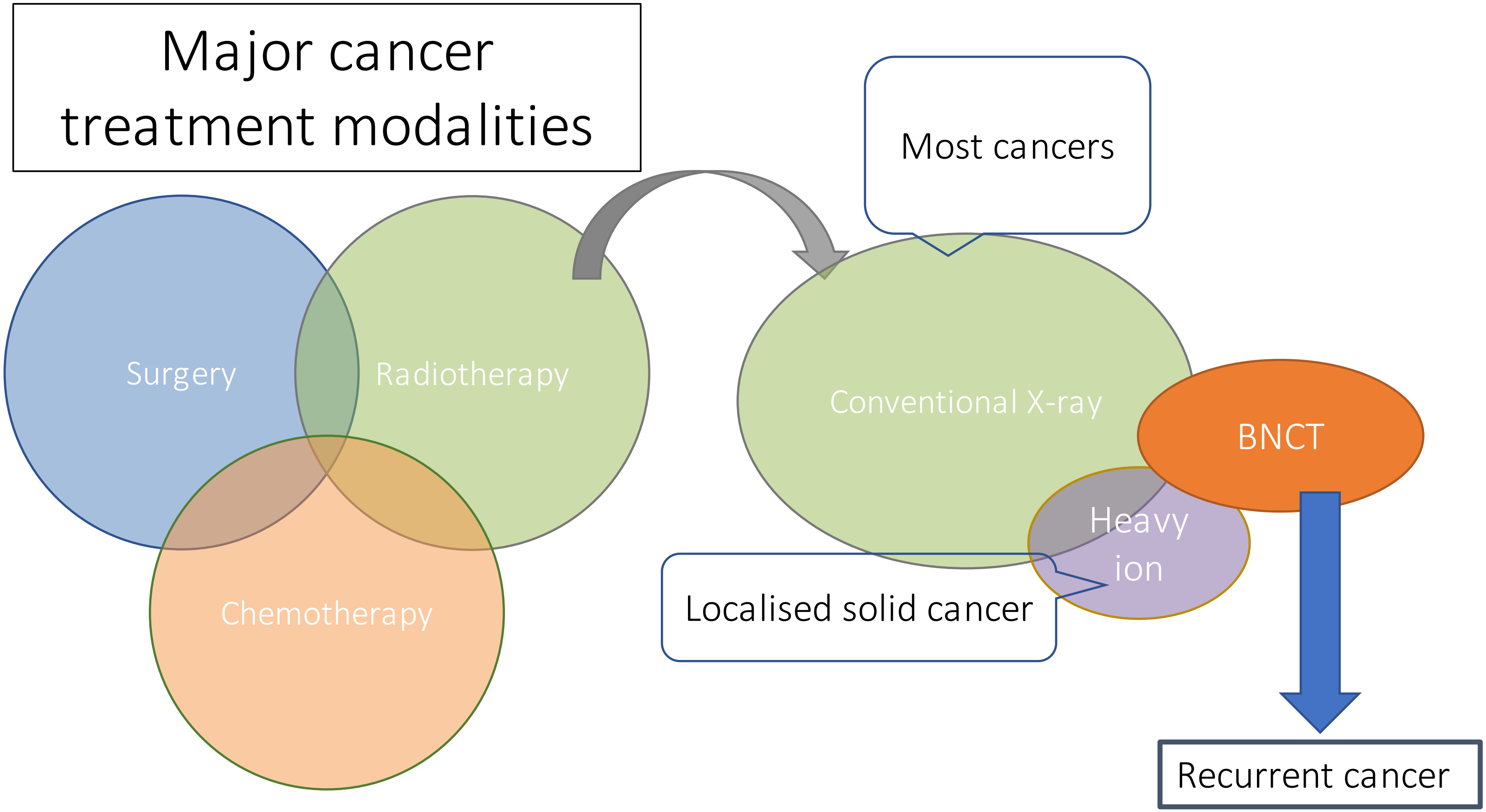
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Surgery
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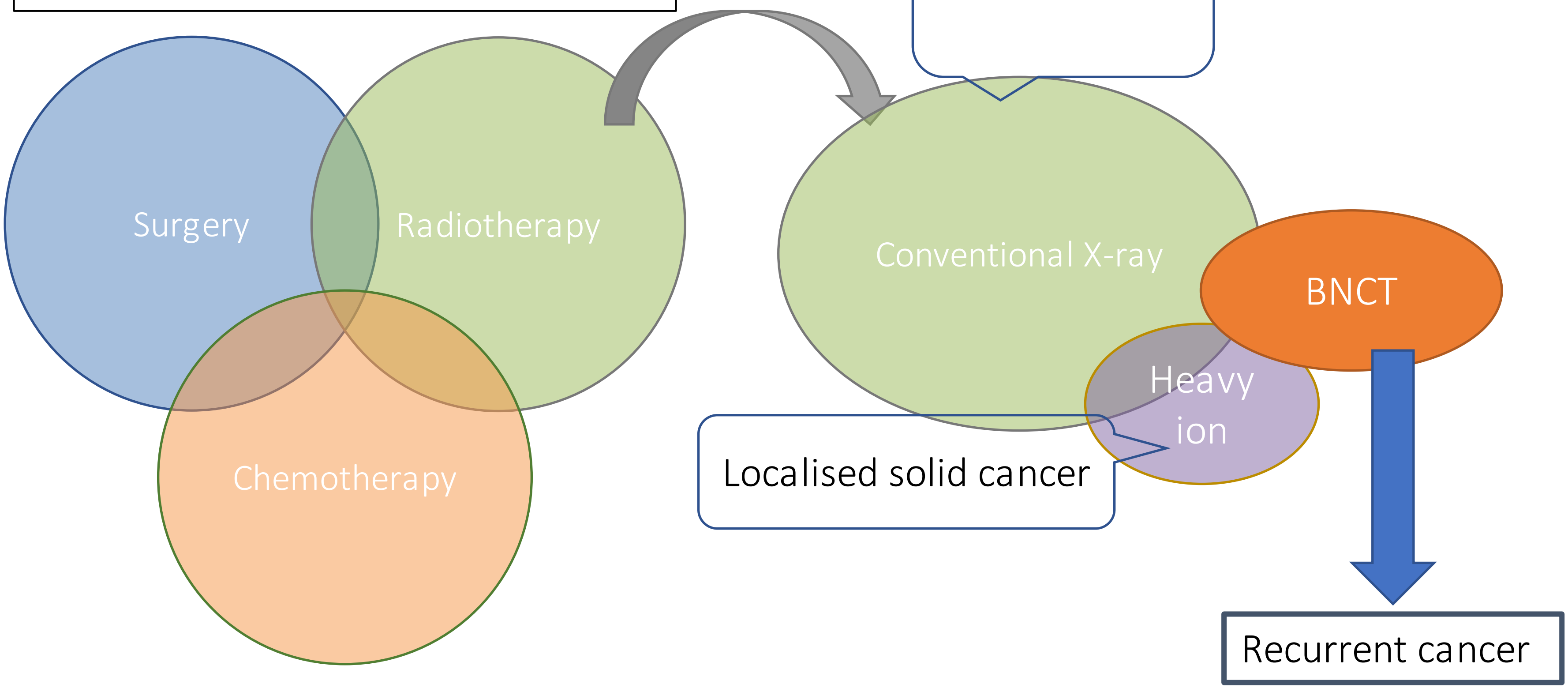
Most cancers
Conventional X-ray
BNCT
Heavy ion
Localised solid cancer
Recurrent cancer

Major cancer treatment modalities



What is BNCT?

Principle of BNCT

- Boron Neutron Capture Therapy (BNCT) is a treatment technique to selectively target high LET particles to tumours at the cellular level.
- A drug containing ^{10}B which accumulates to the tumour is injected into the patient.
- Thermal neutrons are captured by ^{10}B which generates alpha and ^{7}Li ions.
- The range of these particles is in the order of a human cell.

$$^{10}B + n \rightarrow {}^{7}Li + \alpha + 2.79\ \mathrm{MeV} \quad (6.3\%)$$

$$\rightarrow {}^{7}Li^{*} + \alpha + 2.31\ \mathrm{MeV}\ (93.7\%)$$

$$\hookrightarrow {}^{7}Li + \gamma + 0.478\ \mathrm{MeV}$$

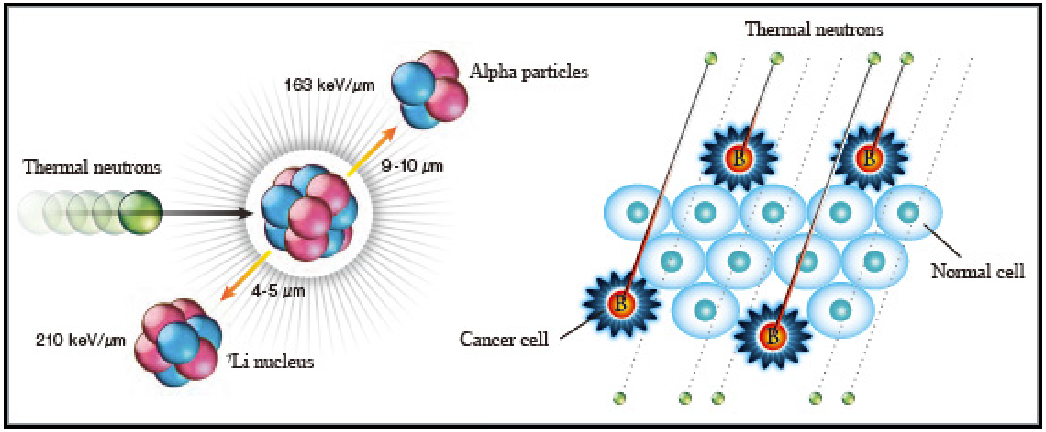


Image from JSNCT homepage http://www.jsnct.jp/about_nct/deep.html accessed on 2019/12/05

History of BNCT: From nuclear reactor to accelerator

History of BNCT

1932	• Neutron was discovered by Sir James Chadwick
1936	• Idea of BNCT by Locher
1950-60	• Clinical application conducted in the U.S. at the Brookhaven National Laboratory

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However, the outcomes were disappointing; the patient's median survival after BNCT was only 87 days.

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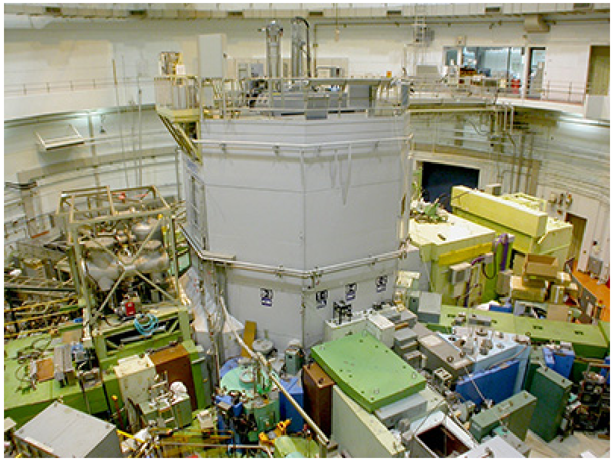
- Clinical application conducted in the U.S. at the Brookhaven National Laboratory

1. Poor selective accumulation of boron in the tumour
2. Poor neutron beam stability/quality

However, the outcomes were disappointing; the patient's median survival after BNCT was only 87 days.

History of BNCT cont.

- 1959: BNCT basic research using JRR-1 and HTR
- 1968: Clinical trial for Malignant brain tumour
- 1975: Clinical trial using Kyoto University Reactor (KUR)
- 1987: BNCT for melanoma using BPA



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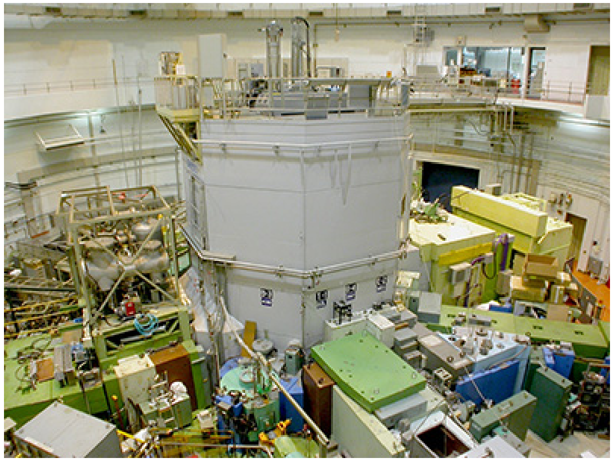
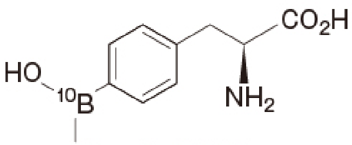
Break through





L-BPA

Major improvement of boron uptake in tumour cells

History of BNCT cont.

1996
- Remodelling of KUR to produce epithermal neutrons for the treatment of deep-seated tumours

2001
- BNCT for recurrent head and neck, liver, malignant meningioma, etc.

2011
- Great East Japan Earthquake, the nuclear reactors were halted for safety measures

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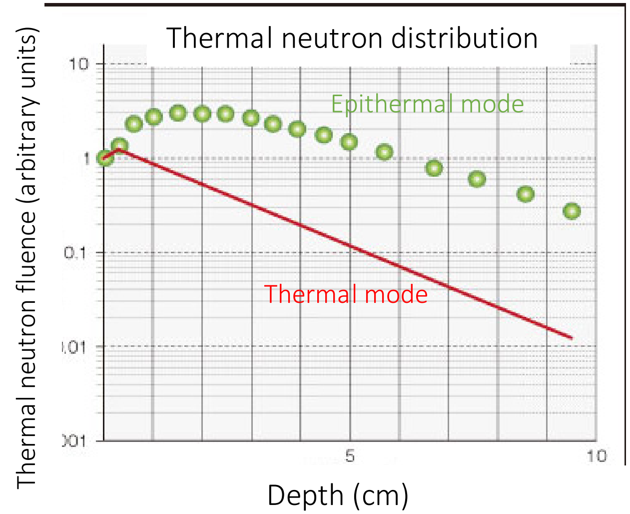

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→ Over 600 clinical cases

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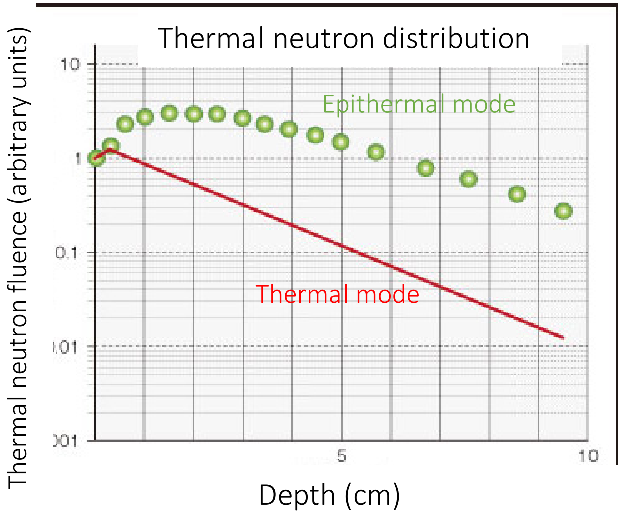

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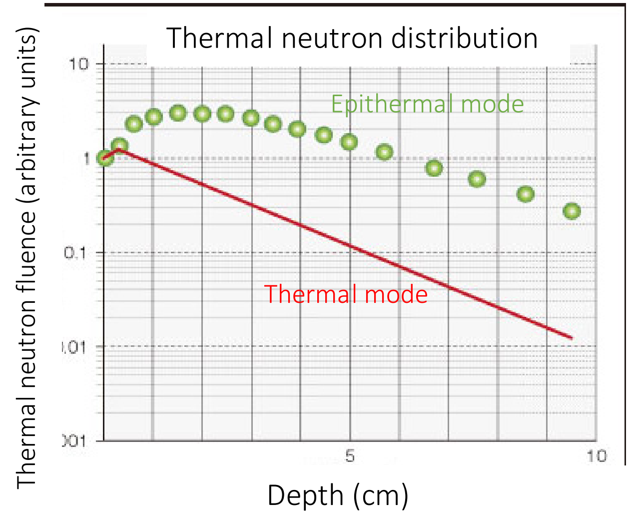

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- Great East Japan Earthquake, the nuclear reactors were halted for safety measures

→ Maintenance and security systems which are necessary for a nuclear reactor is not suited for medical use

History of BNCT cont.

- 2008
  - Development of an accelerator-based neutron source
- 2012
  - Clinical trial of brain BNCT
- 2016
  - Clinical trial of head and neck BNCT
- 2018
  - Opening of the Kansai BNCT Medical Center
- 2020
  - BNCT for unresectable, locally advanced, and recurrent head and neck cancer was approved by the Japanese national health insurance

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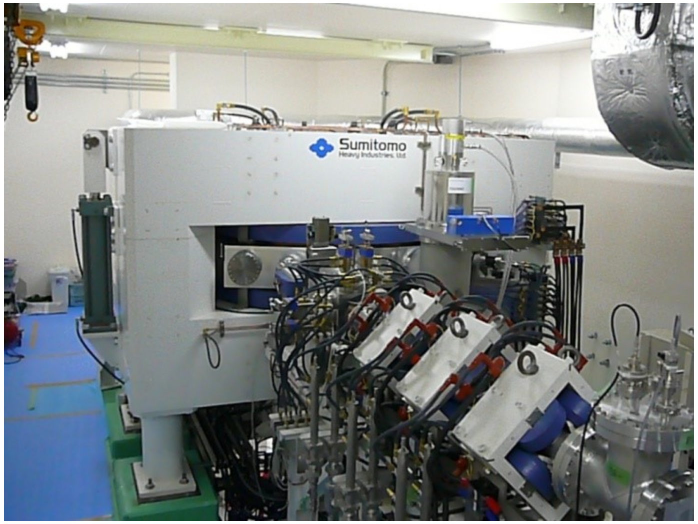

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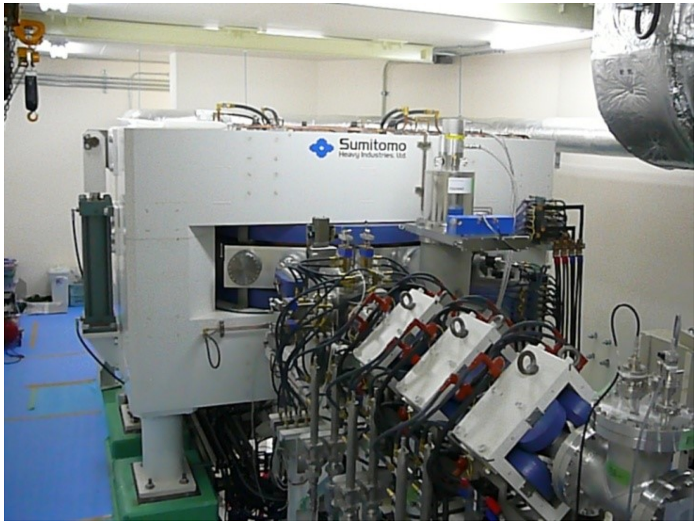


Accelerator for BNCT

Accelerator-based neutron sources worldwide

Accelerator-based Neutron Sources

IAEA International Atomic Energy Agency

Total Sources: **146**

Total Countries: **31**

CANS	Generator	Spallation
51	84	11

Argentina	4
Belgium	1
Canada	3
Chile	1
China	14
Czech Republic	2
Egypt	1
France	4
Germany	7
Greece	3
Hungary	2
India	7
Iran	5
Israel	4
Italy	13
Japan	15
Netherlands	1
Poland	5
Russia	7
Saudi Arabia	1
Slovakia	1
Slovenia	1
South Africa	3
South Korea	12
Spain	3
Sweden	1
Switzerland	3
Tunisia	1
Turkey	1
United Kingdom	4
United States of America	16

IAEA accelerator knowledge portal
Accessed 2022/3/28

BNCT facilities worldwide

BNCT Facilities

IAEA International Atomic Energy Agency
Atoms for Peace and Development

Total BNCT Facilities: **31**

Total Countries: **12**

Linac	Electrostatic	Cyclotron	Reactor
8	12	4	7

Reactor/Accelerator: All

Argentina	3
China	4
Finland	1
Israel	1
Italy	3
Japan	10
Russia	2
South Korea	2
Spain	1
Taiwan, China	1
Thailand	1
United Kingdom	2

IAEA accelerator knowledge portal
Accessed 2022/3/28

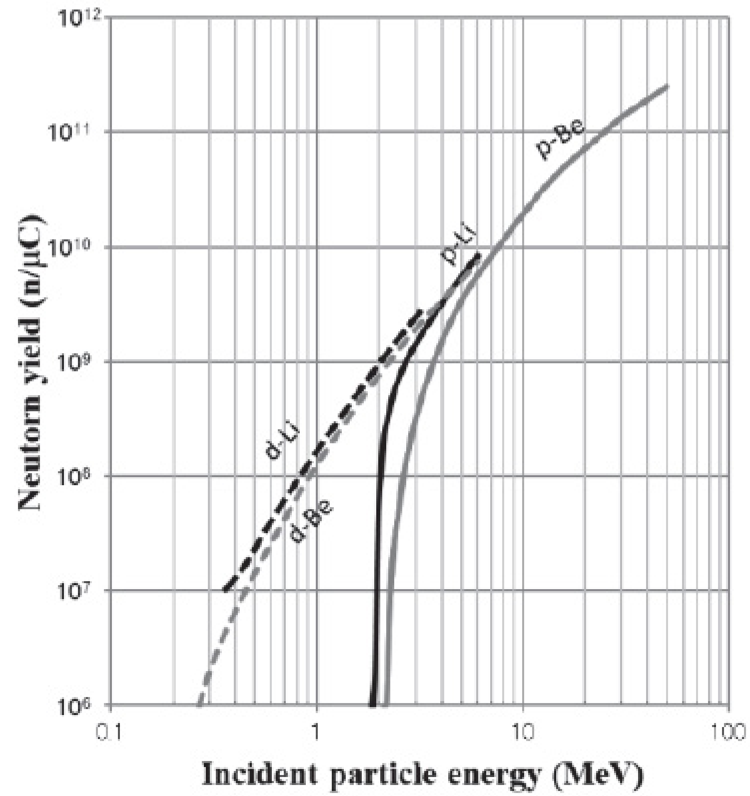
Neutron production using an accelerator

Reaction	Accelerator	Proton energy
$^{7}Li(p,n)^{7}Be$	Electrostatic	Low (~2 MeV)
$^{9}Be(p,n)^{9}B$	Linac	Medium (~10 MeV)
$^{9}Be(p,n)^{9}B$	Cyclotron	High (~30 MeV)

IAEA TecDoc 1223 recommended values

Beam characteristics	Recommended value
Epithermal neutron flux (Φ_{epi})	$\geq 1\times10^{9}$ $n\cdot cm^{-2}\cdot s^{-1}$
Fast neutron component (Fast neutron dose/Φ_{epi})	$\leq 2\times10^{-13}$ $Gy\cdot cm^{2}$
Gamma ray component (gamma ray dose/Φ_{epi}	$\leq 2\times10^{-13}$ $Gy\cdot cm^{2}$
Thermal neutron ratio	≤ 0.05
Current/Flux ratio	≥ 0.7

Soon be updated with the release of the new IAEA TecDoc



*Kiyanagi et. al, AIP conference proceeding 2019

Accelerator-based neutron source for BNCT

Red：Disadvantage
Blue：Advantage

Lithium
- Low melting point
- Tritium production
- ^{7}Be production

Beryllium
- High melting point
- High heat conductivity

Heavy material (tantalum etc.)
- High melting point
- High heat conductivity
- Activation of target

Low energy proton<3MeV
- Neutron production yield ：low
- Activation：Low
- Moderator：small
- Blistering
- High current～20mA

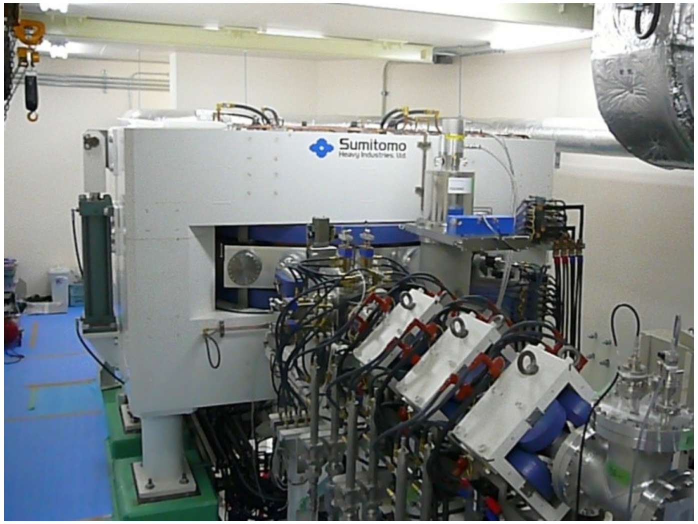
3MeV<Middle energy<8MeV
- Neutron production：middle
- Activation：Low
- Moderator：Middle
- Blistering
- High current～5mA

High energy>30MeV
- Neutron production yield：High
- Activation：High
- Moderator：Large
- No blistering
- Small current～1mA

Cyclotron-based neutron source at KURNS

HM-30 cyclotron

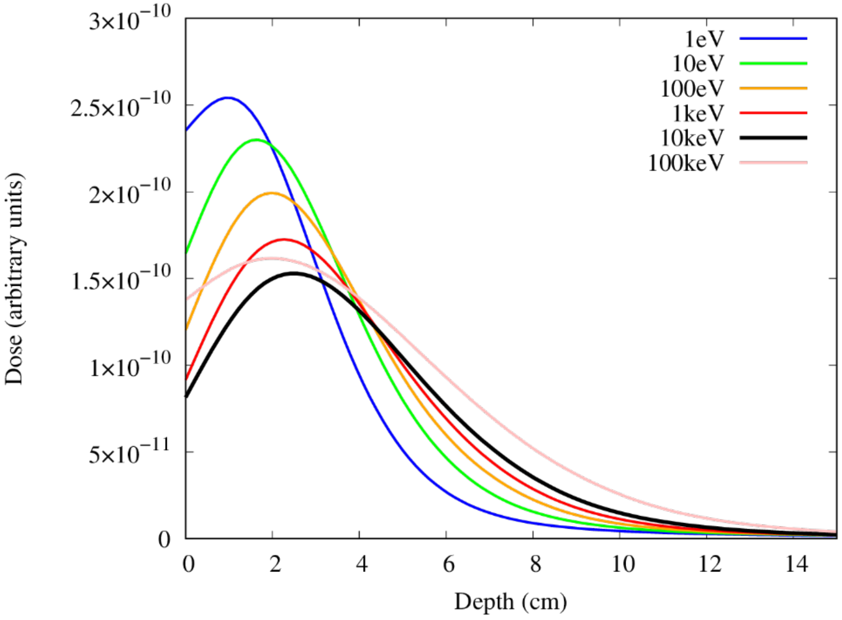
- Negative hydrogen ion acceleration
- High current external ion source that is vertically injected into the cyclotron
- Protons are transported to the neutron production target (Be) through the beam transport system.



Main specification of the cyclotron	
Accelerated particle	Negative hydrogen ion
Extraction energy	30 MeV
Extraction Method	Foil stripping
Maximum beam current	2 mA
Nominal operation current	1 mA
Magnet size	3 m × 1.6 m × 1.7 m
Weight	60 tons

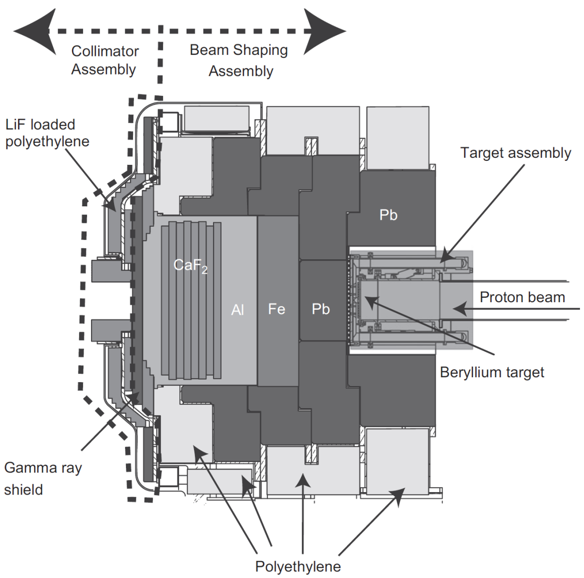
Optimum neutron energy for BNCT

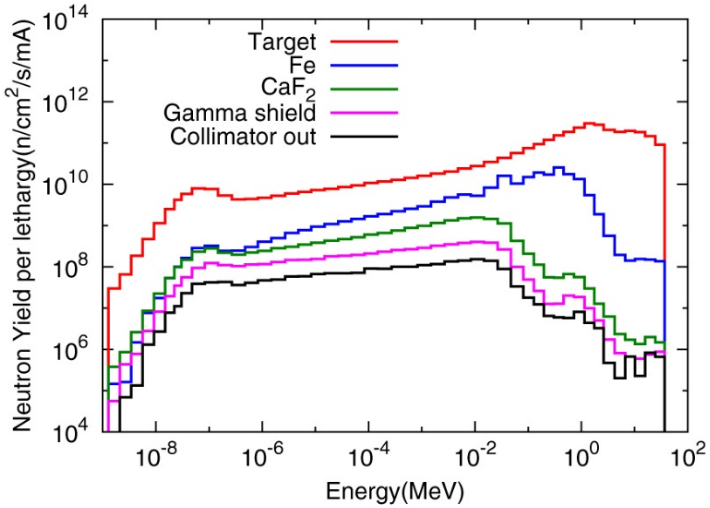
- If the neutron energy is too low, the penetration ability is lost.
- If the neutron energy is too high, the surface dose increases.
- A neutron energy between 10-40 keV is the most effective neutron energy for deep-seated tumours for BNCT

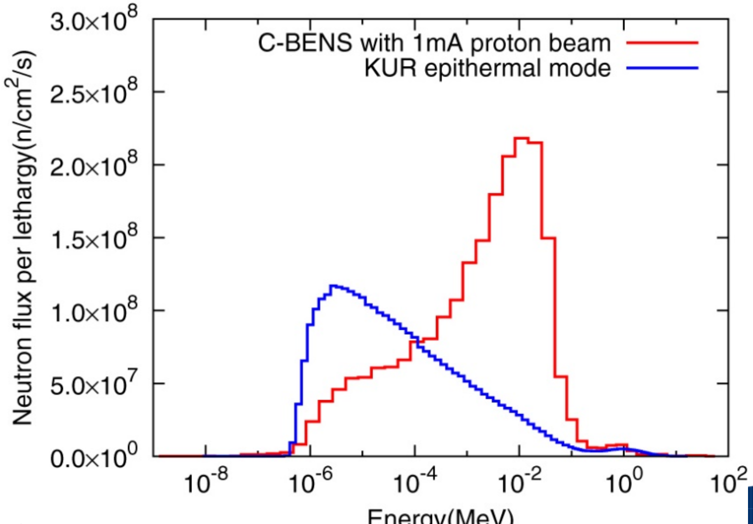


Beam shaping assembly

- Pb act as a breeder and a reflector for high energy neutrons
- Fe act as a moderator
- Al and CaF_2 act as shapers for epithermal region
- Polyethylene used as shielding for high energy neutrons







*Tanaka et. al, Applied Radiation and Isotopes 2011

Introduction to the world's first clinical center situated in a university to offer BNCT

Osaka Medical and Pharmaceutical University (OMPU)

- As of April 2021, union between Osaka Medical College, Osaka University of Pharmaceutical Sciences and Takatsuki High School formed **Osaka Medical and Pharmaceutical University (OMPU)**
- Located in Takatsuki city, Osaka prefecture
- Approximately 15 minutes from central Osaka

Google Maps. Accessed September 13, 2021.
https://goo.gl/maps/bKR7uWBMGwev6yW18

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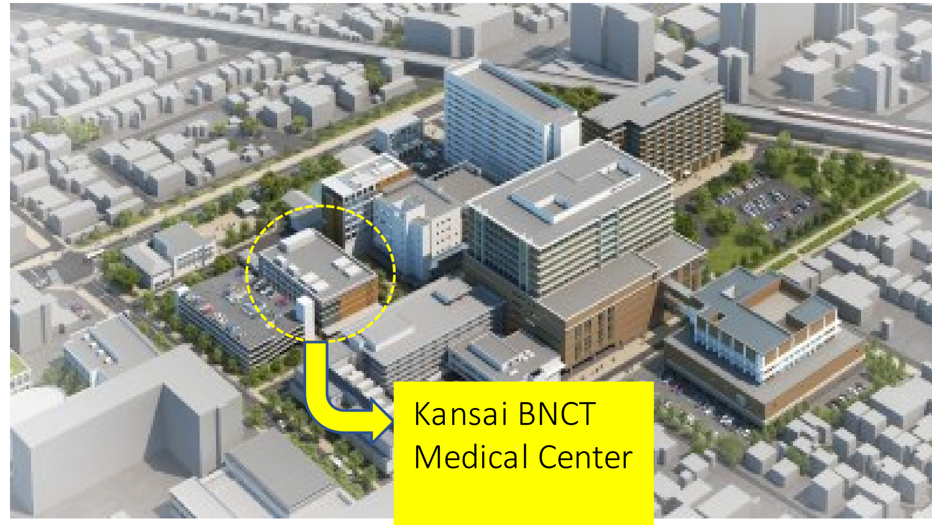


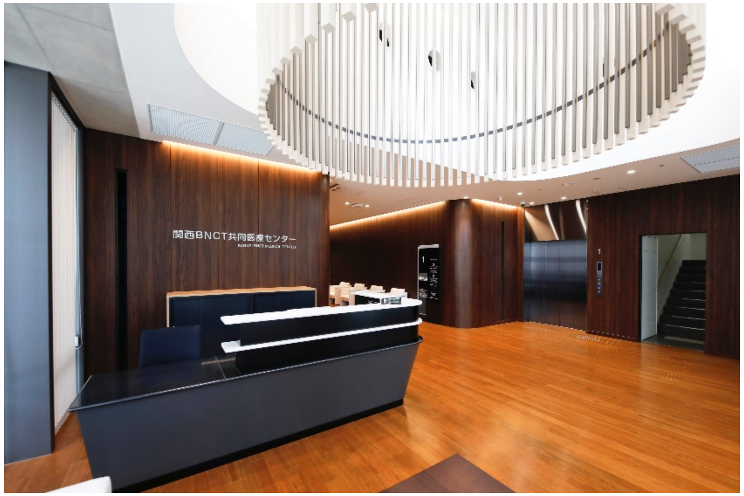
Google Maps. Accessed September 13, 2021.
https://goo.gl/maps/bKR7uWBMGwev6yW18

Kansai BNCT Medical Center

- Located in OMPU
- Performing BNCT for unresectable, locally advanced, and recurrent carcinoma of the head and neck region covered by the national health insurance system since June 2020
- Treated over 100 patients (including patients recruited for the Phase II clinical trial of malignant meningioma)
- In parallel to providing clinical BNCT for patients with head and neck cancer, the center is striving towards approval for insurance covered BNCT for brain tumours

Overview of the facility

Sep. 2016	Building construction works
Sep. 2017	Installation of the system
Jun. 2018	Opening of the center



3F	• Office space	
2F	• BNCT simulation	• PET-CT
1F	•BNCT treatment room	• PET cyclotron
B1	• RI facility	

1F: BNCT area

- Patient preparation room
- Automatic patient transfer system

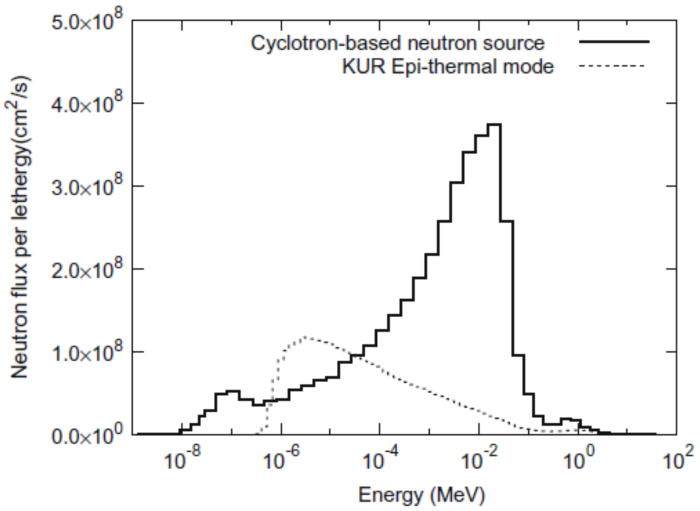
1F: BNCT area

- Treatment console
- Irradiation room
- Horizontal fixed beam port

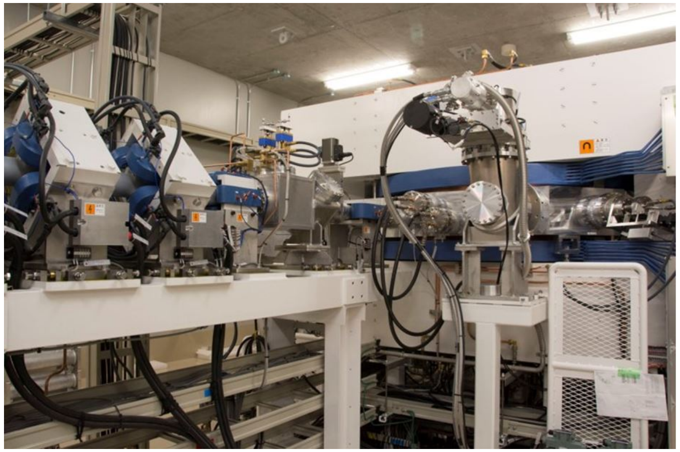
NeuCure® BNCT system

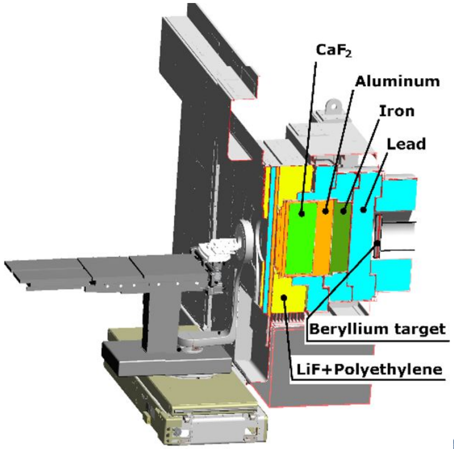
- Developed by Sumitomo Heavy Industries in collaboration with Kyoto University
- Approved as a medical device in Japan in March 2020
- Cyclotron-based accelerator system
- 30 MeV proton beam with a Beryllium target

Epithermal neutron flux > $10^{9} cm^{-2} s^{-1}$



H. Tanaka, et. al, Nucl Instruments Methods Phys Res Sect B 267(11) pp 1970-1977, 2009





World's first BNCT system as a medical device

BNCT System NeuCure®

BNCT dose calculation program NeuCure® Dose Engine

Beam characterisation and clinical commissioning

Neutron interaction with matter (BNCT)

Main dose components:

1. $^{10}B(n,\alpha)^{7}Li$ Boron dose
2. $^{14}N(n,p)^{14}C$ Nitrogen dose
3. $^{1}H(n,n')p$ Hydrogen dose
4. $^{1}H(n,\gamma)^{2}H$ Gamma dose

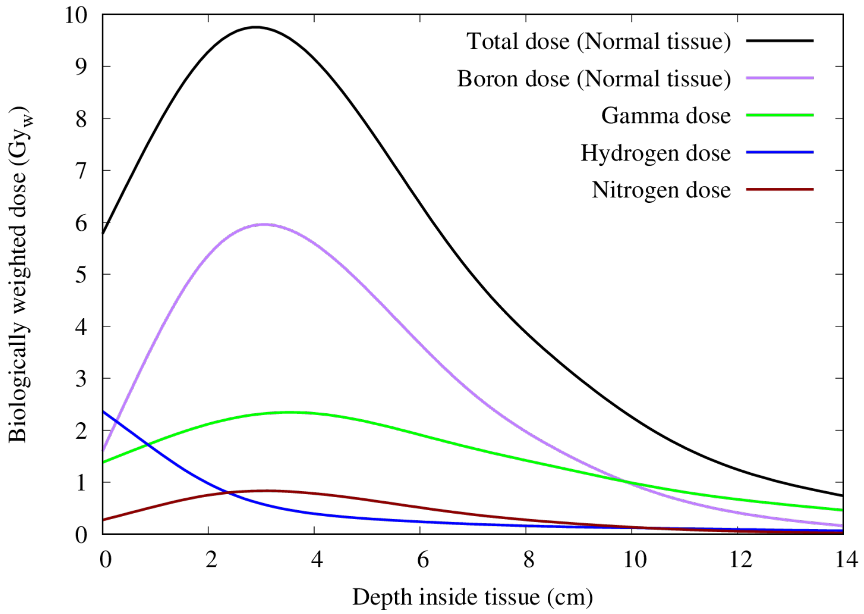
Boron dose and Nitrogen dose → Thermal neutron

Hydrogen dose → Fast neutron

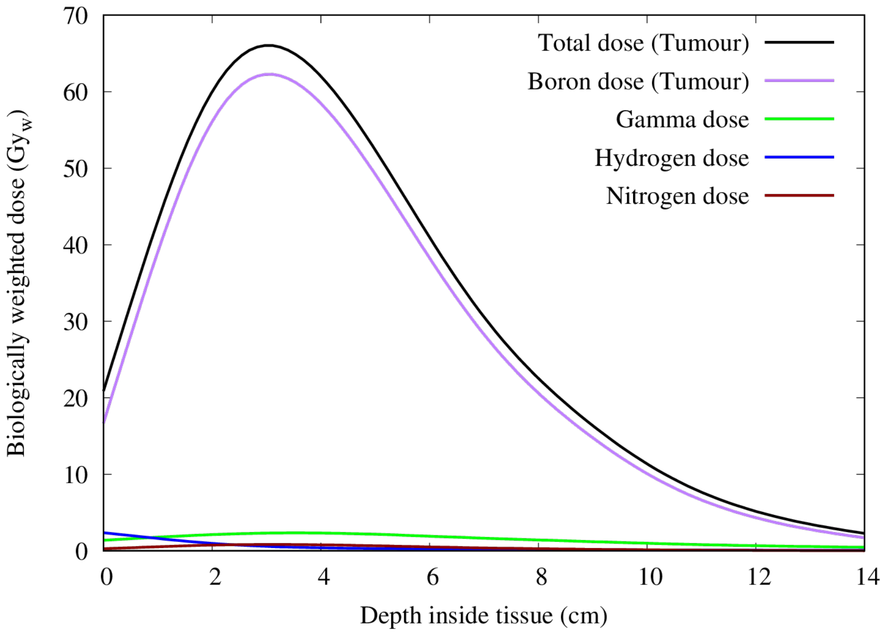
Gamma dose → Gamma ray

→ Important to experimentally measure these components

Normal tissue dose



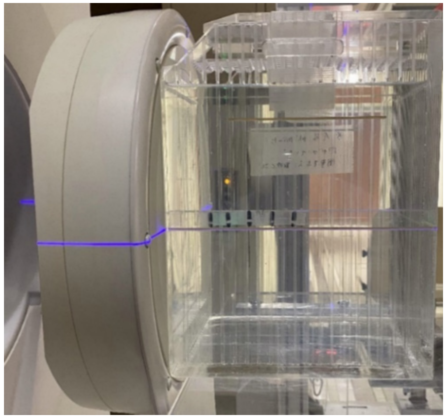
Tumour dose

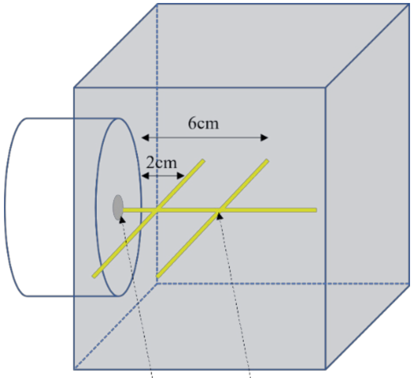


For the tumour, the dominant dose component is the boron dose (>90%).
For the normal tissue, the boron dose component accounts for approximately 50% of the total dose

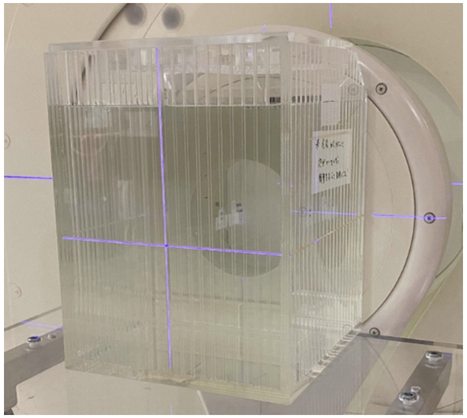
Accurate determination of thermal neutron distribution is crucial

Experimental measurement





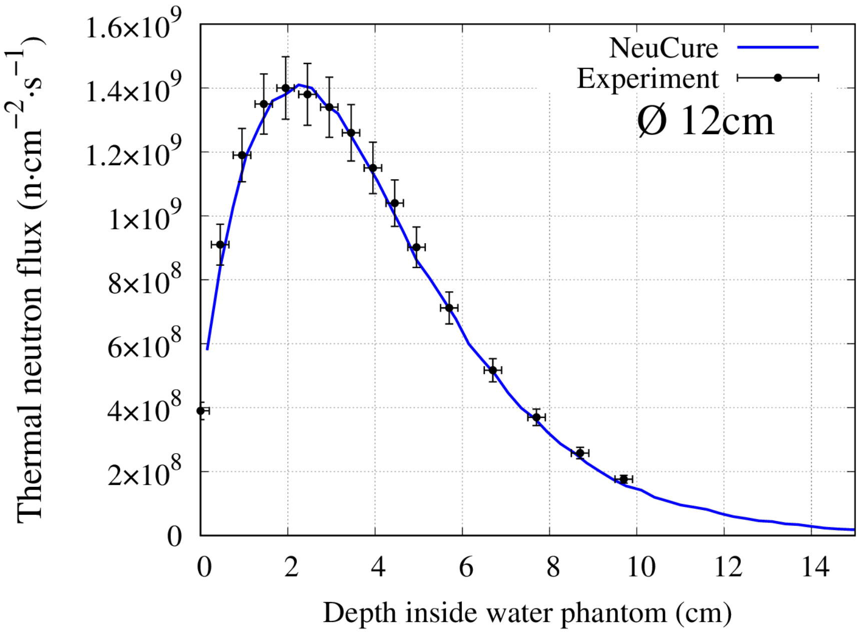
- Performed inside a water phantom
- Neutron activation method
  - Gold foil for thermal neutron detection
  - Indium and aluminium foils for fast neutron detection
- Neutron insensitive TLDs for gamma ray detection



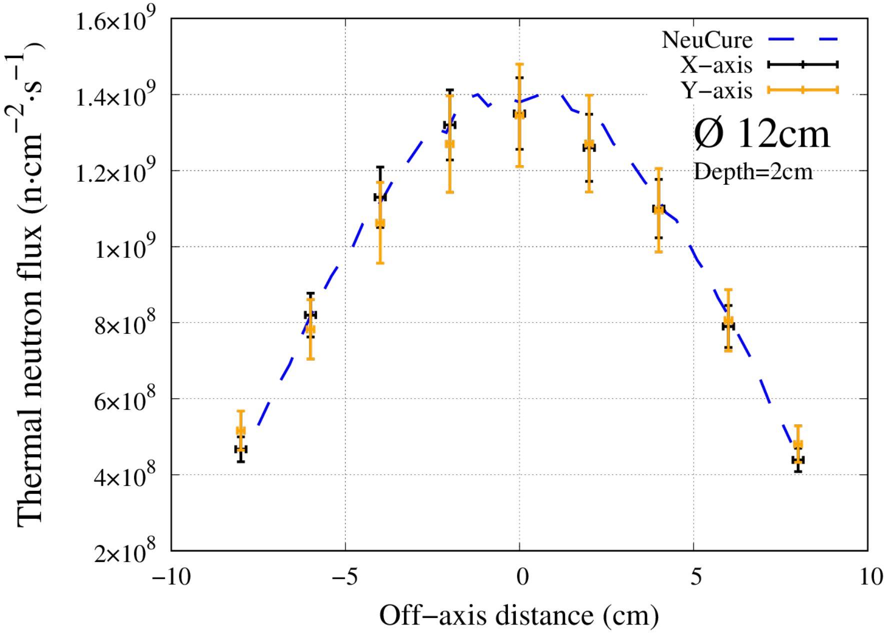
Component	Measuring device
Thermal neutron	Gold activation + HPGe detector
Fast neutron	Indium and aluminium activation + HPGe detector
Gamma ray	Thermoluminescent dosimeters + TLD reader

Thermal neutron distribution

CAX

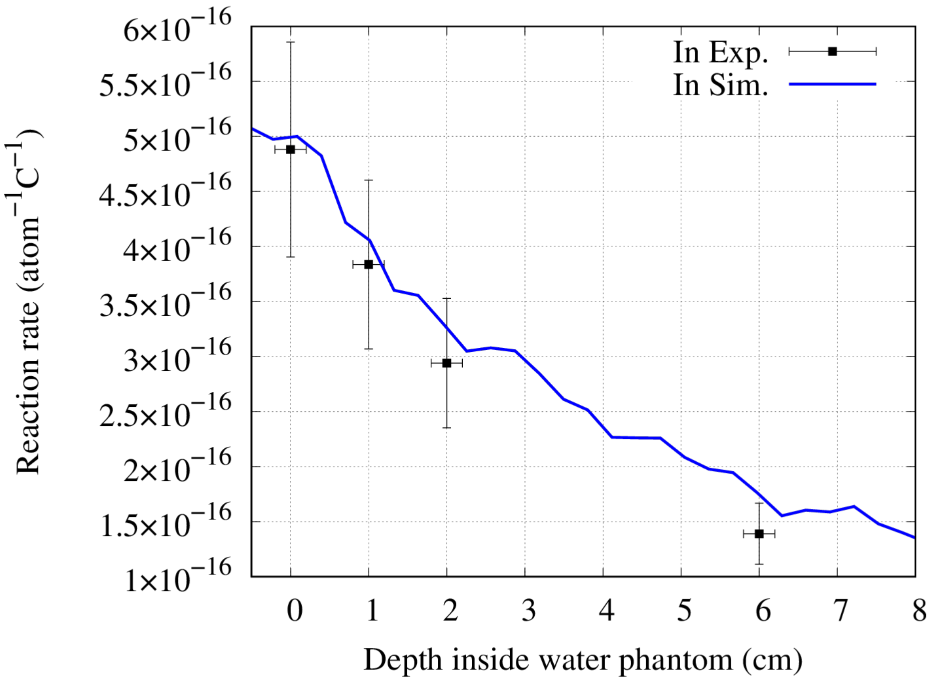


OAR

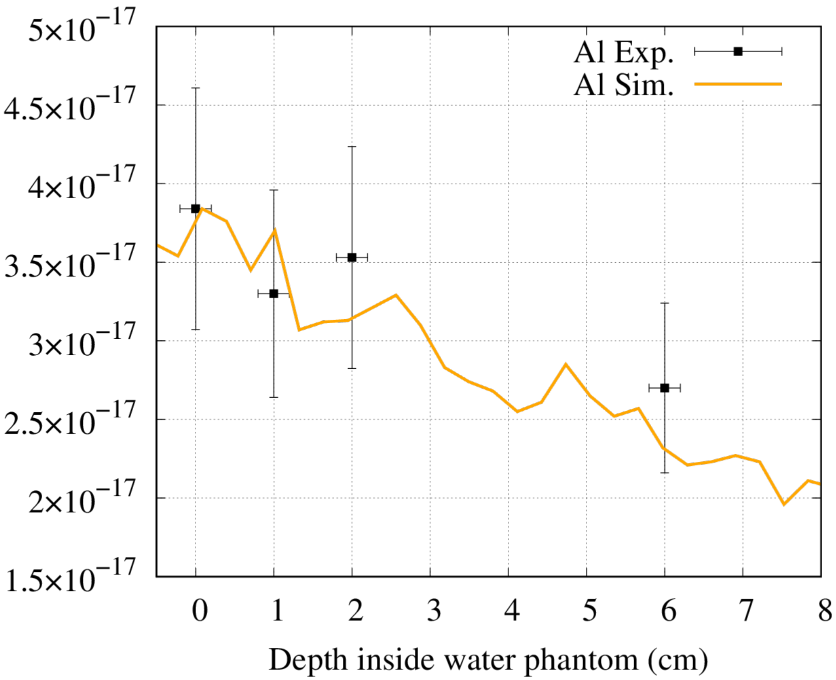


CAX Fast neutron distribution

In (>1.2 MeV)

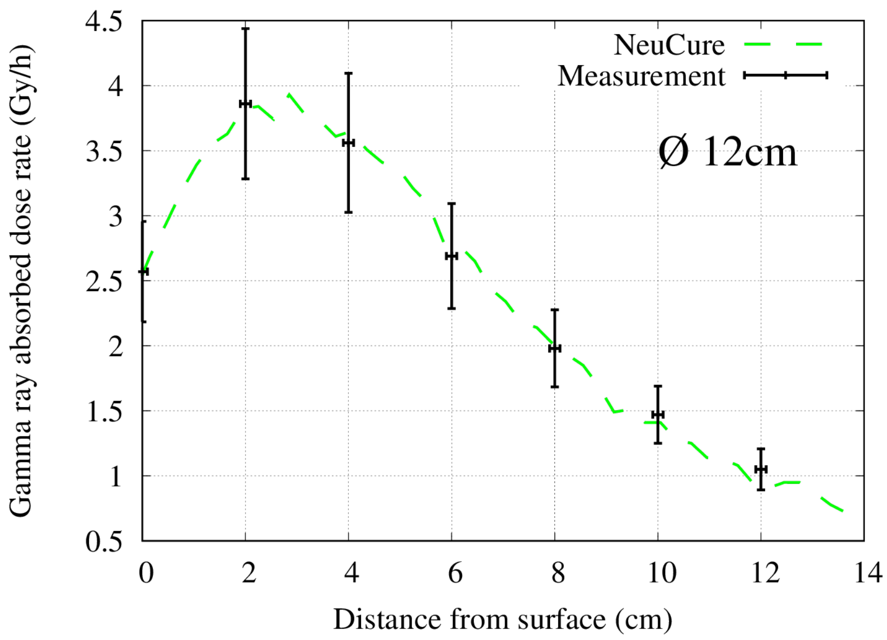


Al(>5 MeV)



Gamma ray distribution

CAX



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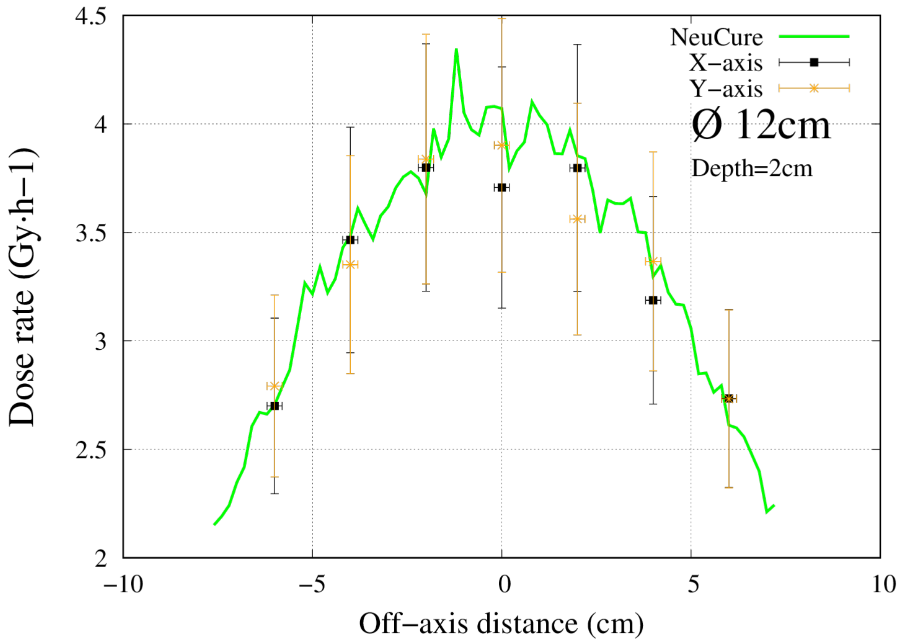
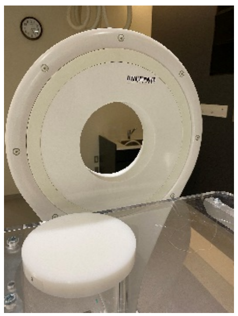
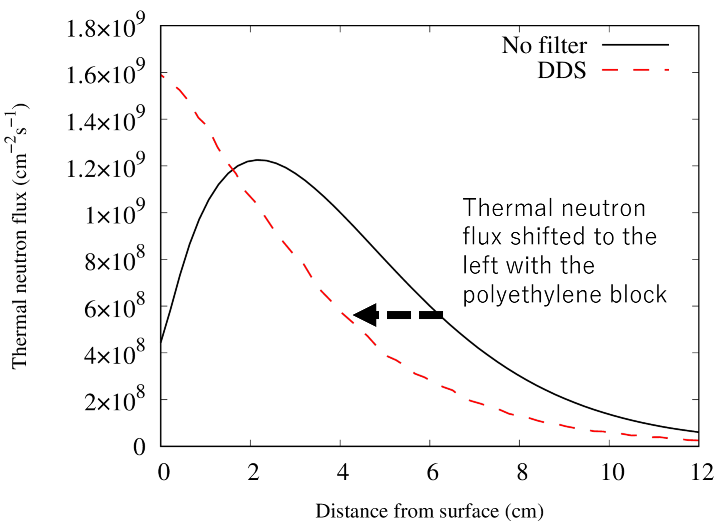


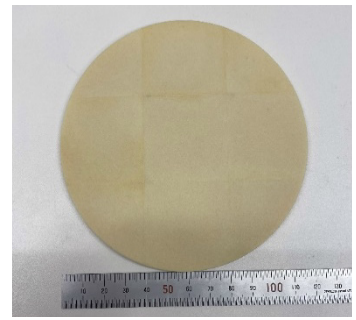
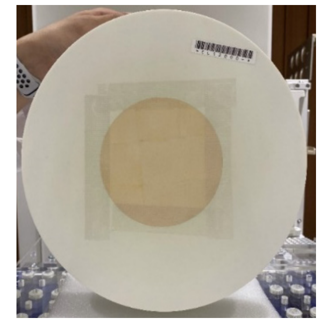
Beam optimization (spectrum shifter)

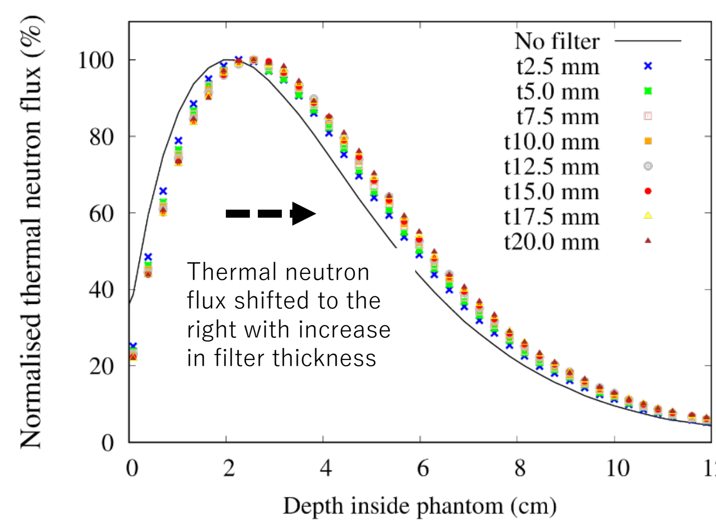
Polyethylene disc to shift the thermal neutron peak to the surface



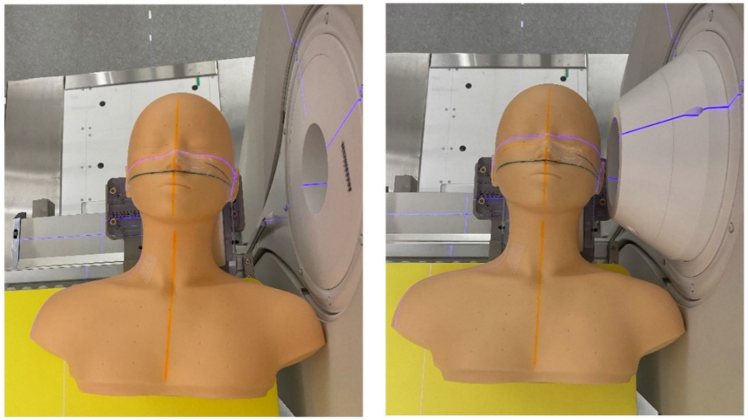



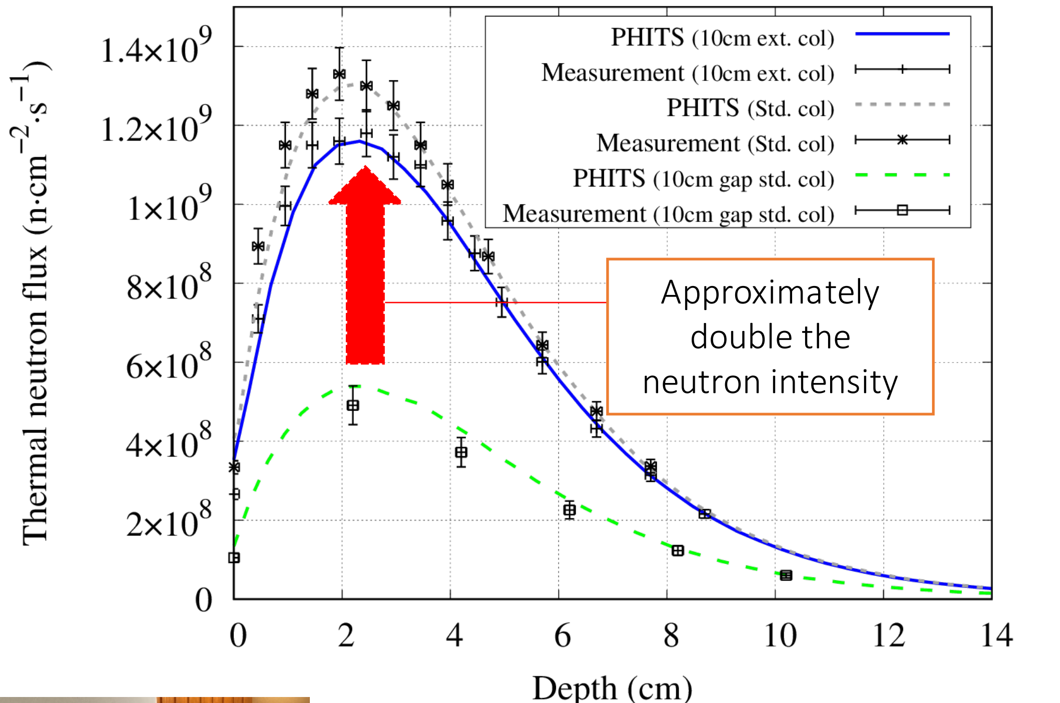
^{6}Li disc to shift the thermal neutron peak to the deeper range



Extended collimators





- ✓ Patient can receive BNCT in a much more comfortable position
- ✓ Irradiation time is reduced
- ✓ Set up position (CT simulation) and treatment position is reproducible

BNCT workflow

Professions related to BNCT (Multidisciplinary team)

- Radiation dosage prescription
- Consultation

Radiation Oncologist

- Treatment planning
- Research and development
- QA/QC

Medical Physicist

- Patient set up
- QA/QC

Radiation Therapist

- Patient care before, during and after treatment

Registered Nurse

- Examine nuclear medicine images
- Perform diagnosis

Nuclear radiologist

- PET drug QA/QC
- Research and development

Pharmacist

- BNCT and PET Cyclotron operation

Cyclotron operator

- Handling of patient fees

Reception staff

BNCT flow

Referral
- Pre-planning
- BNCT indication decision

Consultation
- Head and neck consultation
- BNCT consent
- Tumour review board
- Second opinion

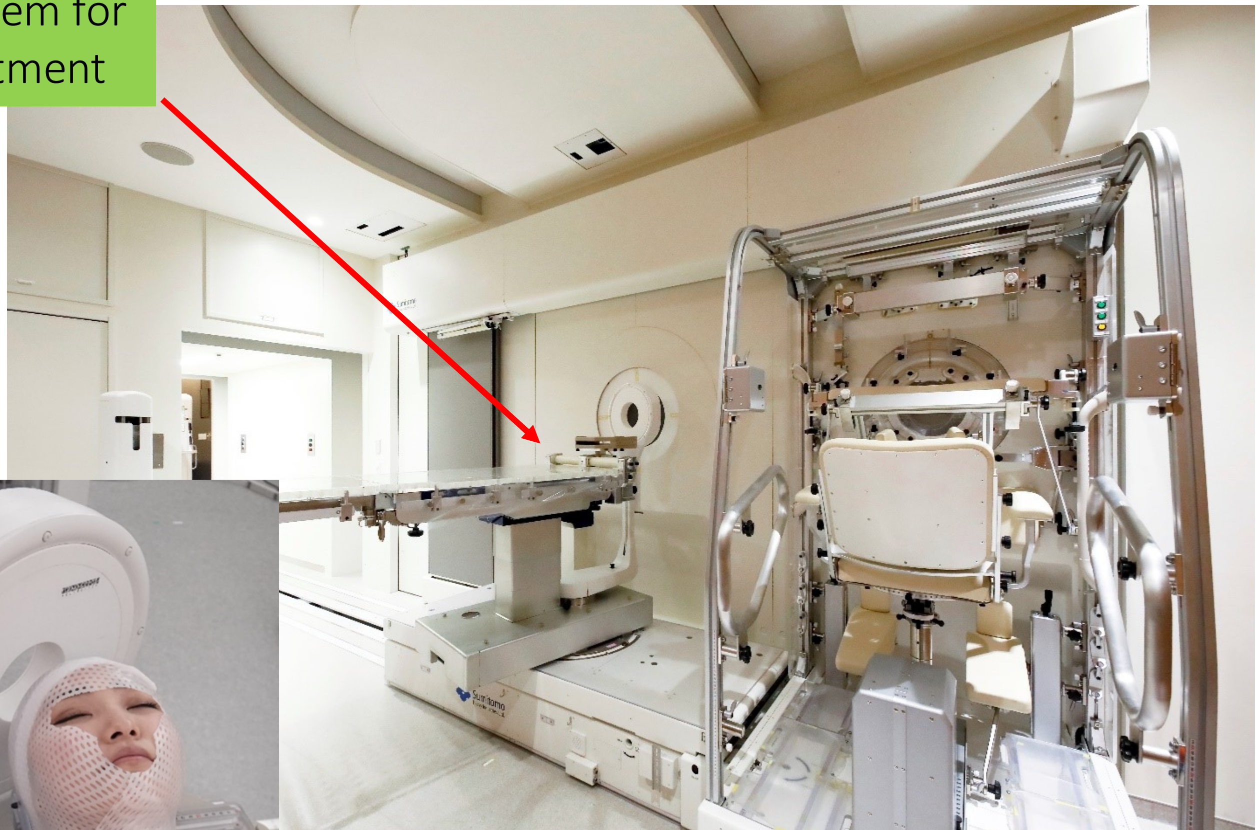
Preparation
- FDG-PET imaging (^{18}F-FBPA if possible)
- BNCT patient positioning and CT simulation
- Treatment planning
- Neutron output measurement

Treatment
- Hospital admission before treatment day
- BNCT treatment
- Discharged from the hospital 48 hours after treatment (if no complications arise from the treatment)

6) BNCT workflow

6) BNCT workflow

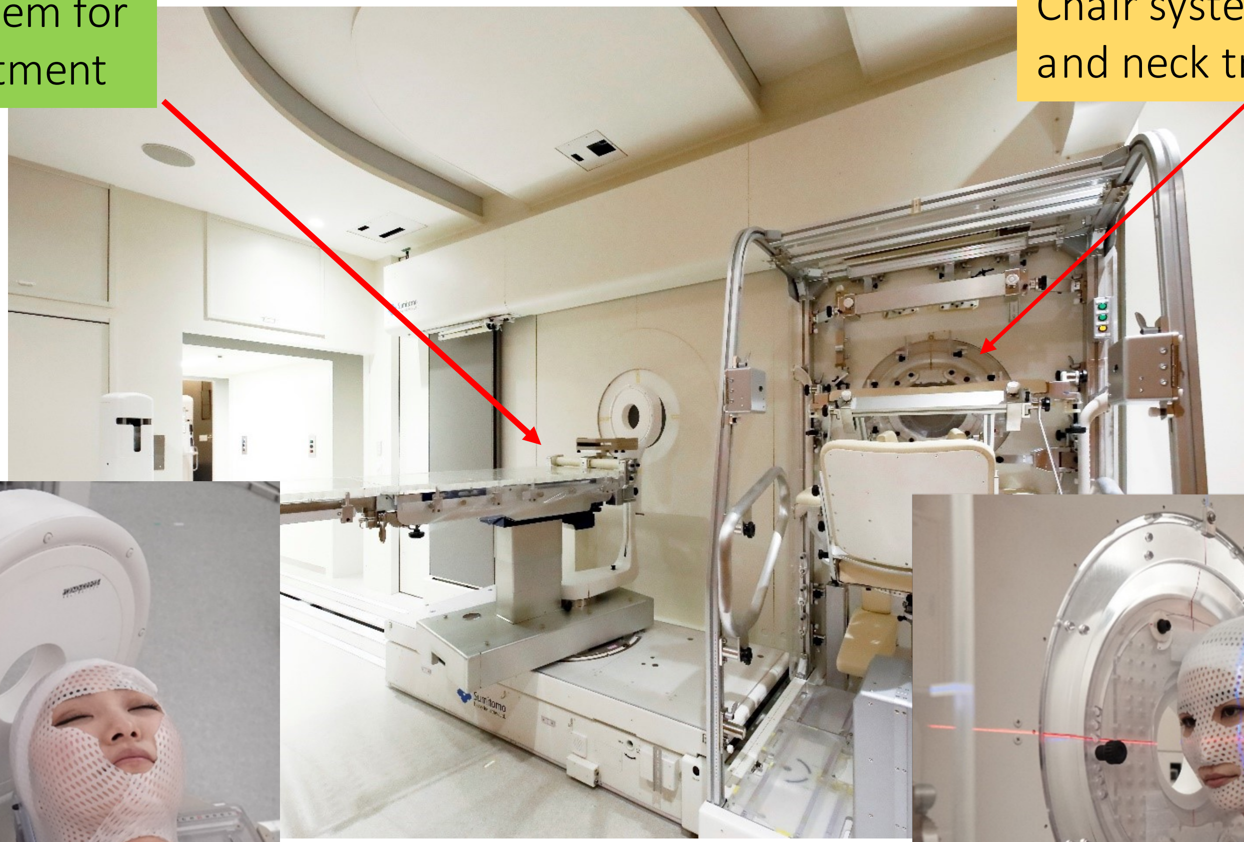
Couch system for brain treatment

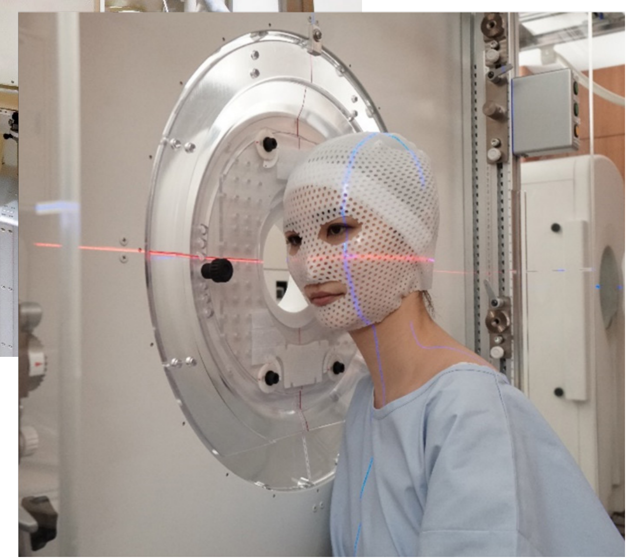


6) BNCT workflow

Couch system for brain treatment

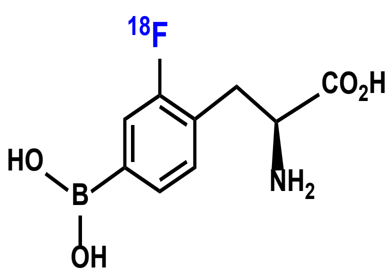
Chair system for head and neck treatment

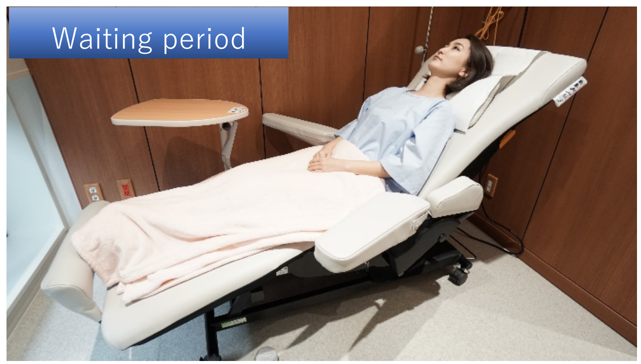




PET/CT

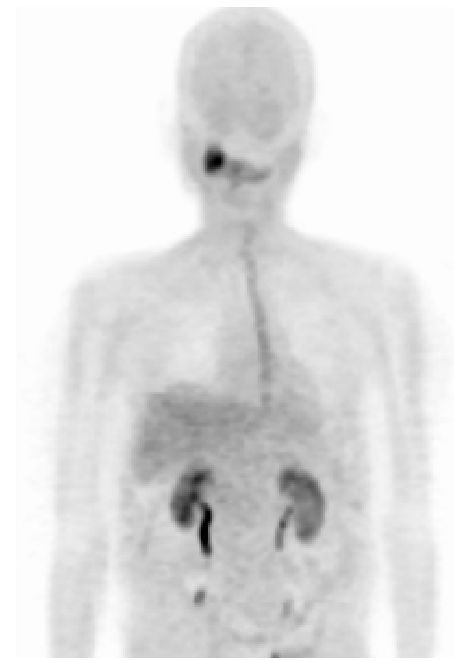
- PET/CT scan to check for any distant metastasis
- FBPA PET to check the indication for BNCT
- ^{18}F-FDG (or ^{18}F-BPA) is injected into the patient intravenously
- After a short waiting period, the scan is performed





Performed 1-2 weeks prior to treatment

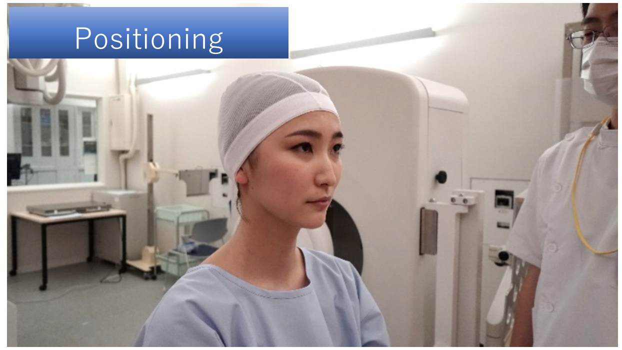
^{18}F-BPA image

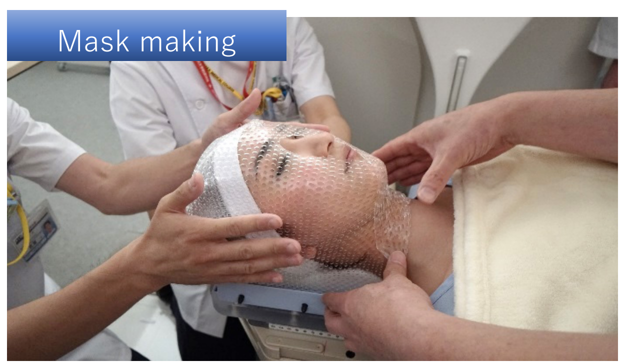


Patient positioning

Performed 1 weeks prior to treatment

- Patient set up and positioning is performed according to the pre-plan parameters
- Thermoplastic mask is created for each individual patient
- Position markers are placed for reproducibility
- 2D orthogonal x-ray images are taken
- CT scan is performed for treatment planning
- The whole process may take up to 3 hours

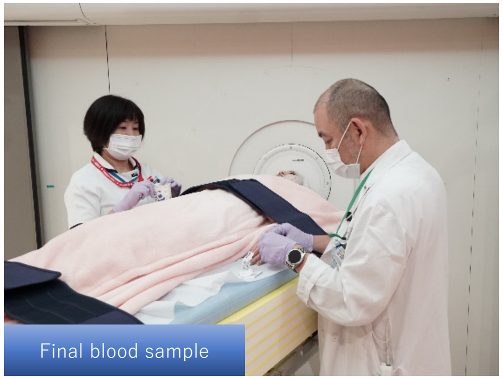




Treatment day

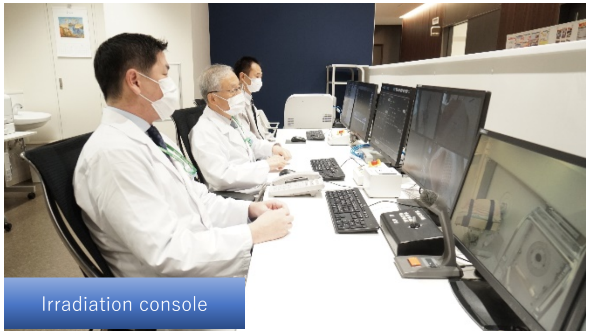
- Patient arrives to the center and ^{10}B infusion begins 2 hour prior to irradiation
- One hour after infusion, the patient is relocated to the pre-treatment room
- Patient is set up according to the final plan and x-ray images are taken to verify the set up
- Patient moves into the treatment room and the final blood sample is taken
- The irradiation is performed (maximum 1 hour)

^{10}B infusion

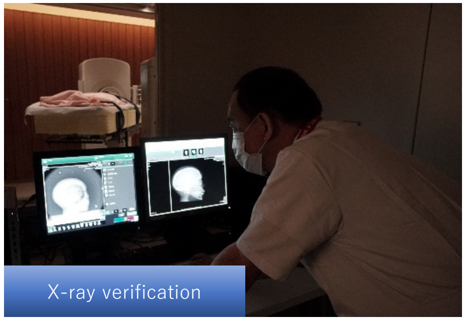


Final blood sample

Patient positioning



Irradiation console



X-ray verification

Patient returns to the hospital after irradiation and is discharged 24-48 hours after

Summary

- An accelerator-based neutron source designed for clinical BNCT is undergoing/being prepared around the world.
- BNCT for head and neck cancer is approved in Japan and so far, the results are excellent.
- We hope the use of an accelerator-based neutron systems increase globally and the indication of BNCT for other sites also increase.

Thank you for your kind attention