BNCT - The past and the challenges for its further development

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BNCT TEAM
The European BNCT Project

SOUTHERN TOHOKU RES. INST. FOR NEUROSCI. 総合南東北病院

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Philipps Universität Marburg

Universitätsklinikum Essen

Today's Menu

A cancer problem and its hypothetical solution

BNCT: Principles

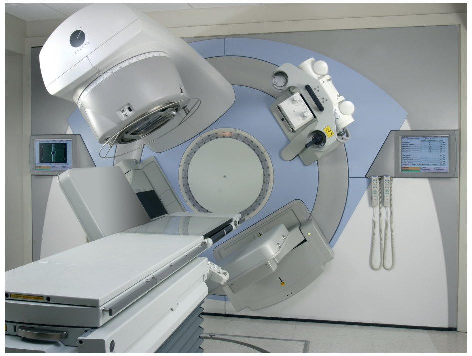
BNCT: does it work?

BNCT: the past

BNCT: What's going on?

Treatment modalities against cancer

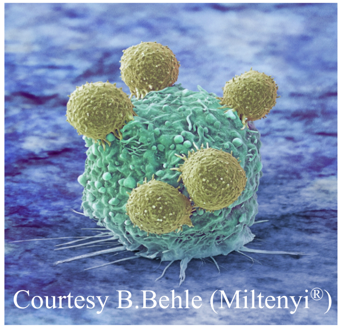
Radiation Therapy



Surgery

Drugs

Cellular Therapies



Radiation Therapy

Europe Union

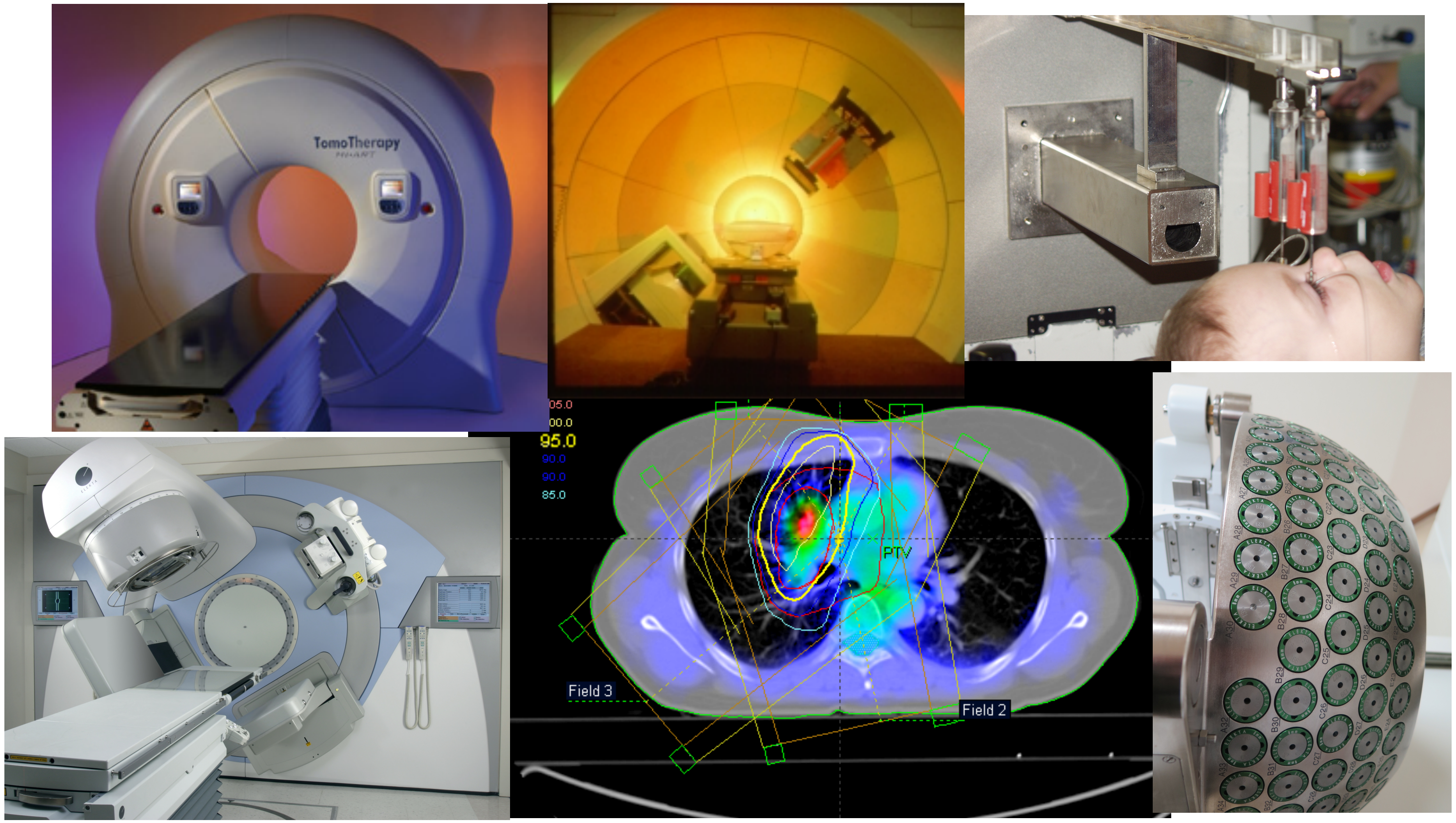
3 Mio. new cancers per year

1,7 Mio. cancer deaths

- 70 % of all patients present loco-regional limited disease
- 60 % of these patients will be definitely cured
- 80 % of all cancer patients receive radiotherapy
- 60 % of all patients who die have an uncontrolled local tumor

Modern advanced radiotherapy techniques

allow a highly precise dose distribution in a defined complex volume

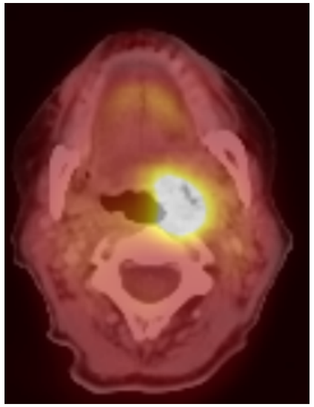


Inherent Problems with Current Radiation Therapy Techniques

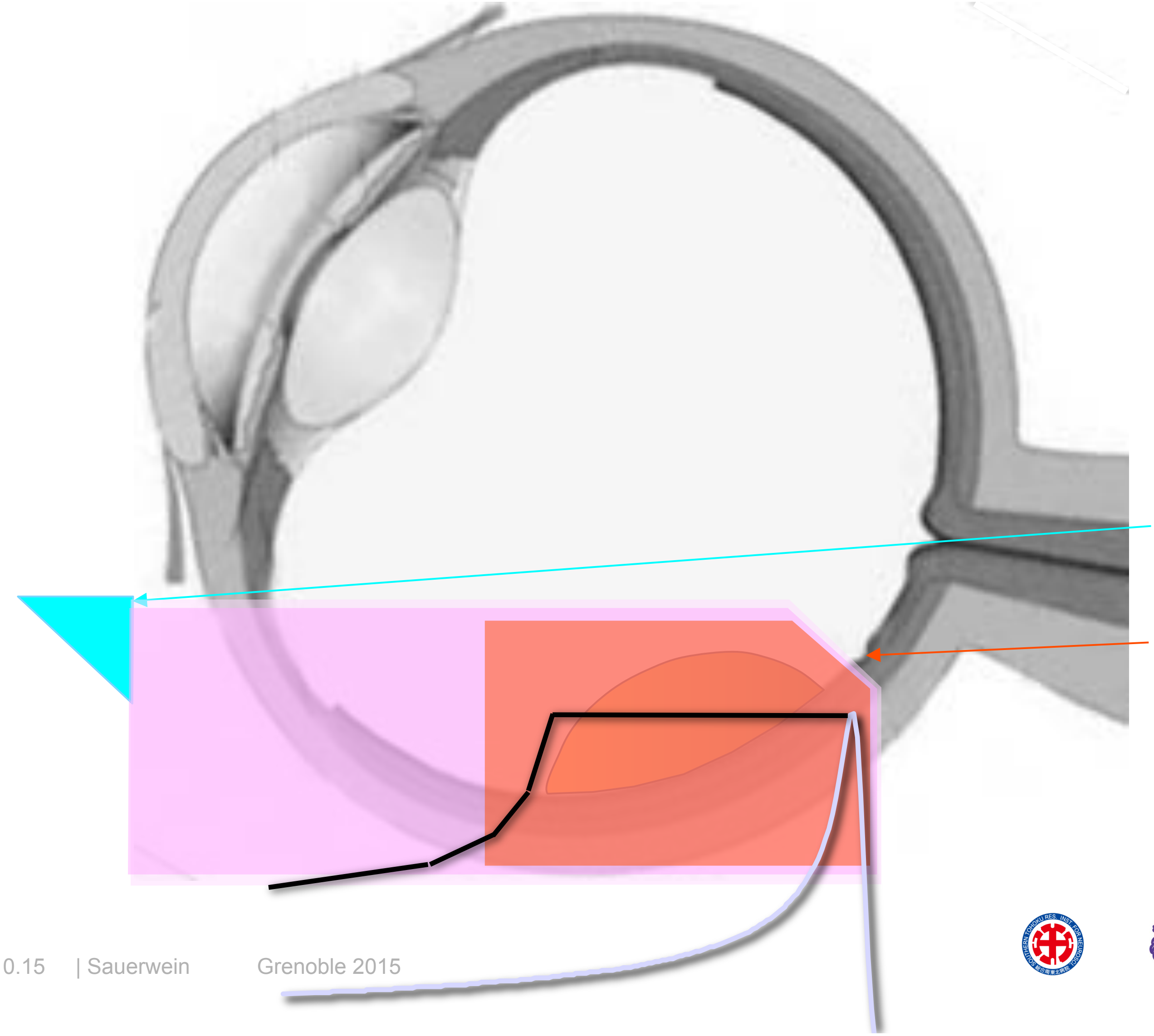
1) Treatment is delivered to a volume of tissue
   Normal tissue in target volume is treated

3) Image guidance techniques are not perfect
   Target volume will vary imaging modalities

4) Physicians define target volume
   Target volume will vary with physician and imaging modalities



Irradiation of a tumor in the eye using protons



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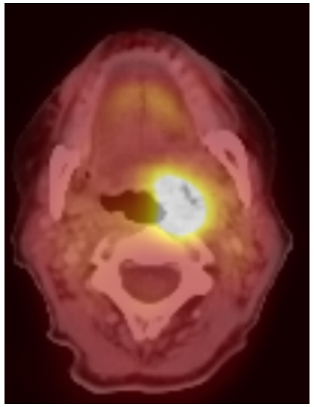


How far are we from the truth ?

TABLE 1
GTVs in Patients with Oropharyngeal Tumors

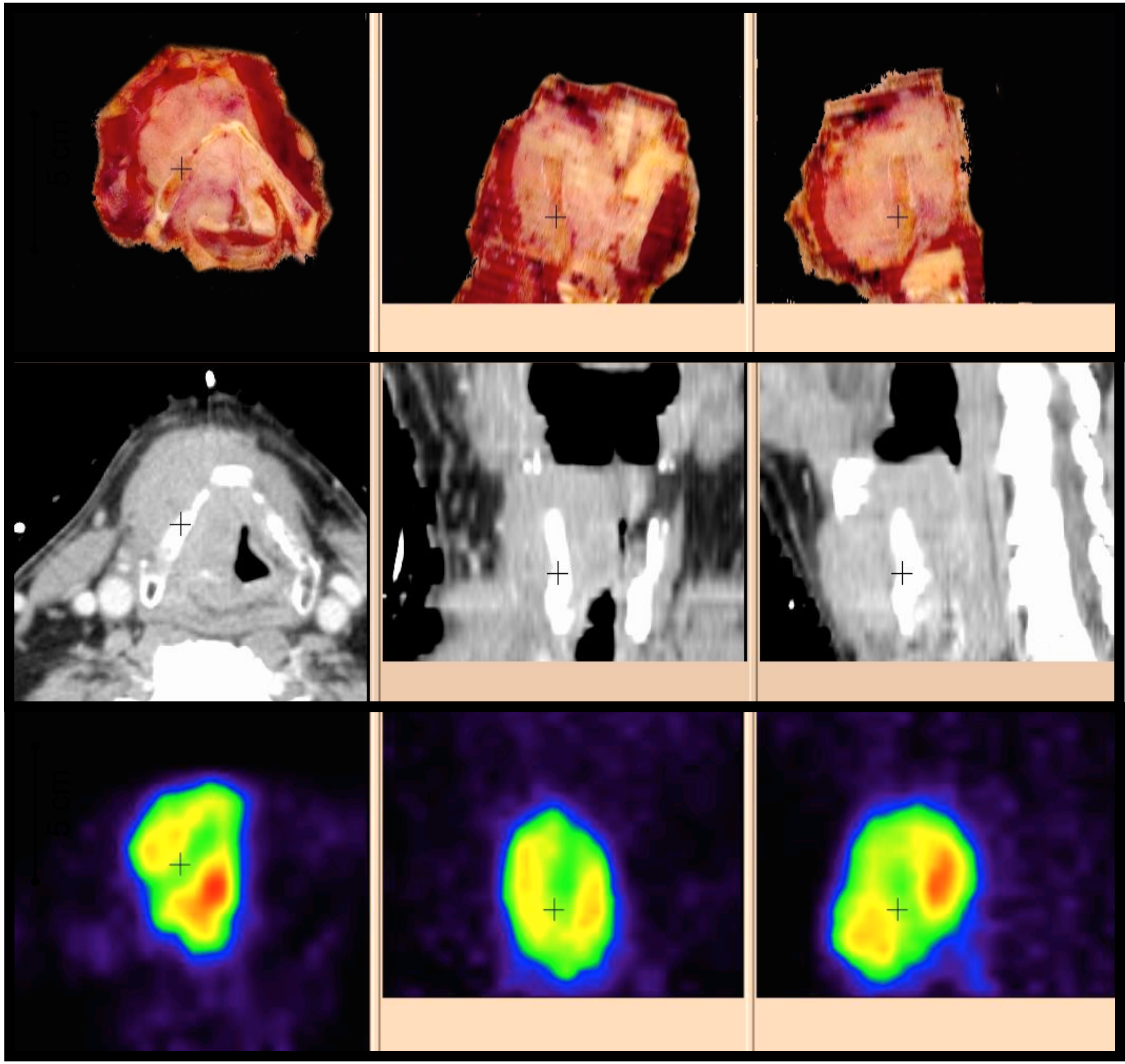
			GTV (cm³)		
Patient No.	Tumor Site	T Stage	CT	MR Imaging	FDG PET
1	BoT	T3	34.6	29.9	22.1
2	TF	T4	14.2	16.9	13.1
3	TF	T2	21.9	19.8	13.3
4	GTS	T2	7.7	5.5	8.1
5	BoT	T2	10.4	11.2	9.7
5	MT	T2	8.8	6.4	9.1
6	PPW	T4	52.0	65.4	28.5
7	PPW	T0	137.7	92.8	88.96
8	BoT	T2	5.1	0.0	5.1
9	BoT	T2	41.4	34.4	17.9
10	TF	T3	18.0	24.0	7.8
Mean	. . .	. . .	32.0	27.9	20.3*

Note.—BoT = base of tongue, GTS = glossotonsillar sulcus, MT = mobile tongue, PPW = posterior pharyngeal wall, TF = tonsillar fossa.

* In the comparison with CT and MR imaging, $P = .02$ and $P = .10$, respectively.

Daisne *et al*, 2004

How far are we from the truth ?



Macroscopy

CAT Scan

^{18}F-FDG PET

Daisne *et al*, 2004

How far are we from the truth ?

Validation with a "gold standard"

	Vol. (ml)	Mismatch $_{x/CT}$	Mismatch $_{x/MR}$	Mismatch $_{x/PET}$	Mismatch $_{x/Macro}$
CT	20.8	-	26%	48%	81%
MR	23.8	45%	-	67%	107%
FDG-PET	16.3	17%	15%	-	47%
Macroscopy	12.6*	10%	9%	13%	-

?

*$p<0.05$ (Wilcoxon rank test)

Daisne *et al*, 2004

Courtesy of Vincent Gregoire, Bruxelles

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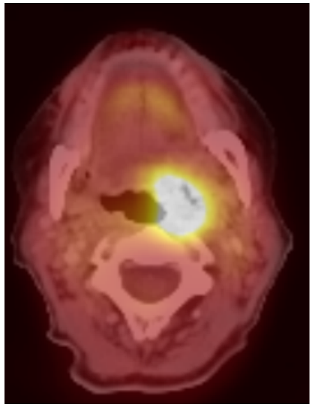
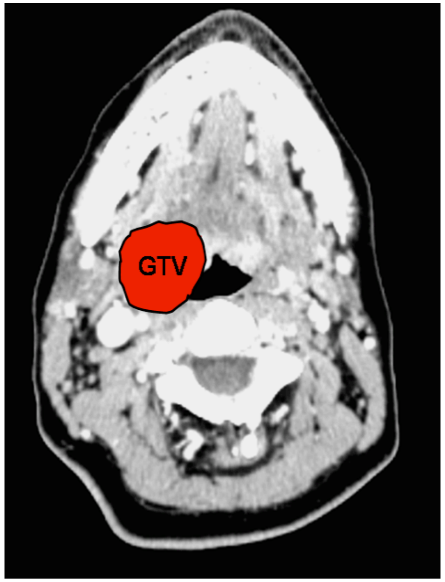
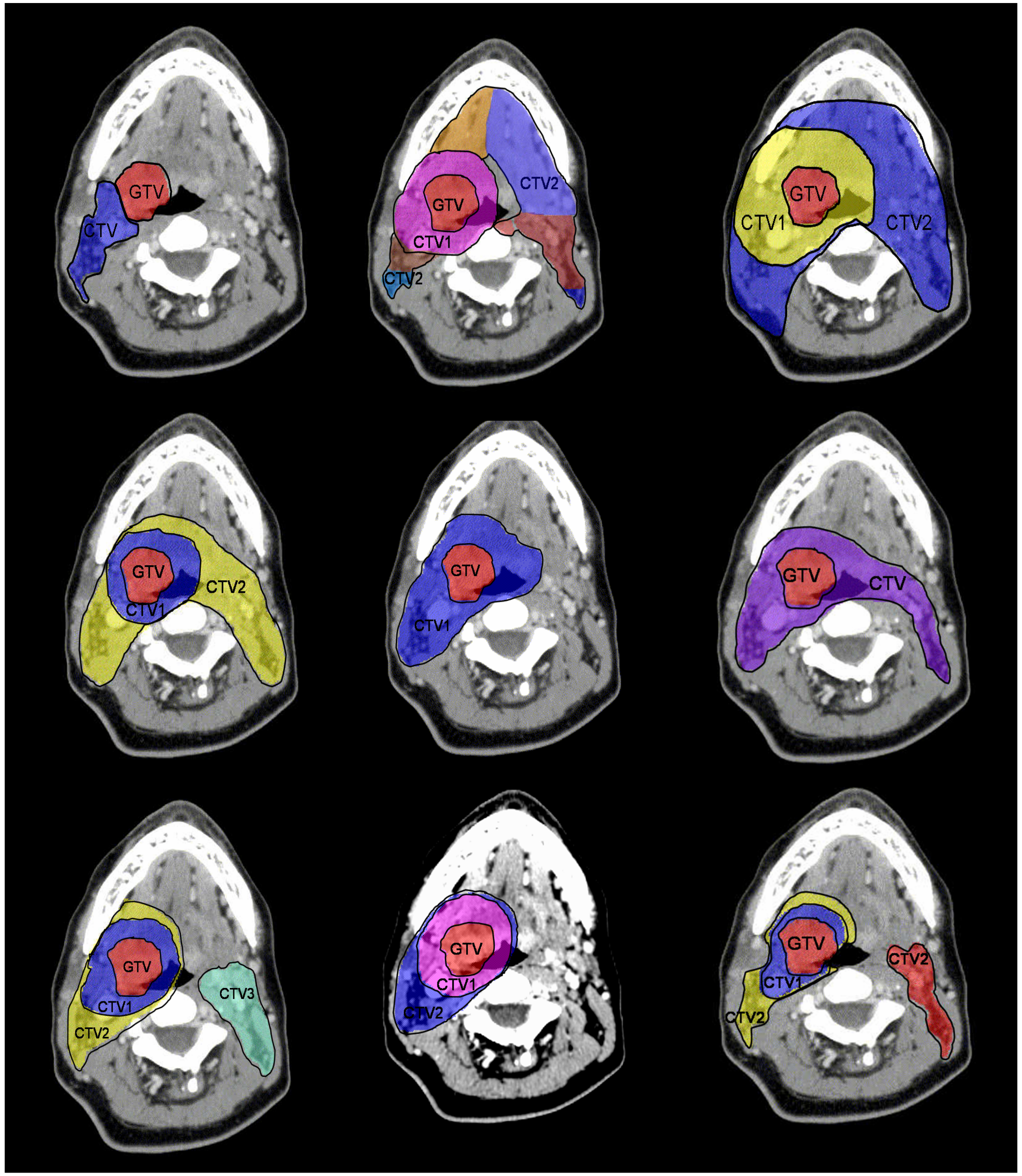


Practice Heterogeneity





Courtesy of Vincent Gregoire, Bruxelles

Harari et al., 2005

4D

La cathédrale de Rouen

C. Monet, 1894

Disease Targeted Therapy

The target volume is determined and labeled at the biological level.

The treatment is designed to damage only cancer cells wherever they are, sparing normal cells even in immediate proximity to the tumor.

Boron Neutron Capture Therapy (BNCT)

Prototype of the radiotherapy of the future

Targeting of single tumor cells by a ^{10}B-compound
Selective destruction by high LET irradiation

THE AMERICAN JOURNAL
OF ROENTGENOLOGY
AND RADIUM THERAPY

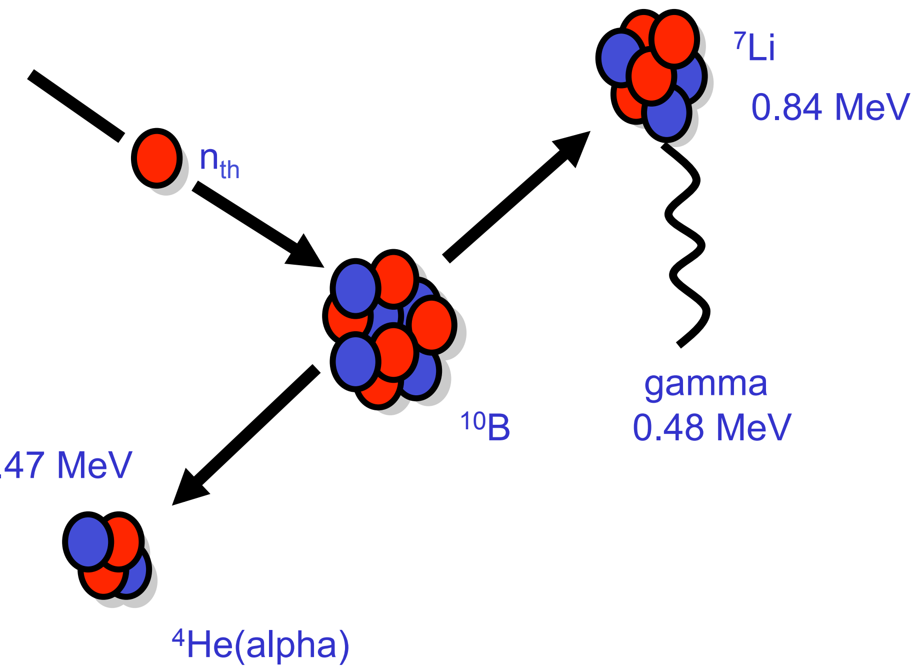
VOL. 36 JULY, 1936 No

BIOLOGICAL EFFECTS AND THERAPEUTIC POSSIBILITIES OF NEUTRONS

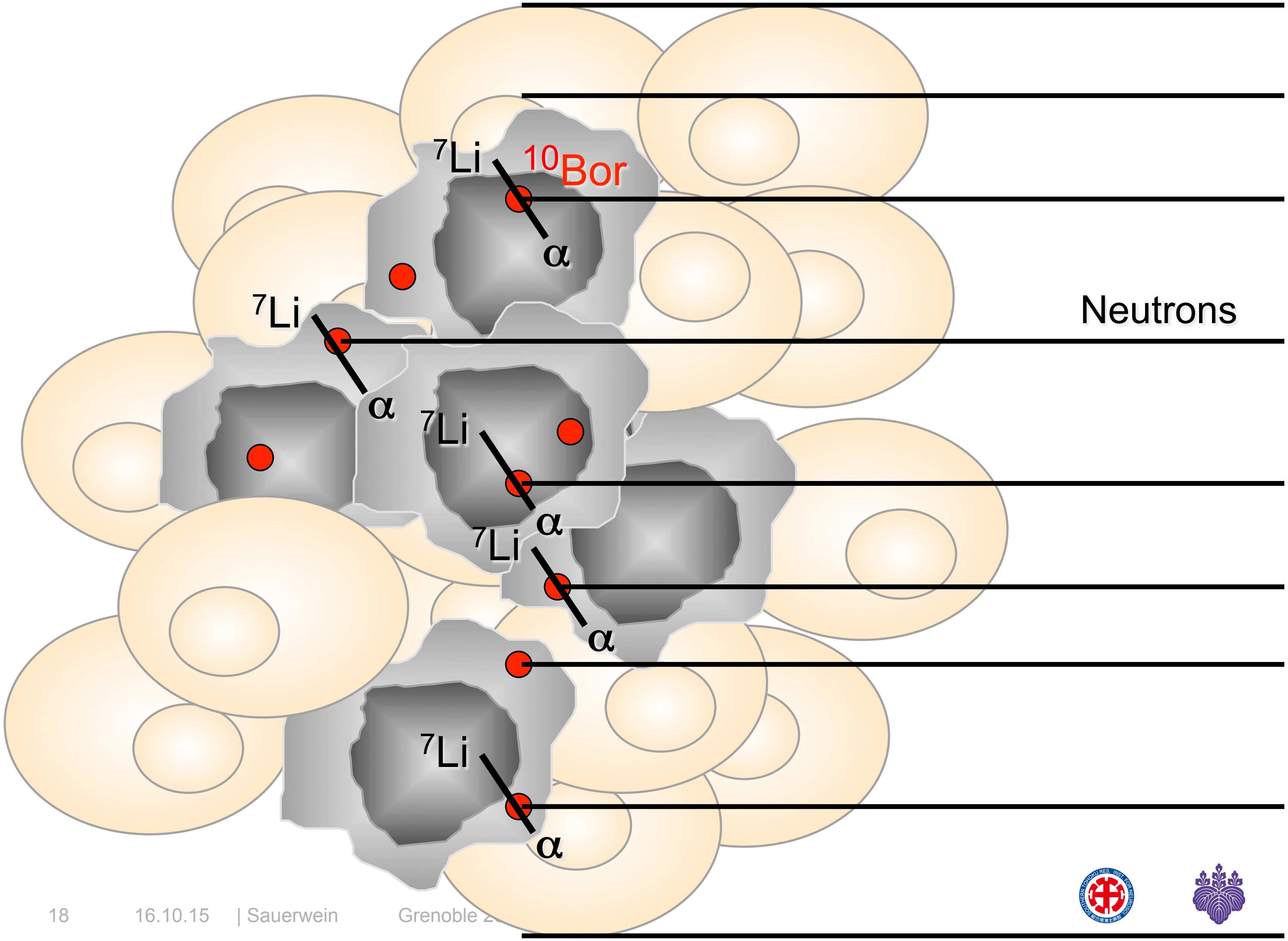
By **GORDON L. LOCHER**, Ph. D.

What is BNCT ?

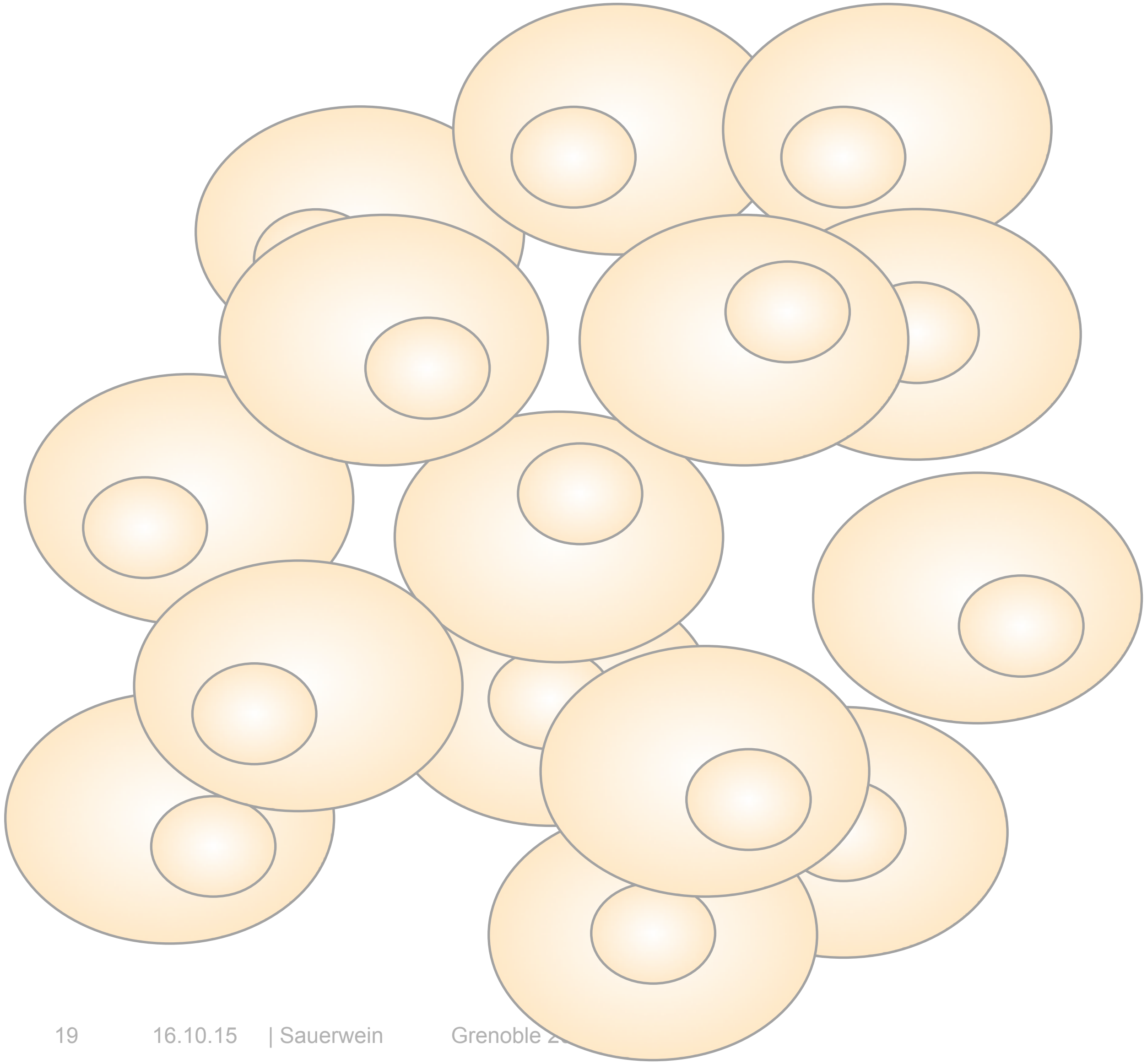
BNCT is based on the ability of the isotope ^{10}B to capture low energy neutrons to produce two highly energetic particles with low range in tissue



BNCT

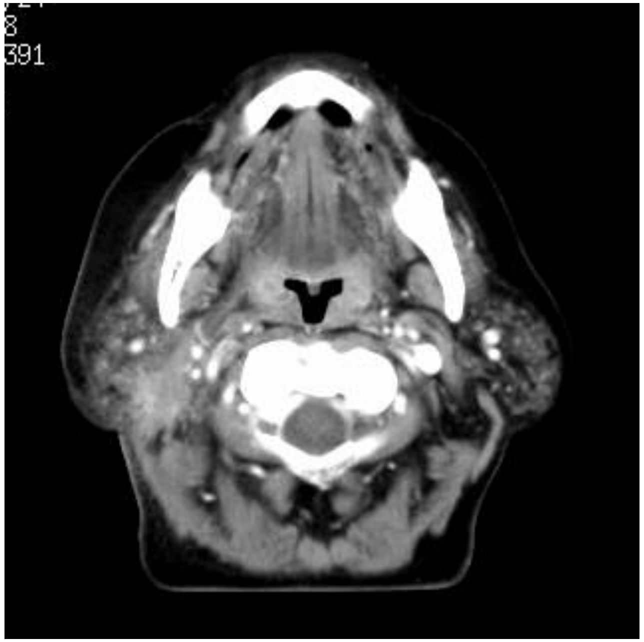


BNCT



BNCT – does it work?

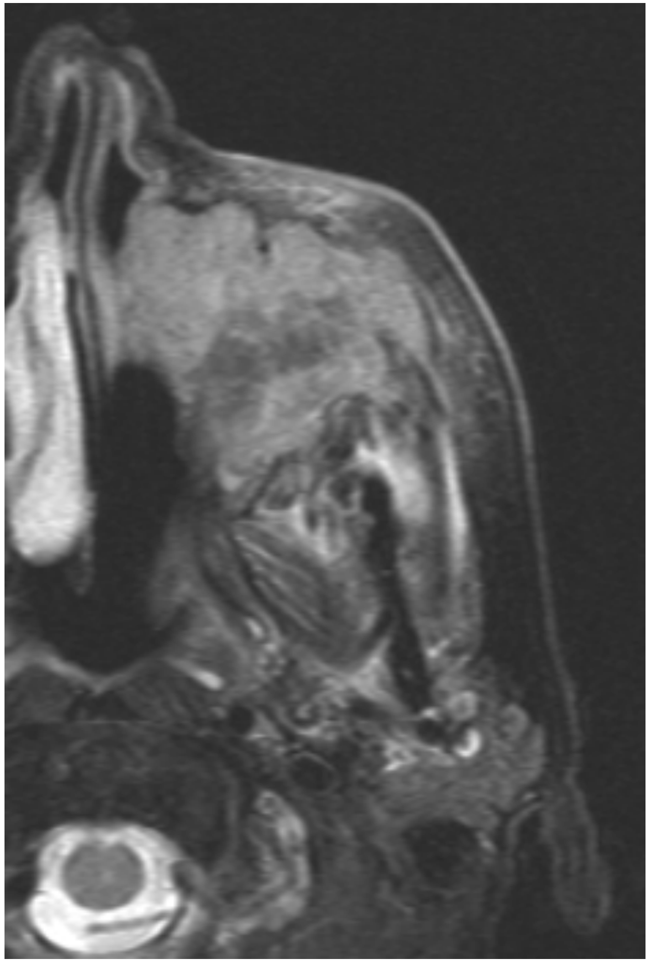
Kawasaki/Kyoto: adenoidcystic carcinoma



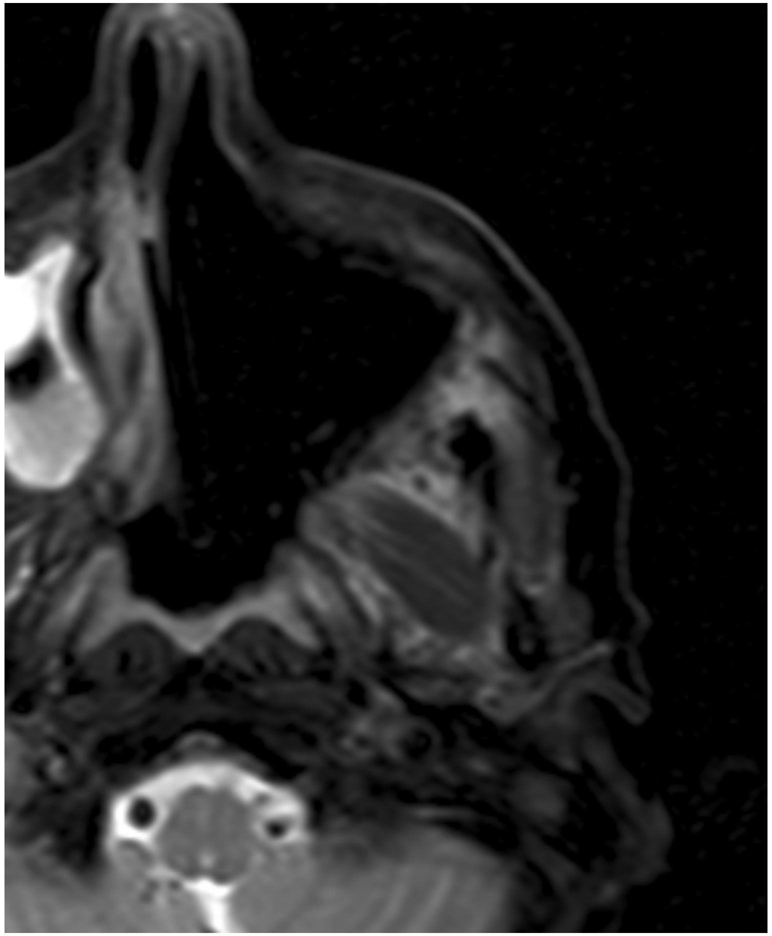
Follow up: 6 months

Courtesy: J. Hiratsuka and T. Aihara

BNCT – does it work?

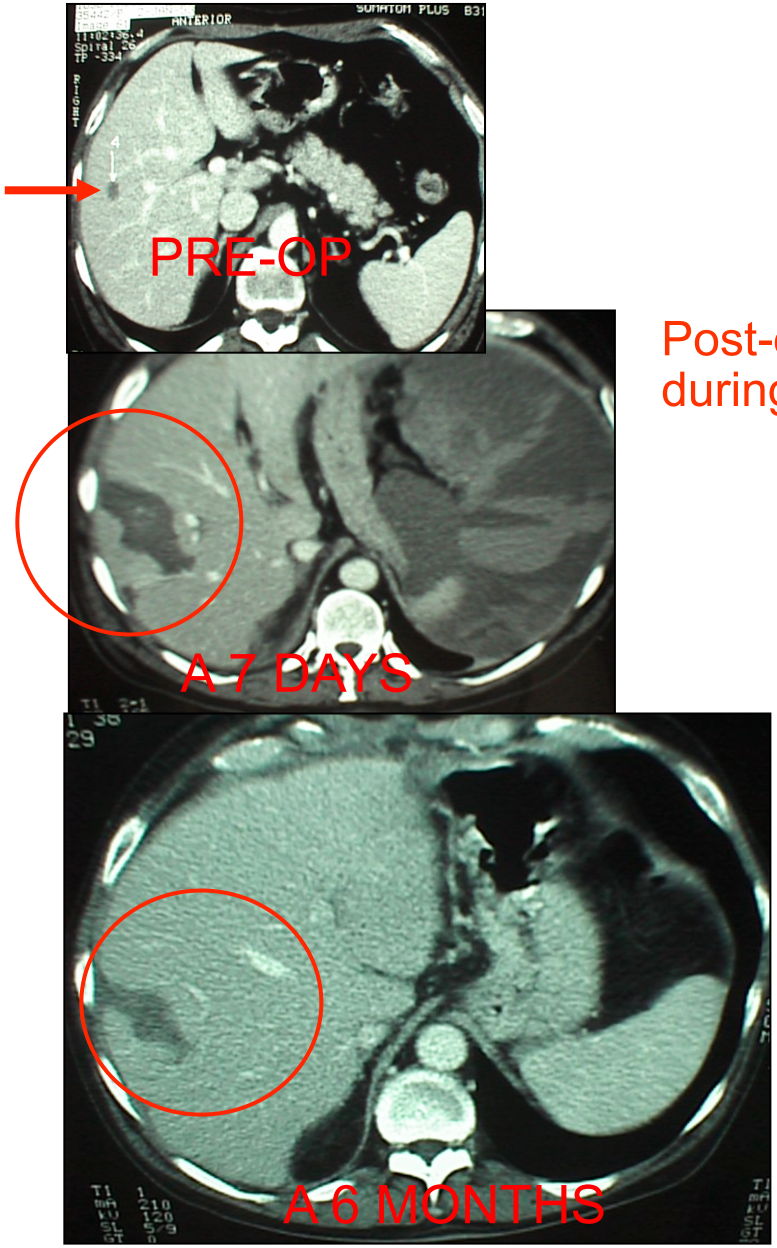


Recurrent head & neck squamous cell carcinoma after full dose radiotherapy



Kankaanranta *et al., 2007* IJROBP

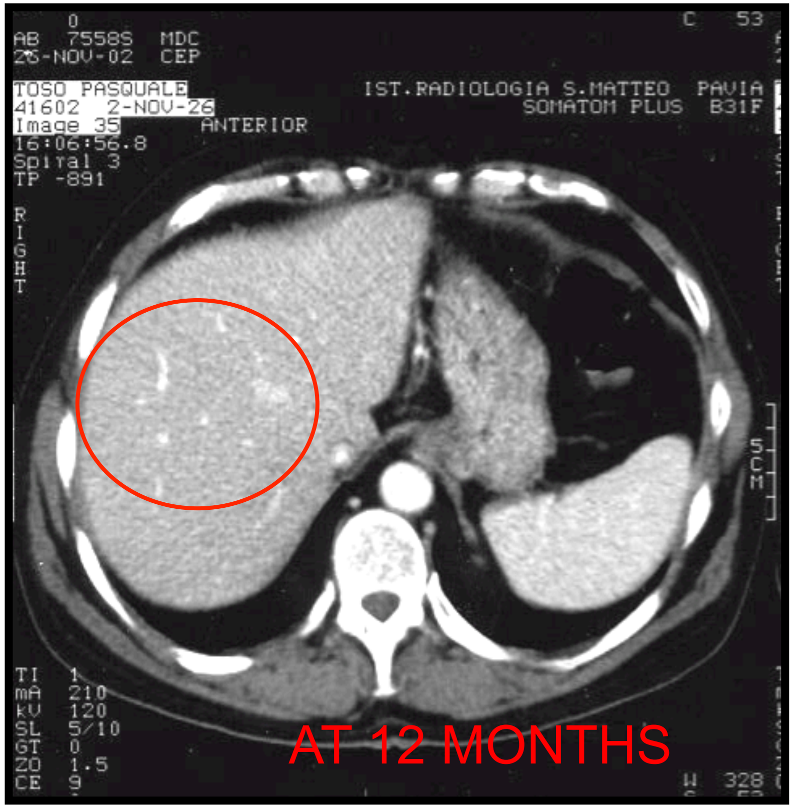
BNCT – does it work?



Post-op follow-up
during 12 months

PAVIA
CASE REPORT

Courtesy A. Zonta

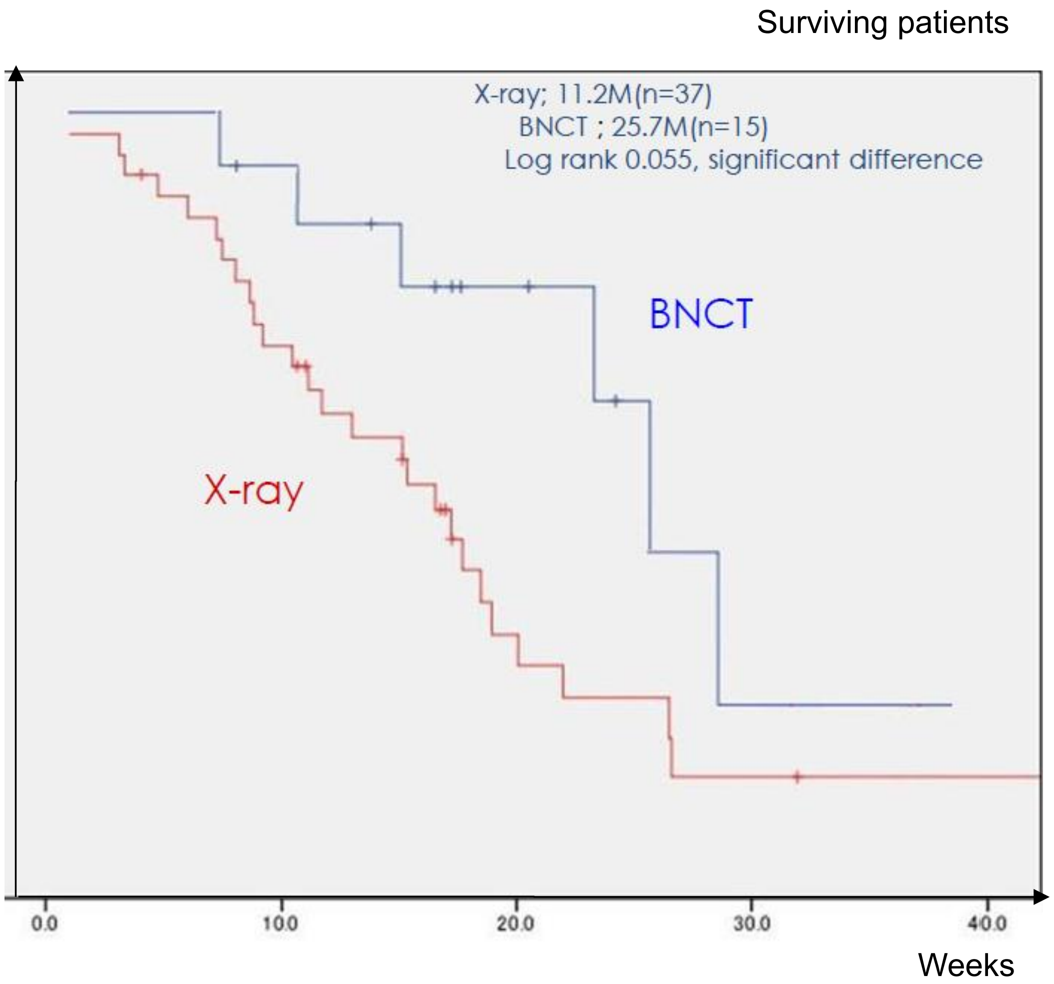


BNCT – does it work?

Glioblastoma treated at Tsukuba University

conventional radiotherapy vs. BNCT

Conclusion: Results for BNCT were significantly better,



BNCT – does it work?

Yes

But

Why was BNCT in more than 60 years never a success?

Some reflections

± 600 patients treated in 55 years

Little clinical advantage with present techniques

Most complex of all radiation therapy modalities

Dosimetry problems not solved

Only reactor beams have been used

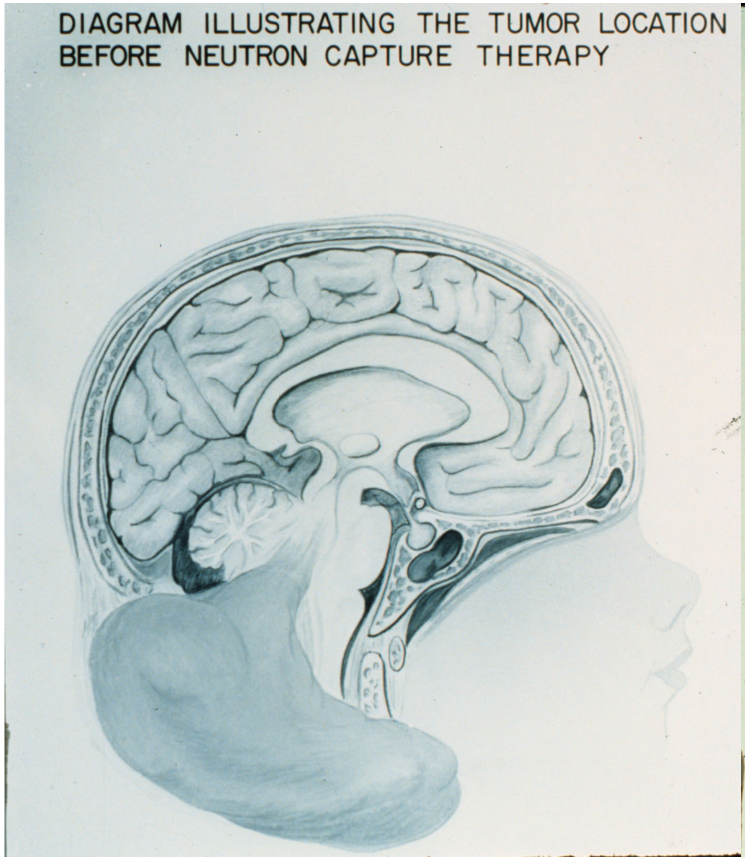
- fixed beam directions
- long treatment times (≥ 40 minutes)
  - ➜ fractionation difficult
- fixed collimators

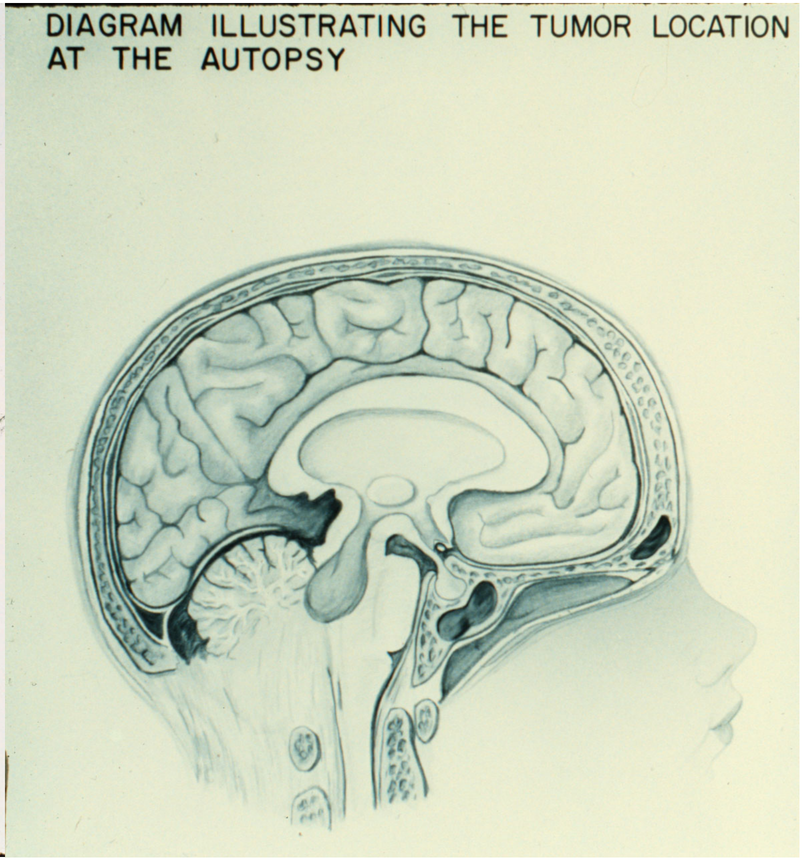
Inadequate specificity of boron compounds

- presently used compounds (BSH, BPA) were developed in early 1960s

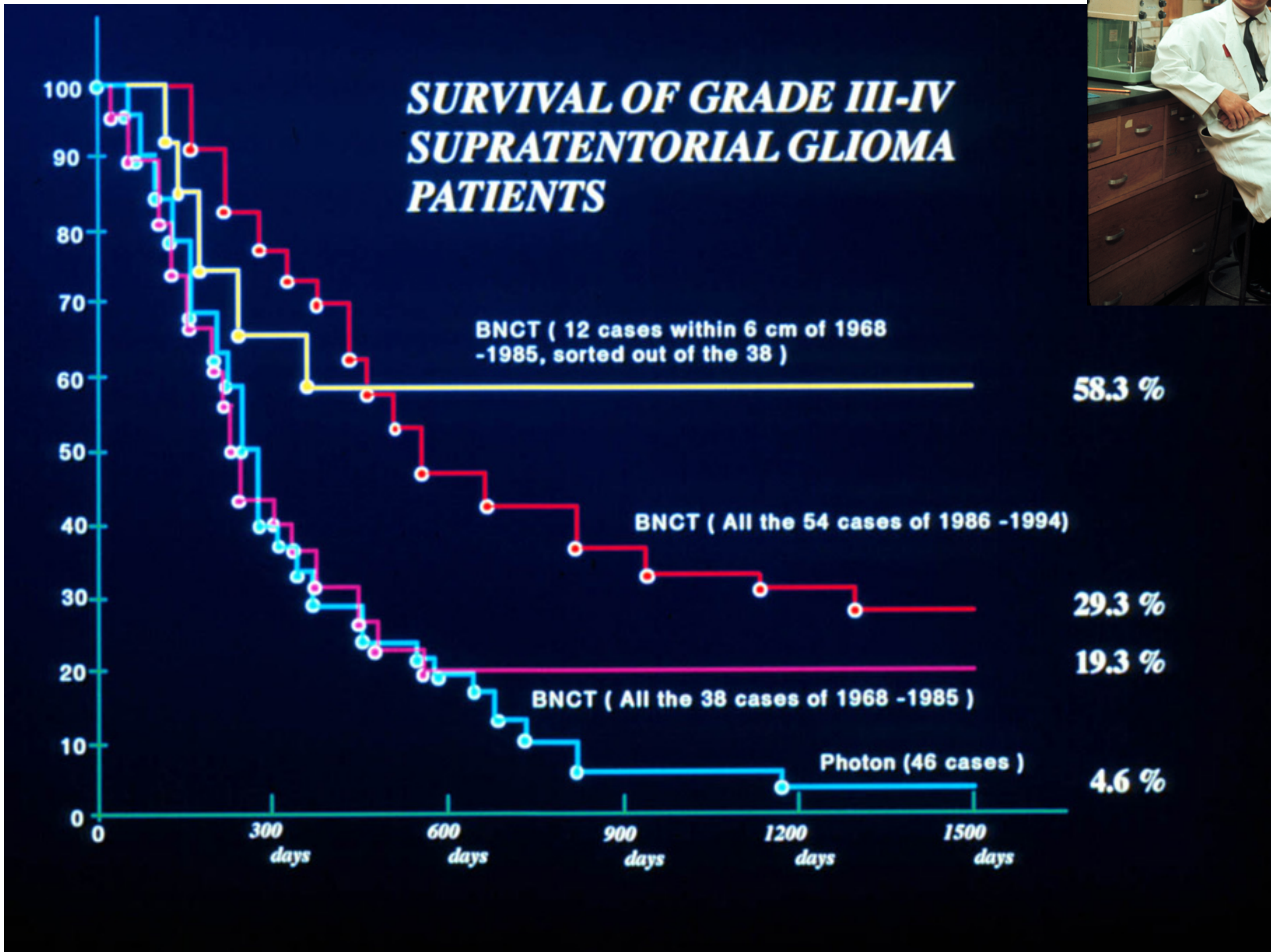
Courtesy by Dan Jones, South Africa

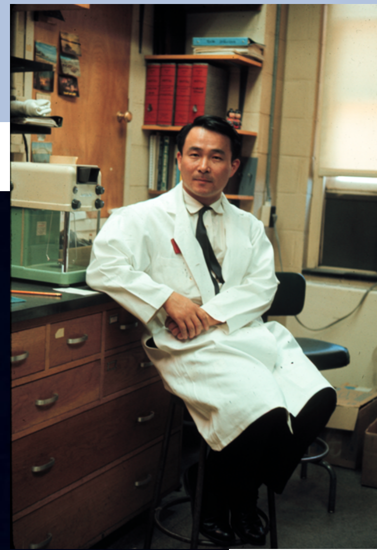
BNCT – the fifties: a disaster





BNCT – the seventies: exciting results





BNCT: History

- 1936 G.L. Locher (USA) proposes neutron capture reactions to be applied in radiation therapy
- 1951-1961 (USA) First pioneering trials of BNCT, with mixed results, effectively a failure
- 1963-1980s Professor Hatanaka (Japan) demonstrates impressive results
- Late 1980s Re-start of US and European efforts
- 1994 New US trials start at Brookhaven and Harvard/MIT (2002-2004)
- 1997 Start of first European trial in Petten (EORTC 11961)
- 1999 stop of BNCT trials in Brookhaven / 2003 at MIT
- 1999-2010 clincial trials started in Finland (1999 - 2010), Czech Republic (2000-2002), Sweden (2001-2005) Argentina (2003), Taiwan (2010)
- 2002 Extra-corporal BNCT in Pavia for liver metastases
- 2012 Start of accelerator based BNCT at KURRI
- 2015 First hospital based BNCT facility opened in Koriyama (Japan)

Our Goal

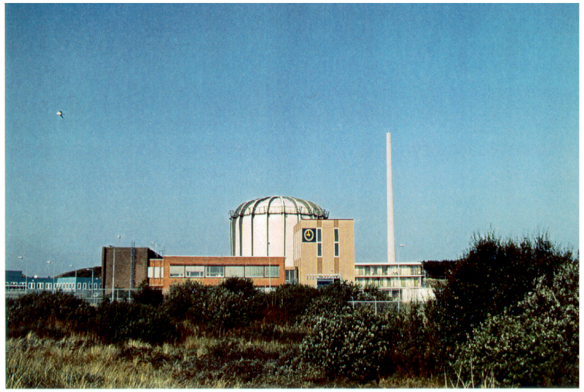
Development of BNCT as a new treatment modality in oncology

Strategies

We try to reach our goal by performing carefully designed clinical trials to collect the data and information necessary for regulatory authorities to approve BNCT as a treatment modality

We support and perform basic and applied research activities to prepare and assist our trials

BNCT in Europe 1996



A specific situation

Funding by the European Commission

International collaboration

Use of a centralized non hospital based facility

Regulatory authorities in 5 different countries involved

BNCT in Europe 1996

How to overcome the obvious problems?

Clear organisational structures

Rigorous quality management procedures

Rigorous application of international accepted rules and standards

Following as much as possible "established ways"

↓

EORTC

EORTC

Creation of the EORTC BNCT Study Group

Supported by the EORTC New Drug Development Office NDDO

Supervised by the New Treatment Committee NTC

Now part of EORTC Laboratory Research

Evaluated by the Scientific Audit Committee SAC

EORTC BNCT Group

Independent data management and monitoring by NDDO Oncology

Reference Centers for

Pathology (Prof. Wiestler, Univ. Bonn)

Neuroradiology (Prof. Zanella, Univ. Frankfurt)

Trained investigators at the patient referral centers to perform the follow up

Tasks

Development of

- global strategies for clinical trials to evaluate a binary treatment modality
- standards for the reporting of dose

Creation of

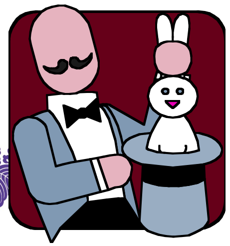
- a collaboration between NCI and EORTC to perform research on BNCT
- a central facility to provide worldwide boronated drugs under GMP for clinical trials

From boron compounds to new medicaments

- support activities necessary for drug development

The European Aspect

- distribute the knowledge to other EU scientists and research institutions
- support the creation of other BNCT irradiation facilities



BNCT – the nineties: The EORTC trials

Strategies

BNCT as binary treatment needs specific trial designs that have to be further developed

The following trials were performed (1996 – 2008)

11001	translational research
11961	phase I
11011	phase II

EORTC
European Organization for Research and Treatment of Cancer

^{10}B-uptake in different tumours using the boron compounds BSH and BPA

- translational research
- phase I aspect: toxicity of the drugs

Study coordinator: Wolfgang Sauerwein

Endpoint

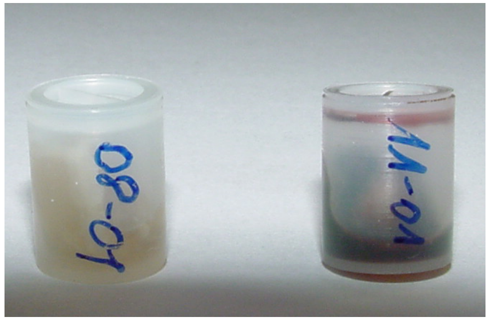
Boron-10 in a

macroscopic Volume

measured by

PGRS

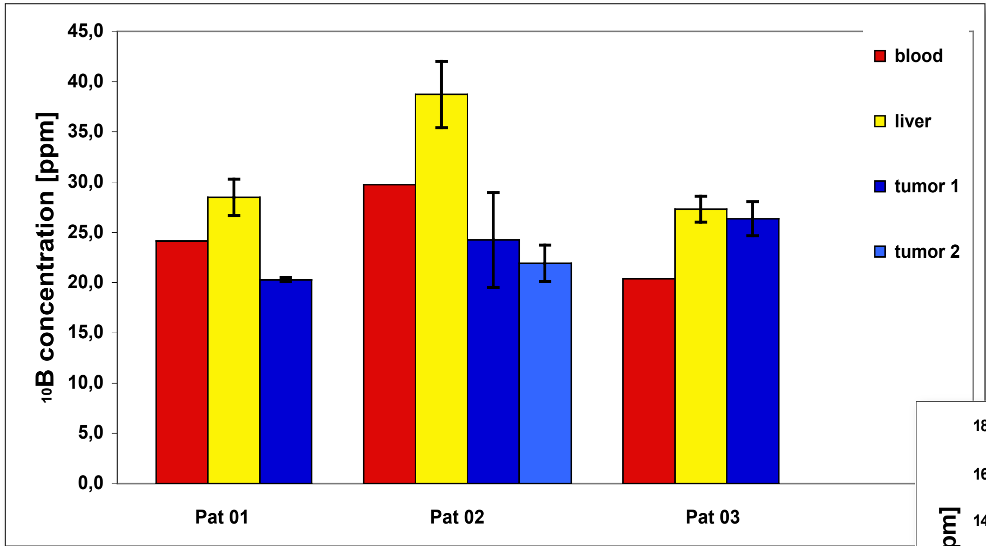
(prompt gamma ray spectroscopy)



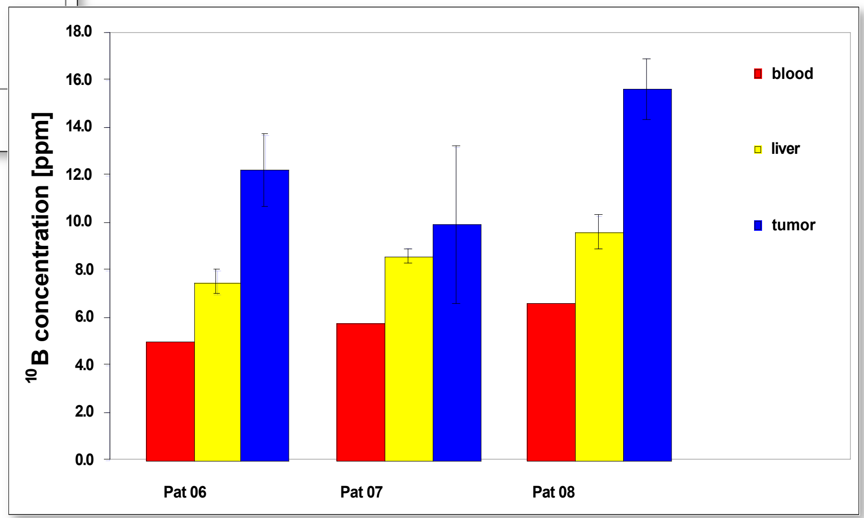
No toxic effects related to the drugs observed

EORTC 11001

BSH administration



BPA administration

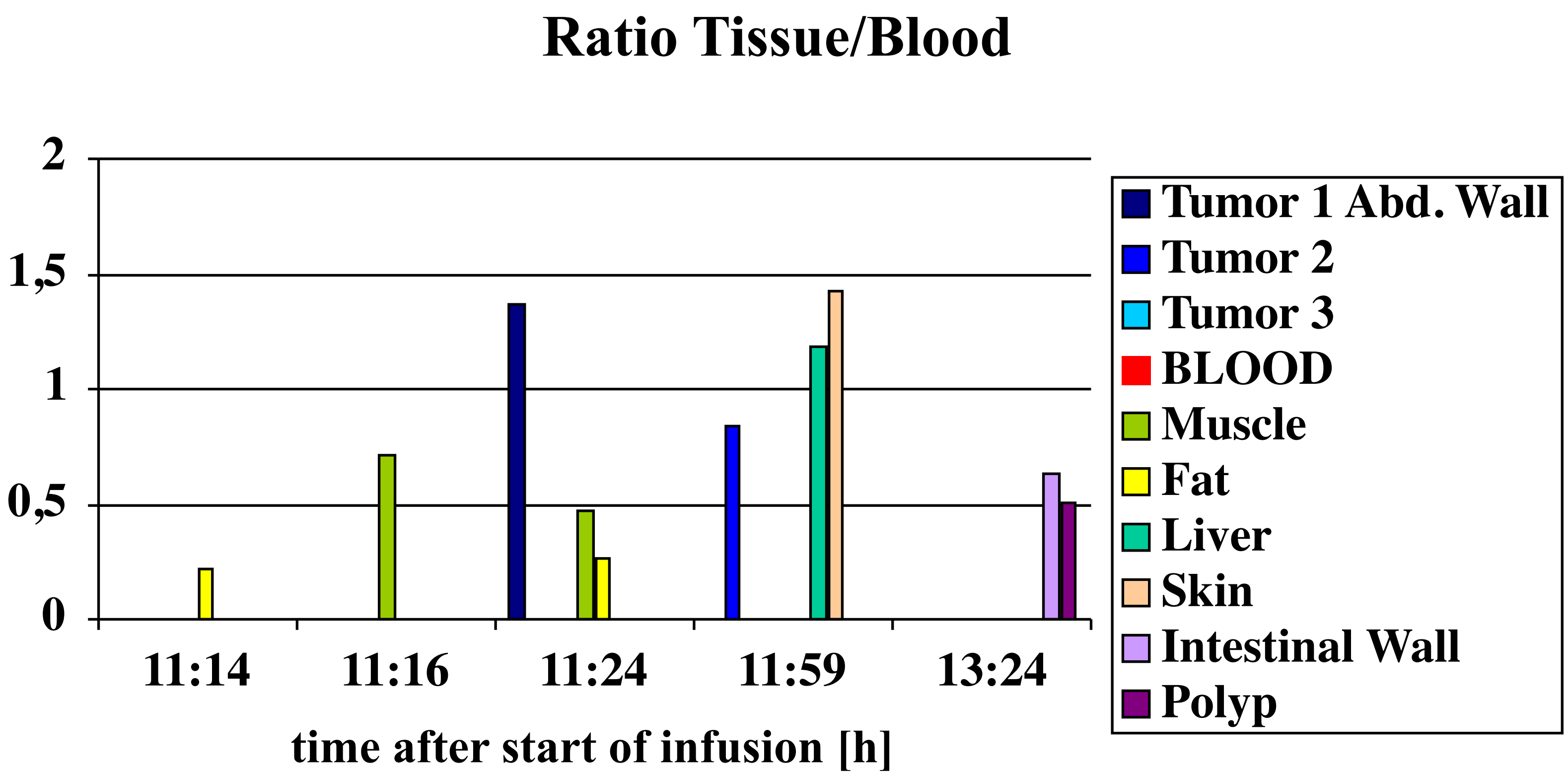


EORTC 11001

Patient 1

tumor type: liver metastases

drug: BSH



EORTC 11001: selected publications

WITTIG A., MALAGO M., COLLETTE L., HUISKAMP R., BÜHRMANN S., NIEVAART V., KAISER G.M., JÖCKEL KH., SCHMID KW., ORTMANN U., SAUERWEIN W. (2008): Uptake of two 10B-compounds in liver metastases of colorectal adenocarcinoma for extracorporeal irradiation with boron neutron capture therapy (EORTC trial 11001). Int J Cancer: 122, 1164–1171

WITTIG A., SHEU S.-Y., KAISER G.M., LANG S., JÖCKEL K.-H., MOSS R., STECHER-RASMUSSEN F., RASSOW J., COLLETTE L., SAUERWEIN W. (2008): New Indications for BNCT? Results from the EORTC trial 11001. In: Neutron Capture Therapy: A new option against cancer (eds.: Zonta A., Altieri S., Roveda L., Barth R.), ISBN 88-8286-176-8, ENEA (Italian National Agency for New Technologies, Energy and the Environment) 2008, p. 39-42

WITTIG A., COLLETTE L., MOSS R., SAUERWEIN W.A. (2009): Early clinical trial concept for boron neutron capture therapy: a critical assessment of the EORTC trial 11001. Appl Radiat Isot. 67, S59-S62

WITTIG A., COLLETTE L., APPELMAN K., BÜHRMANN S., JÄCKEL M.C., JÖCKEL KH., SCHMID K.W., ORTMANN U., MOSS R., SAUERWEIN W.A. (2009): EORTC trial 11001: distribution of two (10)B-compounds in patients with squamous cell carcinoma of head and neck, a translational research/phase 1 trial. J Cell Mol Med 13,1653-1665

BENDEL P., WITTIG A., BASILICO F., MAURI P., SAUERWEIN W. (2010): Metabolism of Borono-phenylalanine-fructose complex (BPA-fr) and Borocaptate Sodium (BSH) in cancer patients – results from EORTC trial 11001. Journal of Pharmaceutical and Biomedical Analysis 51, 284-287

WITTIG A., SHEU-GRABELLUS S.-Y., COLLETTE L., MOSS R., BRUALLA L., SAUERWEIN W. (2011): BPA uptake does not correlate with LAT1 and Ki67 expressions in tumor samples (results of EORTC trial 11001). Appl. Radiat. Isotopes 69, 1807-1812

Phase I trial:
Postoperative Treatment of Glioblastoma with BNCT at the Petten Irradiation Facility

Study coordinator: Wolfgang Sauerwein

Aims of the study

- save irradiation dose for brain tumours
- toxic effects on healthy tissues
- maximum tolerated dose
- dose limiting toxicity

- anti-tumour effect

EORTC 11961

Trial Design

Cohorts of glioblastoma patients treated with:

Surgery (^{10}B uptake study in the 1st cohort)

BNCT

dose escalation by 10% per cohort after 6 months in the absence of dose limiting toxic events

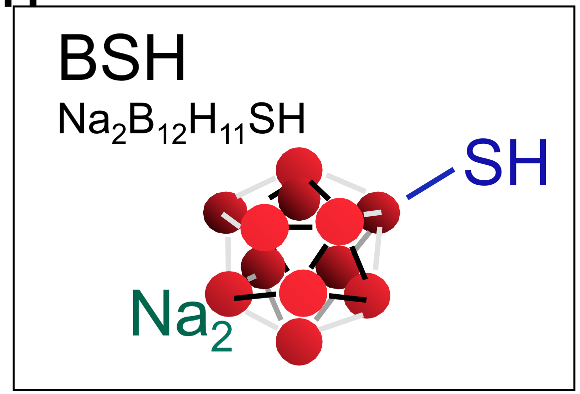
Treatment

BSH infused prior to each fraction
average boron concentration in blood
over the 4 fractions: 30 ppm ^{10}B

planning target volume:
gross tumor volume + 2 cm margin

4 fractions

first 5 patients: 1 field
later: 2 fields



EORTC 11961

Results

4 cohorts of patients were foreseen

4 cohorts have been treated

data of all patients monitored

Final report of NDDO: continue with new cohort

Study closed by EORTC

Systemic toxicity due to BSH

Grade 1-2 (CTC):
hematological changes, hypokaliemia, hyponatremia, erythema, urticaria, flash like sensation,
nausea, vomiting, fever

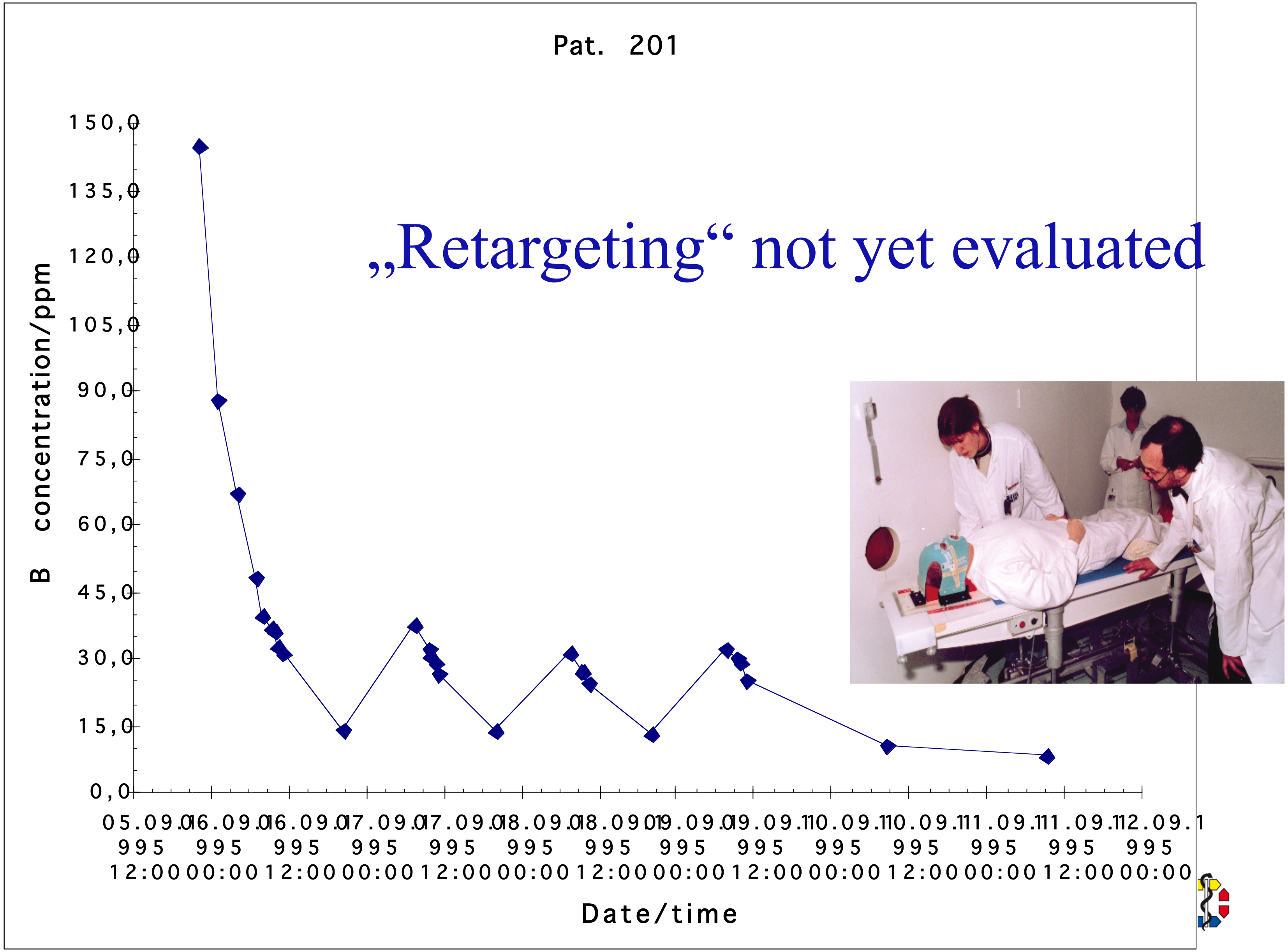
Grade 3 (CTC):
fever, leukopenia

Grade 4 (CTC):

possibly related to BSH:
- neutropenia: treated by G-CSF, resolved within 36 h

unrelated to BSH/BNCT:
- seizure immediately post GBM-surgery

Fractionated treatment: an option?



„Retargeting“ not yet evaluated

Early radiation toxicity

mild erythema, mild pruritus

taste change, mild dry mouth

decreased lacrimation, tinnitus

headache, seizure

Late radiation toxicity

slight atrophy of the skin, skin pigmentation changes, lens opacity, low grade blurred vision, low grade hearing loss, slight atrophy of oral mucosa, hormonal changes, seizure, motor weakness, behavioral change, dysphasia

all patients: alopecia, hair regrow after 3-6 month

EORTC 11961

Follow up patient 403

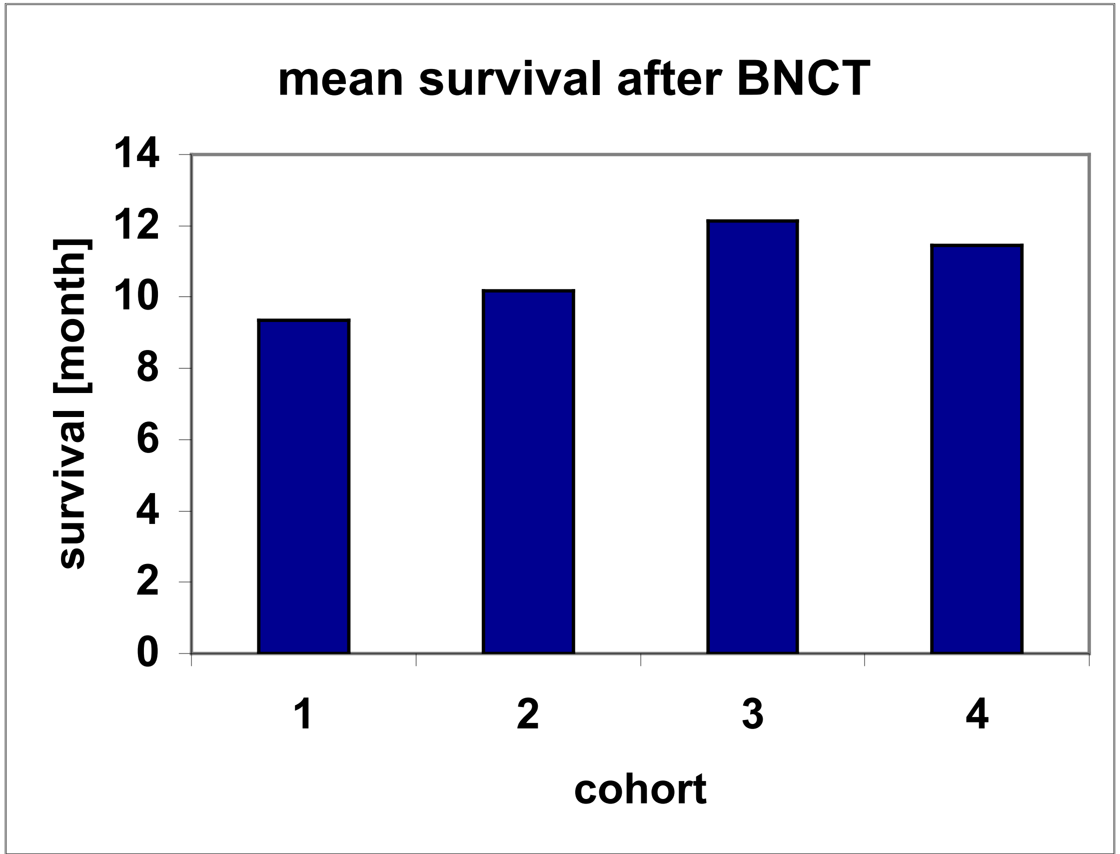
1 week after BNCT

2 month after BNCT

1 month after BNCT

6.5 month after BNCT

Survival


mean survival after BNCT
survival [month]
14
12
10
8
6
4
2
0
1
2
3
4
cohort

Results 2004

- No limiting toxicity due to BNCT
- No organ specific toxicity different from conventional radiotherapy

- Survival equal to conventional therapy

EORTC 11961

4 cohorts treated but no final endpoint reached

Conclusion:
Starting dose was much too low

How to proceed ?

How to proceed?

A new trial should be started with a different dose-escalation schedule:

- 30% increase instead of 10%
- de-escalation in case of severe toxicity as already foreseen by the protocol

Costs ca. 3 Mio € (2004)

EORTC trial 11961: other aspects

- In the frame of 11961 the first BNCT treatment in Europe took place
- First “state of the art” prospective controlled clinical trial to develop the modality “BNCT”
- It was an international trial – important organizational issues to be solved,
- Quality management aspects played a crucial role – this trial and the facility were ISOO certified
- All this made Petten a crystallization point for BNCT research. A lot of basic research could be performed in the frame of the BNCTeam, which never had been possible in a hospital. This research was performed in a decentralized way, but coordinated through Essen (having the irradiation facility in Petten)

EORTC trial 11961: selected publications

SAUERWEIN W., MOSS R., RASSOW J., STECHER-RASMUSSEN F., HIDEGHÉTY K., WOLBERS J.G. SACK H. (1999): Organisation and management of the first clinical trial of BNCT in Europe (EORTC Protocol 11961). Strahlenther. Onkol. 175, 108-111

HIDEGHÉTY K., SAUERWEIN W., HASELSBERGER K., GROCHULLA F., FANKHAUSER H., MOSS R., HUISKAMP R., GABEL D., DE VRIES M. (1999): Postoperative treatment of glioblastoma with BNCT at the Petten Irradiation facility (EORTC Protocol 11961). Strahlenther. Onkol. 175, 111-114

SAUERWEIN W., MOSS R.L. et al. (2001): Status report of the European clinical trial of BNCT at Petten (EORTC Protocol 11961). In: Frontiers in Neutron Capture Therapy. (eds.: Hawthorne F., Shelly K., Wiersema R.J.), Kluwer Academic/Plenum Publishers New York 2001, p. 81-86

HIDEGHÉTY K., SAUERWEIN W. et al. (2001): Report on the first patient group of the European phase I trial (EORTC protocol 11961) at the High Flux Reactor Petten. In: Frontiers in Neutron Capture Therapy. (eds.: Hawthorne F., Shelly K., Wiersema R.J.) Kluwer Academic/Plenum Publishers New York 2001, p. 105-111

HIDEGHÉTY K., SAUERWEIN W., WITTIG A., GÖTZ C., PAQUIS P., GROCHULLA F., HASELSBERGER K., WOLBERS J., MOSS R., HUISKAMP R., FANKHAUSER H., DE VRIES M., GABEL D. (2003): Tissue uptake of BSH in patients with glioblastoma in the EORTC 11961 phase I BNCT trial. J. Neuro-Oncology 62, 145-156

VOS M.J., TUROWSKI B., ZANELLA F.E., PAQUIS P., SIEFERT A., HIDEGHÉTY K., HASELSBERGER K., GROCHULLA F., POSTMA, T.J., WITTIG A., HEIMANS J.J., SLOTMAN B.J., VANDERTOP W.P., SAUERWEIN W (2005):v Radiologic findings in patients treated with boron neutron capture therapy for glioblastoma multiforme within EORTC trial 11961. Int. J. Rad. Oncol. Biol. Phys. 61, 392-399

WITTIG A., MOSS R.L., STECHER-RASMUSSEN F., APPELMAN K., RASSOW J.,ROCA A., SAUERWEIN W. (2005): Neutron activation of patients following boron neutron capture therapy of brain tumors at the High Flux Reactor (HFR) Petten (EORTC trials 11961 and 11011). Strahlenther. Onkol. 181, 774-782

EORTC 11011

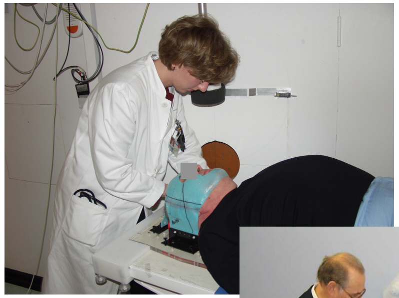
Early phase II study on BNCT in metastatic malignant melanoma using the boron carrier BPA

Study coordinator and PCI:
Andrea Wittig MD PhD (Essen)

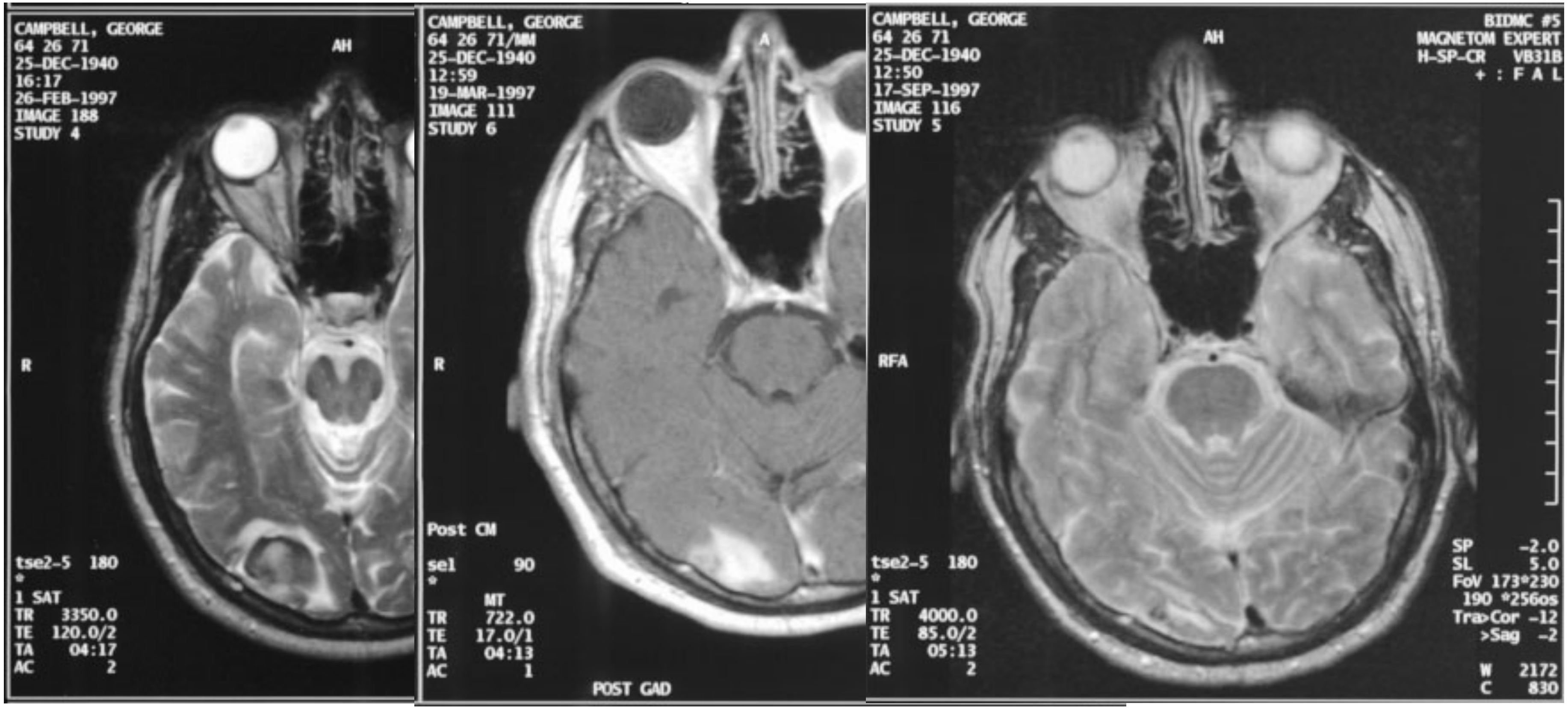
Multi-centre trials:
physical differences of the neutron beams make a comparison of results difficult

First approach of a "multicenter" trial in BNCT (Essen/Petten - Harvard/MIT)

- New degree of complexity
- Organizational challenges



EORTC 11011



The Harvard/MIT experience

Paul Busse

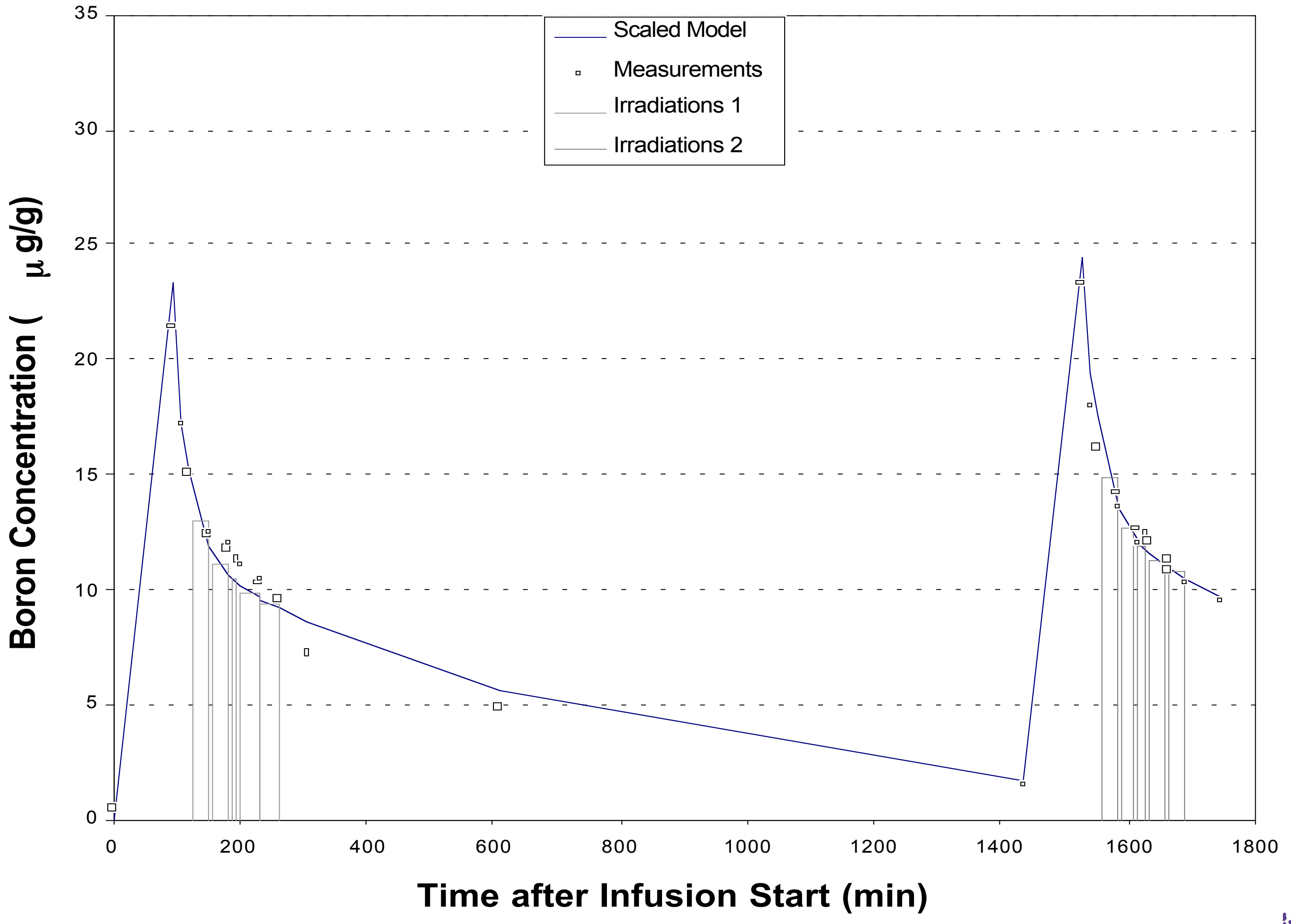
EORTC 11011

Objectives

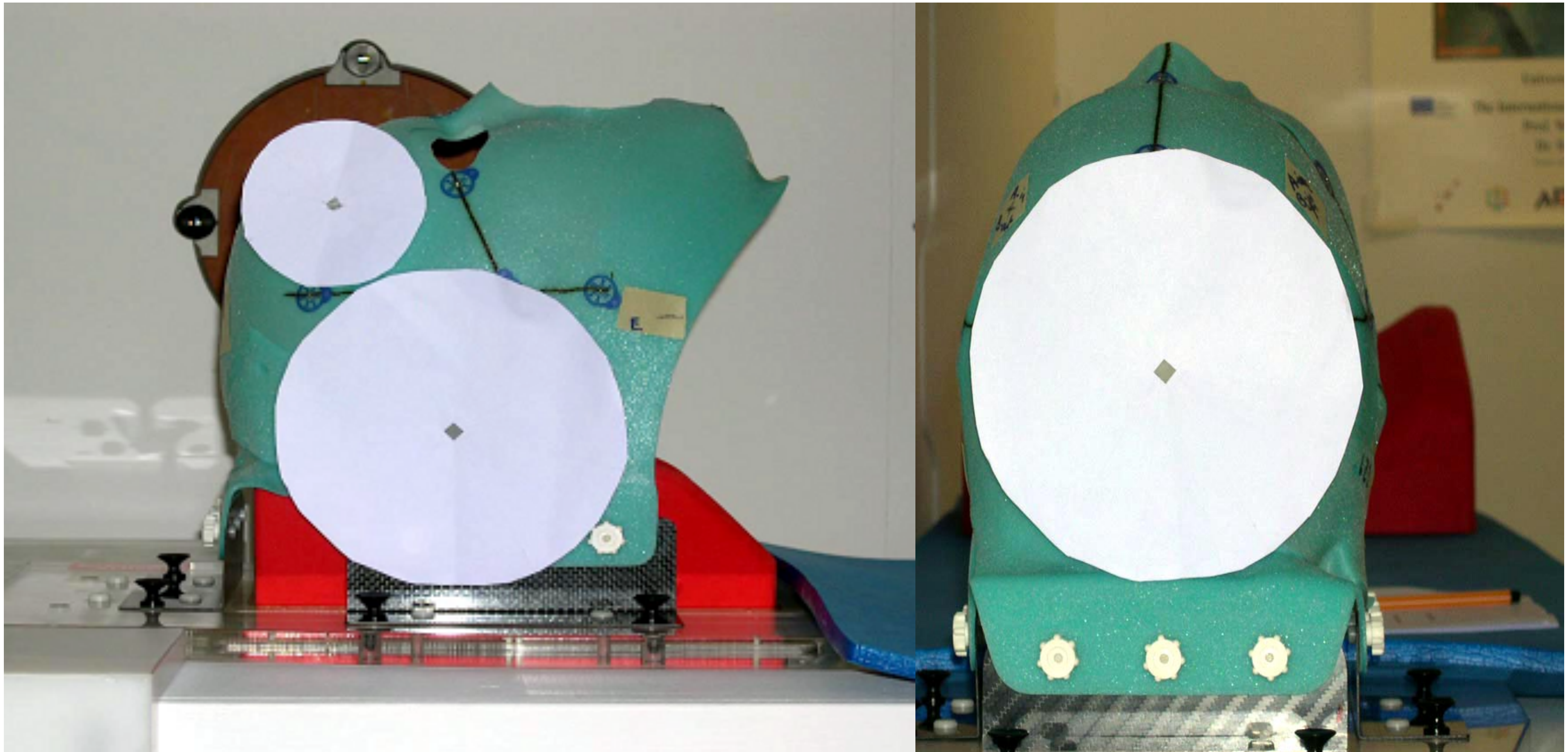
- therapeutic activity and efficacy of BNCT using BPA as palliative radiotherapy in metastatic melanoma (local response)
- safety (systemic toxicity of BPA after repeated administration, early and late radiation toxicity)
- ^{10}B concentration in blood after repeated administration of BPA
- Optional biodistribution study

Pharmacokinetic of ^{10}B

Patient #2



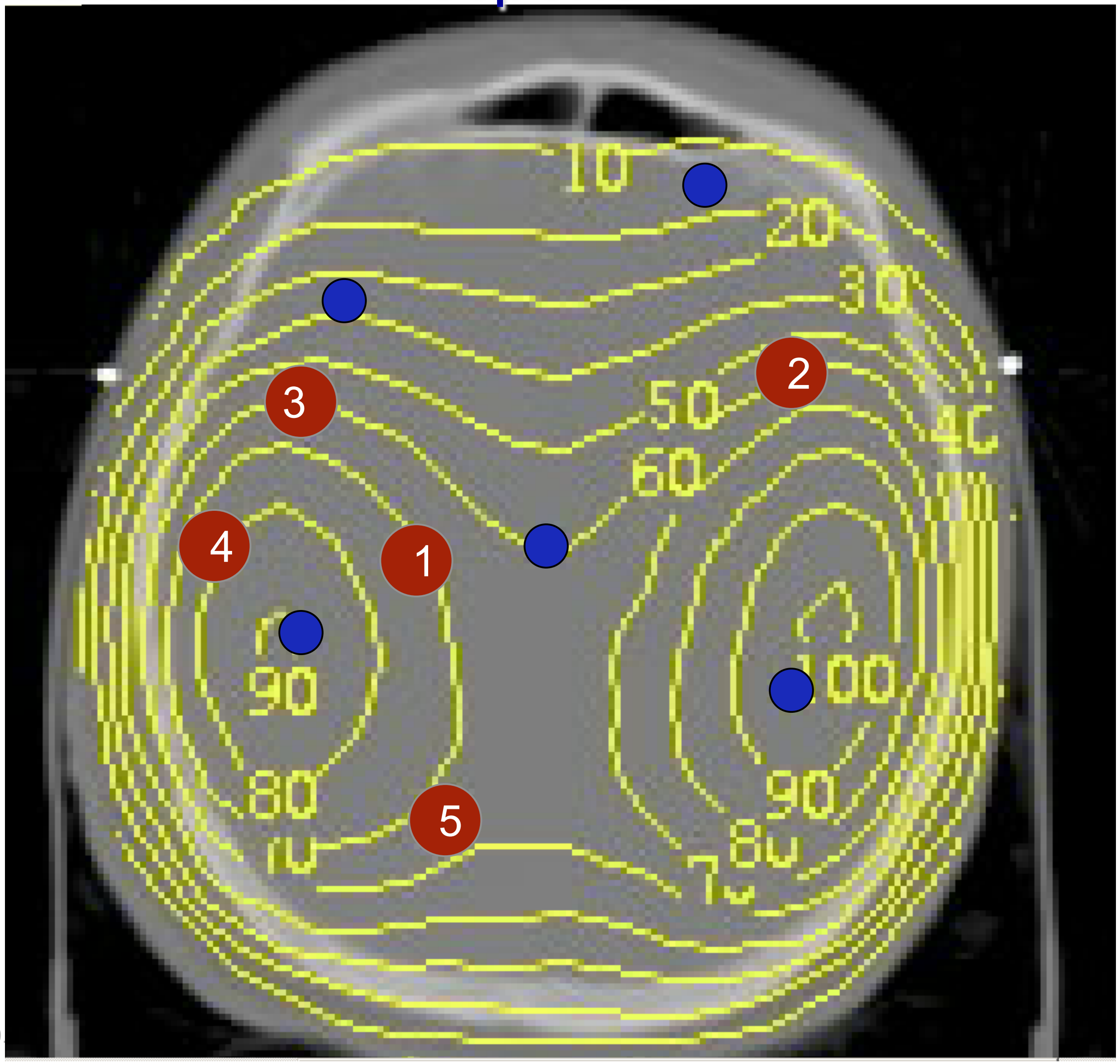
Total brain irradiation using 5 fields



Evaluation of tumor response

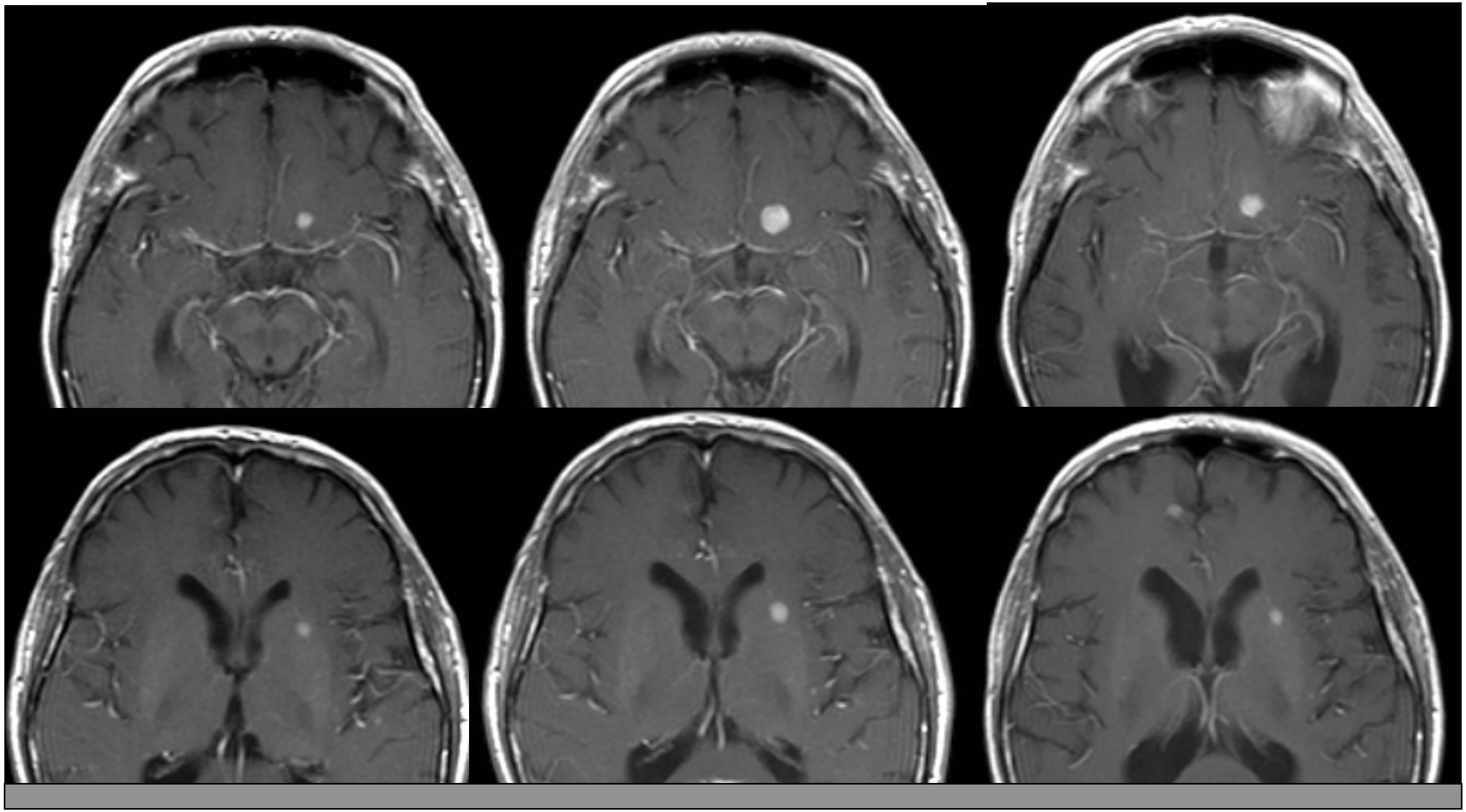
target lesions

non-target lesions



measurable and non-measurable lesions

EORTC 11011



12/2004 01/2005 03/2005

Follow up

15.07.2004

21.07.2004

Standardised, prospective follow up investigations

Case report forms

Trained investigators

Evaluation of toxicity: allopecia

Nuclear Research Reactors for BNCT

Generation 1: Early US trials

1. Brookhaven Graphite Research Reactor (BGRR), 1951-61
2. Brookhaven Medical Research Reactor (BMRR), 1959-61
3. M.I.T. Reactor, 1959-61

- In total 63 patients

Generation 2: Japanese Reactors

1. Hitachi Training Reactor, 1968-75 [13]
2. JRR-3 (JAERI), 1969 [1]
3. JRR-4 (JAERI), 1990 … 1999 [13]
4. Musashi I.T.R., 1977-89 [>100]
5. Kyoto Univ. Research Reactor (KURR), 1975, 1981, 1990… [>60]
6. JRR-2 (JAERI), 1990 [33]

all above reactors use(d) thermal neutrons

-In total, over 200 patients

Generation 3: Next wave of US trials (epithermal neutron beams)

1. M.I.T.R.-II, 1994-1999 [18]
2. BMRR, 1994-1999 [53]

- In total, 71 patients

Generation 4: new generation

~~1. HFR Petten~~	~~1997~~	~~[26 glioblastoma, 4 melanoma metastases]~~
~~2. JRR-4 (JAERI), Japan~~	~~1998~~	~~[>20, glioma, meningioma]~~
3. KUR, Kyoto, Japan	1998	[>60 Head and neck](?)
~~3. VTT, Finland~~	~~1999~~	~~[>200, mainly head and neck]~~
~~4. Rez, Czech Rep.~~	~~2000~~	~~[5, glioblastoma]~~
~~5. Studsvik, Sweden~~	~~2001~~	~~[>50]~~
~~6. MIT, USA~~	~~2002~~	~~[7]~~
~~7. Pavia, Italy~~	~~2001~~	~~[2, extracorporeal liver]~~
8. Bariloche, Argentina	2003	[7, skin melanoma] (?)
9. THOR, Taiwan	2010	[24, head and neck]

BNCT TEAM

The European BNCT Project
Project Co-ordinator: Prof. Dr. med. W. Sauerwein

The BNCT Facility

The basic requirements to house a complete BNCT facility are:

there should be a sufficient and adequate fluence rate of neutrons that emanate through a large diameter beam tube, that itself preferably faces a large source area of the neutron source.

there must be sufficient space at the exit side of the beam, to accommodate a large working area for building the irradiation room.

the facility should be freely accessible such that the patient can be readily brought into the irradiation room from outside.

there should be sufficient space outside the reactor building to house facilities for the reception and preparation of the patient prior to entering the facility for treatment.

Neutron Beam requirements

The required radiation beam should be essentially an epithermal neutron beam with the following characteristics:

- epithermal neutron flux ≅ 10^9 neutrons/cm^2s (at the therapy position)
- neutron energy ~ 1 eV to ~ 10.0 keV
- gamma dose rate ≤ 1.0 Gy/hr
- fast neutron dose rate ≤ 0.5Gy/hr
- current:flux ratio (J/Φ) > 0.8

and

- directed beam (!)

beam parameters of epithermal neutron beams

Reactors	Epithermal neutron flux ($10^9/cm^2s$)	Fast neutron dose per epithermal neutron ($10^{-13}Gy/cm^2$)	Gamma dose per epithermal neutron ($10^{-13}Gy/cm^2$)	Current/flux J/Φ
BMRR	1.8	4.3	1.3	0.67
MITR-II	0.2	12.5	14.0	0.55
HFR	0.33	8.6	10.3	0.98
KURR	9.5	2.9	0.4	0.82
GTRR	4.0	1.5	-	-
MITR/fission plate	18.0	1.3	1.0	-
BMRR/ fission plate	12.0	2.8	1.0	0.78
FiR I	3.5	2.6	1.0	-

Nuclear Research Reactors for BNCT

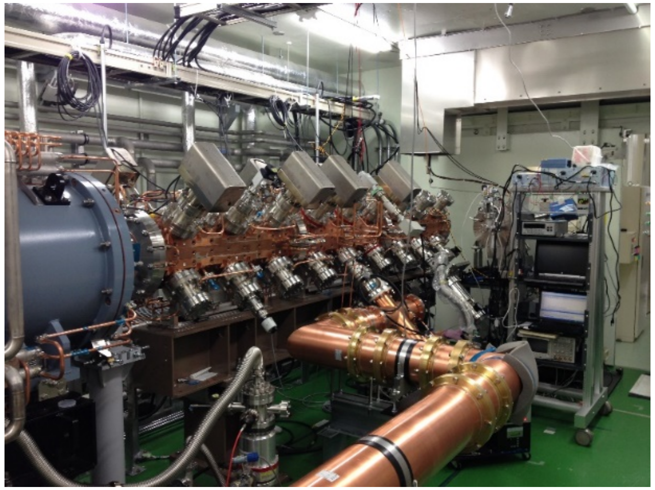
Excellent research facilities but not hospital based and therefore not suitable for clinical trials

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

New Neutron Sources in BNCT: Accelerators

Our wishes

- Safe
- Reliable
- Compact
- Hospital based
- Easy to operate
- No radiation protection challenges
- Reasonable price (twice a linac?)



→ Collaboration with heavy industries
→ Collaboration with Japan

Why partners in Japan?

- One facility is already treating patients
  - Kyoto University Research Institute
    (in collaboration with Sumitomo Heavy Industries
    and Stella Pharmaceutical)

C-BENS at Kyoto Univ.

- Three facilities are under construction
  - Tsukuba University, Tokay Village
    (in collaboration with Mitsubishi Heavy Industries)
  - National Cancer Research Hospital, Tokyo
    (n collaboration with Hitachi Ltd and CICS)
  - Southern Tohoku Group, Koriyama
    (in collaboration with Sumitomo Heavy Industries)

The partners (linked by bilateral agreements)

国立研究開発法人
国立がん研究センター

National Cancer Center Hospital

Tsukuba University

Southern Tohoku Group

SOUTHERN TOHOKU RES. INST. FOR NEUROSCI.
総合南東北病院

University Hospital Essen

Essen University Hospital runs Germany’s largest Comprehensive Cancer Center:
The West German Cancer Center (WTZ)

21 Clinical Departments

16 Research Institutes

Particle Therapy in Essen since 1978

1978 Start Fast Neutron Treatments

1991 Start Proton Treatments for Eye Tumors (Cooperation with Centre Antoine-Lacassagne Nice, F)

CAL Nice
Centre Antoine-Lacassagne
Centre Régional de Lutte contre le Cancer

1996 Clinical Trials for BNCT (Petten, NL) The European BNCTeam

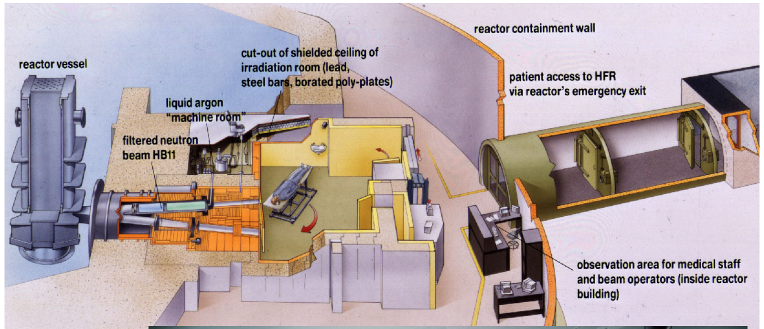
EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

2007 Treatments with High Energy Neutrons (Cooperation with iThemba LABS, South Africa)

2013 Westdeutsches Protonenzentrum Essen

2014 2nd Department for Radiotherapy

Actually 3 cyclotrons running at the University Hospital Essen

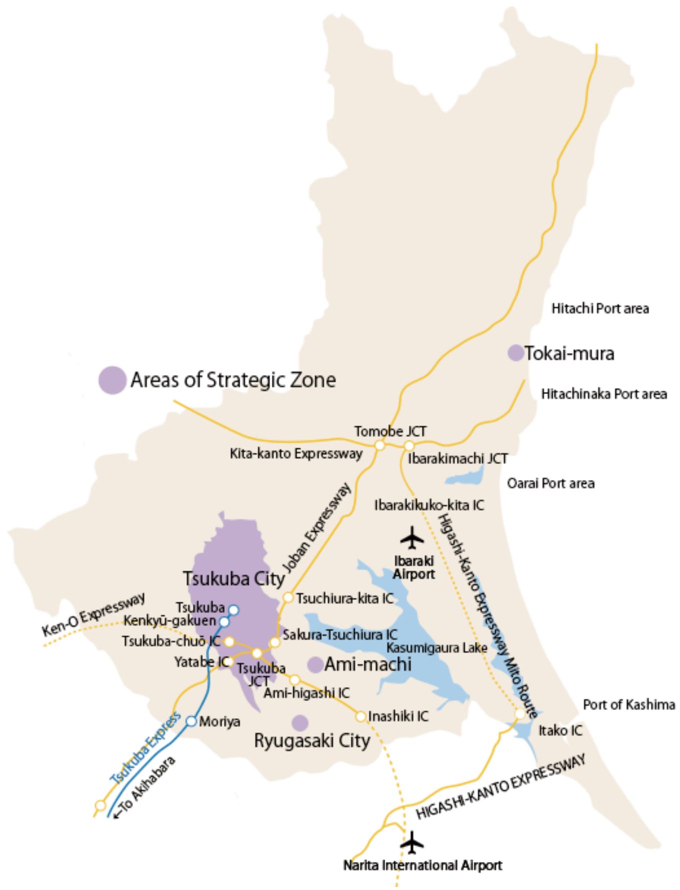


University of Tsukuba

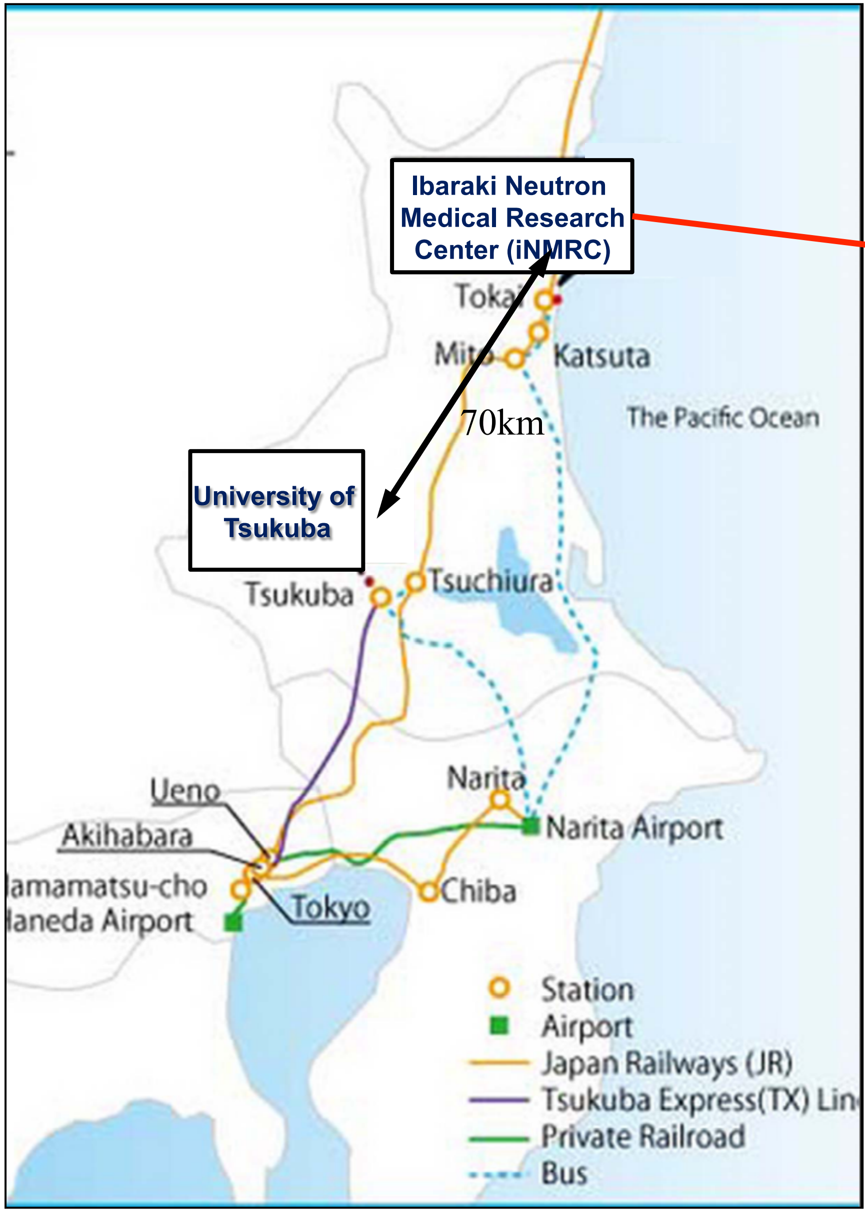
University of Tsukuba (筑波大学), was established in October 1973, due to the relocation of its antecedent, the Tokyo University of Education, to the Tsukuba area. The University has 28 college clusters and schools with a total of around 16,500 students (as of 2014). The main Tsukuba campus covers an area of 258 hectares (636 acres), making it the largest single campus in Japan.

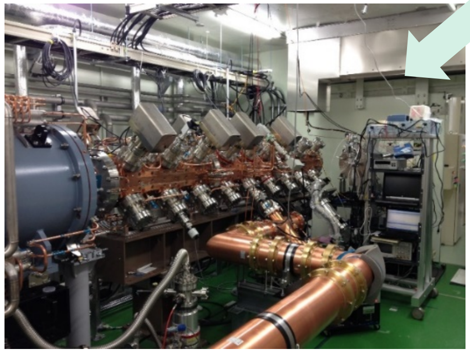
University of Tsukuba

In 2011, seven areas in Japan including Tsukuba were designated as **„International Strategic Zone“**.
International Strategic Zones commit to industrial promotion given advantage on regulatory standards requirement/ financial help from governmental body and local autonomy. **BNCT** is part of Tsukuba‘s International Strategic Zone as **„New Generation of Cancer Radiotherapy“.**



Tsukuba University

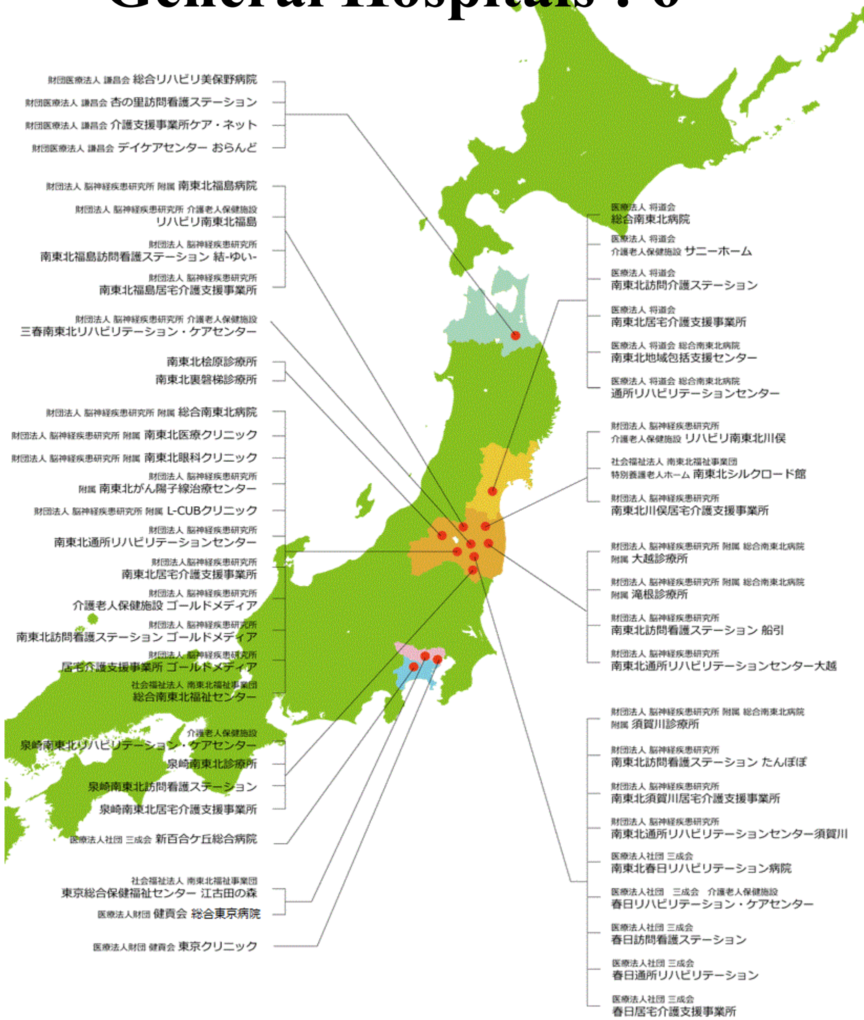




Ibaraki Neutron Medical Research Center

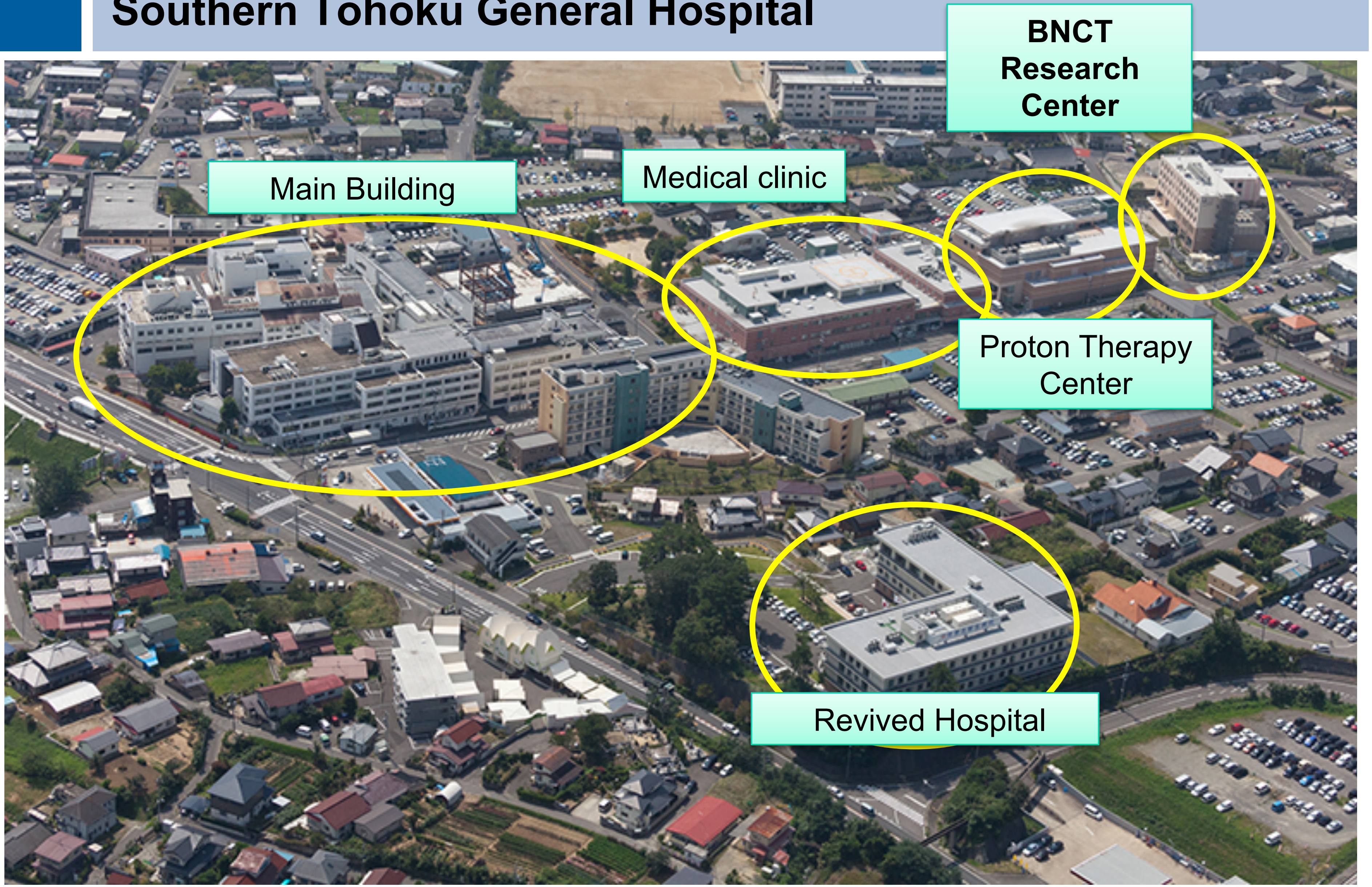
The Southern Tohoku Group

Health Facilities: 70
General Hospitals : 6



Fukushima Prefecture

Southern Tohoku General Hospital



http://www.minamitohoku.or.jp/index.php

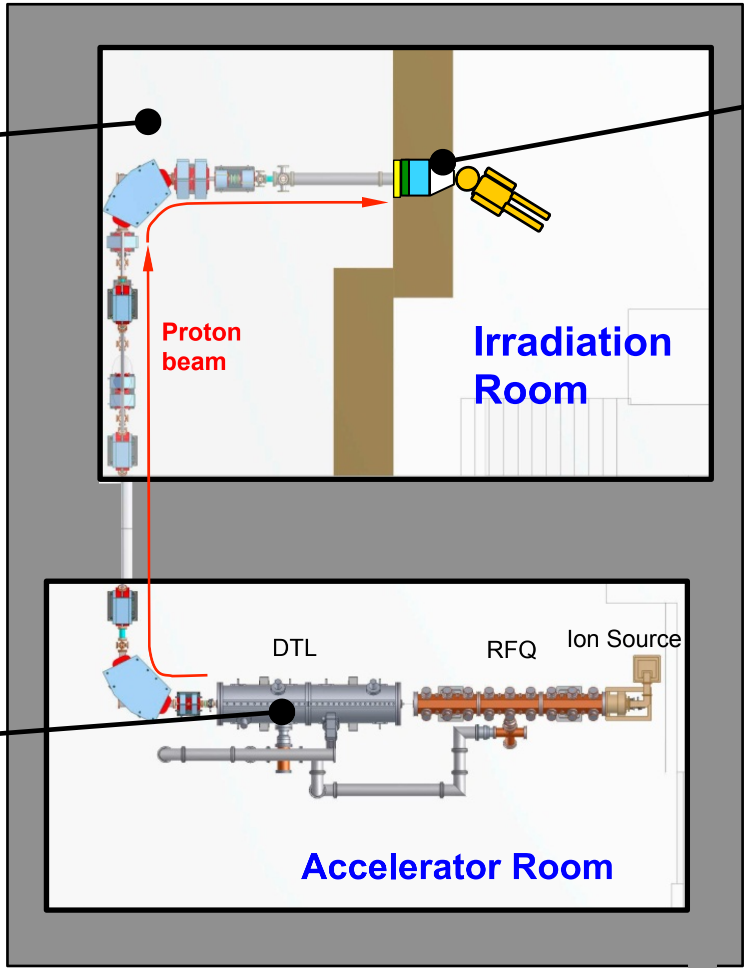
The BNCT Research Center in Koriyama

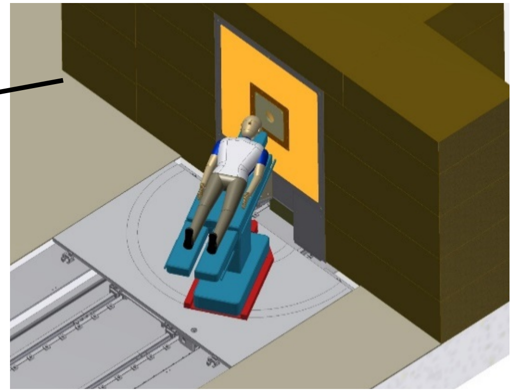
The Southern Tohoku General Hospital owns the first hospital based BNCT facility using a cyclotron produced by Sumitomo HI

Koriyama: A hospital based BNCT facility

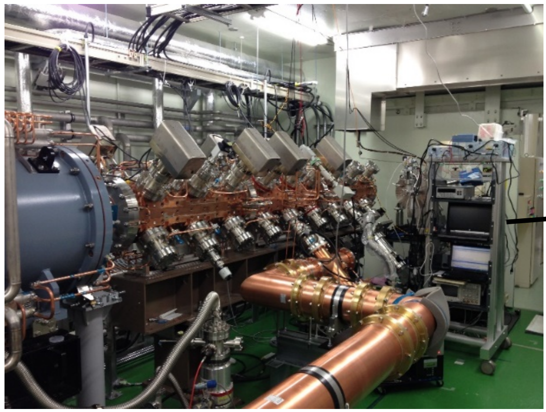
Tsukuba: A high intensity neutron source for BNCT

Proton beam transport





Irradiation room image



Accelerator

Building of iNMRC

Ibaraki Neutron Medical Research Center (iNMRC)
Tsukuba's iBNCT building in Tokai Village

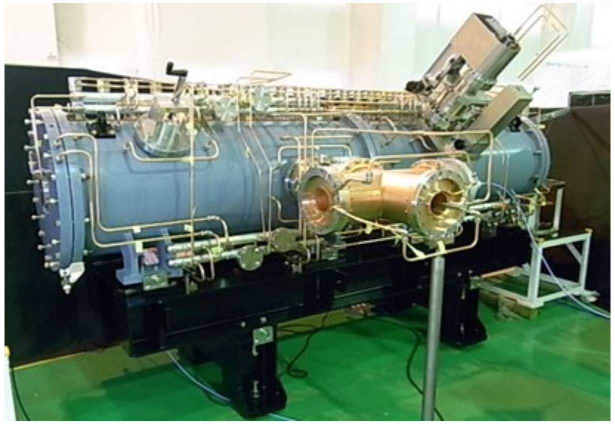
Tsukuba: A high intensity neutron source for BNCT

J-PARC Linac (300m)

Type	RFQ＋DTL Type Linac
Proton Energy	8MeV
Peak Current	50mA
Average Current	>5mA （Max.10mA）
Beam plus	1msec.
Duty	20%
Power to Target	>40kW （Max. 80kW）
Dimension	Length: <7m, Footprint: <50m^2

RFQ Type Accelerator

+

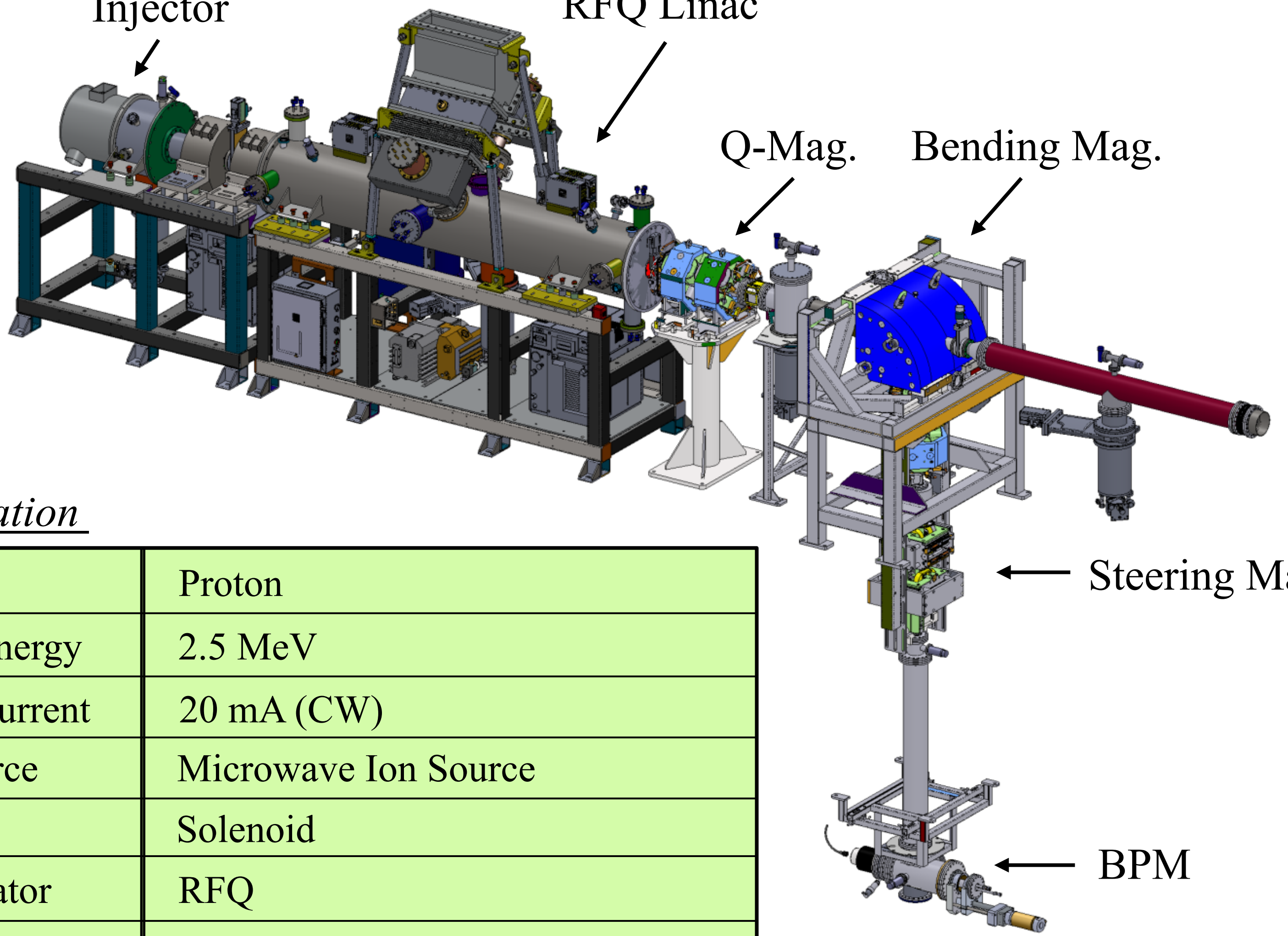


DTL Type Accelerator

Built by Mitsubishi HI

National Cancer Center Hospital: an innovative design

High Current Proton RFQ Linac



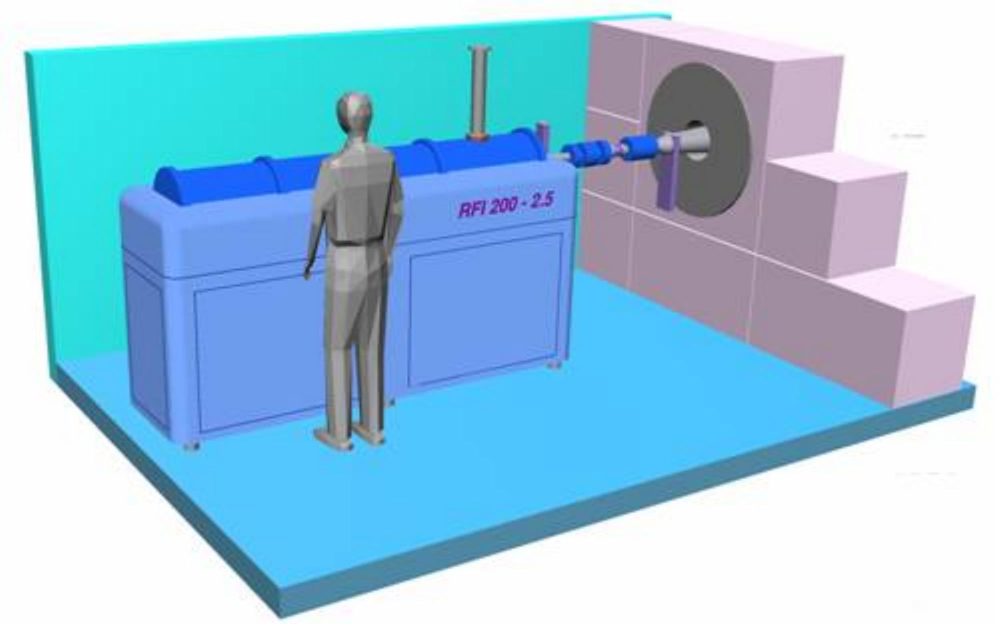
Specification

▪Particle	Proton
▪Beam Energy	2.5 MeV
▪Beam Current	20 mA (CW)
▪Ion Source	Microwave Ion Source
▪LEBT	Solenoid
▪Accelerator	RFQ
▪RF	Klystron (330kW CW, 400MHz)

Accelerator-Based Epithermal Neutron Source (ABENS)

An economical Accelerator-Based Epithermal Neutron Source (ABENS) for the **BNCT** application! Based on the latest development in linac technology, the revolutionary **RFI Linac Structure**, this unit offers higher efficiency operation from smaller units at lower cost.

<u>Features:</u>
ECR Microwave Ion Source
Einzel Lens LEBT
RFQ Linac to 0.5 MeV
RFI Linac to 2.5 MeV
Resonantly Coupled Linacs
Single Rf Power Drive Point
Tetrode Rf Power System



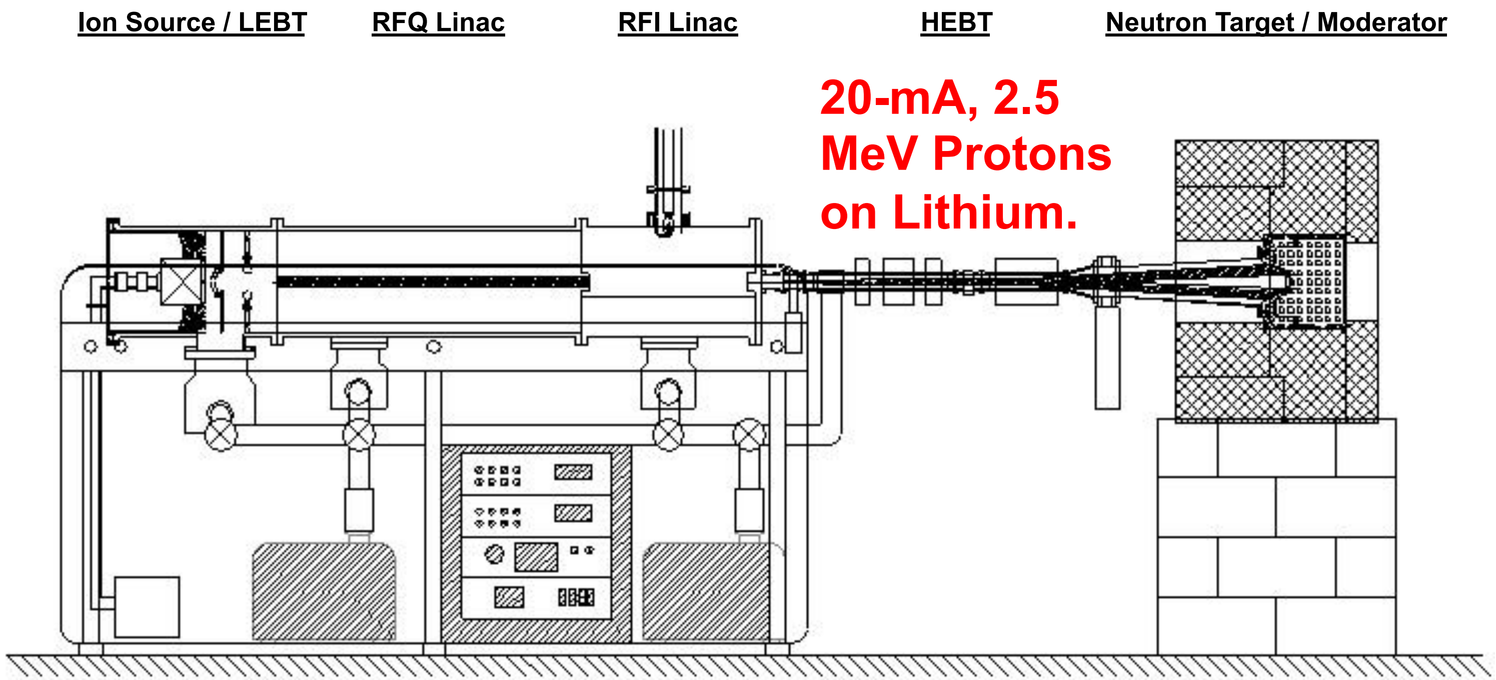
<u>Parameters:</u>

Beam Particle	Proton	
Energy	2.5	MeV
Rf Frequency	200	MHz
Beam Current (peak)	20	mA
(average)	20	mA
Beam Duty Factor (CW)	100	%
Beam Power (CW)	50	kW
Rf Cavity Power (CW)	70	kW
Rf Power (total)	120	kW
Electrical Power	200	kVA

Solid Lithium Target	50 kW
Moderator Assembly	Fluental
Epithermal Neutron Flux	2.2×10^9 n/cm^2/s

Linac Systems 2004

Linac Structure



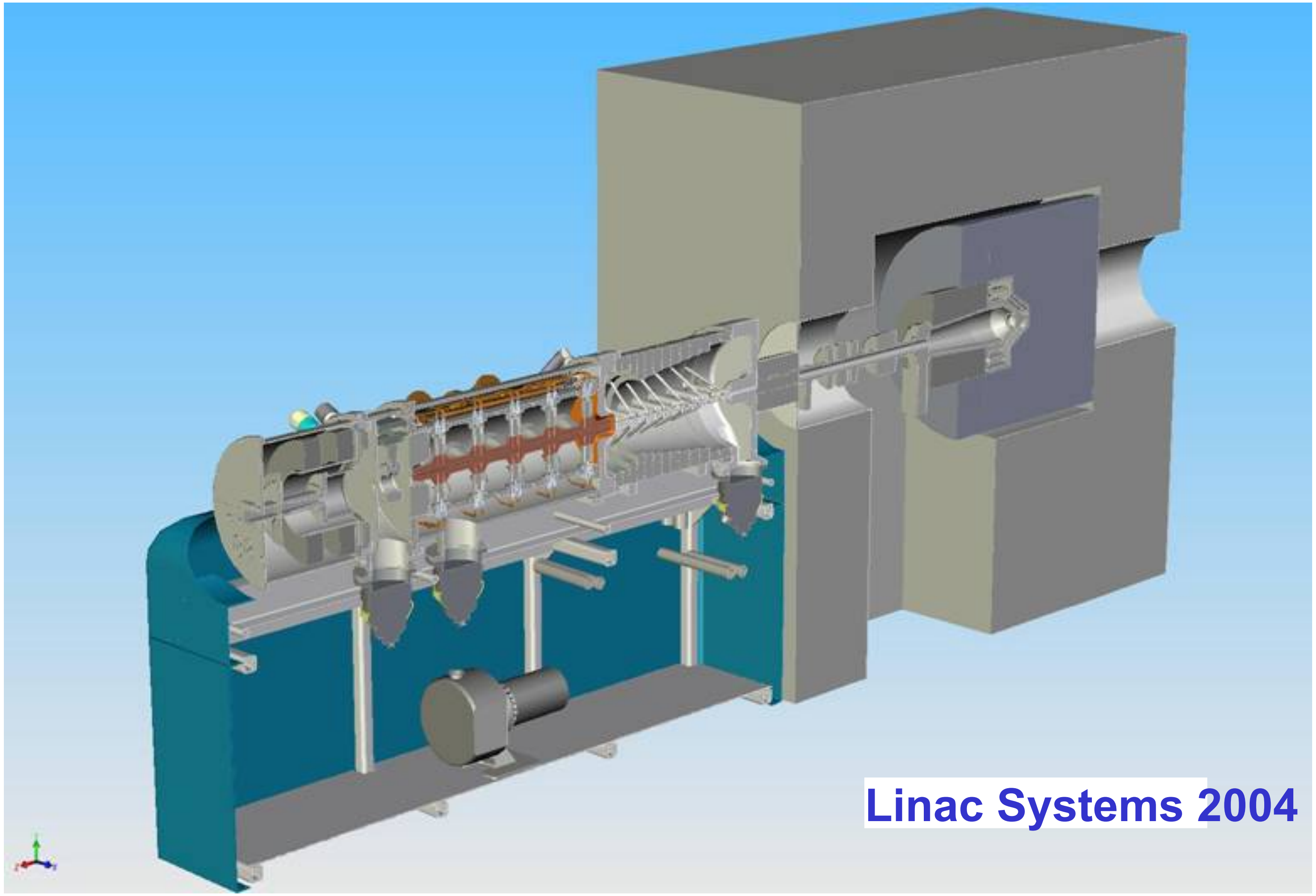
The RFI Linac does:

twice the acceleration of the RFQ
in half the length of the RFQ
with one third the power of the RFQ.

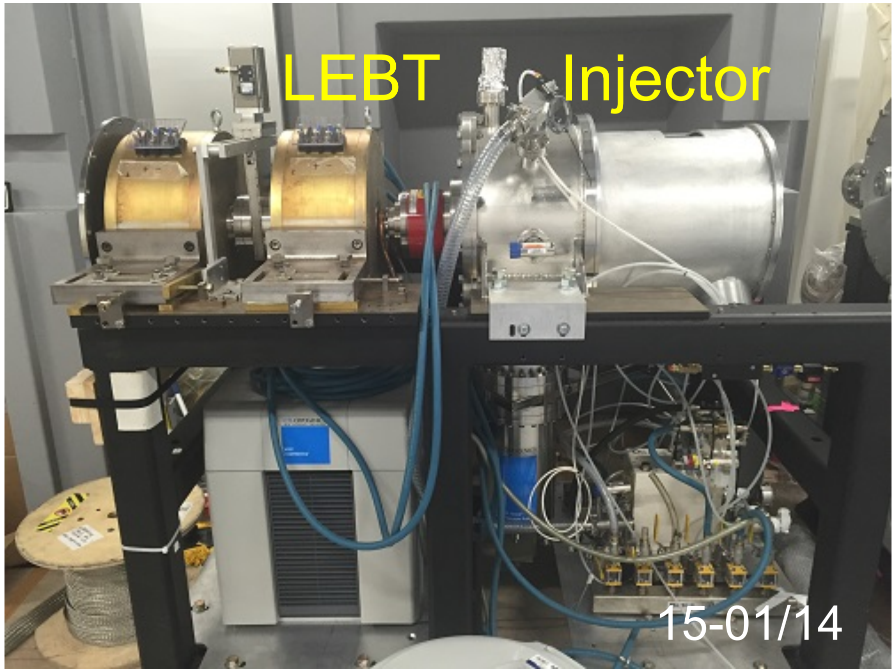
Shunt Impedance, $Z \sim DW^2 / (P * L)$
$Z_{(RFI\ to\ RFQ\ Ratio)} = DW^2_{Ratio} / (P_{Ratio} * L_{Ratio})$
$Z_{(RFI\ to\ RFQ\ Ratio)} = 2^2 / (1/3 * 1/2) = 24$ times!

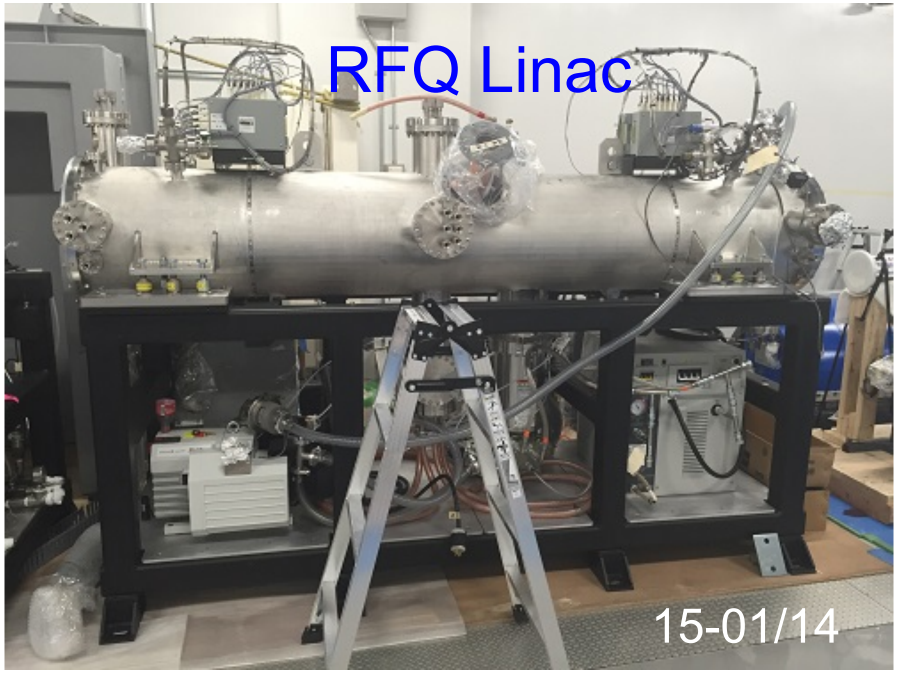
Linac Systems 2004

Linac Structure



The accelerator

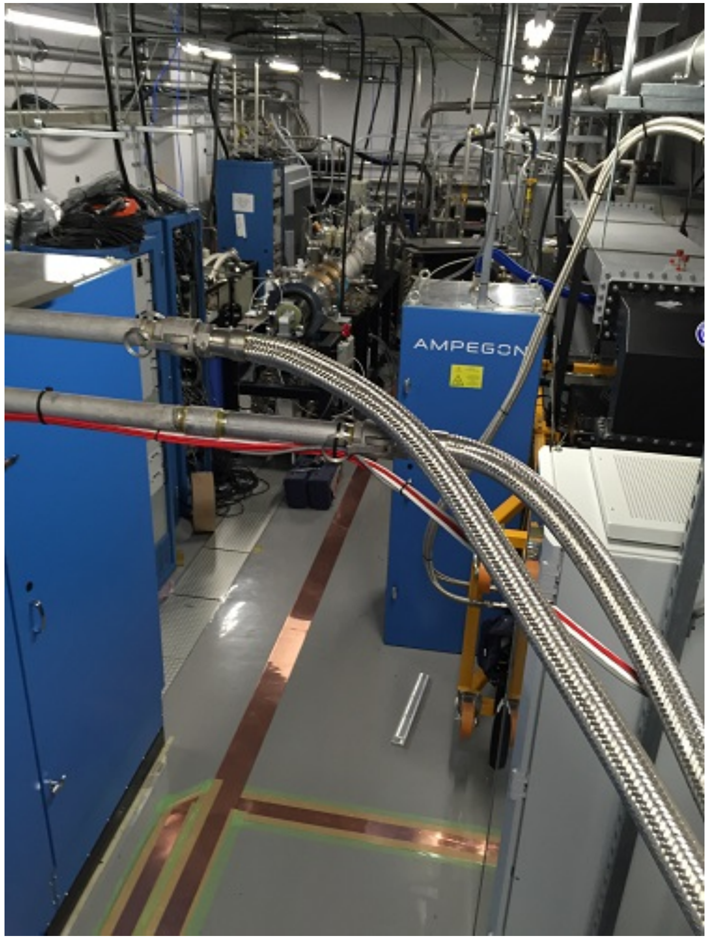




国立研究開発法人
国立がん研究センター

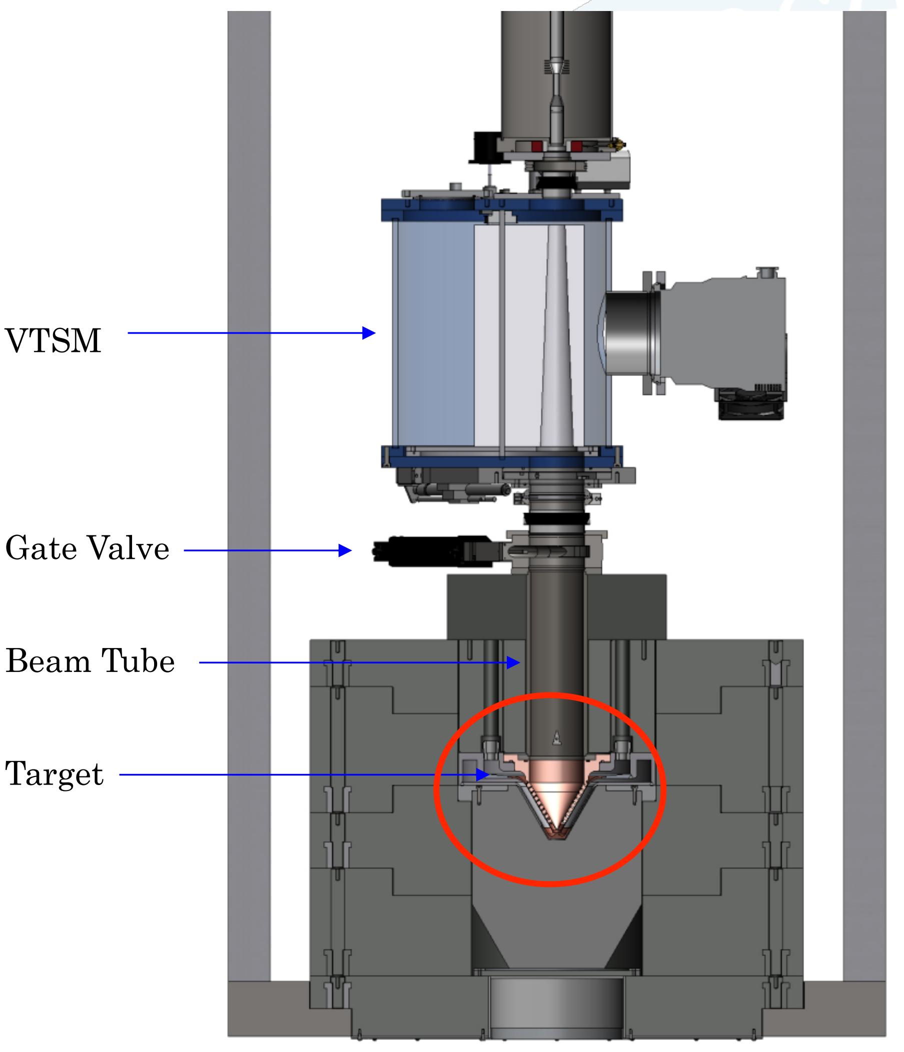
Courtesy Jun Itami and Yoshio Imahori

Accelerator System



Courtesy Jun Itami and Yoshio Imahori

National Cancer Center Hospital



陽子線加速装置及びHEBT
AccSys Technology, Inc.

リチウムターゲット自動再生装置
CICS, Inc.

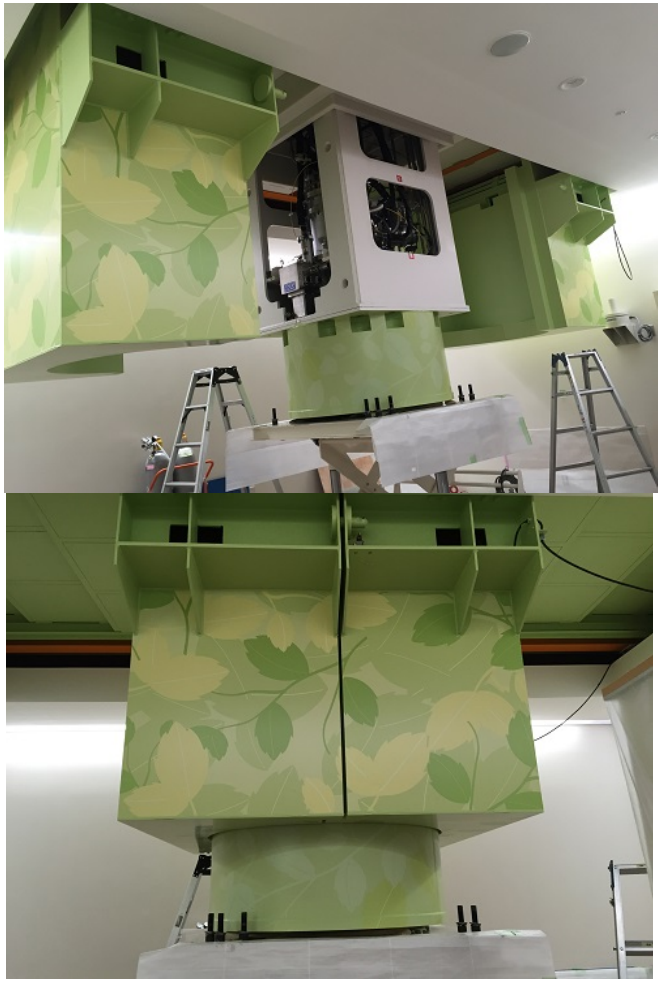
リチウムターゲットおよびモデレータ
CICS, Inc.

Courtesy Jun Itami and Yoshio Imahori

National Cancer Center Hospital

Target system in place
Vertical beam delivery
Beam size: 25cm ϕ

Courtesy Jun Itami and Yoshio Imahori



Is this a realistic approach?

Yes

But

neutrons

^{10}B

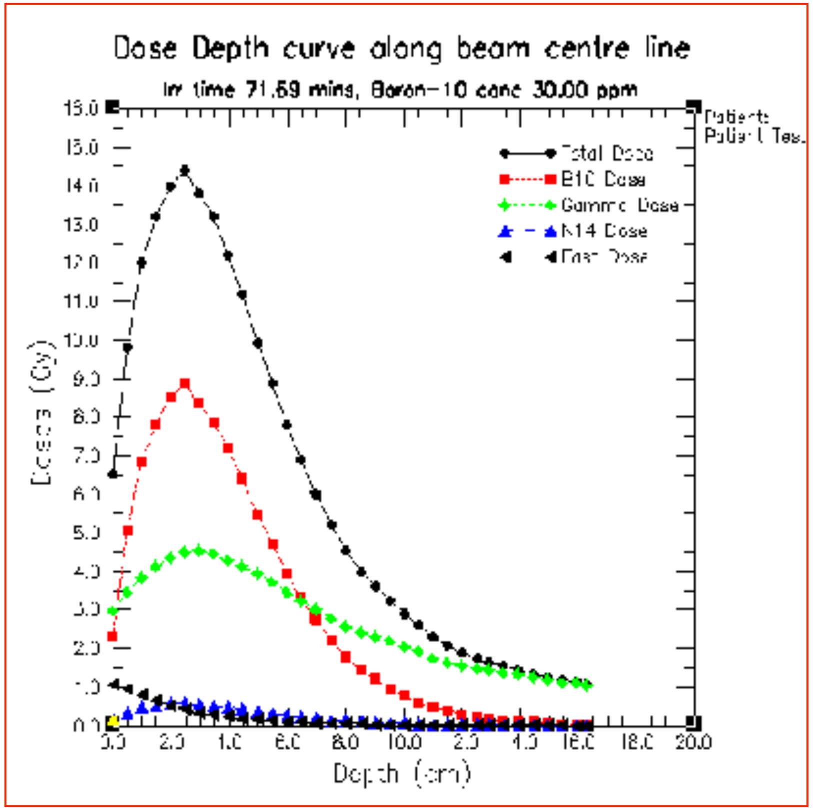
Dose
a special challenge in BNCT

In BNCT different dose components have to be handled

Different biological effects

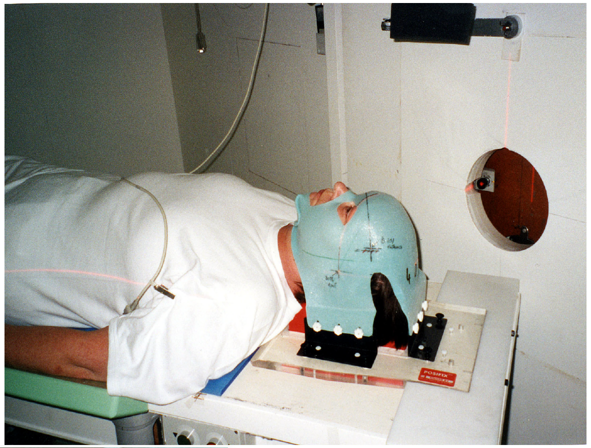
Dosimetry

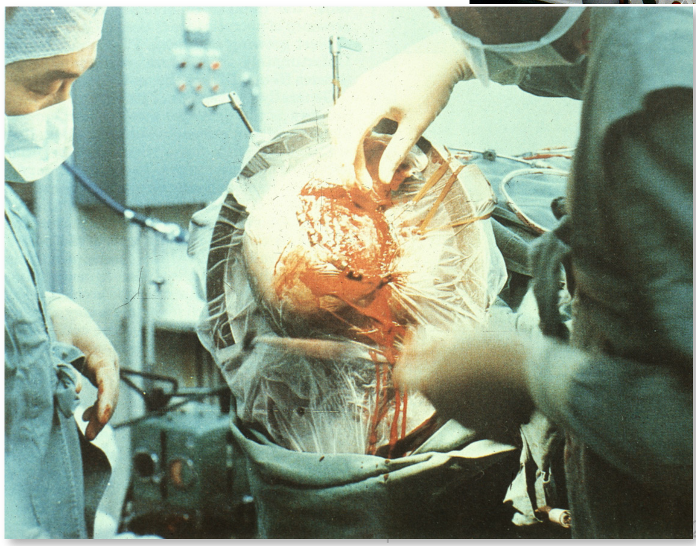
Treatment Planning



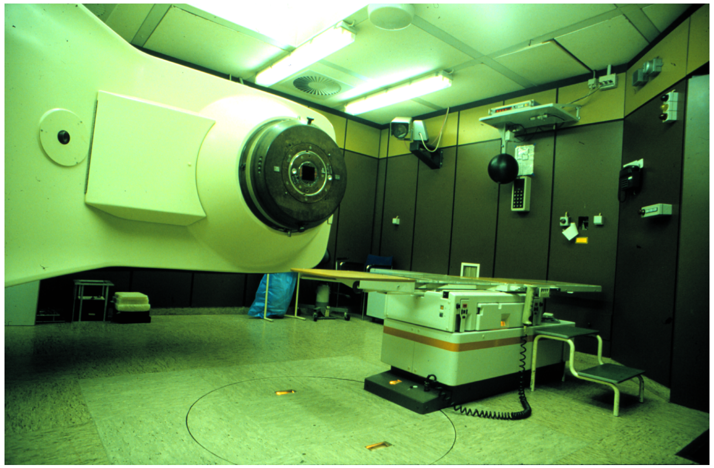
Optimized beam delivery

What is the best beam?





2015



Is this a realistic approach?

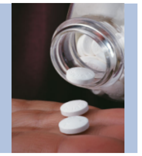
Yes

But

neutrons

^{10}B

Drug development

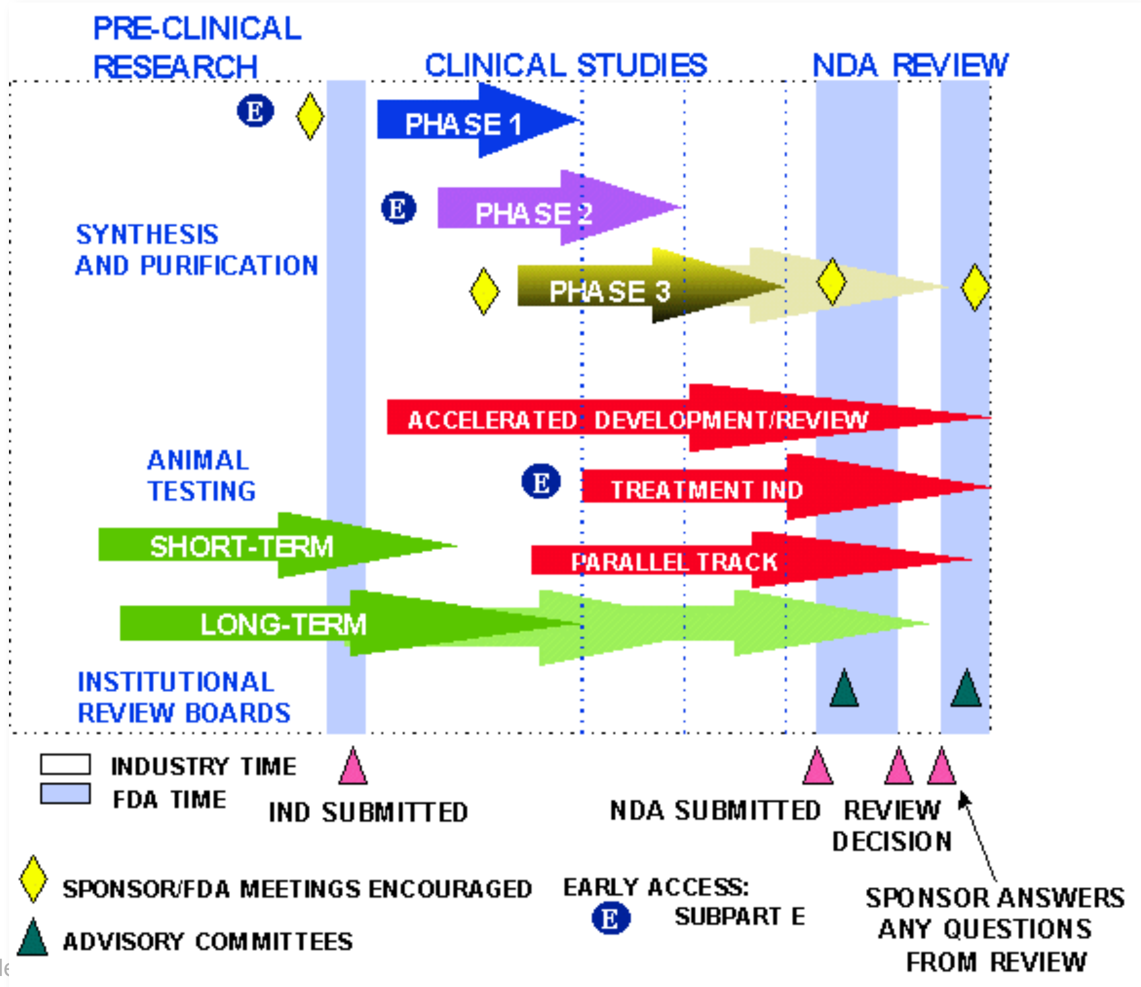


U.S. Department of Health and Human Services
FDA Food and Drug Administration

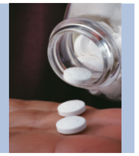
1 out of 5000 compounds

12 years

$ 400 Millions



Drug Development for BNCT



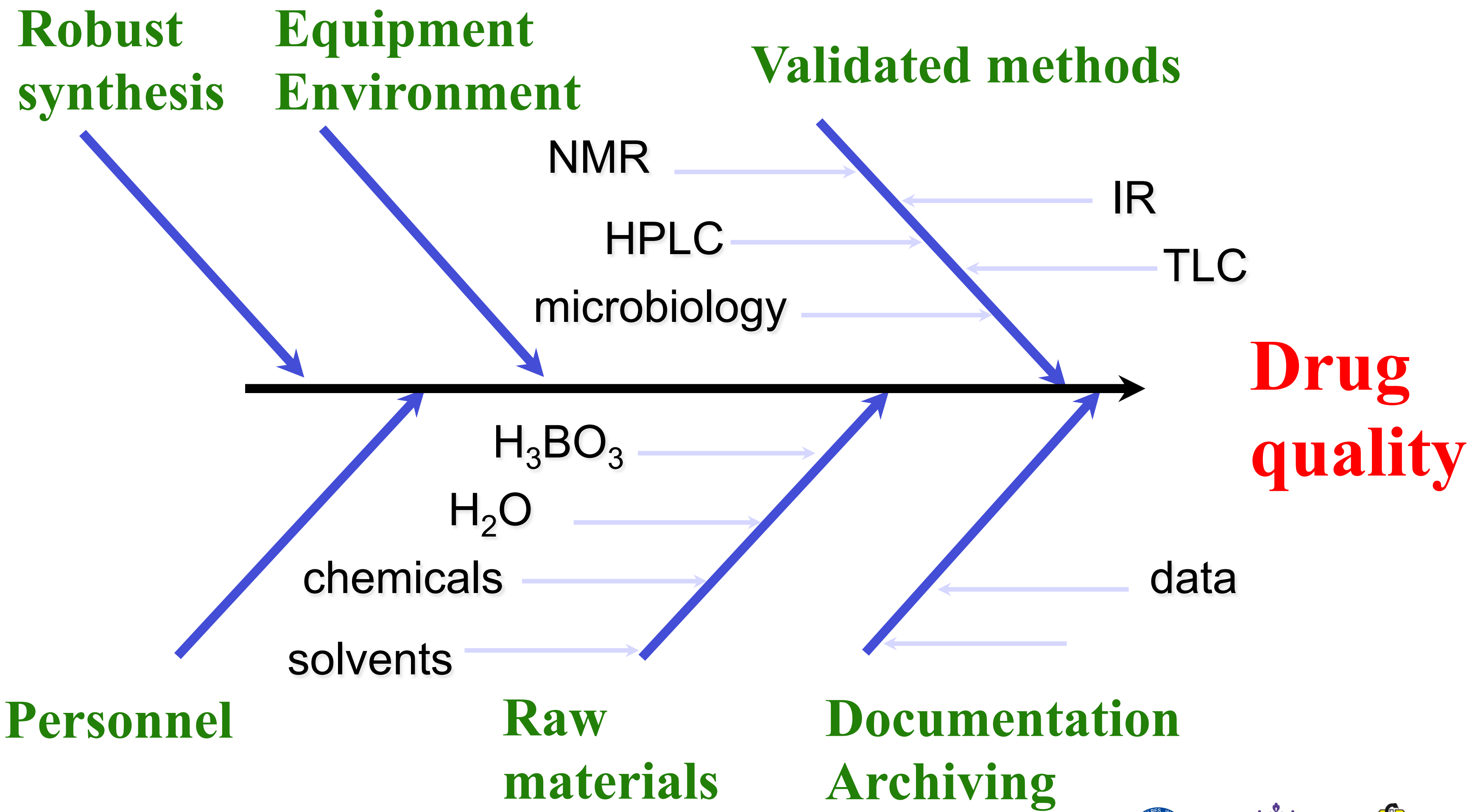
- Drug development is research driven by industry
- There was no interest from industry in BNCT (no market)
- Isotope enriched compounds
- No single sponsor can pay the amount of money needed

Coordinated efforts combining academic research and SME's may help to overcome the problem

Within the frame of the EU research project "Boron Imaging", it was possible for one of the partners to develop the production of BPA under the rules of GMP.

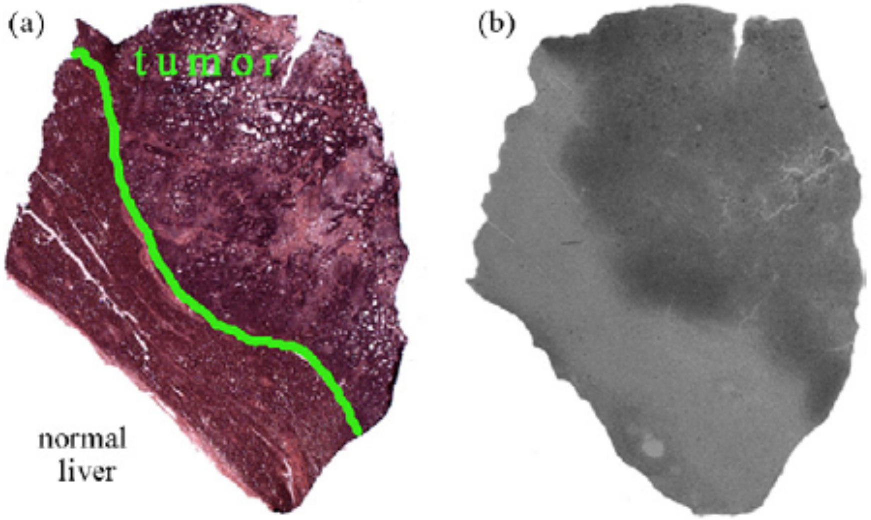
Industrial Production Under GMP

BNCT TEAM
The European BNCT Project



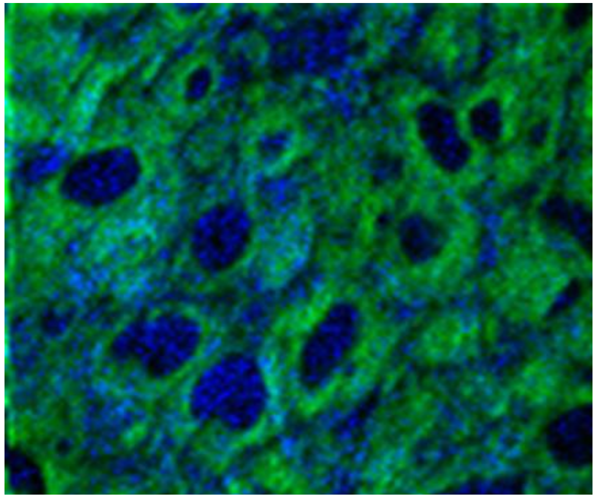
Courtesy of Otomar Kriz, Rez

2 Drugs available for BNCT Clinical Trials



Neutron Capture Radiography of a liver metastases

Courtesy Saverio Altieri



Blue = ^{10}B

Laser-SNMS of a sarcoma

Wittig, Sauerwein et al.
Mol Cancer Ther, 2008

The long-lasting process for approval of BNCT as a treatment modality in Japan

Basic research

Preclinical Studies

Clinical Trials*

Application

Treatment

Phase I : Safety

Phase II : Efficacy

* only for Japanese citizens

Accelerator based BNCT@ KURR

2008～ Basic research → 2009～ Preclinical Studies → 2012～ Clinical Trials → Application → Treatment

2008～ Basic research

Medicinal Product:

Neutron Source

Drug:

Boron Compound

2009～ Preclinical Studies

Mechanical
Electronic
Electromagnetic
Radiological
Biological
Performance…

Pharmacokinetic
Safety
Toxicity…

2012～ Clinical Trials

Phase Ⅰ: Safety

2012~2015 Brain tumor

2014~ Head & Neck Cancer

Phase Ⅱ: Efficacy

Application

Medicinal Product:

Neutron Source

Drug:

Boron Compound

Treatment

BNCT

Accelerator based BNCT@ KURR

2008～ Basic research → 2009～ Preclinical Studies → 2012～ Clinical Trials → Application → Treatment

Basic research

Medicinal Product: completed
Neutron Source

Drug: completed
Boron Compound

Preclinical Studies

Mechanical
Electronic
Electromagnetic
Radiological
Biological
Performance…

Pharmacokinetic completed
Safety
Toxicity…

Clinical Trials

Phase Ⅰ: Safety completed
2012~2015
Brain tumor

2014~
Head & Neck Cancer

Phase Ⅱ: Efficacy

Application

Medicinal Product:
Neutron Source

Drug:
Boron Compound

Treatment

BNCT

Accelerator based BNCT@ Southern TOHOKU BNCT Center

2013-14
BNCT facility

2014～
Preclinical Studies

2015～
Clinical Trials

2017?
Application

2018?
Treatment

Clinical research project?

Construction of a BNCT Hospital

Equivalency tests between KURR & BNCT Center

Mechanical
Electronic
Electromagnetic
Radiological
Biological
Performance…

Phase Ⅱ : Efficacy

Medicinal Product:

Neutron Source

Drug:

BPA

BNCT

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