The Current Status of the Accelerator Neutron Source and Dosimetry for Boron Neutron Capture Therapy

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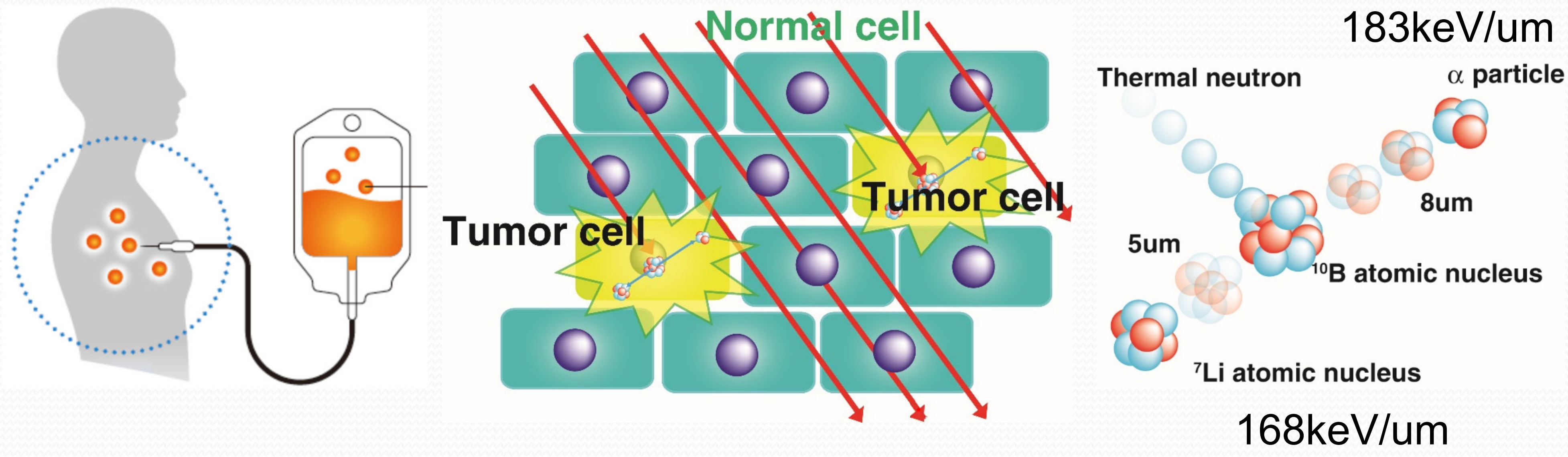
23th January 2025 CCRI Webinar

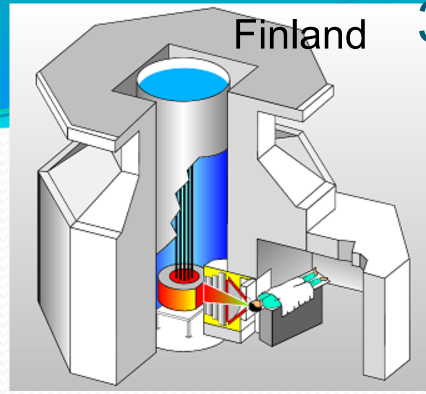
Boron Neutron Capture Therapy



Expectations

- Indications for recurrent cancer after radiation therapy and invasive cancer
- Indications for radiation-resistant cancer due to high LET particles

BNCT histories



1932：Chadwick

1936：Dr. Locher BNCT principal

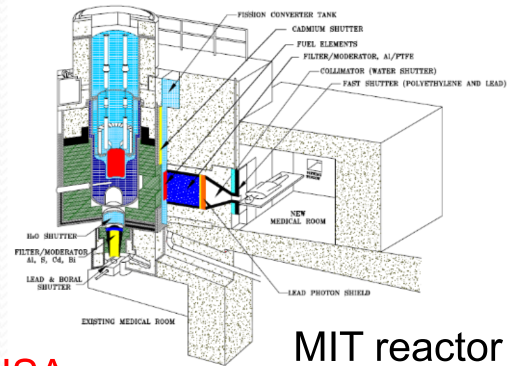
1940-1950：USA basic research accelerator based thermal neutron

1951：First BNCT in USA Brookhaven reactor

1951-1961：USA 63 clinical studies

1962-1993： basic research in USA

http://www.bnl.gov/bgrr/"



MIT reactor

1994-1999： Brookhaven・epithermal neutron

1994-2003：MIT・ epithermal neutron

1997：Petten・ epithermal neutron

1999-2012：Finland・ epithermal neutron

2000：Czech ・ epithermal neutron

2001-2005：Sweden ・ epithermal neutron

2002-：Italy・ epithermal neutron

2003-：Argentina ・ epithermal

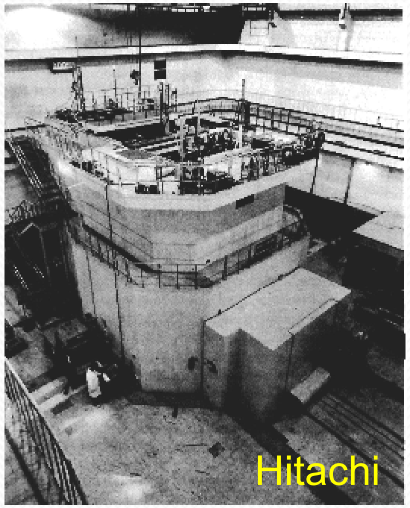
2010：Taiwan・ epithermal neutron

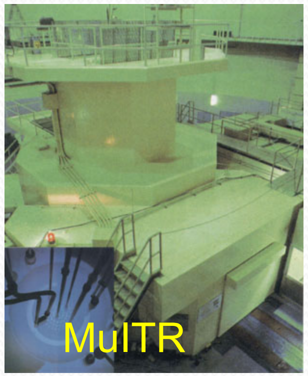
BNCT in USA

1940	1950	1960	1970	1980	1990	2000	2010

BNCT in Japan

BNCT using epithermal





1968：First BNCT in Japan

1968-75：Hitachi reactor

1974：KUR

1977-89 ： MuITR

Accelerator-based neutron source

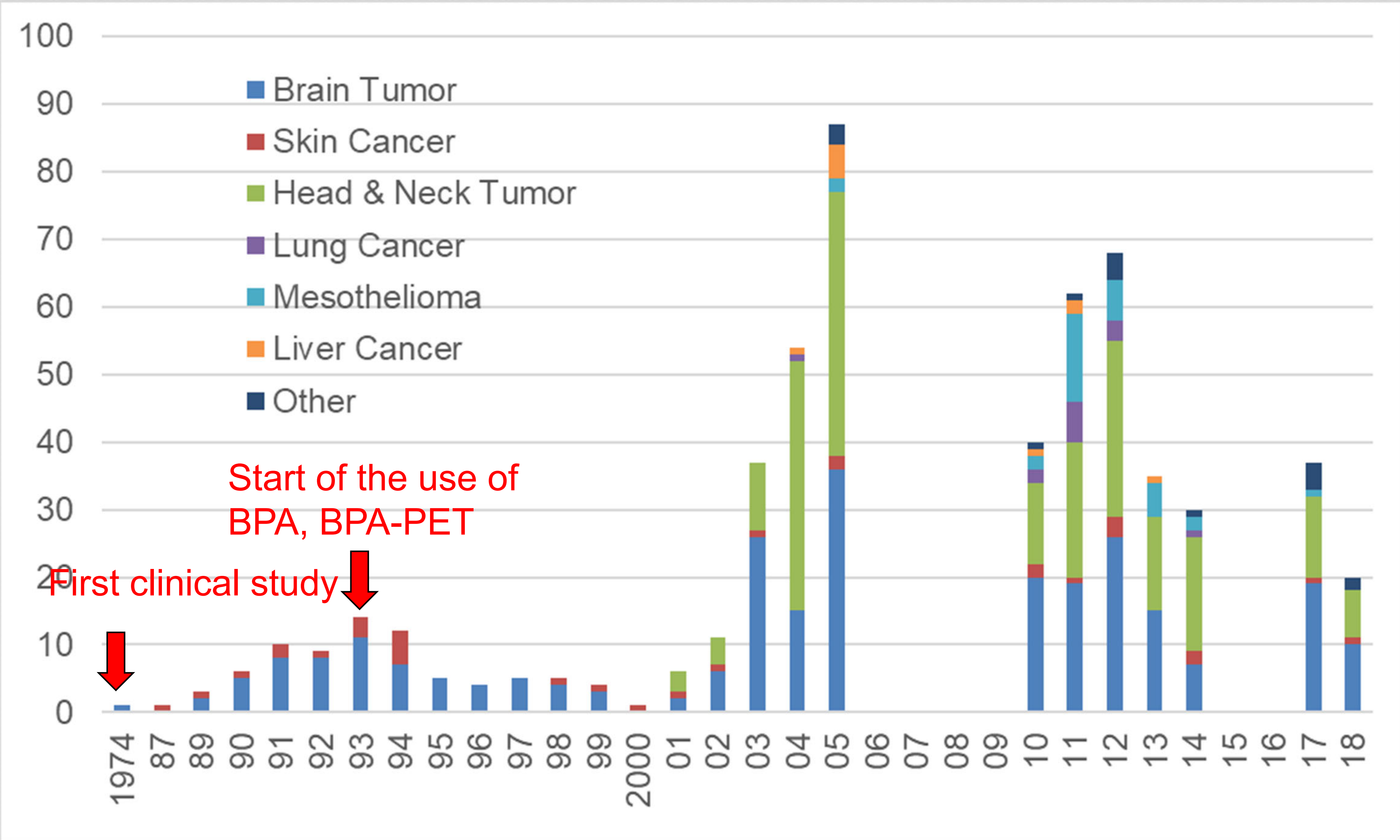
1990-96：JRR-2

1996-：KUR-M

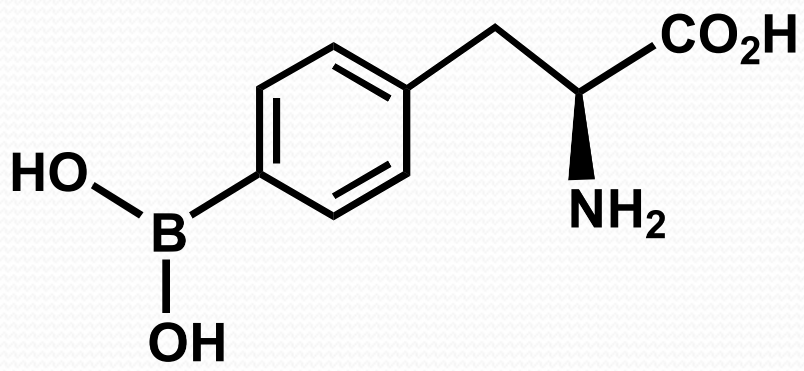
1999-2011：JRR-4・ epithermal neutron

Boron-Neutron Capture Therapy for Tumors", edited by H.Hatanaka (1986)

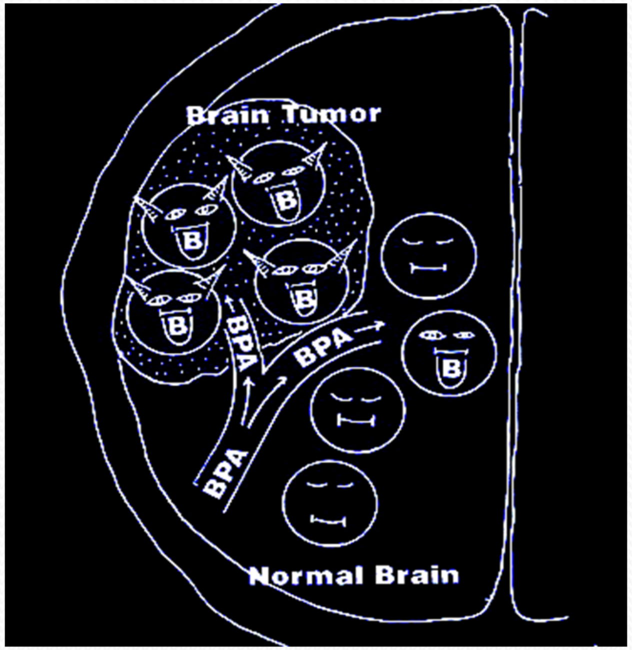
Clinical studies at KURNS using research reactor: KUR



BPA (*para*boronophenylalanine)

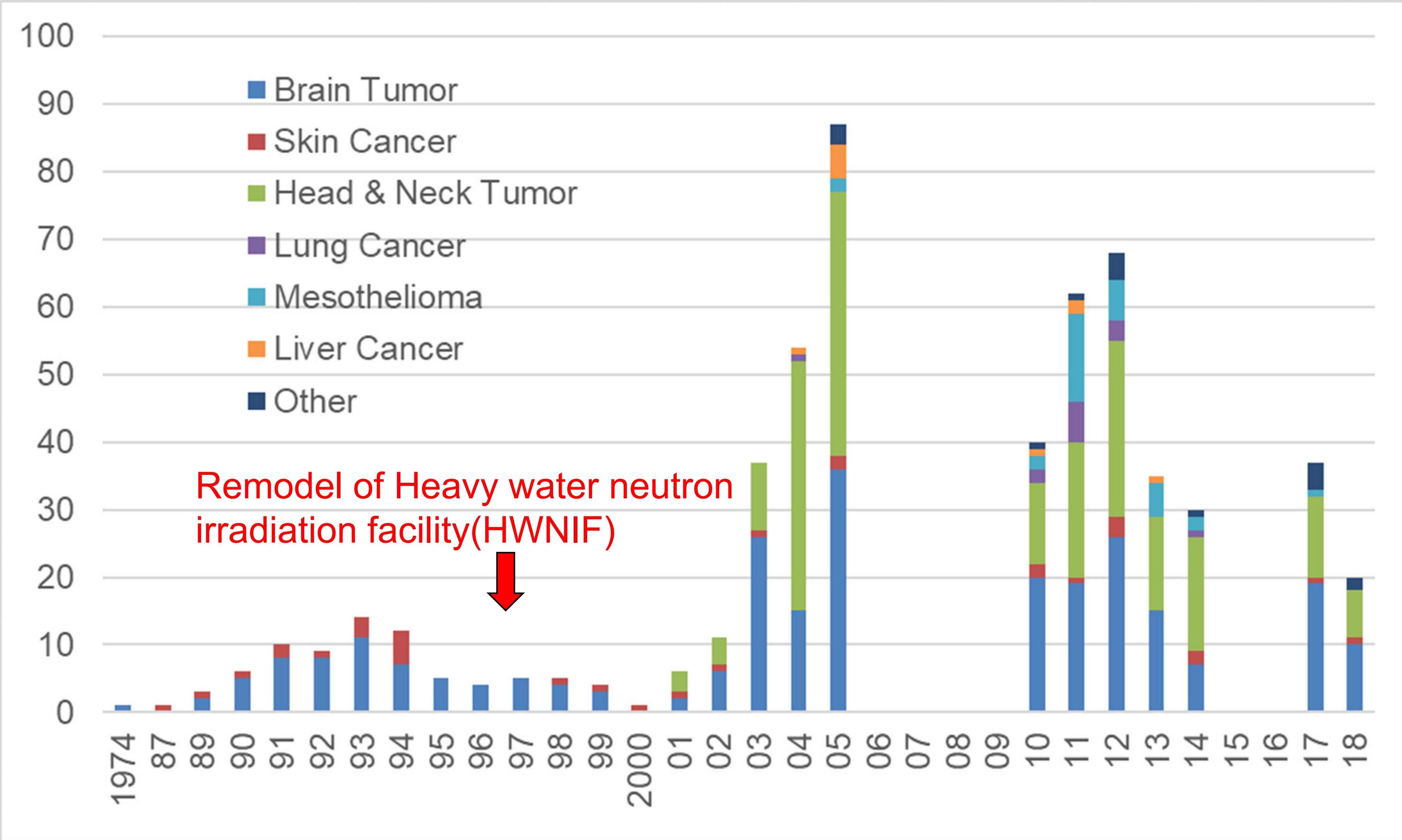


L- *p* - BPA

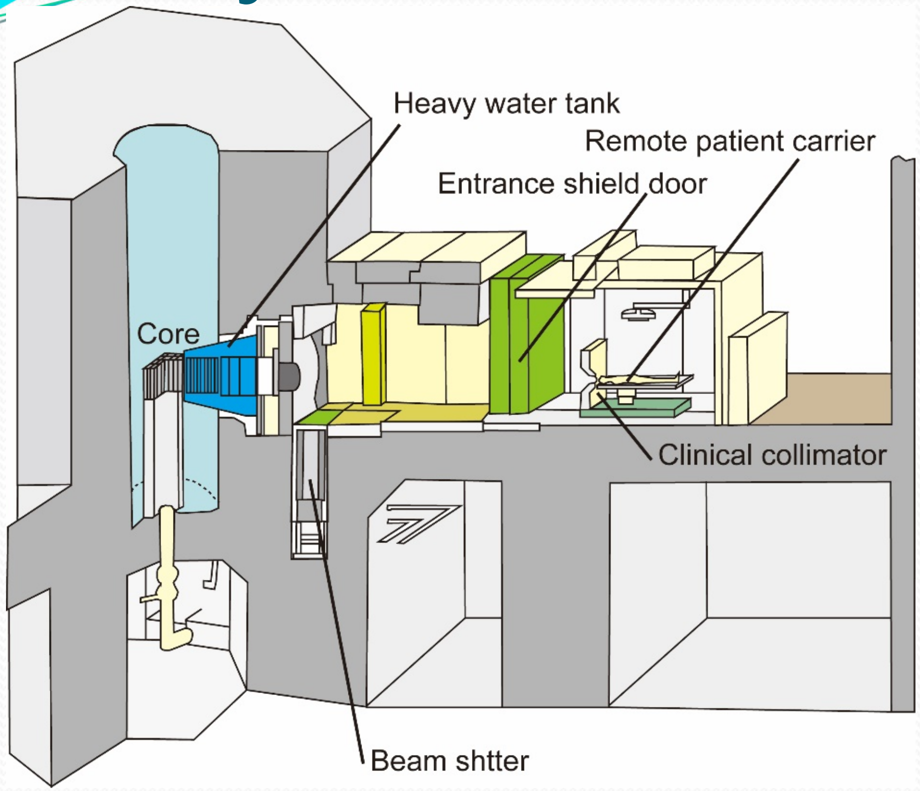


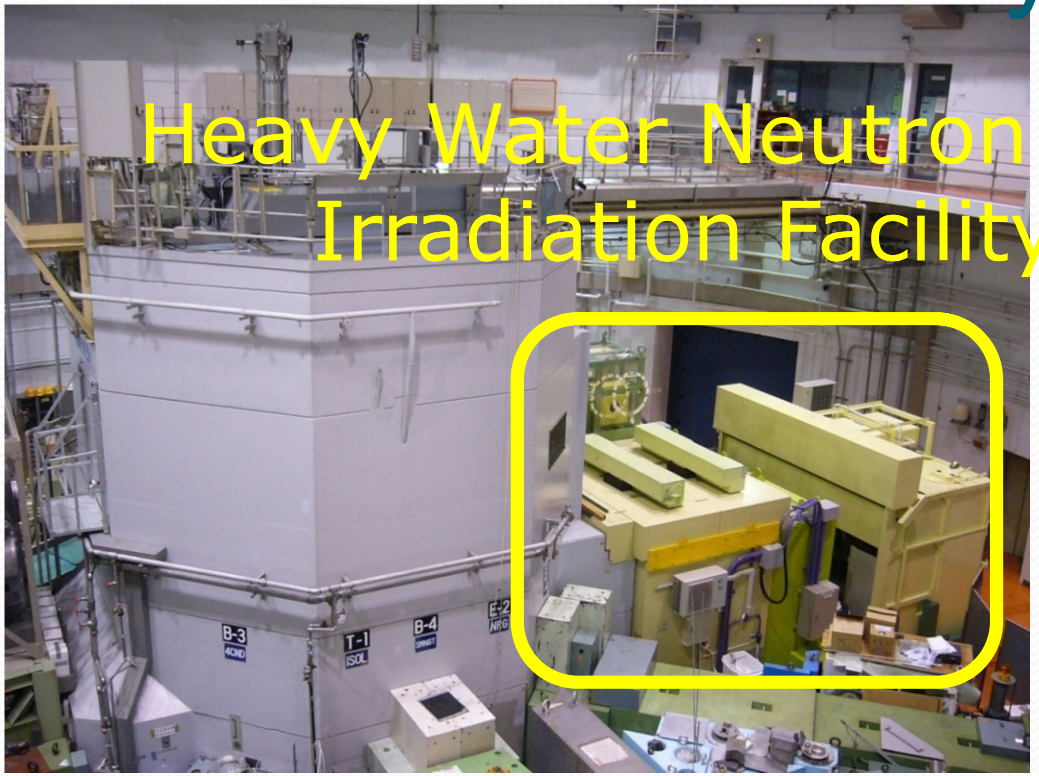
- ✓Taken into the cells through amino acid transport .
- ✓Uptake level depends on cell proliferation.
- ✓Therefore, it accumulate more in tumor cells than in normal cells.
- ✓ Low toxicity.

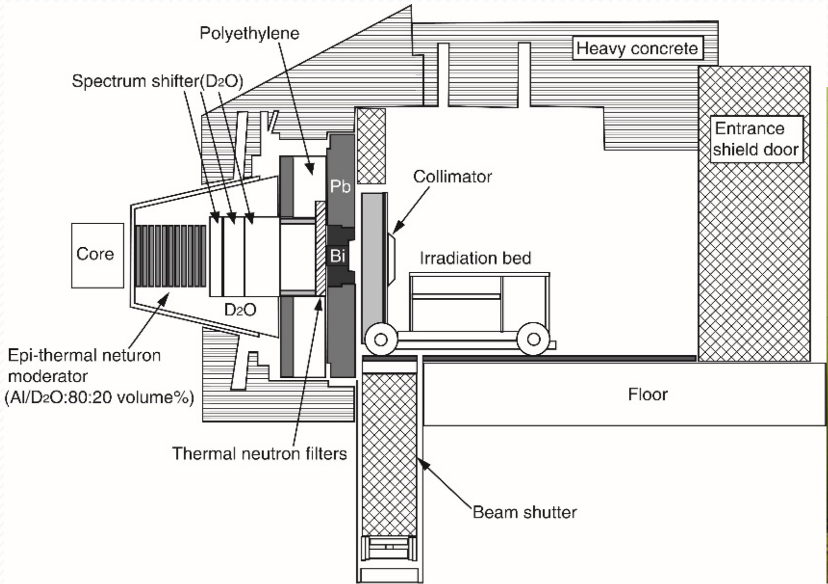
Clinical studies at KURNS using research reactor: KUR



Heavy Water Neutron Irradiation Facility



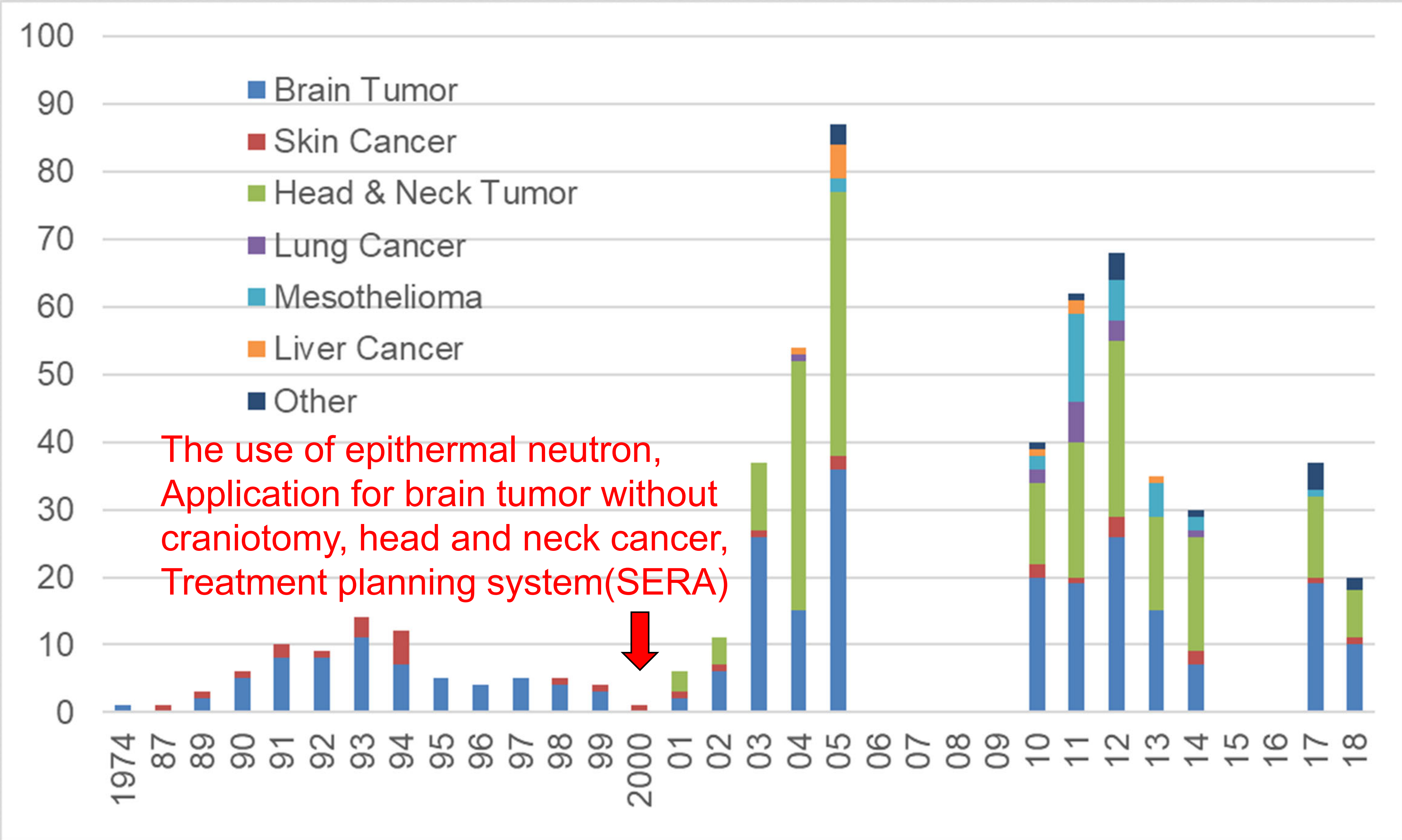




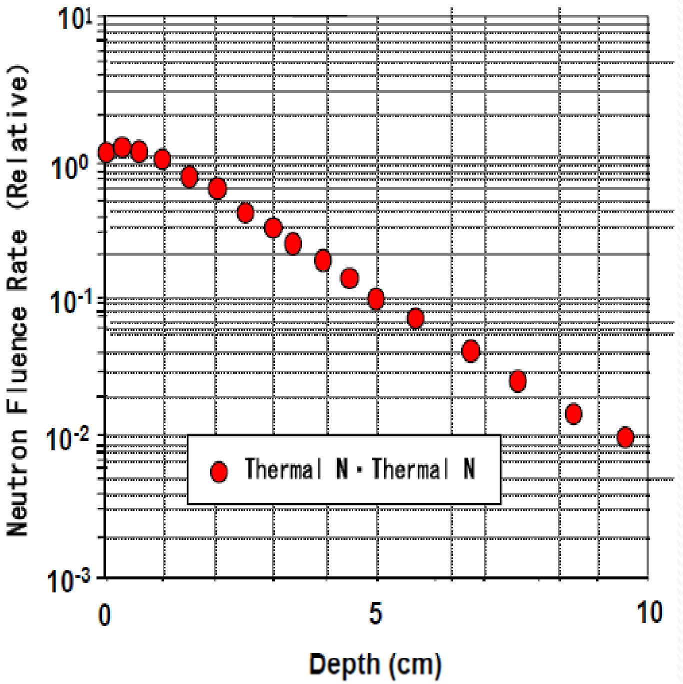
Brain tumor

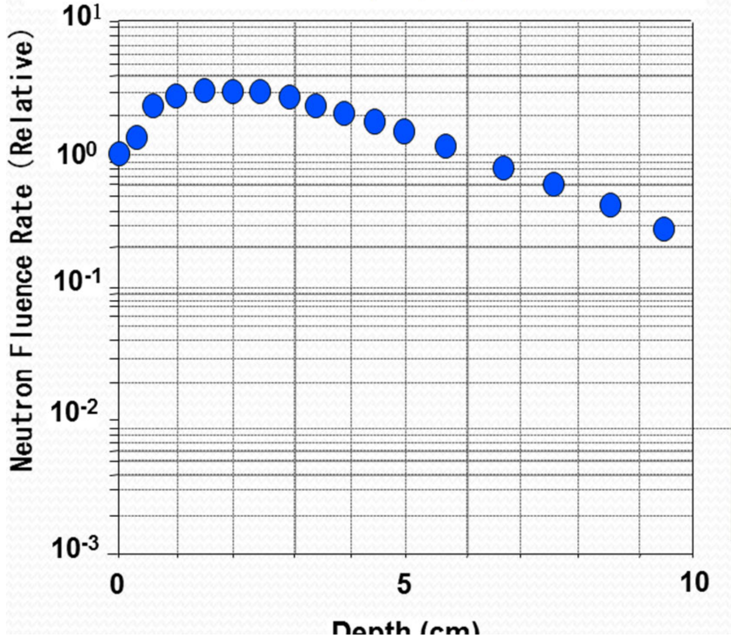
Head and neck

Clinical studies at KURNS using research reactor: KUR



BNCT by Using Epithermal Neutron Beam

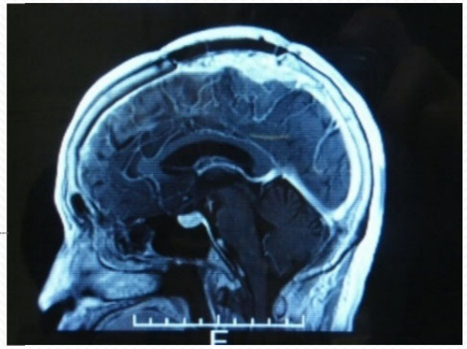




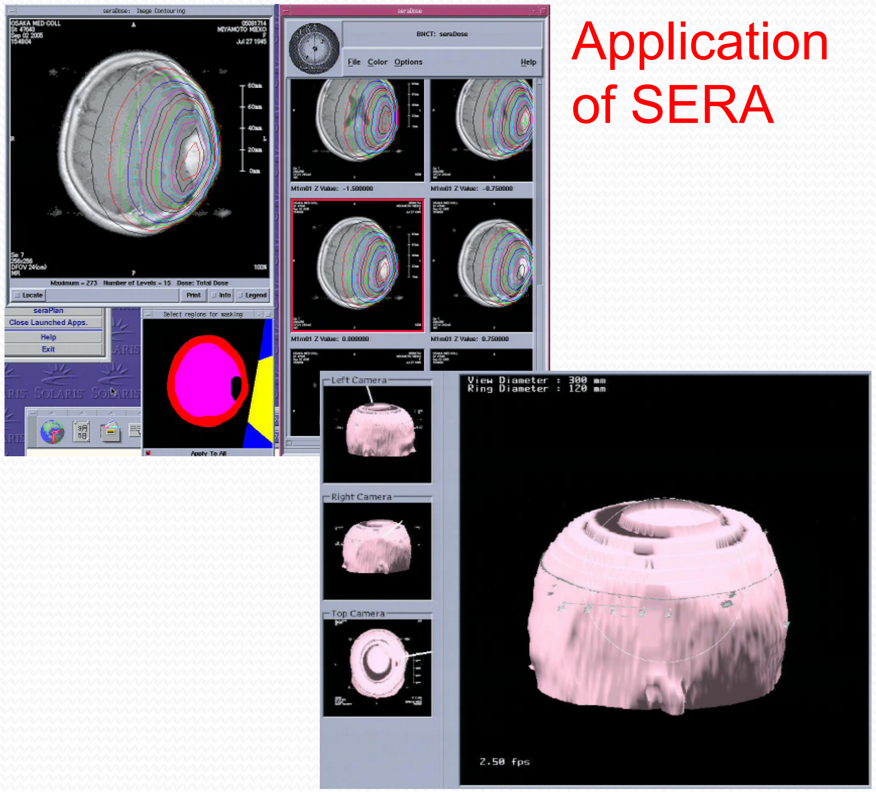
Multi-leaf collimator

New irradiation bed

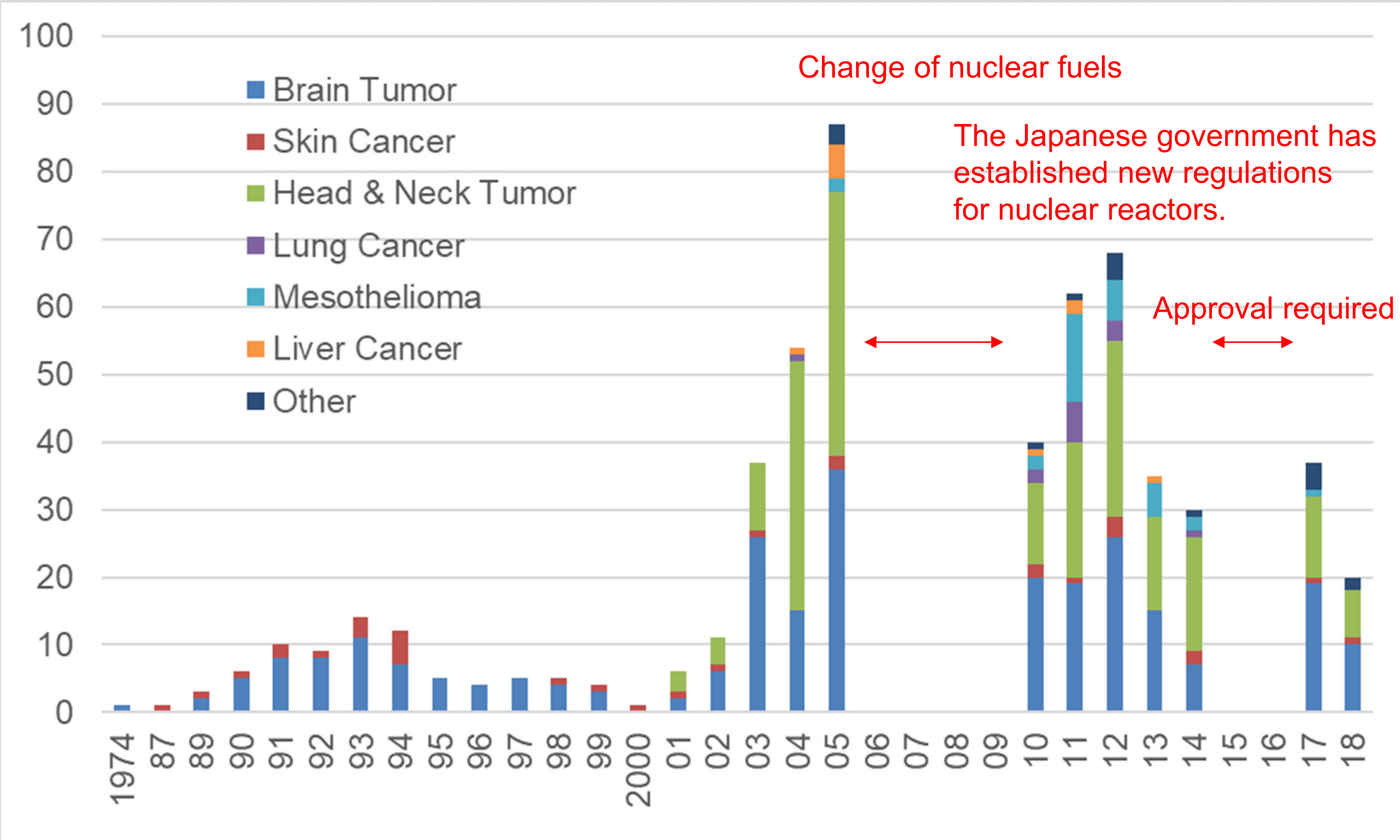
Application for brain tumor without craniotomy,



Application of SERA



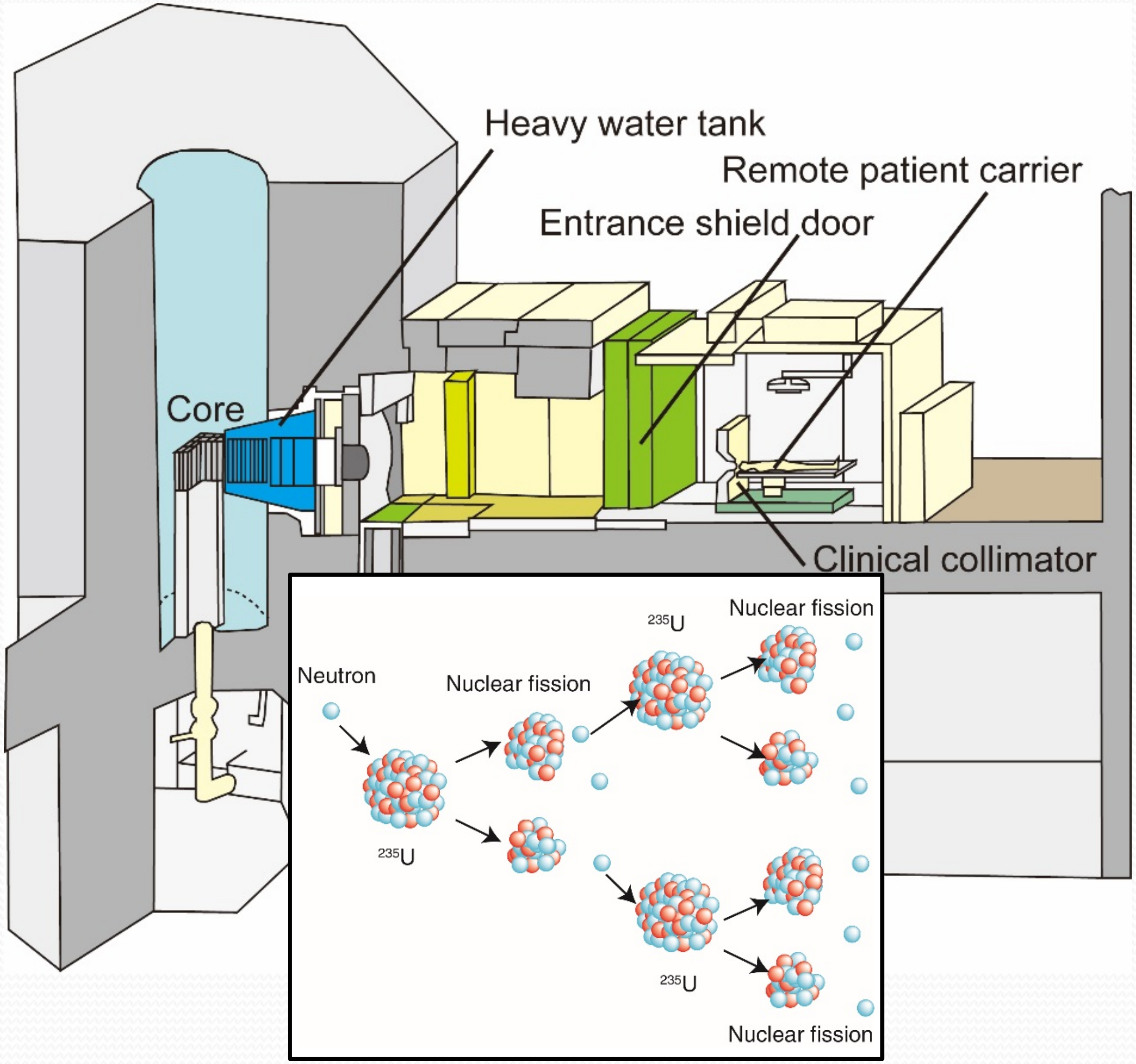
Clinical studies at KURNS using research reactor: KUR



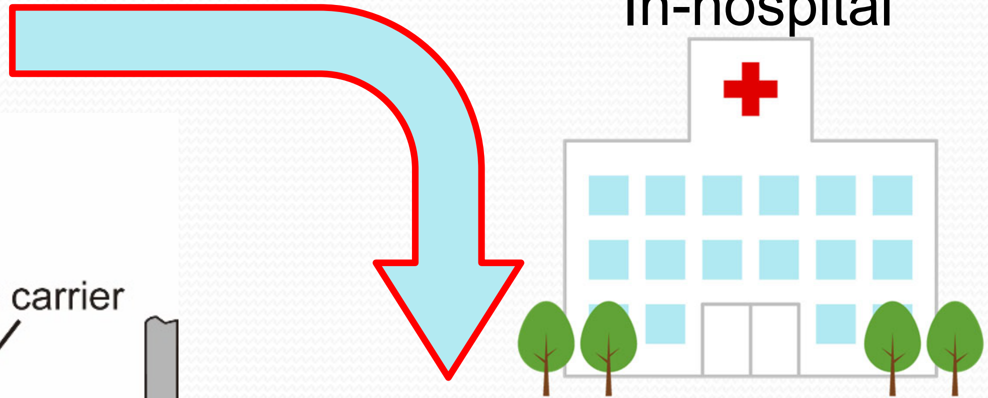
Reactor-based BNCT facility in the world

From nuclear reactor to accelerator

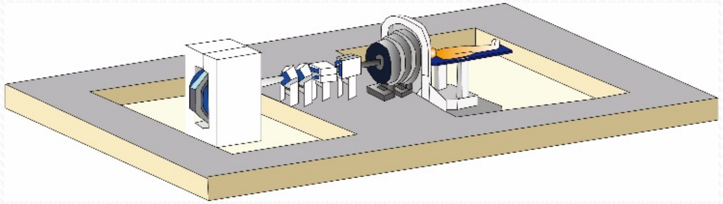
Conventional System
(Nuclear Reactor-based)



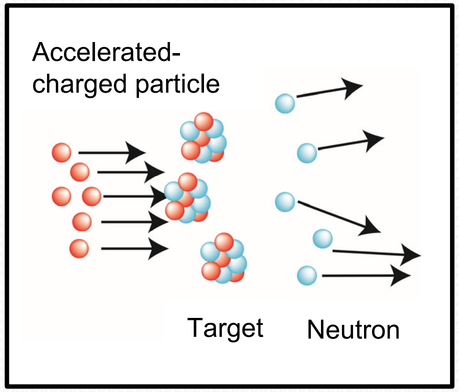
In-hospital



New Generation System
(Accelerator-based)



In Safe, Compact,
Easy to use

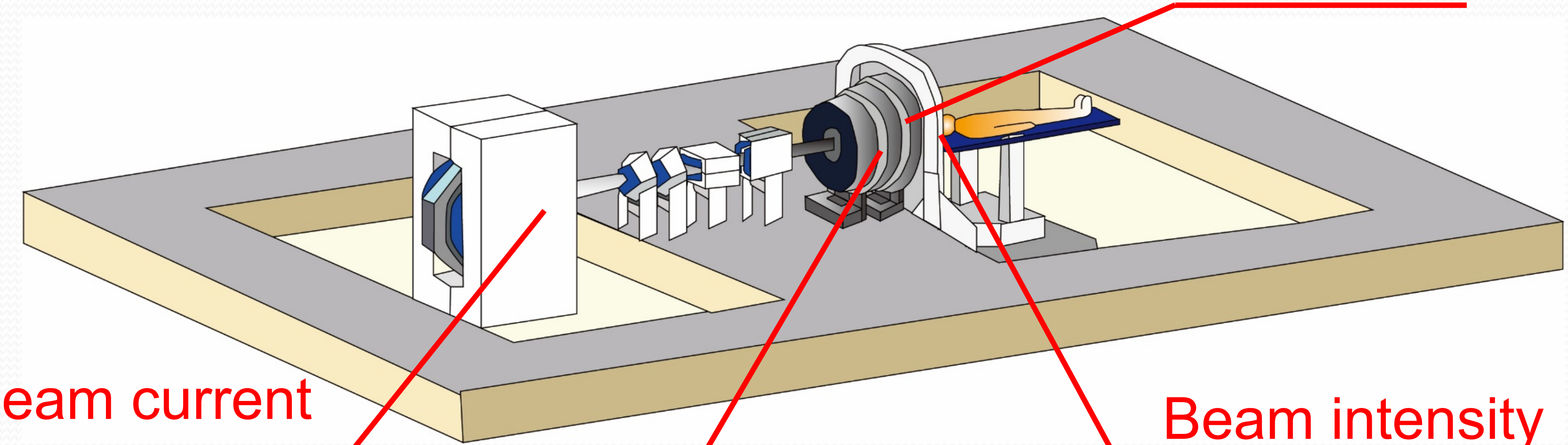


Accelerator based neutron source

Accelerator

Moderator

Activation



Beam current

Current 1-30 (mA)

Beam intensity

Epithermal neutron flux>5×10^{8} cm^{-2}s^{-1}

Fast neutron contamination<7×10^{-13} Gy cm^{2}

Gamma-ray contamination<2×10^{-13} Gy cm^{2}

Heat reduction of target

Blistering

Neutron yield 10^{13}-10^{14}(n/s)

Plan of accelerator based neutron source

Proton Energy	**Accelerator**
Ep<3MeV	Electrostatic accelerator、RFQ
3MeV<Ep<11MeV	Linac、Cyclotron
11MeV<Ep<100MeV	Cyclotron、FFAG

Reaction	Proton Energy (MeV)	Yield (Neutron/ Proton)	Melting (°C)	Conductivity(W/m/K)	Neutron Energy	Moderator Size
^{7}Li(p,n)^{7}Be	2.5	1.46x10^{-4}	180	84.7	0.1〜0.5MeV	Small
^{9}Be(p, n)^{9}B	4	1.6x10^{-4}	1278	201	Depend on proton energy	Large
^{9}Be(p, n)^{9}B	30	3.0x10^{-2}	1278	201		Large
Ta(p,xn)	50	7.0x10^{-2}	3017	57.5		Large

Beam current ⟺ Reduction of heat on target

Trade off

Size of moderator ⟺ Neutron intensity penetrated after moderator

Accelerator-based neutron source for BNCT

Blue: Items to consider
Red: Merit

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

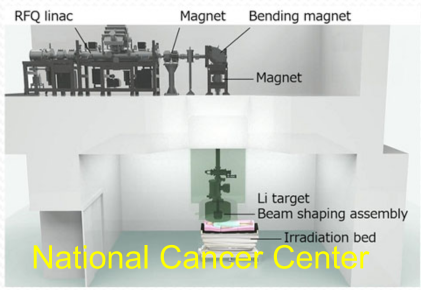
Beryllium
- High melting point
- High heat conductivity

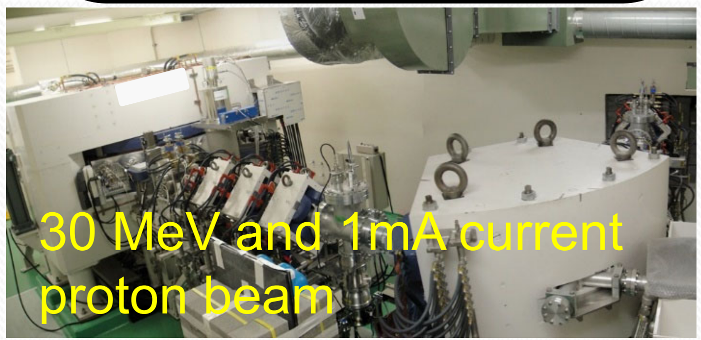
Heavy material(tantalum etc.)
- High melting point
- High heat conductivity
- Activation of target

Low energy proton<3MeV
- Neutron production yield ：Low
- Activation：Low
- Moderator：small
- Blistering(Backing material)
- High current～10mA

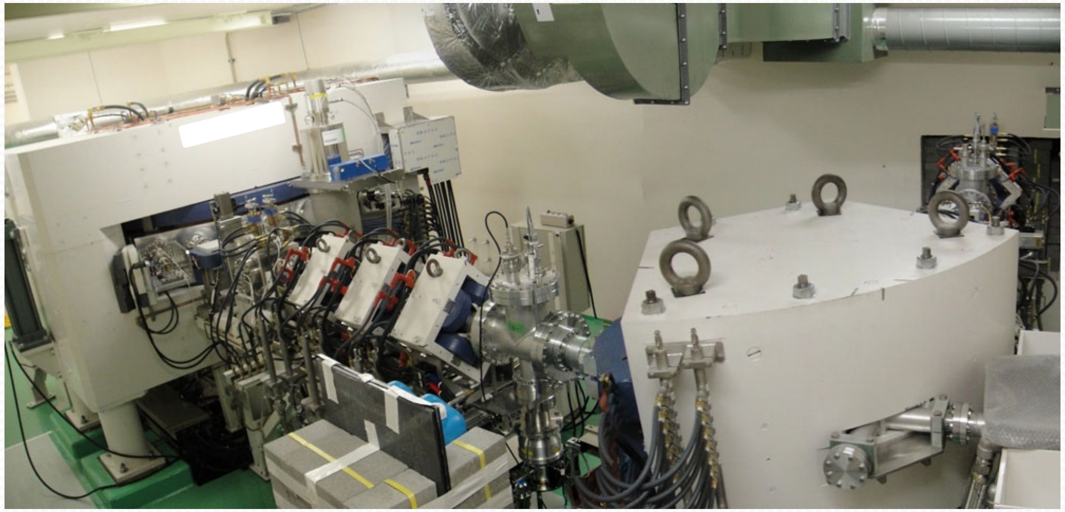
3MeV<Middle energy<8MeV
- Neutron production yield ：Middle
- Activation：Low
- Moderator：Middle
- Blistering(Backing material)
- Middle current～2mA

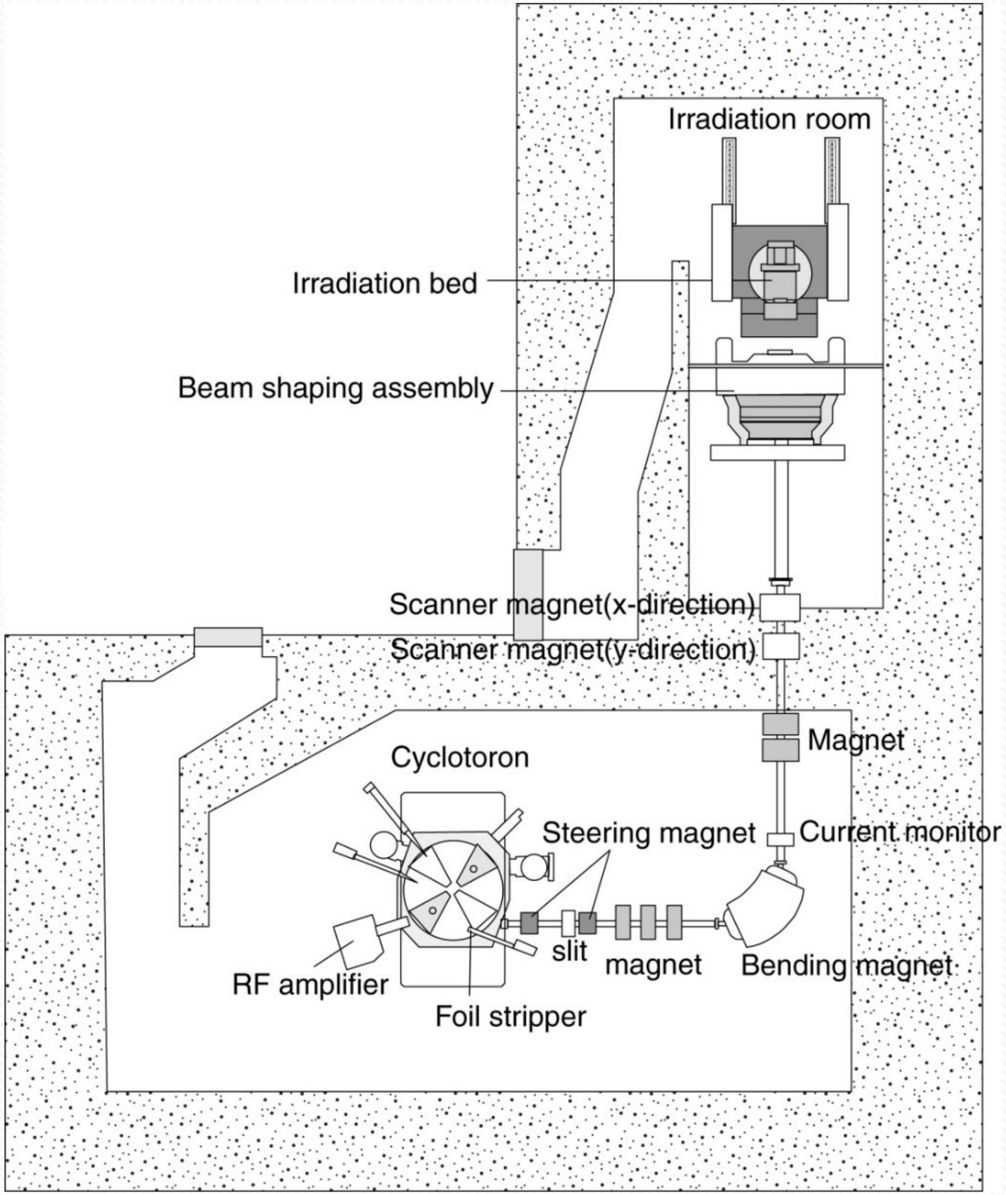
High energy>30MeV
- Neutron production yield ：High
- Activation：High
- Moderator：Large
- No blistering
- Small current～1mA





Cyclotron Based Epithermal Neutron Source(C-BENS)





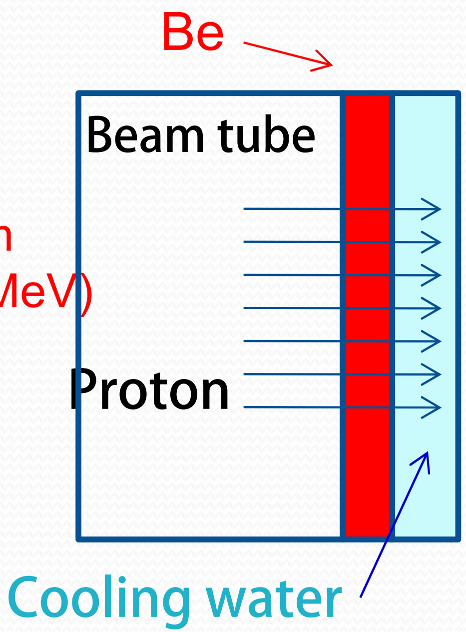
Accelerated particle : negative hydrogen ion(-H)

Maximum Energy:30MeV

Stable beam current: 1mA

Maximum power : 30kW

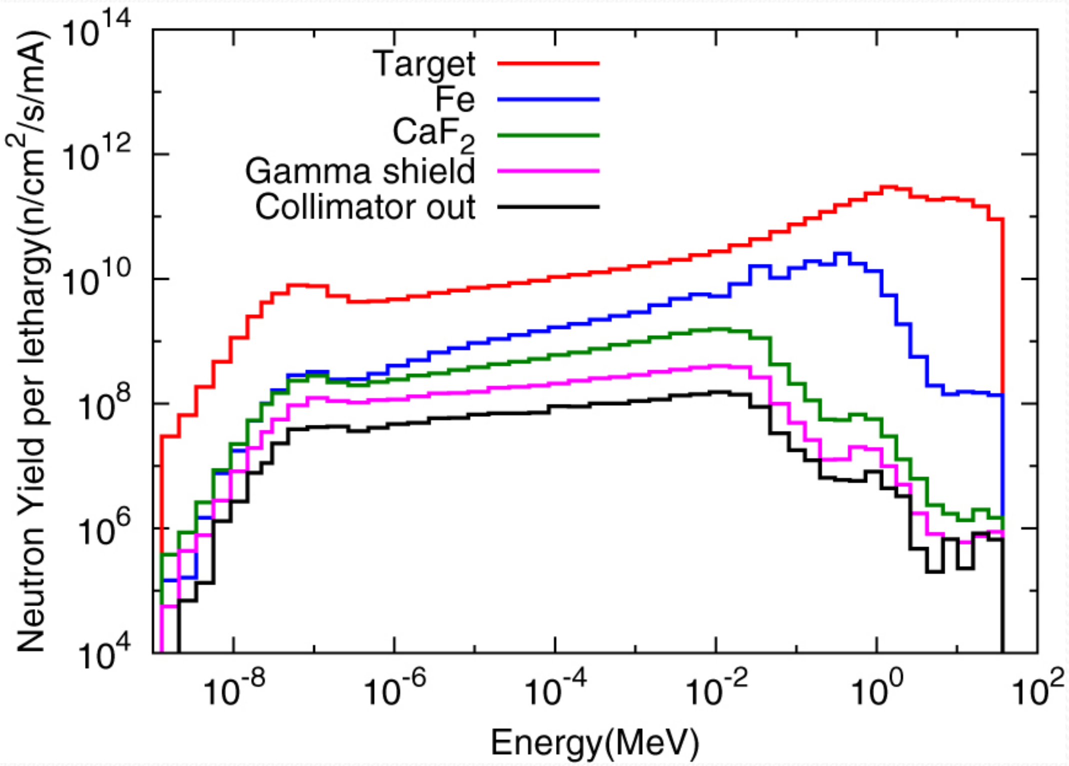
Be target thickness is 5.5 mm
(proton range :5.8 mm at 30MeV)



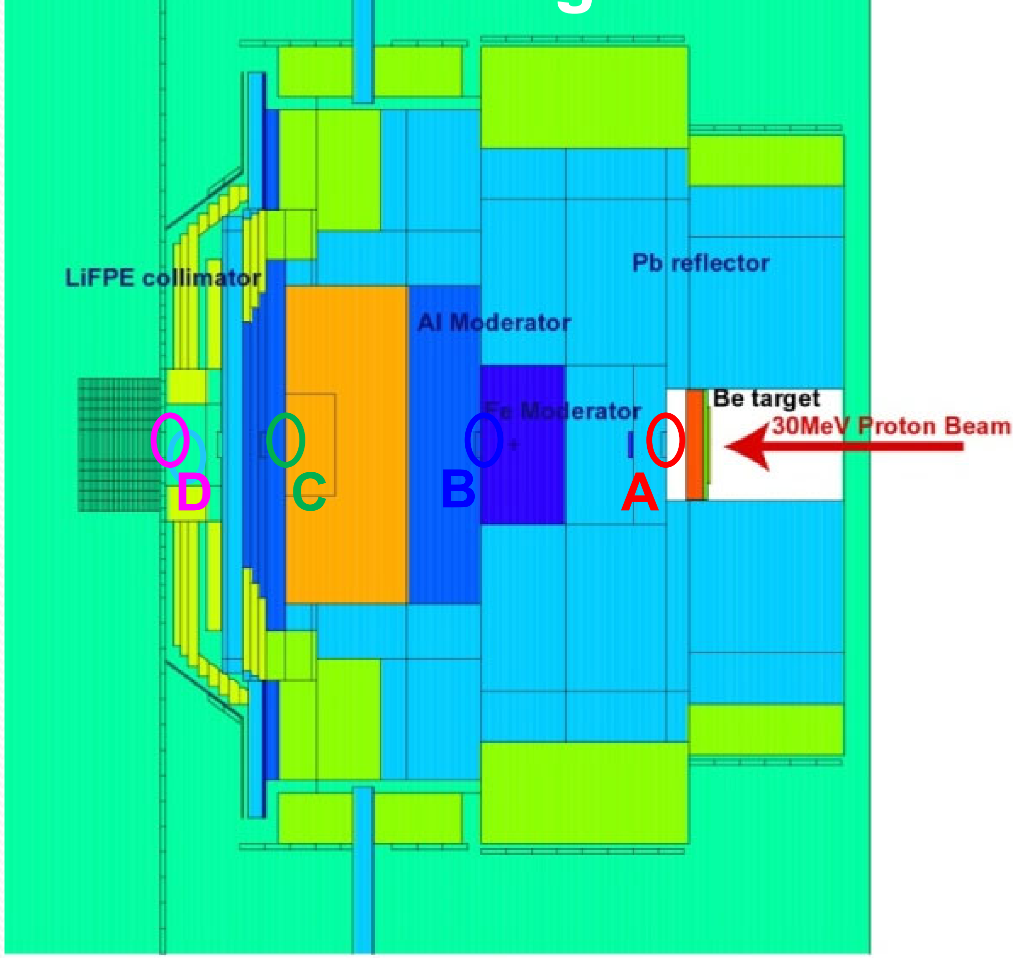
Cyclotron Based Epithermal Neutron Source(C-BENS)

Pb : used as a breeder and a reflector for high energy neutrons
Fe : used as a moderator
Al and CaF_2 : used as a shaper for epi-thermal region
Polyethylene : used as a shielding for high energy neutrons

Inelastic reaction cross section of Pb and Fe



Calculation using MCNPX



Al has the valley of XS at around 27keV. F has the resonance at several hundred keV.

Cyclotron Based Epithermal Neutron Source(C-BENS)
Southern Tohoku BNCT Research Center

Applied Radiation and Isotopes 156 (2020) 108961

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journal homepage: http://www.elsevier.com/locate/apradiso

Design and construction of an accelerator-based boron neutron capture therapy (AB-BNCT) facility with multiple treatment rooms at the Southern Tohoku BNCT Research Center

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[c] Sumitomo Heavy Industries, Ltd., Tokyo, 141-6025, Japan

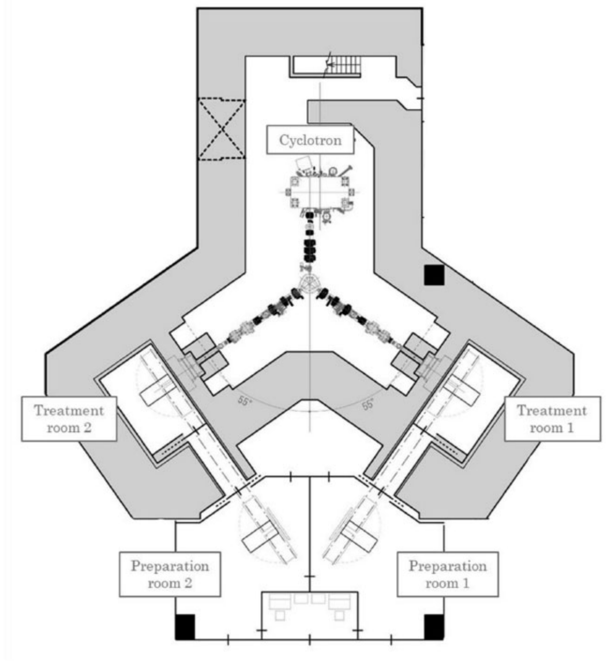
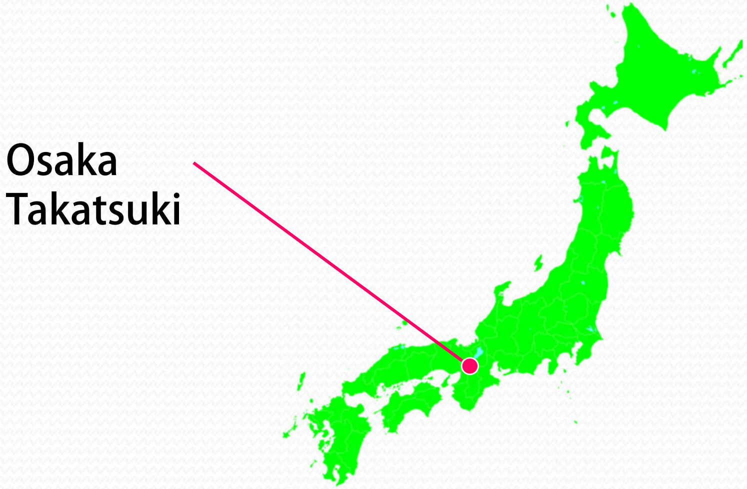
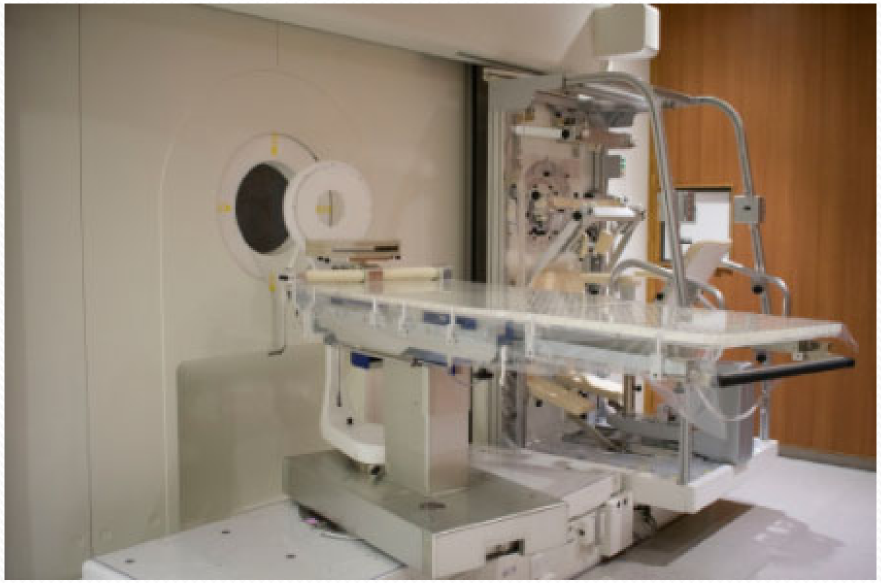


Fig. 1. Schematic layout of the basement floor of the Southern Tohoku BNCT Research Center.

http://southerntohoku-bnct.com/

Cyclotron Based Epithermal Neutron Source(C-BENS)
Kansai BNCT Medical Center





https://www.ompu.ac.jp/kbmc/index.html

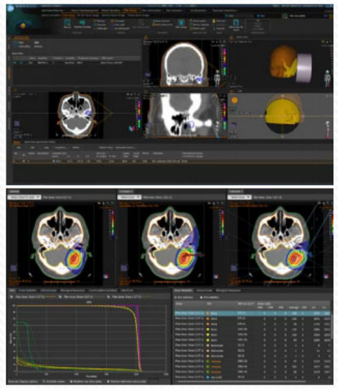
Cyclotron Based Epithermal Neutron Source(C-BENS)
BNCT Treatment system, Treatment planning system, Boron drug
The approvals of medical device and drug

- 2014/4 — Ph1 Clinical trial
- 2016/7 — Ph2 Clinical trial※
- 2017/2,4 — "Sakigake" Designations system
- 2019/10 — Application
- 2020/3 — March 11, 2020 Medical device approved, March 25, 2020 Drug approved
- 2020/6 — National Healthcare Insurance Coverage

※K. Hirose et al., Radiotherapy and Oncology, 155, 182-187,(2021)

Southern Tohoku BNCT Research Center
Kansai BNCT Medical Center

"unresectable locally advanced or locally recurrent head and neck cancer"



AB-BNCT projects in the world

Beryllium 10 projects

Name of the project	Location	Accelerator	Purpose	Current status
C-BENS	Particle Radiation Oncology Research Center of Kyoto University in Kumatori, Japan	Cyclotron	BNCT research	complete clinical trial
NeuCure (BNCT30)	Southern Tohoku BNCT Research Center, Fukushima, Japan	Cyclotron	Clinical BNCT	patient treatment
NeuCure (BNCT30)	Kansai BNCT Medical Center, Osaka Medical College, Osaka, Japan	Cyclotron	Clinical BNCT	patient treatment
NeuCure (BNCT30)	Boao BNCT Center, Boao, China	Cyclotron	Clinical BNCT	under construction
Heron AB-BNCT	China Medical University Hsinchu Hospital, Zhubei City, Hsinchu County, Taiwan	Cyclotron	Clinical BNCT	clinical trial
Heron AB-BNCT	Taipei Veterans General Hospital, Taipei, Taiwan	Cyclotron	Clinical BNCT	under development
CYCIAE-14B	China Institute of Atomic Energy (CIAE), Beijing, China Tai'an Central Hospital, Tai'an, China	Cyclotron	BNCT research	commissioning
iBNCT	Ibaraki Neutron Medical Reserch Center, University of Tsukuba, Japan	RFQ+DTL	Clinical BNCT	clinical trial
A-BNCT	Gachon University Gil Medical Center, Songdo, Incheon, South Korea	RFQ+DTL	Clinical BNCT	clinical trial
Legnaro-RFQ	Legnaro National Laboratory, Italian Institute of Nuclear Physics (INFN), Legnaro (Padova), Italy	RFQ	BNCT research	under development

Lithium 17 projects

Name of the project	Location	Accelerator	Purpose	Current status
NCC CICS-1	National Cancer Center Hospital, Tokyo, Japan	RFQ	Clinical BNCT	phase I clinical trial
CICS-2	Edogawa Hospital, Japan	RFQ	Clinical BNCT	clinical trial
LU AB-BNCT	Fujian Medical University Union Hospital (Mazu Hospital), Putian City, Fujian Province, China	RFQ	Clinical BNCT	commissioning
D-BNCT01	Dongguan Neutron Science Center, Dongguan campus of IHEP, China	RFQ	BNCT research	experimental use
D-BNCT02	Dongguan People's Hospital, China	RFQ	Clinical BNCT	under construction
X-TANS	Xi'an Jiaotong University, Xi'an, China	RFQ	Multi-purpose research	under development
SARAF-LiLiT	Soreq Nuclear Research Center, Israel	RFQ+HWR	Multi-purpose research	experimental use
nuBeam	Helsinki University Hospital, Finland	Electrostatic	Clinical BNCT	commissioning
nuBeam	Shonan Kamakura General Hospital in Kanagawa Prefecture, Japan	Electrostatic	Clinical BNCT	commissioning
HF ADNF	Birmingham University, UK	Electrostatic	Multi-purpose research	commissioning
NeMeSis	Granada University Hospital, Spain	Electrostatic	Clinical BNCT	under development
NUANS (Dynamitron)	Nagoya University, Japan	Electrostatic	BNCT research	experimental use
KIRAMS AB-BNCT	Korea Institute of Radiological and Medical Sciences (KIRAMS), Seoul, South Korea	Electrostatic	BNCT research	under construction
NeuPex	Xiamen Humanity Hospital, Xiamen City, China	Electrostatic Tandem	Clinical BNCT	clinical trial
Alphabeam	Fondazione Centro Nazionale Adroterapia Oncologica (CNAO), Pavia, Italy	Electrostatic Tandem	Clinical BNCT	under construction
VITA	Budker Institute of Nuclear Physics, Novosibirsk, Russia	Electrostatic Tandem	BNCT research	experimental use
VITA	Blokhin National Medical Research Center of Oncology, Moscow, Russia	Electrostatic Tandem	Clinical BNCT	under construction

https://isnct.net/bnct-boron-neutron-capture-therapy/accelerator-based-bnct-projects-2021/

BNCT dosimetry

Dose evaluation of BNCT

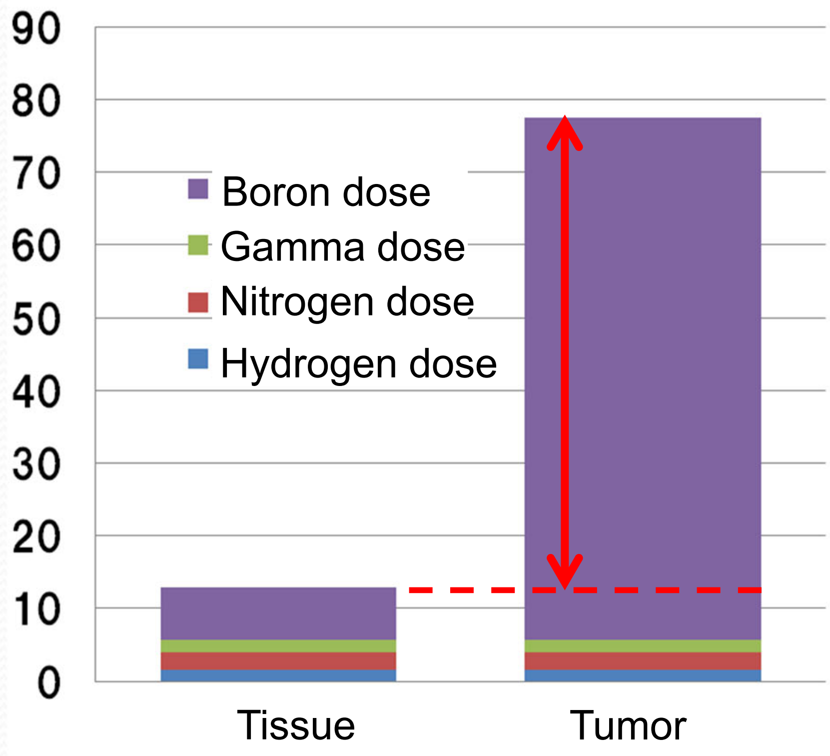
The main doses produced by neutron irradiation in BNCT are,

(1) Boron dose : $^{10}B(n,\alpha)^{7}Li$
Depends on boron concentration, reaction with thermal neutrons

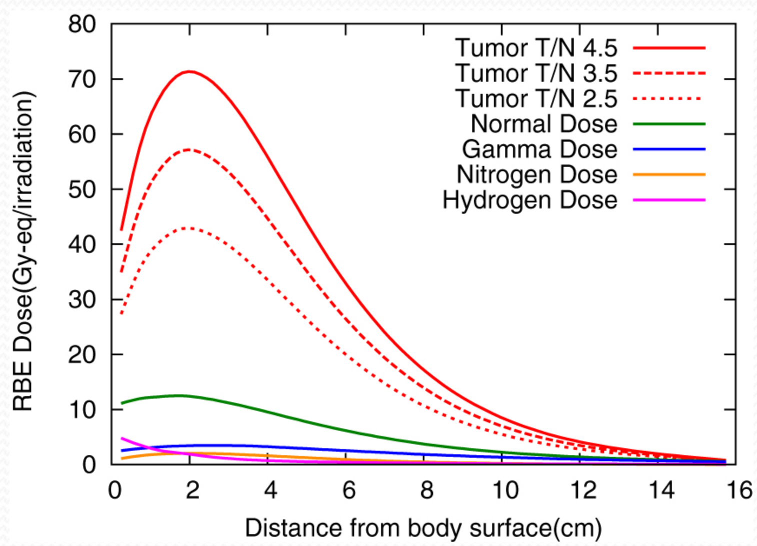
(2) Gamma dose:
from accelerator neutron source
from (n,γ) reaction between thermal neutron and hydrogen in human body

(3)Nitrogen dose: $^{14}N(n,p)^{14}C$

(4)Hydrogen dose: $^{1}H(n,n)p$



In BNCT dosimetry, the total dose from (1) to (4) must be determined for each tumor and tissue.

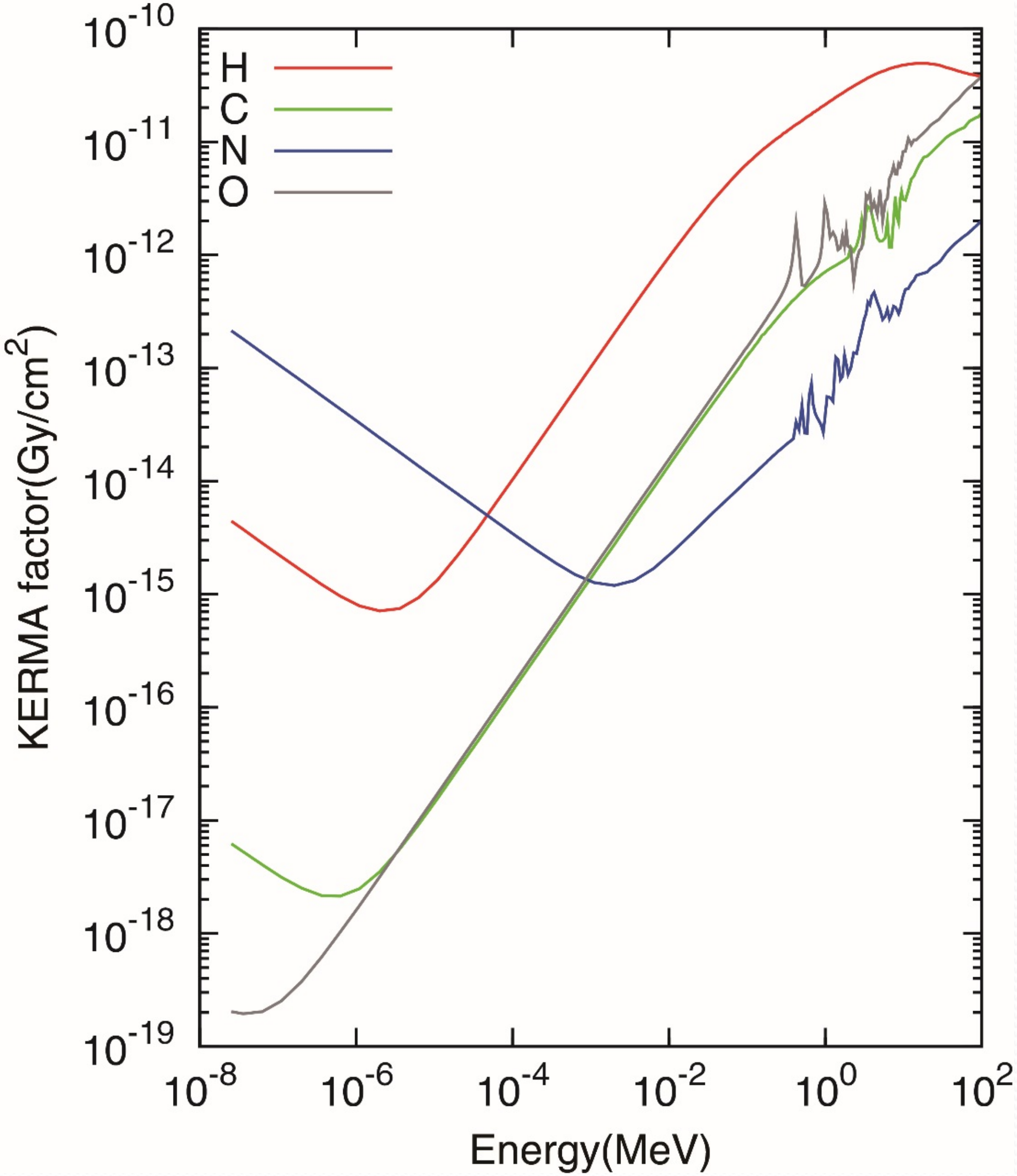


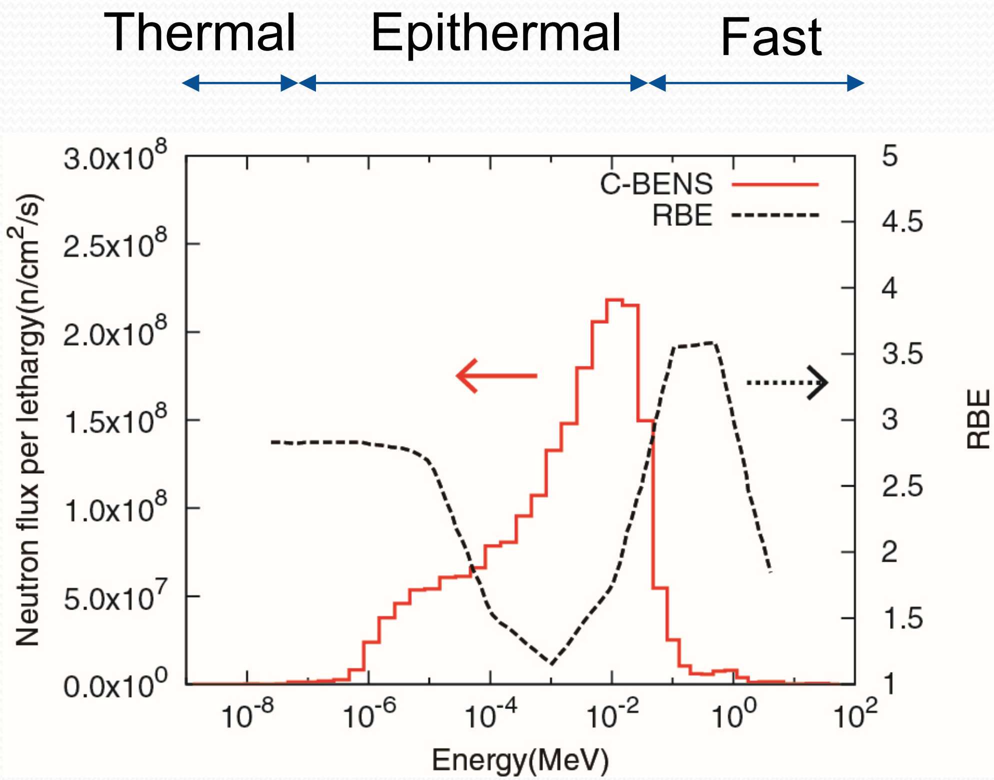
The difference in boron doses can be used as a dose advantage for tumors over normal tissues.

Physical dose (Gy)

kinetic **e**nergy **r**eleased in **ma**terials:Gy

KERMA × Neutron energy spectrum





RBE vs Energy:
T.E. Blue, et al., Phys. Med. Biol., 38, 1693-1712,1993

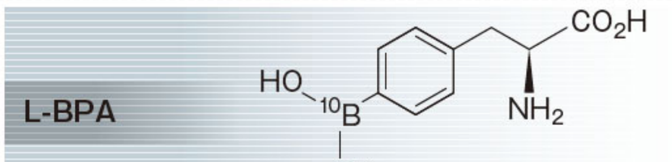
It is difficult to measure the whole energy region. Monte Carlo simulation is necessary.

RBE,CBE

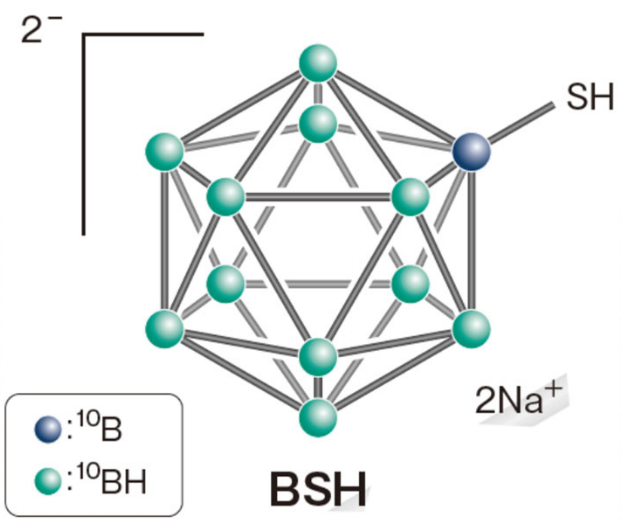
Relative Biological Effectiveness :RBE,
Compound Biological Effectiveness : CBE

Compound	Tumor	Skin	Brain	Mucosa	Liver	Lung
BSH CBE	2.5	0.8	0.37	0.3	?	
BPA CBE	3.8	2.5	1.35	4.9	?	?
Nitrogen RBE	3					
Hydrogen RBE	1.8-3.2(Depended on neutron energy)					

BPA (borono-phenylalanine)



BSH

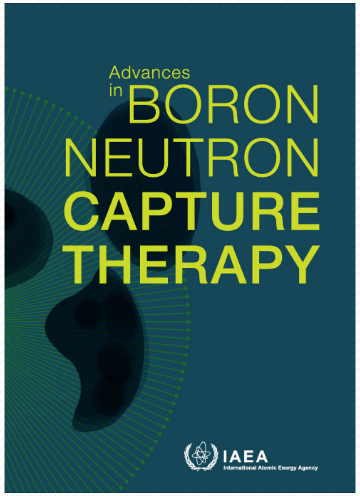


Tumor boron concentration/blood boron concentration = ~3.5

Each physical dose is multiplied by its RBE or CBE. The total X-ray equivalent dose is obtained by multiplying each physical dose by

Boron equivalent dose D_B
= Boron physical dose x CBE
Nitrogen equivalent dose D_N
= Nitrogen physical dose × Nitrogen RBE
Hydrogen equivalent dose D_H
= hydrogen physical dose × Hydrogen RBE
Total equivalent dose
D_{Total} (Gy-Eq) $= D_B + D_N + D_H + D_\gamma$

BNCT dosimetry



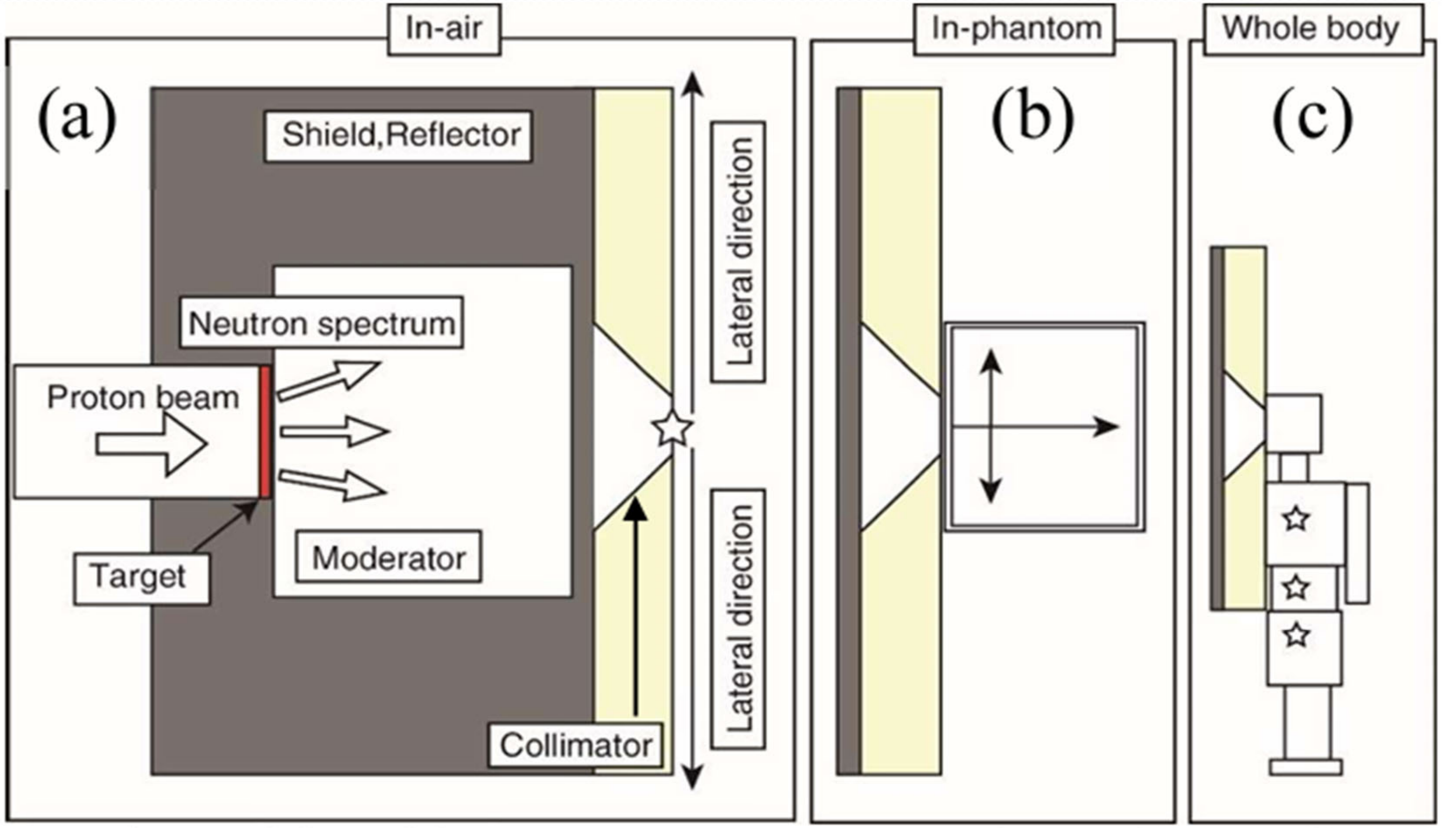
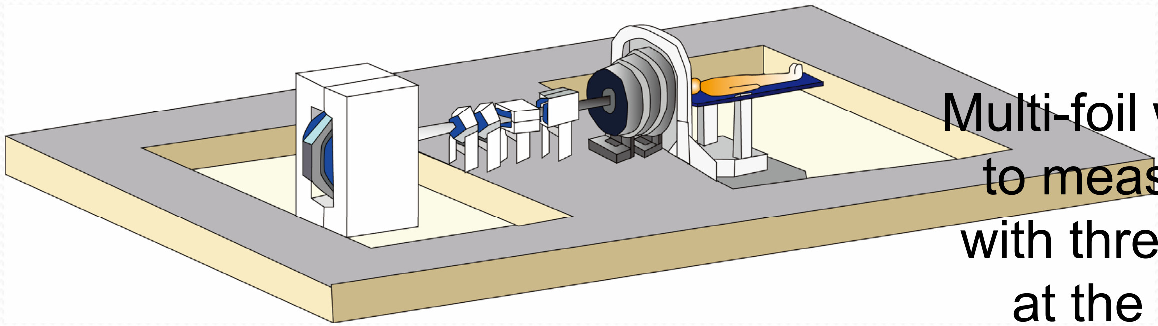
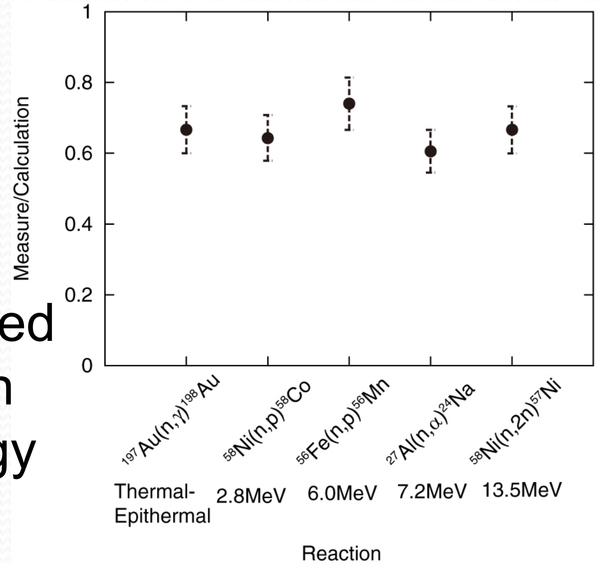


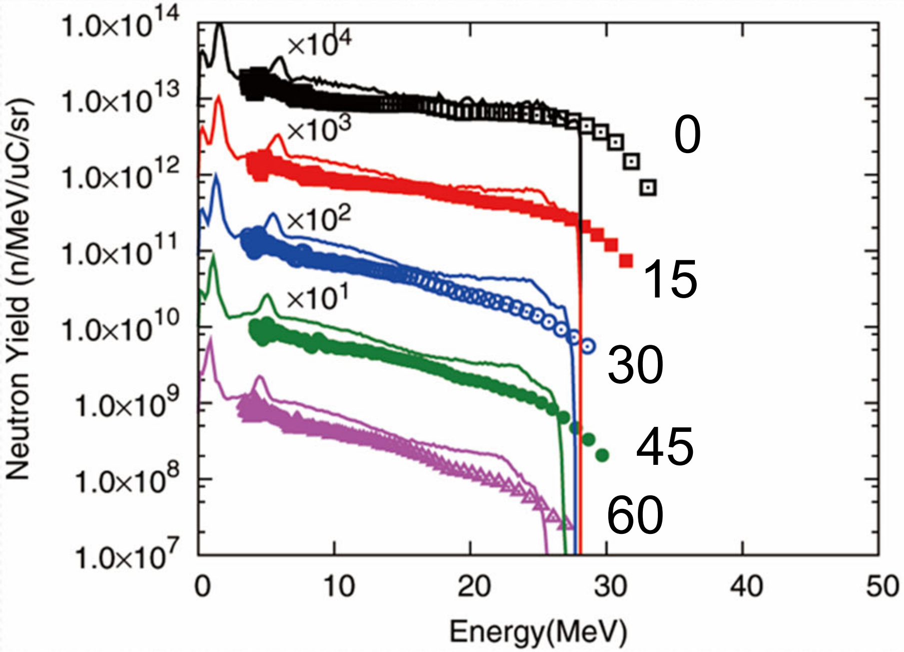
FIG. 17. Schematic layout of physical dosimetry in an AB-BNCT system showing (a) in-air, (b) in-phantom and (c) whole body measurements (courtesy of H. Tanaka, Kyoto University).

Neutron energy spectrum (In-air)

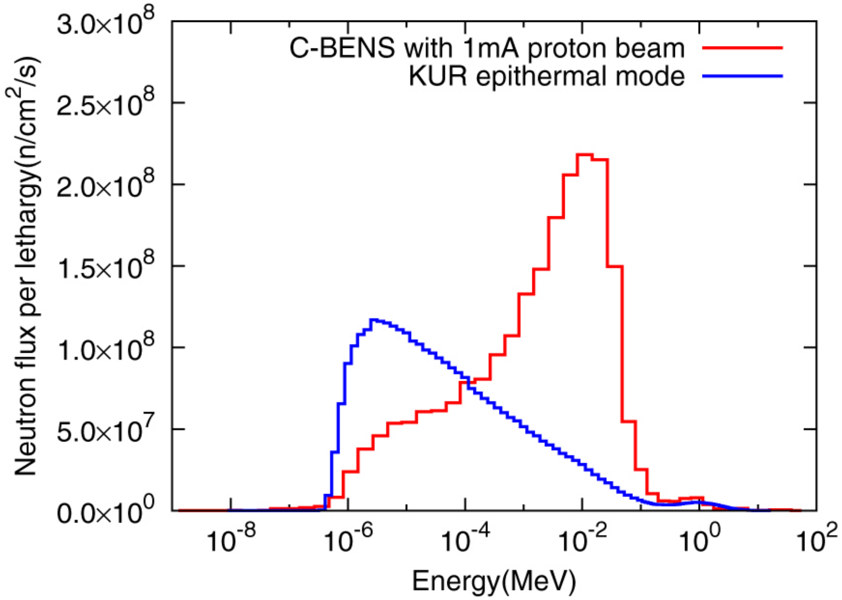




Multi-foil was irradiated to measure neutron with threshold energy at the beam port.



The neutron spectrum is measured by the time of flight at target position.



Neutron energy spectrum at beam port has a wide energy range(10^{-8}-10^{2}MeV). It is difficult to measure in whole energy range.

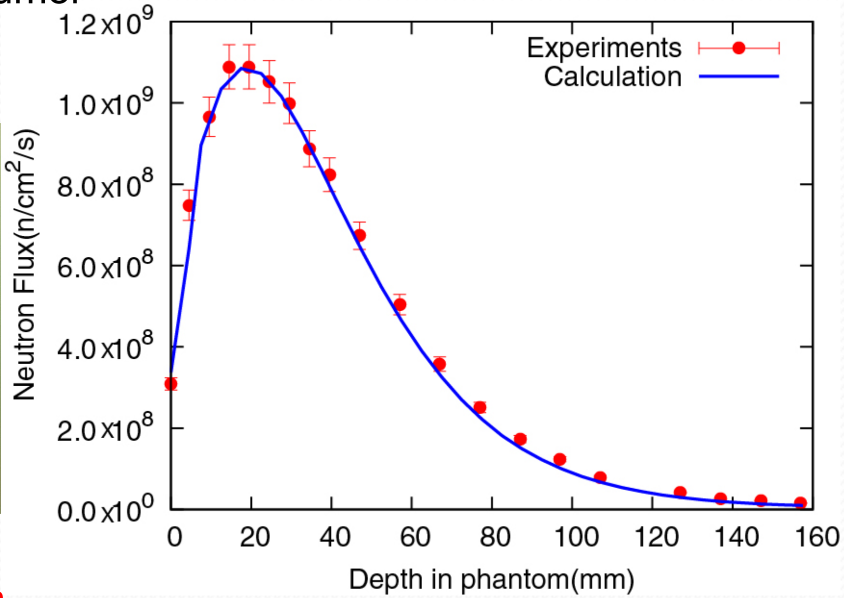
Water phantom

Water phantom

20 × 20 × 20cm cubic phantom was used in the assumption of brain tumor irradiation.

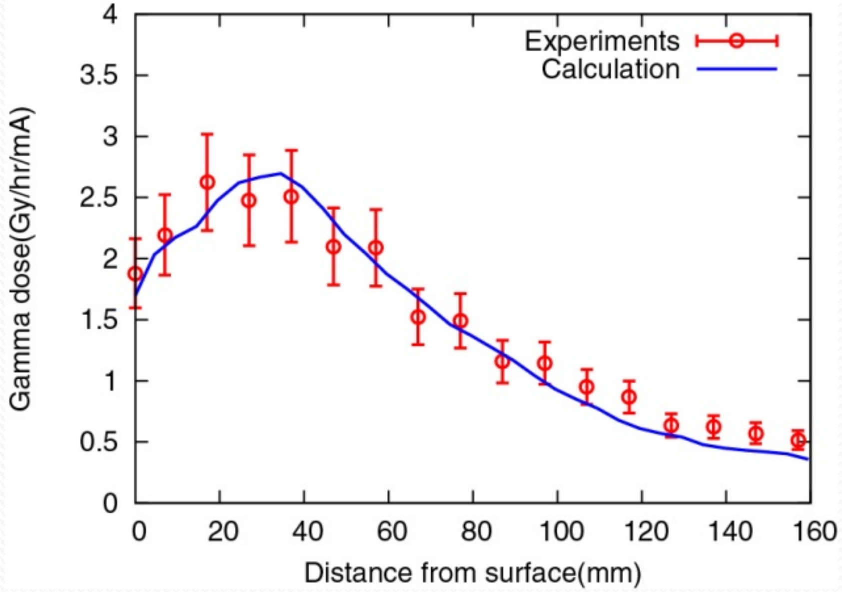
Thermal neutron flux

Gold foil with/without Cd cover



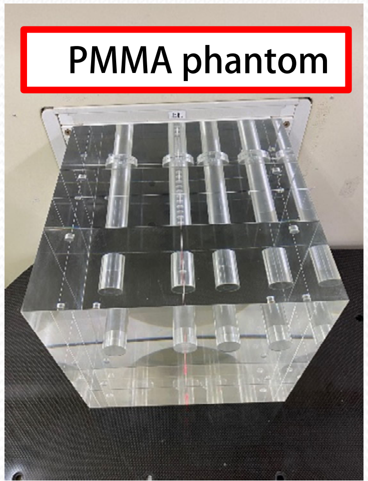
Gamma dose

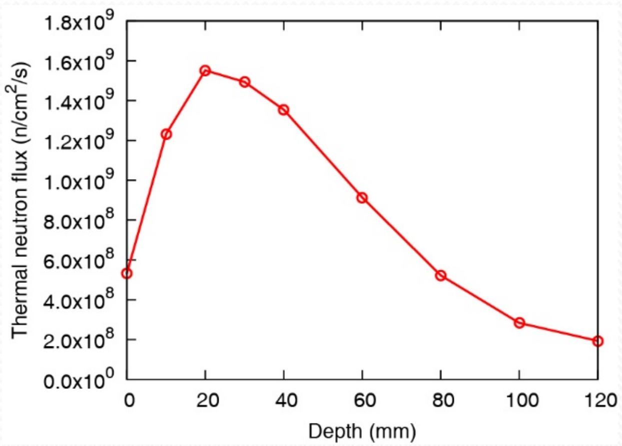
TLD enclosed in quartz glass or Glass dosimeter with LiF shielding to reduce the thermal neutron sensitivity



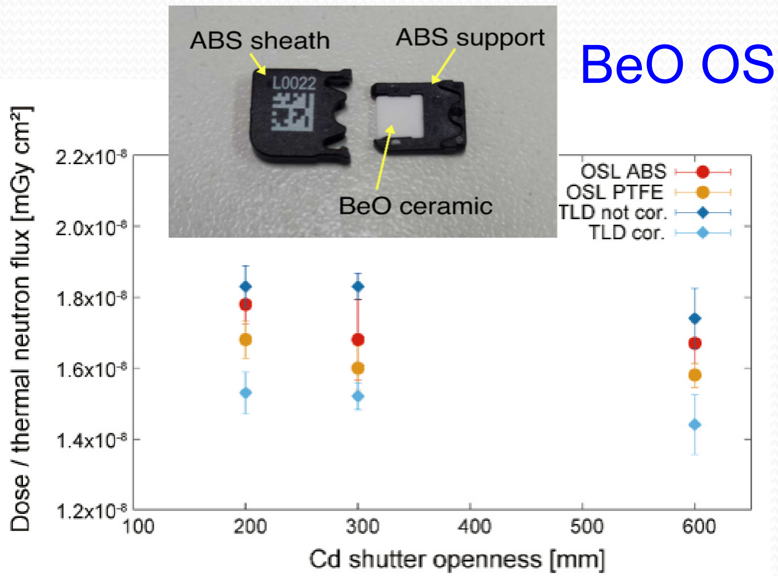
PMMA phantom

The same 30 × 30 × 30cm.





BeO OSLD

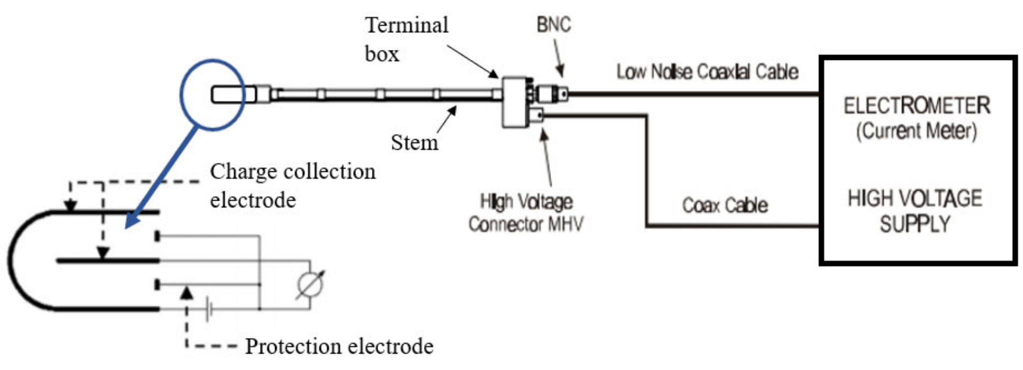


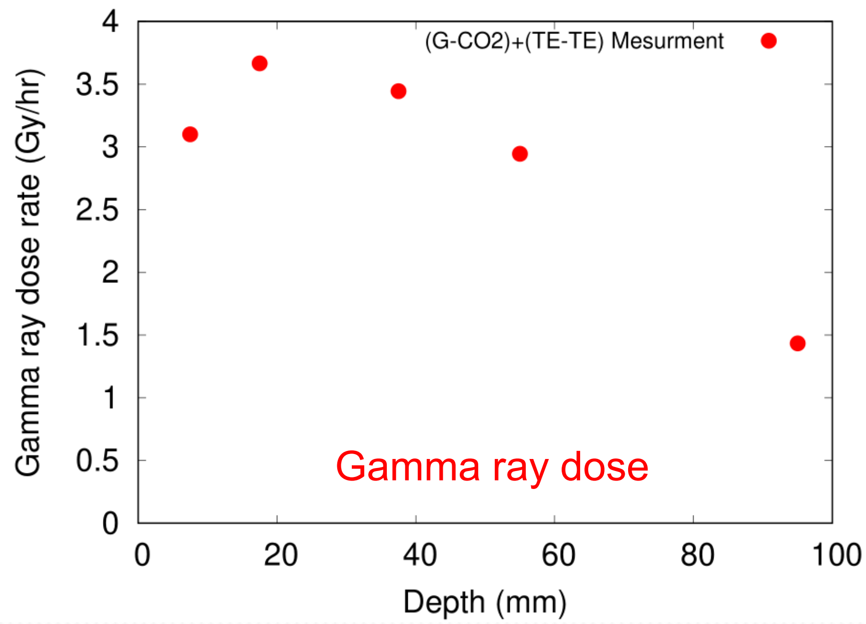
Water phantom

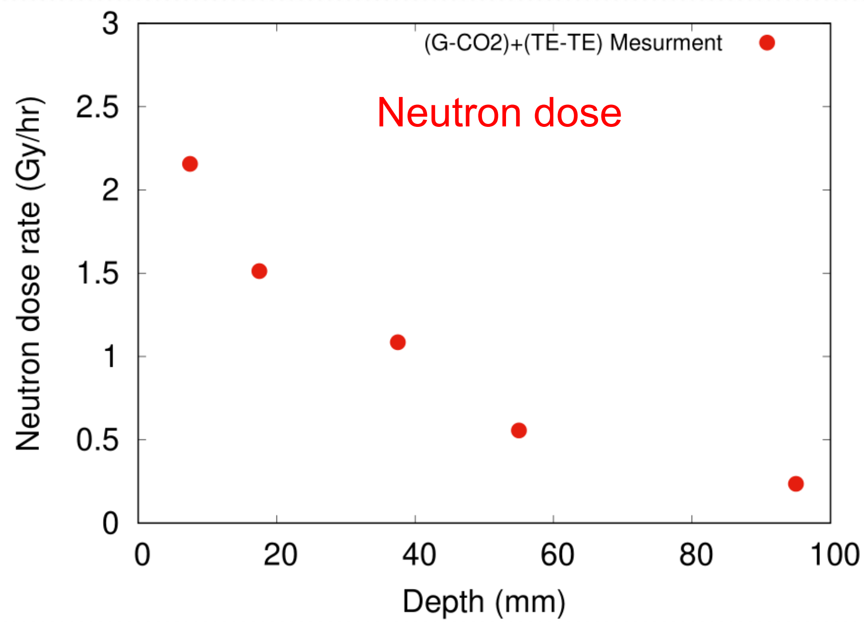
Twin ionization chamber(0.1 cc)

Graphite wall + CO_2 gas

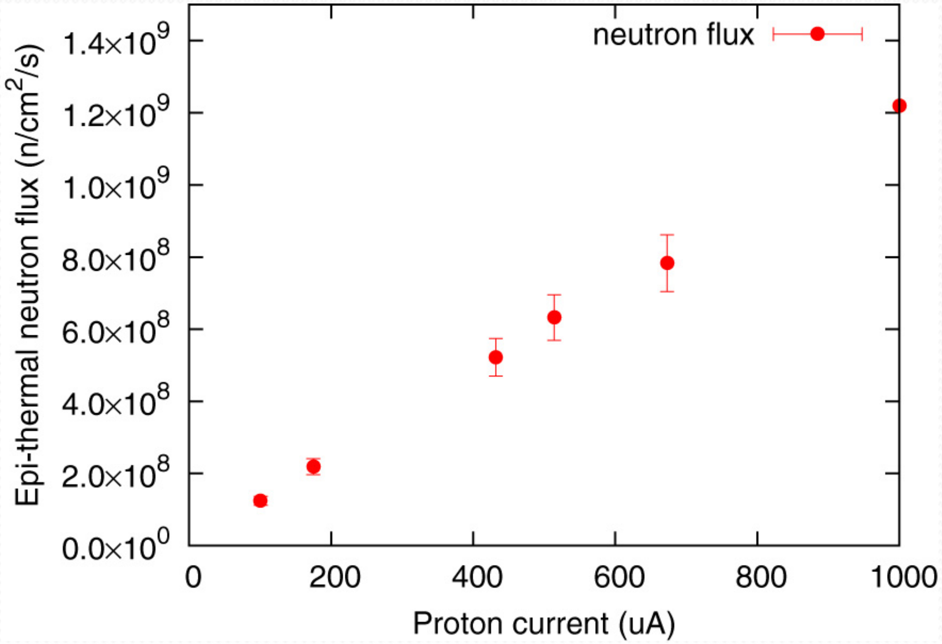
Tissue equivalent wall + TE gas

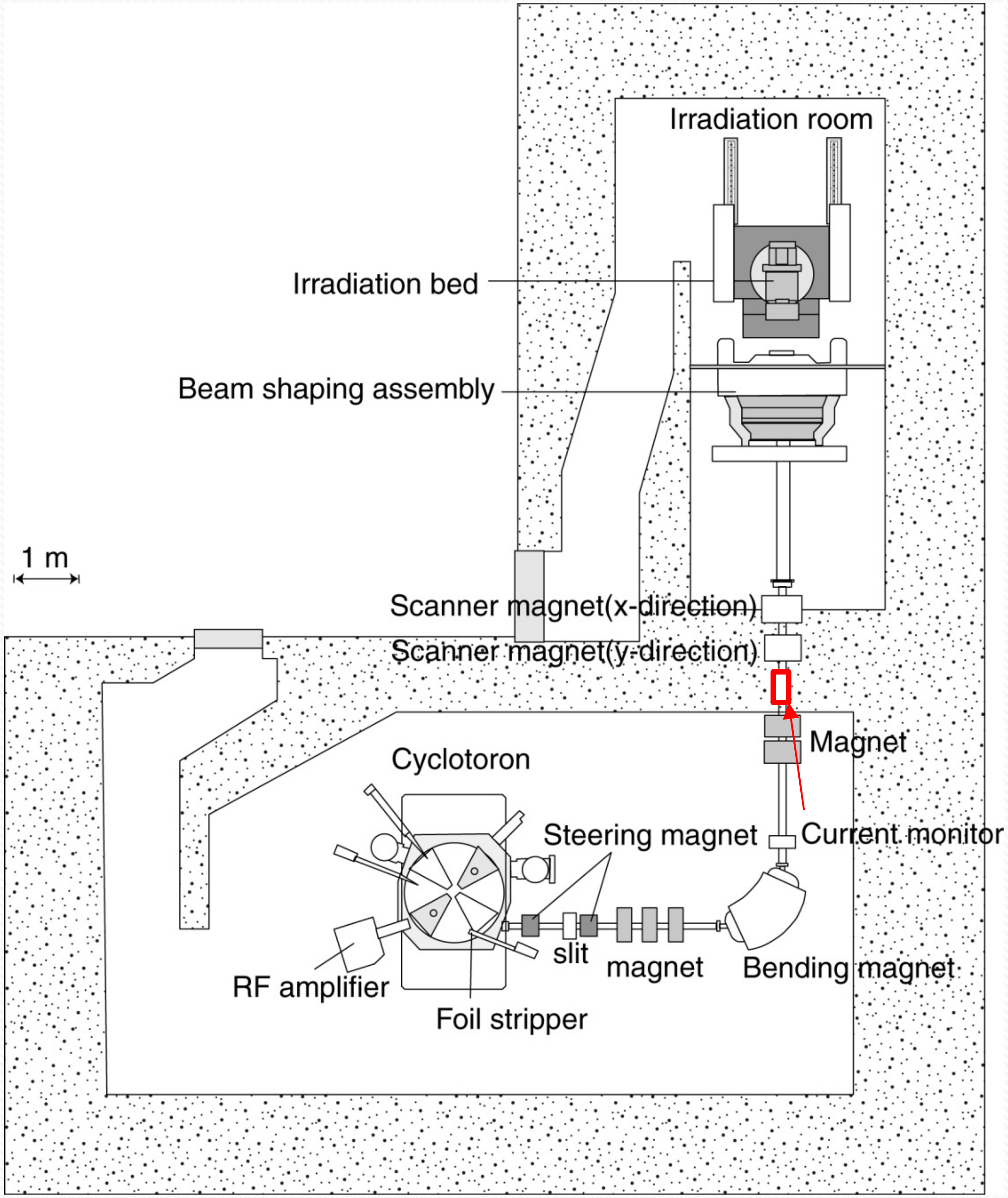






Beam monitor



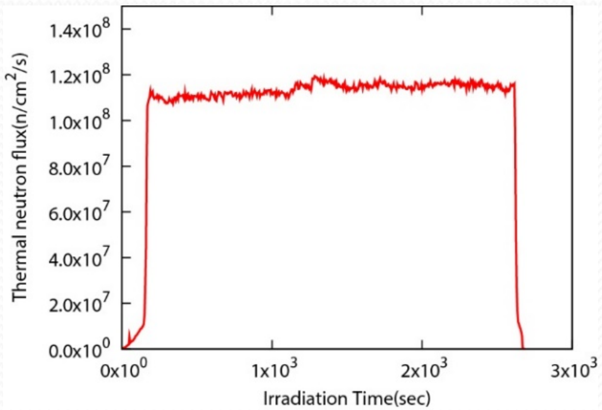


Proton electric current
Proton electric current was measured by a transmission type current monitor. It is needed to confirm the linearity between proton current and neutron flux at beam port using activation foil.

Proton electric charge is act as Monitor Unit like a conventional radiotherapy after the confirmation of the linearity and target stability. Real-time neutron monitor is desirable to determine the prescribed dose to patient.

Real time neutron detector

- Disturbance by detector size
  Small LiCAF scintillator ∼0.4mm
- Radiation resistance
  Quartz fiber∼ϕ0.6mm
- High neutron intensity10^{9}($cm^{-2}s^{-1}$)
  Small scintillator
- Discrimination of gamma ray
  Small scintillator,Pulse height distribution



Calibration

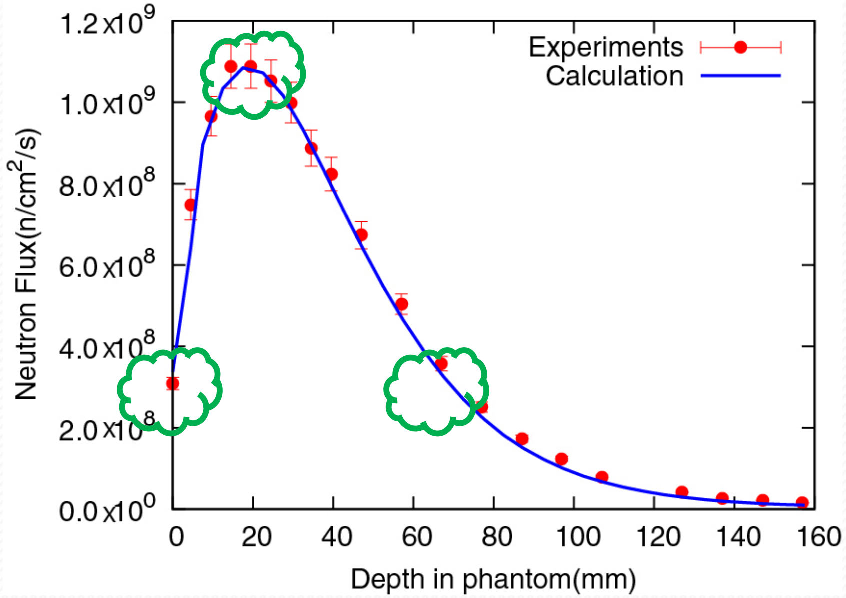
- Calibration field: thermal neutron standard at
  Institute of Japan (NMIJ)
- Source: high emission rate AmBe
- Moderator: graphite bricks
- Source-detector distance: 90 cm
- Thermal flux: ~10^3 n/cm^2/s

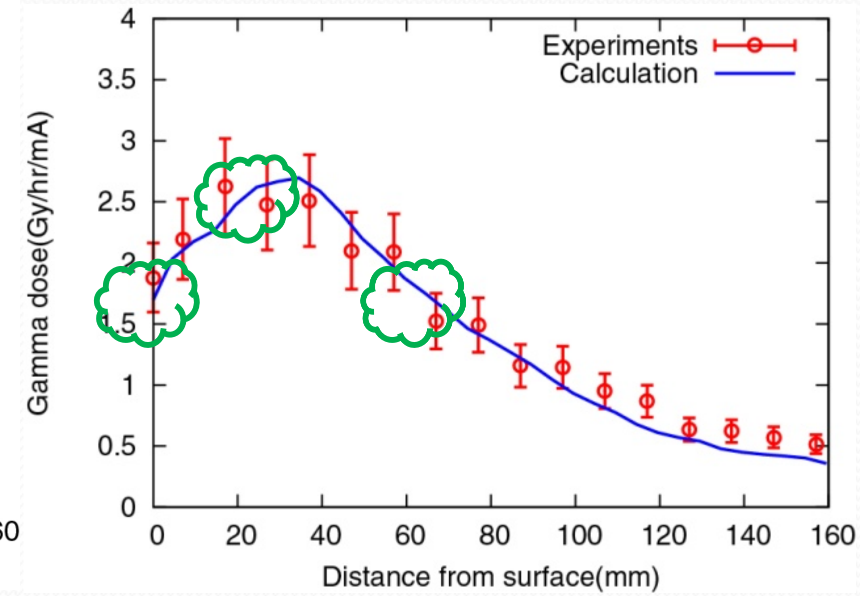
Neuron energy spectrum is practically a Maxwellian distribution

https://unit.aist.go.jp/rima/ract-neu/neutron/souti.html#souti-3

➡ Response for the thermal neutron standard field can be obtained

QA/QC





Gold wire was set at surface, 20 mm, 60 mm position to confirm the output of neutron information and irradiated with same amount of electric charge of proton beam.
Surface position can be checked the fast neutron dose in Annual QA.

Gamma ray dose distribution is similar to thermal neutron flux distribution. The measurement of gamma ray dose is useful to check not only gamma dose but thermal neutron flux.

The repeat measurement of the thermal neutron flux and gamma ray dose distribution was conducted in the commissioning phase.

Source description of neutron and gamma ray was set in treatment planning system. The simulation was performed and compared with the measured distribution of thermal neutron flux and gamma ray dose.

Summary

- **In air**

Neutron energy spectrum at target ⇨ Time of Flight
Neutron energy spectrum at beam port ⇨ Multi-foil, bonner sphere
Neutron/gamma ray dose in lateral direction ⇨ Activation method, TLD/Glass dosimeter

- **Whole body exposure**

Neutron/gamma ray dose at each organ ⇨ Human simulated phantom, Activation method

- **Water phantom**

Thermal neutron flux distribution
(Fast) Neutron dose/flux distribution ⇨ Activation method, TLD/Glass dosimeter
Gamma ray dose rate distribution ⇨ Twin ionization chamber

- **On-lineBeam monitor**

Electric current of proton beam ⇨ Electric current monitor
Real-time neutron monitor ⇨ Fission chamber, BF3,LiCAF + fiber
Calibration

- **QA/QC, Commissioning** ⇨ Activation method, TLD/Glass dosimeter
Bonner sphere

Please join us to develop BNCT dosimetry!


Thank you
email: tanaka.hiroki.3e@kyoto-u.ac.jp