Turku PET Centre

UNIVERSITY OF HELSINKI

Clinical BNCT practice in Finland

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VTT

Outline

- Why BNCT
- Neutron facility FiR 1
- Dosimetry
- BNCT dose
  - Standard RBE dose calculation and it's weaknesses
  - Photon-Isoeffective dose calculation model
- Treatment planning
- BNCT in practice
- Clinical trials in Finland

Why BNCT

1. **High-LET hadron radiotherapy**
   - ➔ Effective against radiation resistant cancers
     - glioblastoma, melanoma, sarcoma, thyroid carcinoma, renal cell carcinoma, some adenocarcinomas

2. **Biologically targeted radiotherapy**
   - ➔ High dose gradient between tumor and healthy tissues
     - Preferential boron carrier uptake of tumor
     - Cancerous tissue is more sensitive to BNCT than healthy tissue

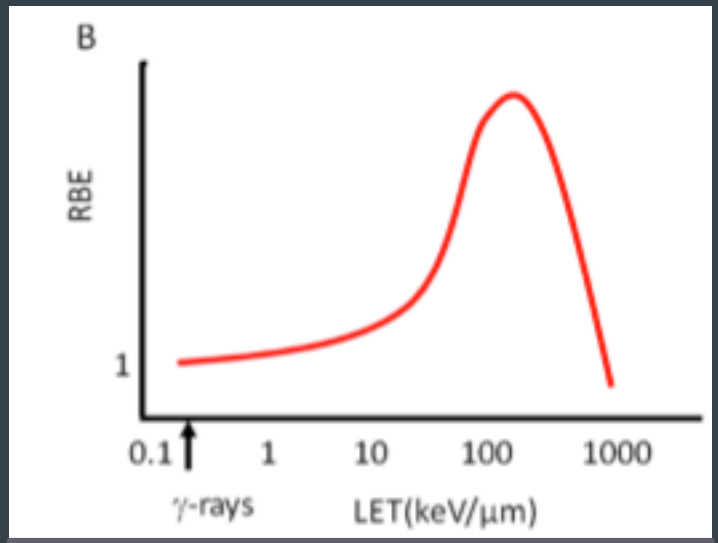
   - ➔ Can be administered
     1. After high-dose radiotherapy
     2. Near or within radiosensitive tissues such as brain, spinal cord, optic nerve, liver or lung etc.

High-LET radiation from BNCT

LET=linear energy transfer

$^{10}B + n \rightarrow \alpha + {}^{7}Li + \gamma\ (95\%)$ Q=2.79 MeV

- Very high cross section at thermal neutron energies, σ = 3840 barns
- Densely ionizing disintegration products



Typical RBE-LET relationship
➔ RBE peaks near 100–200 keV/ μ m
Ledingham et al. Appl Sci 4, 2014.

LET_{ave}

α -particle ~163 keV/μm

^{7}Li nucleus ~200 keV/μm

➔ Range ~10 μm~diameter of a cell

Max LET at clinical energies

Electrons ~ 10 keV/μm

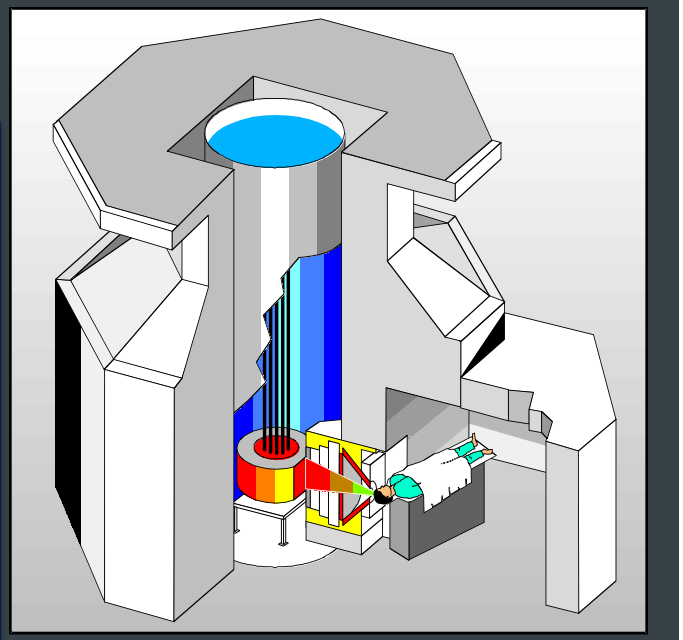
Protons ~90 keV/μm

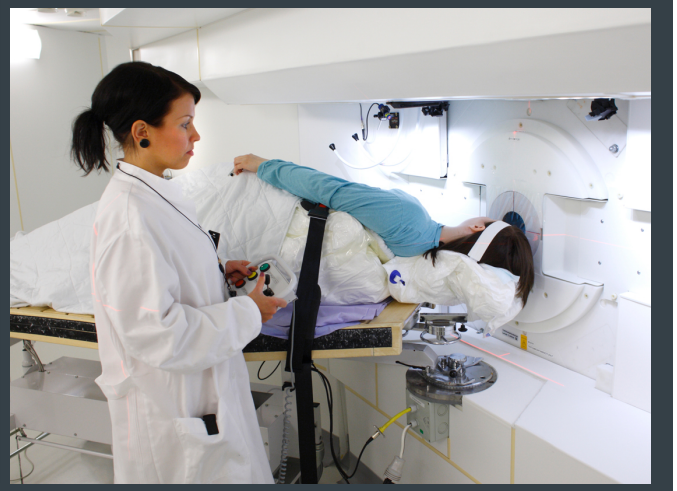
Carbon ~ 150 keV/μm

Clinical BNCT in Finland

- Between years 1999 and 2012
  - 249 patients (>300 BNCT treatments)
    - Primary and recurrent brain tumors
    - Head and neck cancer
    - Melanoma of extremities
  - Patients from Finland, Sweden, Norway, Estonia, Italy, Monaco, Japan and Australia
- Boron phenylalanine (BPA) as the ^{10}B carrier
  - 2 hours intravenous infusion
  - Dose escalation from 290 to 500 mg/kg
- Neutron facility: 250 kW TRIGA mark research reactor FiR 1 (GE, San Diego, CA)
  - Epithermal neutron beam

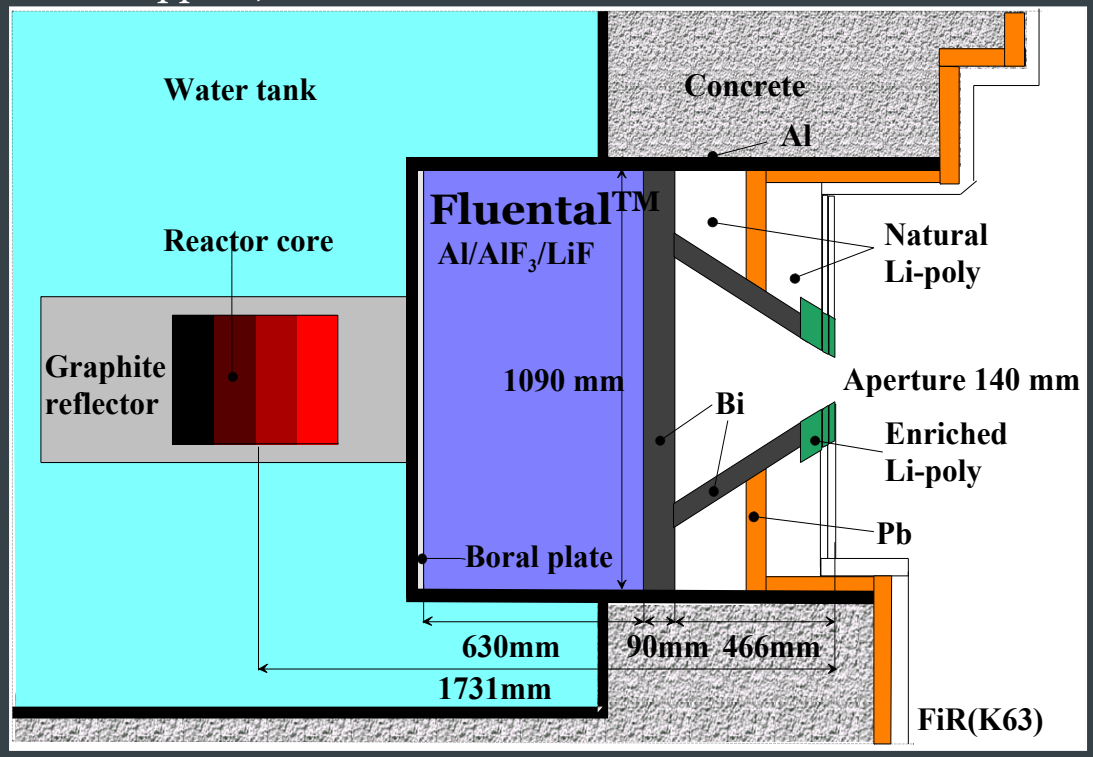
FiR 1 closed due to political and financial reasons





Epithermal neutron beam at FiR 1

Tiina Seppälä, PhD Thesis 2002



Neutron Energy range	Measured neutron fluence rate	Calculated neutron fluence rate	Ratio M/C
	$cm^{-2}s^{-1}$	$cm^{-2}s^{-1}$	
Fast >10 keV	3.45×10^7	3.20×10^7	1.08
Epithermal 0.414 eV - 10 keV	**1.08×10^9**	**1.03×10^9**	**1.04**
Thermal <0.414 eV	6.36×10^7	5.91×10^7	1.08

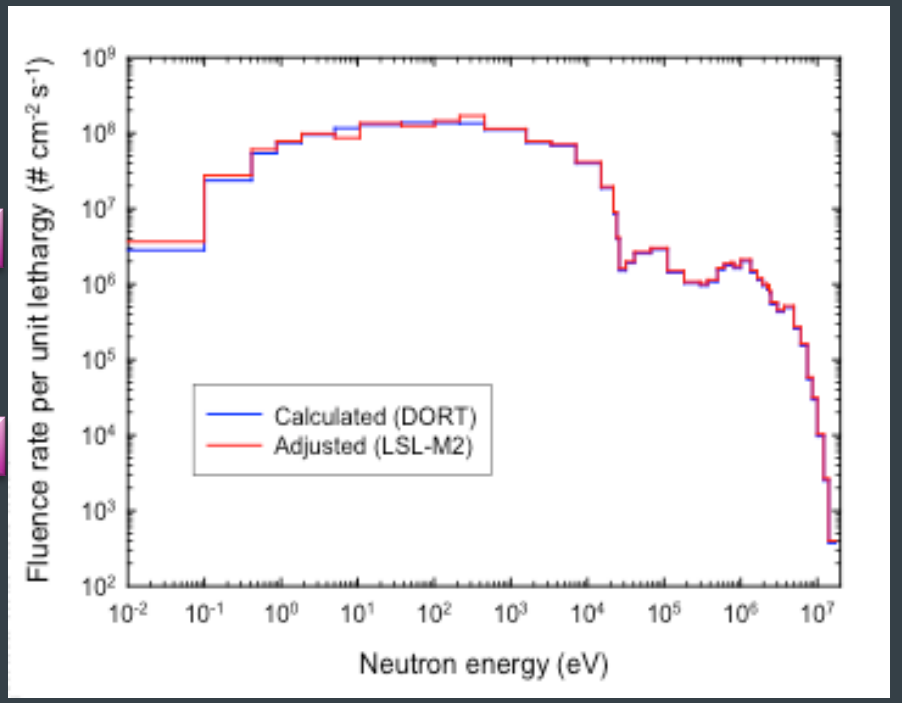
DORT* code used for modelling the reactor core and the beam shaping assembly

*A two-dimensional discrete ordinate (deterministic) transport code

Verification of the neutron beam model

Neutron measurements with set of activation foils

Type	Reaction	Half-life	
In-Al (0.2 %)	$^{115}In(n,\gamma)^{116m}In$	54.41 min	
In (pure)	$^{115}In(n,n')^{115m}In$	4.486 h	Threshold 430 keV
Sc (pure)	$^{45}Sc(n,\gamma)^{46}Sc$	83.79 d	
Au-Al (1 %)	$^{197}Au(n,\gamma)^{198}Au$	2.695 d	**Thermal**+Epithermal
W-Al (1 %)	$^{186}W(n,\gamma)^{187}W$	23.72 h	
^{238}U-Al (22.83 %)	$^{238}U(n,\gamma)^{239}U$	23.47 min	
La-Al (5 %)	$^{139}La(n,\gamma)^{140}La$	40.274 h	
Mn-Al (1 %)	$^{55}Mn(n,\gamma)^{56}Mn$	2.58 h	Thermal+**Epithermal**
Cu-Al (10 %)	$^{63}Cu(n,\gamma)^{64}Cu$	12.70 h	
Cu (pure)	$^{63}Cu(n,\gamma)^{64}Cu$	12.70 h	
Dy-Al (4.7 %)	$^{164}Dy(n,\gamma)^{165}Dy$	2.334 h	
Ni (pure)	$^{58}Ni(n,p)^{58}Co$	70.86 d	Threshold 1.9 MeV
^{54}Fe (99.92 %)	$^{54}Fe(n,p)^{54}Mn$	312.3 d	Threshold 800 keV
^{58}Fe (93.23 %)	$^{58}Fe(n,\gamma)^{59}Fe$	44.51 d	
Nb (pure)	$^{93}Nb(n,n')^{93m}Nb$	16.13 y	
Co-Al (0.491 %)	$^{59}Co(n,\gamma)^{60}Co$	5.27 a	



The measured reaction rates adjusted with the least-squares adjustment code LSL-M2

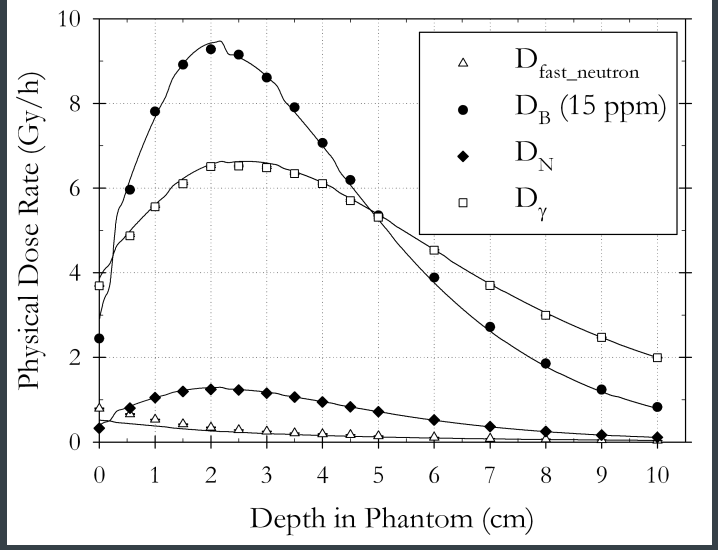
Serén T *et al.* 1999, *15th Europeon TRIGA Conf., VTT Symp.* **197**

BNCT dose components

Thermal neutron induced dose components in tissue

1. Boron dose from $^{10}B(n,\alpha)^{7}Li$ ➔ D_B
2. Nitrogen dose from thermal neutron capture in tissue ➔ D_N
3. Photon dose mainly from $^{1}H(n,\gamma)^{2}H$ $E\gamma$=2.2 MeV ➔ D_γ

FiR 1 - 14 cm diameter circular beam



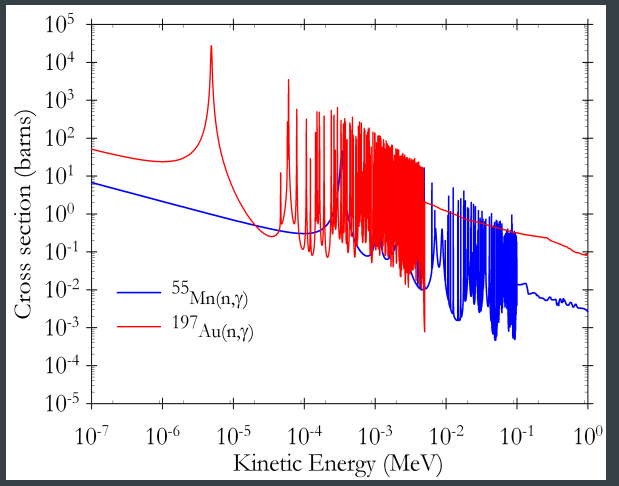
ppm=part per million, μg/g

Beam quality related dose components

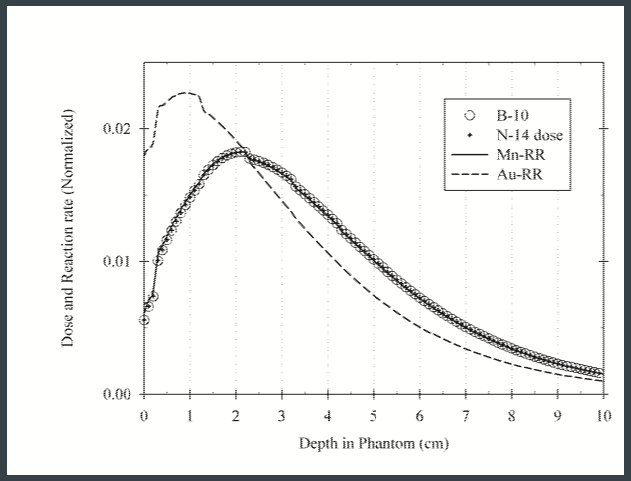
1. Fast neutron, or proton recoil dose from $^{1}H(n, n')p$ in tissue ➔ D_{n_fast}
2. "Primary" photons from the materials around neutron source ➔ D_γ

Primary dosimetry: neutron activation measurements with ^{197}Au and ^{55}Mn foils

- ^{197}Au(n,γ) and ^{55}Mn(n,γ) reactions mainly at thermal and epithermal neutron energy range
- ^{55}Mn(n,γ) activation along the depth in phantom equals ^{10}B and ^{14}N depth dose distributions



- Diluted Al-Mn and Al-Au foils (ø12 mm × 0.2 mm)
  - 1 w-% of Mn or Au
    - ➔ No self-shielding effect
  - Uncertainty ±3%
- ^{197}Au(n,γ) reaction rate @ 2 cm depth in cylindrical PMMA phantom
  - ➔ Dose calculation normalization
- MnAl foils applied for *in vivo* dosimetry



Dosimetry at FiR 1

1. Diluted Al-Mn and Al-Au foils
2. Ionization chambers of Exradin™ *Uncertainty 5-20%*
   - **Mg(Ar)** chamber for photon dose ~*"neutron insensitive"*
   - **TE(TE)** chamber for total and neutron dose ~*tissue equivalent*

Cylindrical solid PMMA phantom

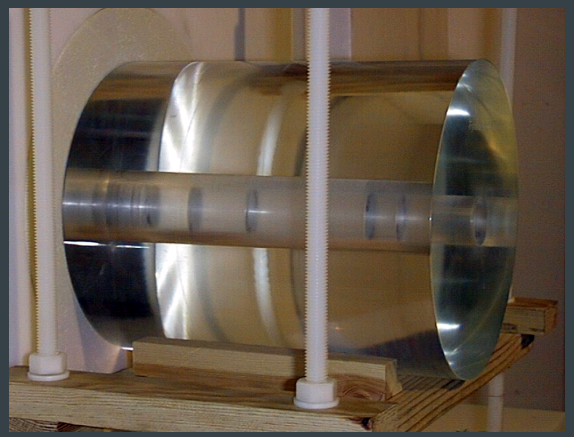
ø 20 cm, length 24 cm

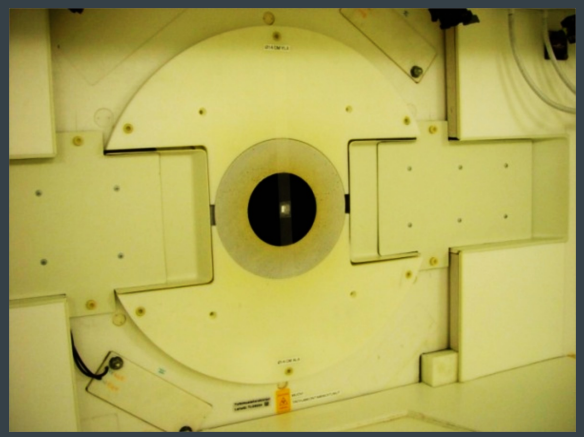
- Activation measurements
- Normalization of the beam models
- Beam stability check measurements

Large cubical water phantom with cylindrical extension

$W \times L \times D$ = 51 cm × 51 cm × 47 cm

- Depth and radial profiles
  - Neutron activation measurements
  - Ionization chamber measurements





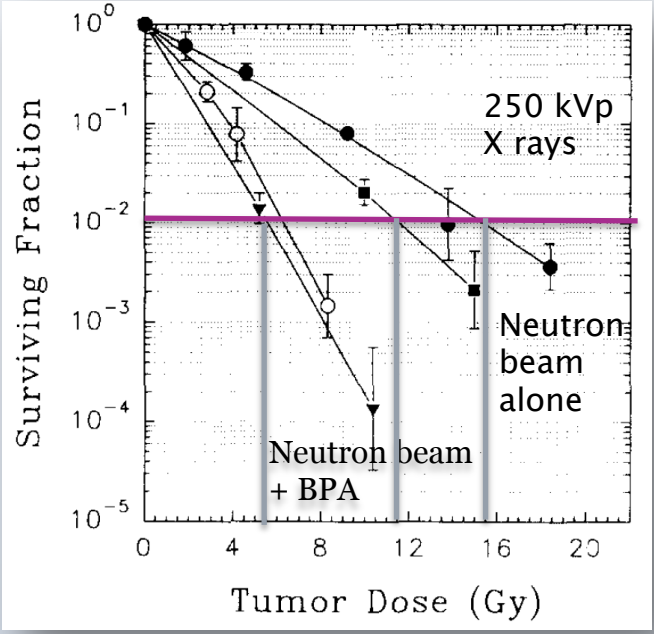
Total RBE dose – traditional approach

Coderre et al. 1993, Coderre and Morris 1999

$$D_W = RBE_B \times [B10] \times D_{B,ppm} + D_g + RBE_N \times D_N + RBE_n \times D_n$$

Coderre *et al.* [IJROBP 1993; 27(5), 1121-29]:

- Intracerebral 9L rat gliosarcoma model
- radiobiological parameters from *in vivo/in vitro* clonogenic cell survival assays
- Irradiated at Brookhaven Medical Research Reactor



Commonly applied RBE values defined at 1%

Component	RBE
X rays / Beam gamma photons	1
Neutrons (BMRR minus photons)	3.2
Boron (BPA)	3.8

PROBLEMS

- Radiobiological effect depends on the dose rate and total dose
  - → biological effect should be derived for each irradiation condition individually
- RBE's were derived for given cell type and given end point

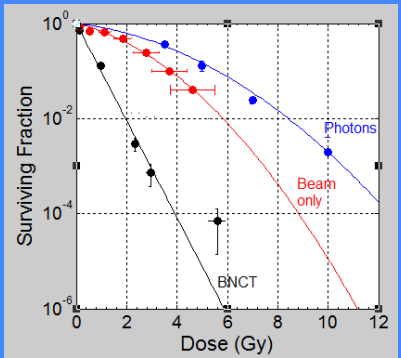
Photon-isoeffective dose calculation model

González and Santa Cruz, Rad Res. 178, 2012

- Takes into account the dose rate of each dose component
- Takes into account the cumulative dose per fraction
  - first-order repair of sublethal lesions by means of the generalized Lea-Catcheside time factor (G)added in the modified linear-quadratic model
- Considers the synergistic interactions between different radiation components
- Predicts significantly lower tumor doses than constant RBE and CBE factors
- Predicts response of melanoma lesions to BNCT better than the fixed RBE approach

Photon-isoeffective doses in BNCT: parameters of the model

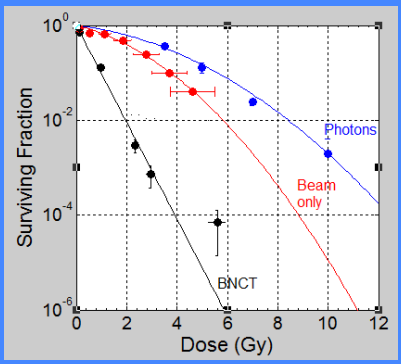
1) Determination of the photon radiation parameters α_R ,β_R (2 param.):



$$-\ln\left(S_R(D_R)\right) = \alpha_R D_R + G_R(\theta')\beta_R D_R^2,$$

Survival Model + photon data: parameters are obtained explicitly including the dependence of irradiation time (G_R with θ') in the fitting.

2) Determination of the BNCT radiation parameters α_i ,β_i (8 param.):



$$-\ln\left(S(D_1,\dots,D_4)\right) = \sum_{i=1}^{4}\alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i\beta_j}\,D_i D_j\,.$$

Four-parameter survival model

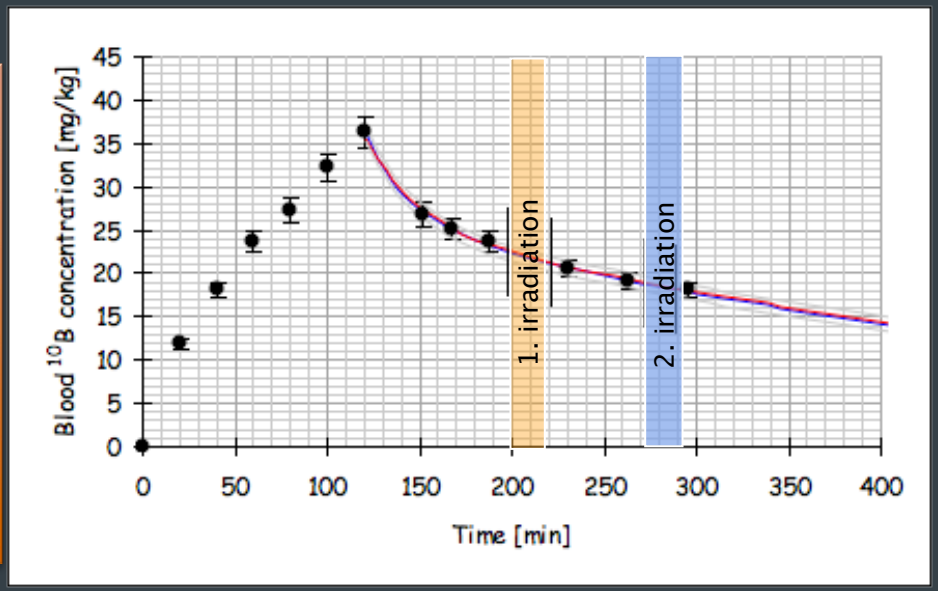
Suvival model + n Beam only & n+^{10}B-BPA data: parameters are simultaneously obtained explicitly including the dependence of (G factor) the irradiation time.

^{10}B concentration evaluation in Finland

- Blood samples collected every 10 or 20 minutes
  - during and after BPA infusion
  - Analyzed with inductively coupled plasma–atomic emission spectrometry (ICP-AES)
- Boron dose calculated based on the average whole blood ^{10}B concentration at the time of irradiation
  - Tissue-to-blood ^{10}B estimated based on literature (Coderre et al. 1998 etc)

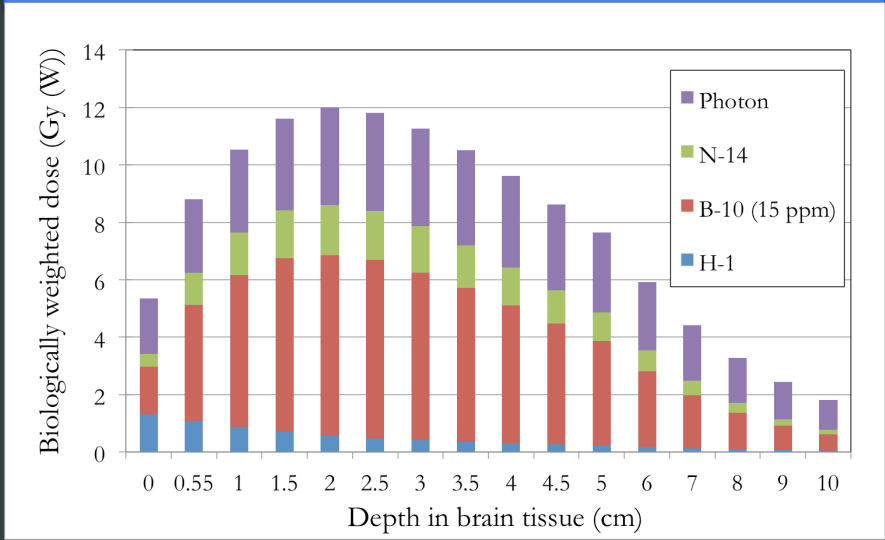
^{10}B concentrations for tissues [B10]

Blood	15 -20 mg/g
Brain (or spine)	same as blood
Mucosal membrane	2 × blood
Tumor cells (GTV and PTV)	3.5 × blood
Skin	1.5× blood
Lung	same as blood

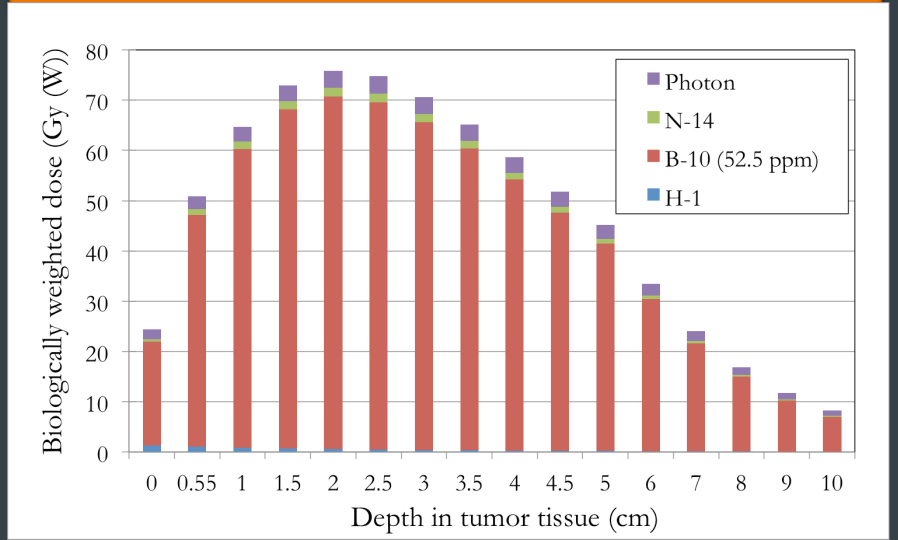


Depth doses in phantom at FiR 1

Dose to normal brain



Dose to tumor

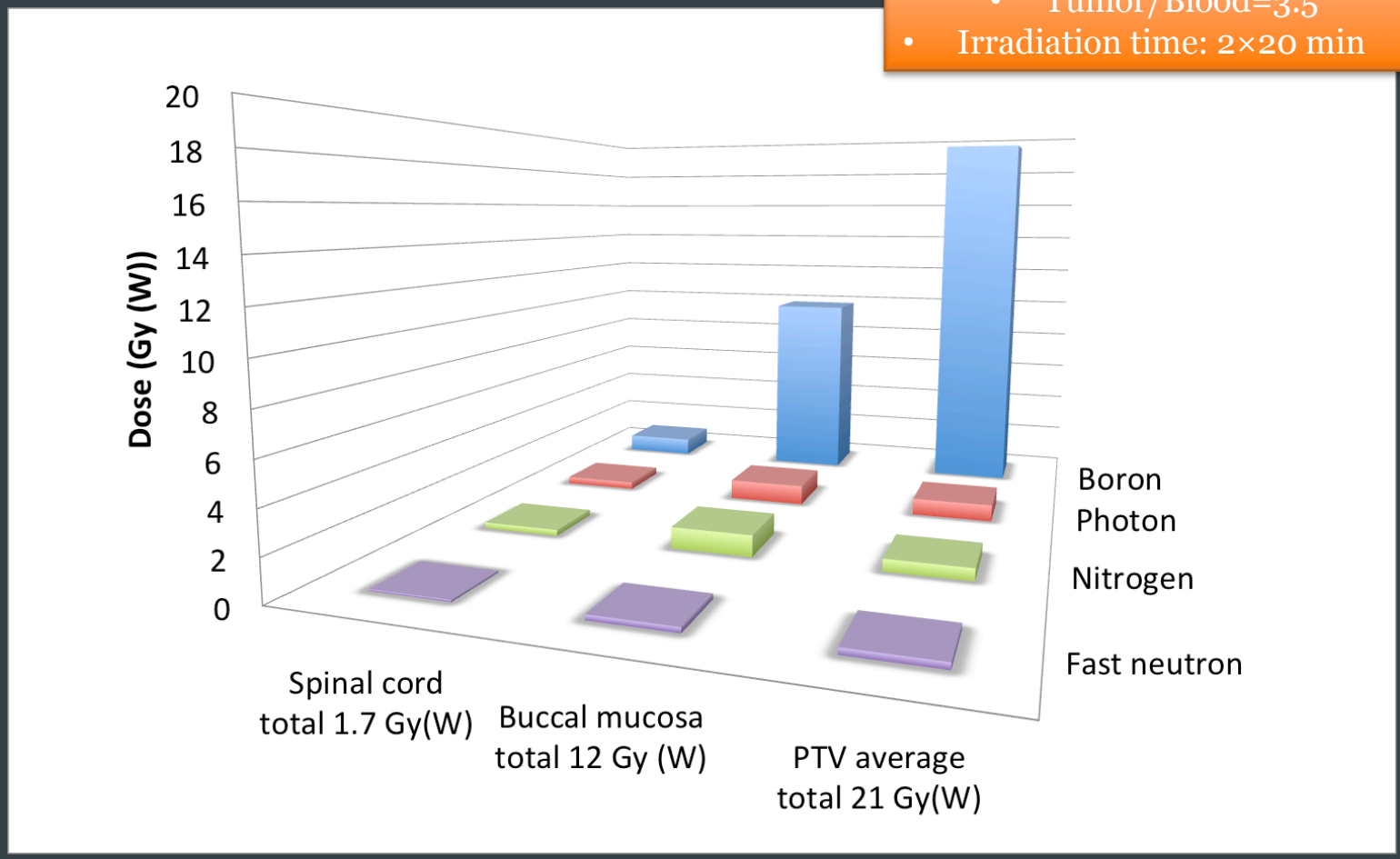


MCNP calculation in a water phantom

BNCT dose components in head&neck cancer

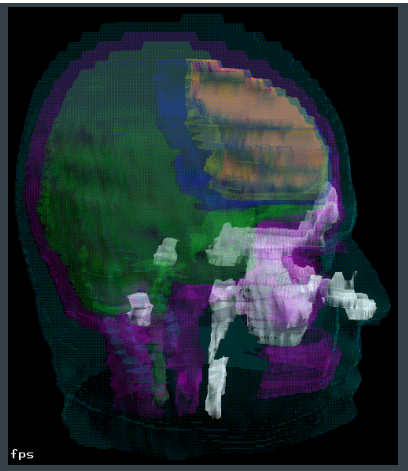
Patient 24HN, BNCT×2, CR response, grade 3 mucositis

- Blood ^{10}B concentration 19 μg/g
  - Tumor/Blood=3.5
- Irradiation time: 2×20 min

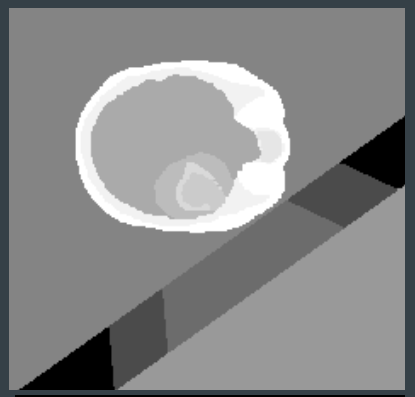


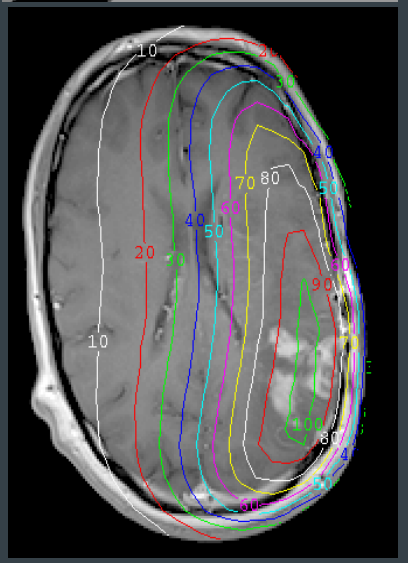
Kankaanranta *et al.* . Int J Radiat Oncol Biol Phys. 69, 2007 & 82, 2012

SERA
treatment planning system



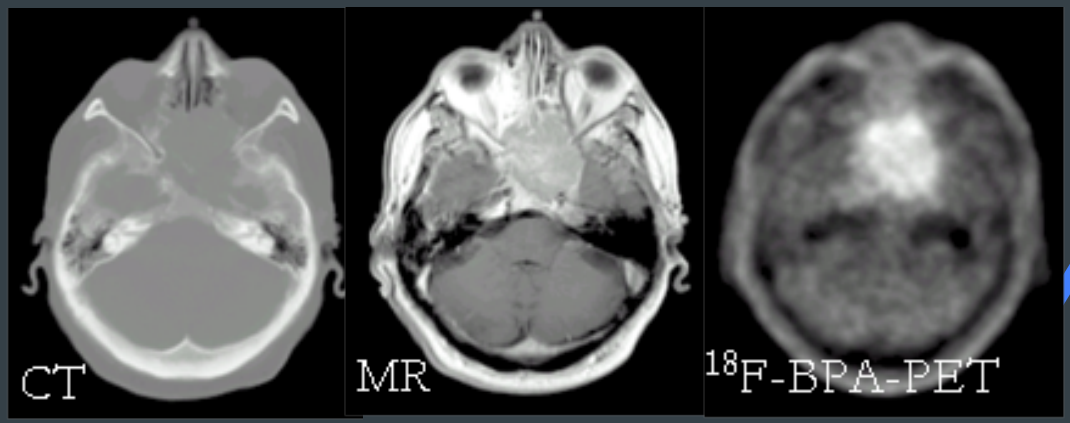
- Developed for BNCT dose calculations at Idaho National Engineering and Environment Laboratory and Montana State University, USA
- Used for clinical BNCT in the Netherlands, Sweden, Japan and Finland
- Specially tailored Monte Carlo code **seraMC**
  - Particle transport in the patient geometry using the local material composition of each pixel
  - Requires creation of 3-D patient model

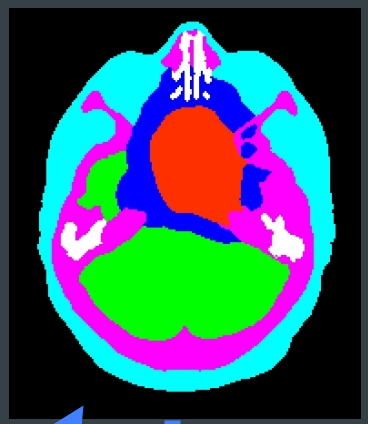


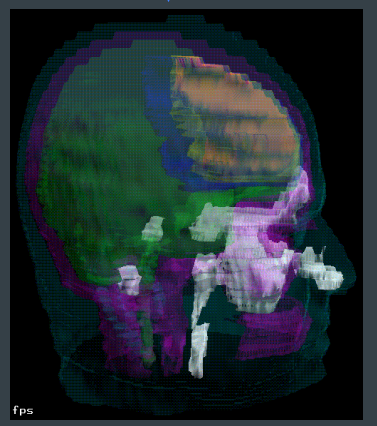


Patient model for treatment planning

- 3-D patient model based on medical images (CT or MRI)
- Contrast-enhanced T1 weighted MRI and ^{18}F-BPA-PET images applied to define the target volume
  - All macroscopic tumors included in the gross tumor volume (GTV)
  - Planning target volume (PTV): GTV with a margin of ~1.5 cm
- Tissue compositions defined according to ICRU Report 46
  - Average soft tissue, brain, skull, lung and air cavities

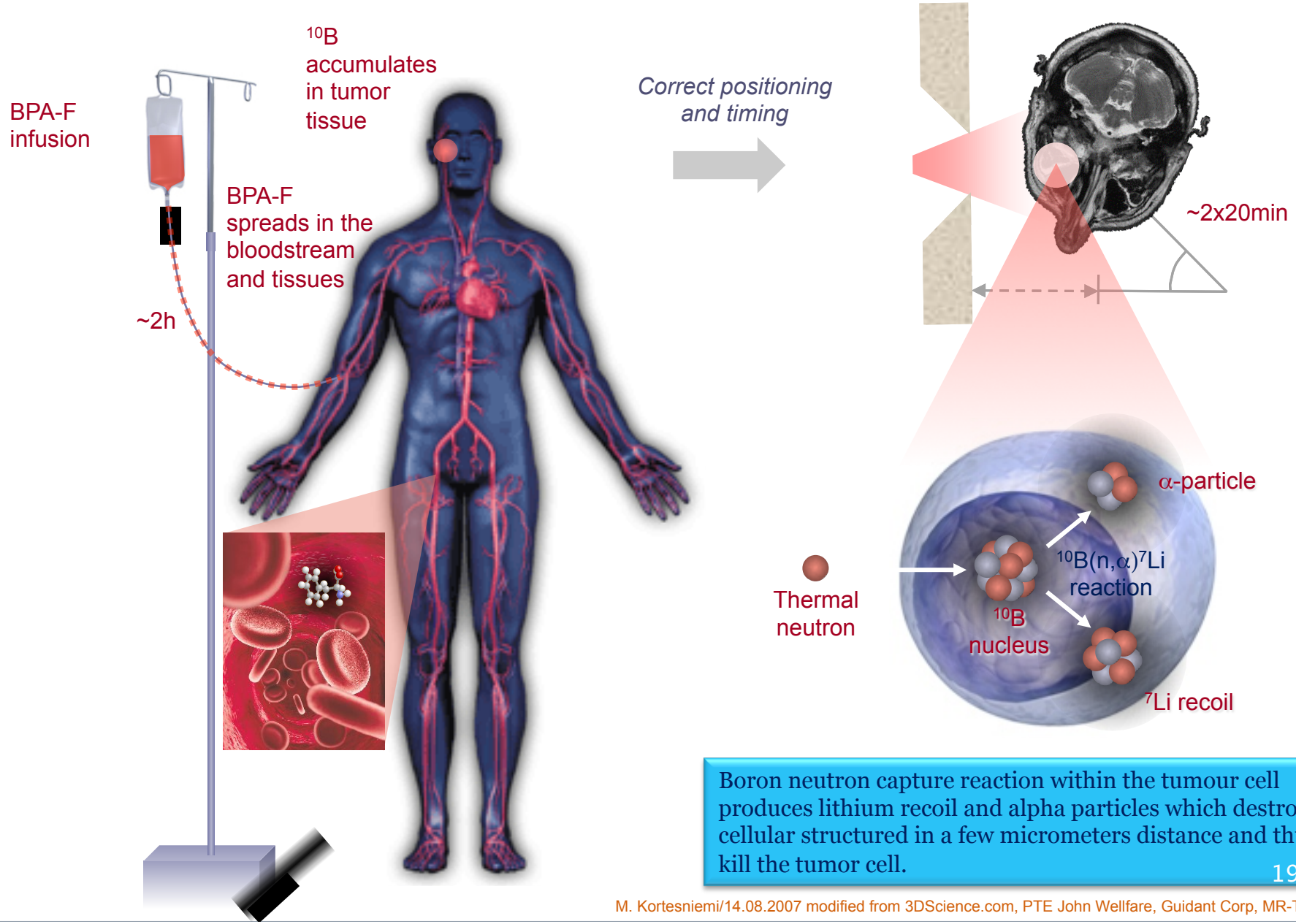






Pixel-by-pixel uniform volume element 'univel' reconstruction for Monte Carlo transport in SERA

BNCT IN PRACTICE



Boron neutron capture reaction within the tumour cell produces lithium recoil and alpha particles which destroy cellular structured in a few micrometers distance and thus kill the tumor cell.

M. Kortesniemi/14.08.2007 modified from 3DScience.com, PTE John Wellfare, Guidant Corp, MR-Tip.com

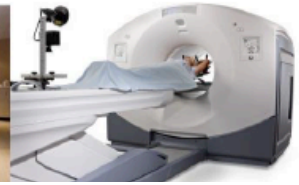
Helsinki University Central Hospital (HUCH)

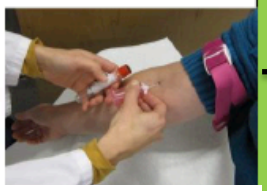
HN-BNCT-process at HUCH

Referral

Reception

CT/MRI/PET/laboratory tests





Day 1

Dose plan

Day 2

Hospitalization

Day 3

Positioning at FiR 1

Boron Infusion

Day 4

Transportation

Irradiation at FiR 1

Day 4

Follow-up

Day 5

BNCT treatments in Finland

- **Starter with registered prospective clinical trials** www.clinicaltrials.gov
  1. BNCT as the first post operative treatment in GBM
  2. BNCT in the treatment of irradiated and recurrent GBM and AA III
  3. BNCT in the treatment of locally recurrent HNC
  4. BNCT in the treatment of locally recurrend HNC combined with Cetuximab

- Based on the wide experience and good results in the clinical trials, BNCT was requested and given to compassionate case patients, who were not eligible for the trials, but who were considered to benefit from BNCT
- Pilot cases
  - Primary treatment for large head and neck cancer (2010)
  - Melanoma
  - Meniongeoma, etc…

Glioma BNCT in Finland

- Altogether 98 glioma patients treated
  - Newly diagnosed glioblastoma (n=39)
  - Malignant glioma progressed after conventional radiotherapy (n=59)
- Based on Brookhaven clinical trials (Chanana *et al* Neurosurgery 44, 1999)
  - 2-hour i.v. infusion of BPA-F (290-500 mg/kg)
  - ^{10}B measured from whole blood
  - Irradiation started >45 min after end of BPA infusion
  - Constant tissue-to-blood ^{10}B concentration ratios + RBE factors

- Recently, doses reanalysed

1. BPA uptake of brain and glioma modelled based on dynamic ^{18}F-BPA imaging study by Imahori et al. 1998 (Koivunoro et al., 2015)
2. Instead of fixed RBEs, doses calculated with Photon-Isoeffective model **(González and Santa Cruz, Rad Res. 178, 2012)**

Trial P01: BNCT as the first post operative treatment in GBM

Boron Neutron Capture Therapy in the Treatment of Glioblastoma Multiforme

- To determine the value of BNCT in the treatment of subjects who have undergone surgery for glioblastoma, but glioblastoma has not been treated with radiation therapy or chemotherapy
- BPA dose escalation from 290 mg/kg to 500 mg/kg
- Radiation dose escalation: normal brain maximum from 8 to 14 Gy (W)
- 38 patients treated

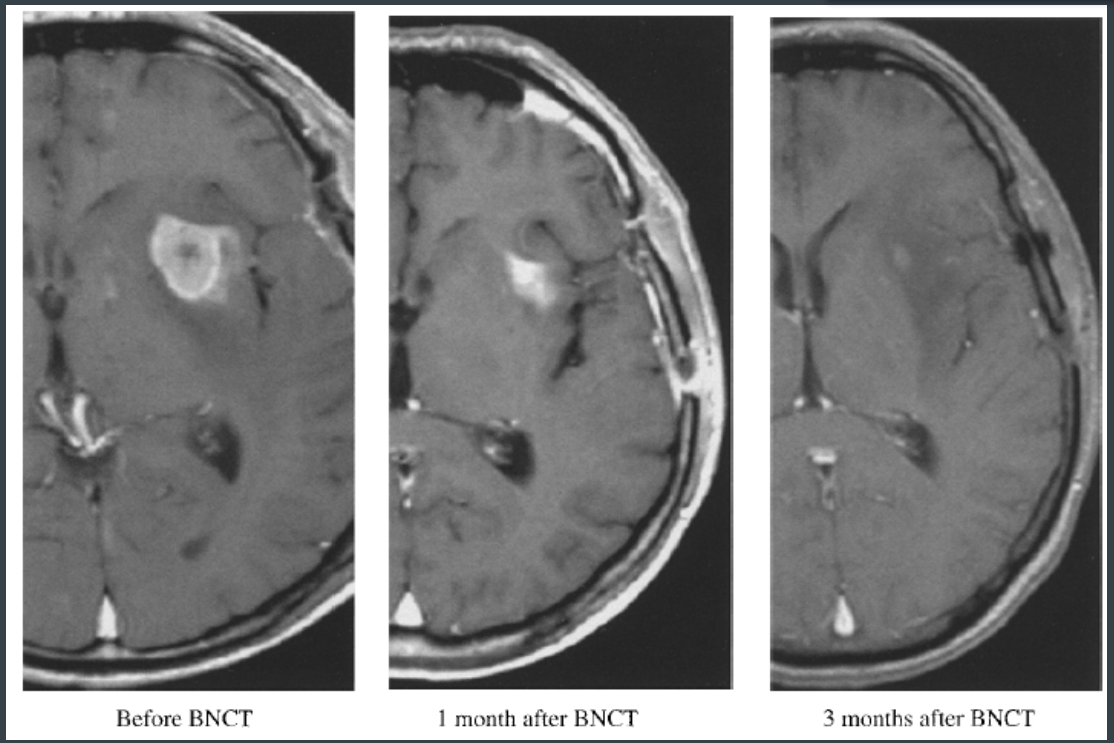
Preliminary results for 18 patients (Joensuu *et al.* J of Neuro-Oncology 62, 2003)

- BNCT is relatively well tolerated
- Efficacy comparisons with conventional photon radiation are difficult due to patient selection and confounding factors such as other treatments given
- The results support continuation of clinical research on BPA-based BNCT

An example of BNCT irradiation result:

39-year-old man with histologically confirmed glioblastoma multiforme

Joensuu *et al.* J of Neuro-Oncology 62, 2003



Left:

A transaxial MRI scan taken 10 days after brain surgery showing an enhancing tumor in the left insular lobe.

Middle:

An MRI taken one month following BPA-based BNCT suggesting tumor response. The patient used dexamethason 6 rag/day.

Right: A MRI three months following BNCT. The patient has been without corticosteroids for 1.5 months

Trial P03: BNCT for recurrent GBM

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 2, pp. 369–376, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.02.031

CLINICAL INVESTIGATION **Brain**

L-BORONOPHENYLALANINE-MEDIATED BORON NEUTRON CAPTURE THERAPY FOR MALIGNANT GLIOMA PROGRESSING AFTER EXTERNAL BEAM RADIATION THERAPY: A PHASE I STUDY

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- 22 patients (20 glioblastoma, 2 anaplastic astrocytoma)
- Escalation of BPA-F dose
  - 290, 350, 400 or 450 mg/kg
- Dose limits
  - Normal brain dose
    - max 8 Gy (W)
    - average <6 Gy (W)
  - Tumor dose: ≥17 Gy (W)

- Adverse effects evaluated according to the National Cancer Institute common terminology criteria version 3.0
- Treatment response evaluated by use of the RECIST (Response Evaluation Criteria in Solid Tumors)

Results & conclusions

- Four patients (18%) responded to BNCT.
  - All responses were partial.
- Nine patients (41%) had stable disease for 3–18+ months (median, 6 months)
- Median overall survival 7.3 months after BNCT
  - 1 patient was alive at the time of analysis 18 months after BNCT
- ≥290 mg/kg BPA dose and mean PTV dose of ≥34 Gy(W) improved survival

- BNCT administered with BPA-F dose up to 400 mg/kg as a 2-hour infusion is feasible in the treatment of malignant gliomas that recur after conventional radiation therapy
- The effect of L -BPA-F mediated BNCT on survival compared with conventional external beam radiation therapy in recurrent glioma remains to be investigated in a prospective randomized clinical trial

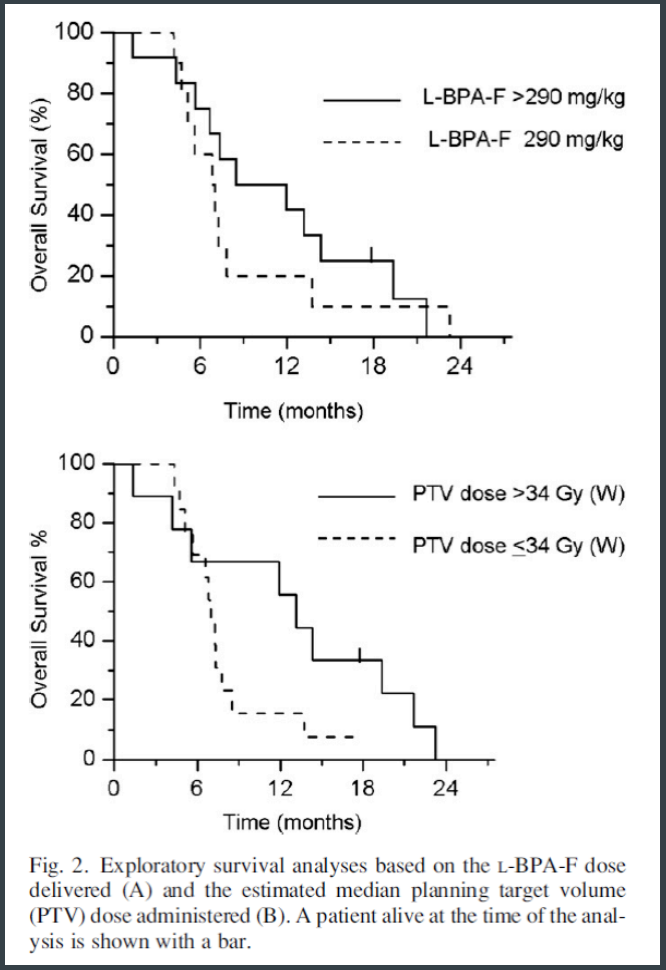


Fig. 2. Exploratory survival analyses based on the L-BPA-F dose delivered (A) and the estimated median planning target volume (PTV) dose administered (B). A patient alive at the time of the analysis is shown with a bar.

Kankaanranta *et al.* IJOROP 80, 2011

Adverse effects: recurrent glioma

- In general, BNCT was relatively well tolerated
- Most adverse effects were graded mild or moderate (grade 1 or 2) in severity
- The most frequent acute adverse effects:
  - alopecia (82%)
  - insomnia (50%)
- The most common severe (grade 3) acute adverse effect was seizures (18%)

L -BPA-F infusion-related adverse effects

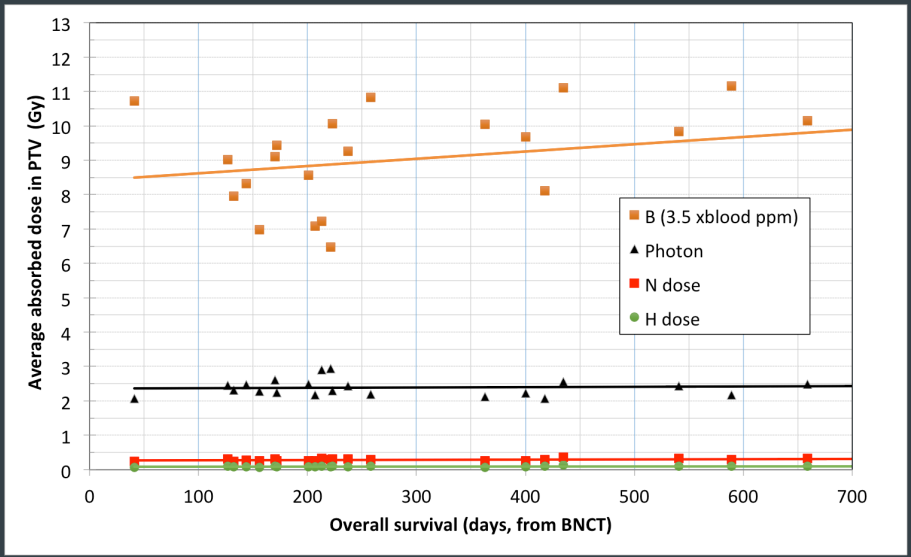
- Grade 3
  - orbital edema, n=1
- Grade 1or 2
  - fatigue, n = 2
  - hypertension, n = 1
  - vomiting, n = 1

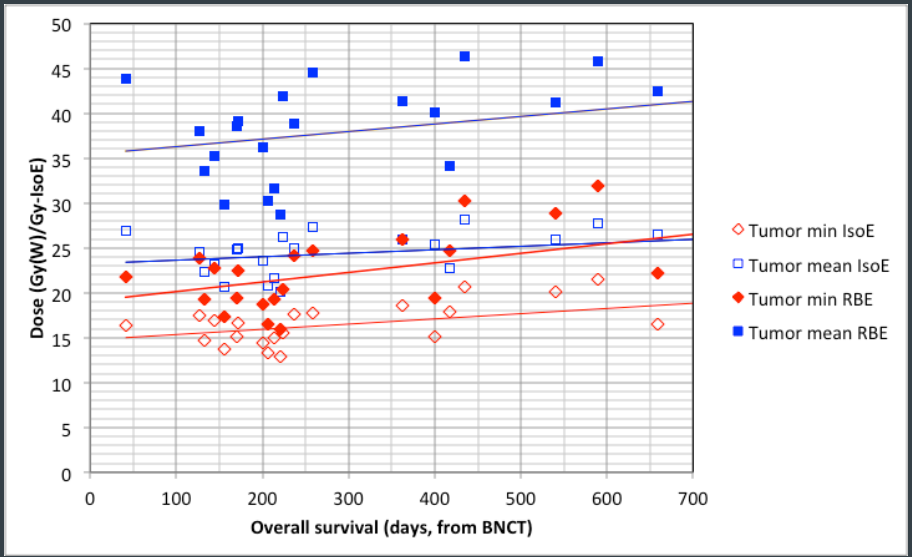
Table 3. Acute and late adverse effects recorded

	Patients with acute effects ($n = 22$)		Patients with late effects ($n = 18$)	
	Grade 1 or 2	Grade 3[†,‡]	Grade 1 or 2	Grade 3[†]
Adverse effect*	No. (%)	No. (%)	No. (%)	No. (%)
Alopecia	18 (82)	1 (5)	0 (0)	0 (0)
Insomnia	11 (50)	1 (5)	1 (6)	0 (0)
Headache	5 (23)	1 (5)	0 (0)	0 (0)
Memory loss	5 (23)	1 (5)	0 (0)	0 (0)
Motor neuropathy	5 (23)	1 (5)	0 (0)	0 (0)
Serous otitis	5 (23)	0 (0)	0 (0)	0 (0)
Mouth dryness	4 (18)	0 (0)	1 (6)	0 (0)
Dry eye	4 (18)	0 (0)	1 (6)	0 (0)
Hypertension	4 (18)	0 (0)	0 (0)	0 (0)
Skin edema	3 (14)	3 (14)	1 (6)	0 (0)
Fatigue	3 (14)	2 (9)	2 (11)	0 (0)
Muscle weakness	3 (14)	2 (9)	2 (11)	1 (6)
Brain edema	3 (14)	0 (0)	2 (11)	0 (0)
Skin atrophy	2 (9)	0 (0)	2 (11)	0 (0)
Cognitive disturbance	2 (9)	1 (5)	0 (0)	1 (6)
Somnolence	1 (5)	0 (0)	0 (0)	0 (0)
Seizures	1 (5)	4 (18)	0 (0)	0 (0)
Speech impairment	1 (5)	1 (5)	1 (6)	0 (0)
Blurred vision	1 (5)	1 (5)	0 (0)	0 (0)
Teleangiectasia	1 (5)	0 (0)	0 (0)	0 (0)
Glaucoma	0 (0)	0 (0)	1 (6)	0 (0)
Duodenal ulcer	0 (0)	1 (5)	0 (0)	0 (0)

Kankaanranta *et al.* IJOROP 80, 2011

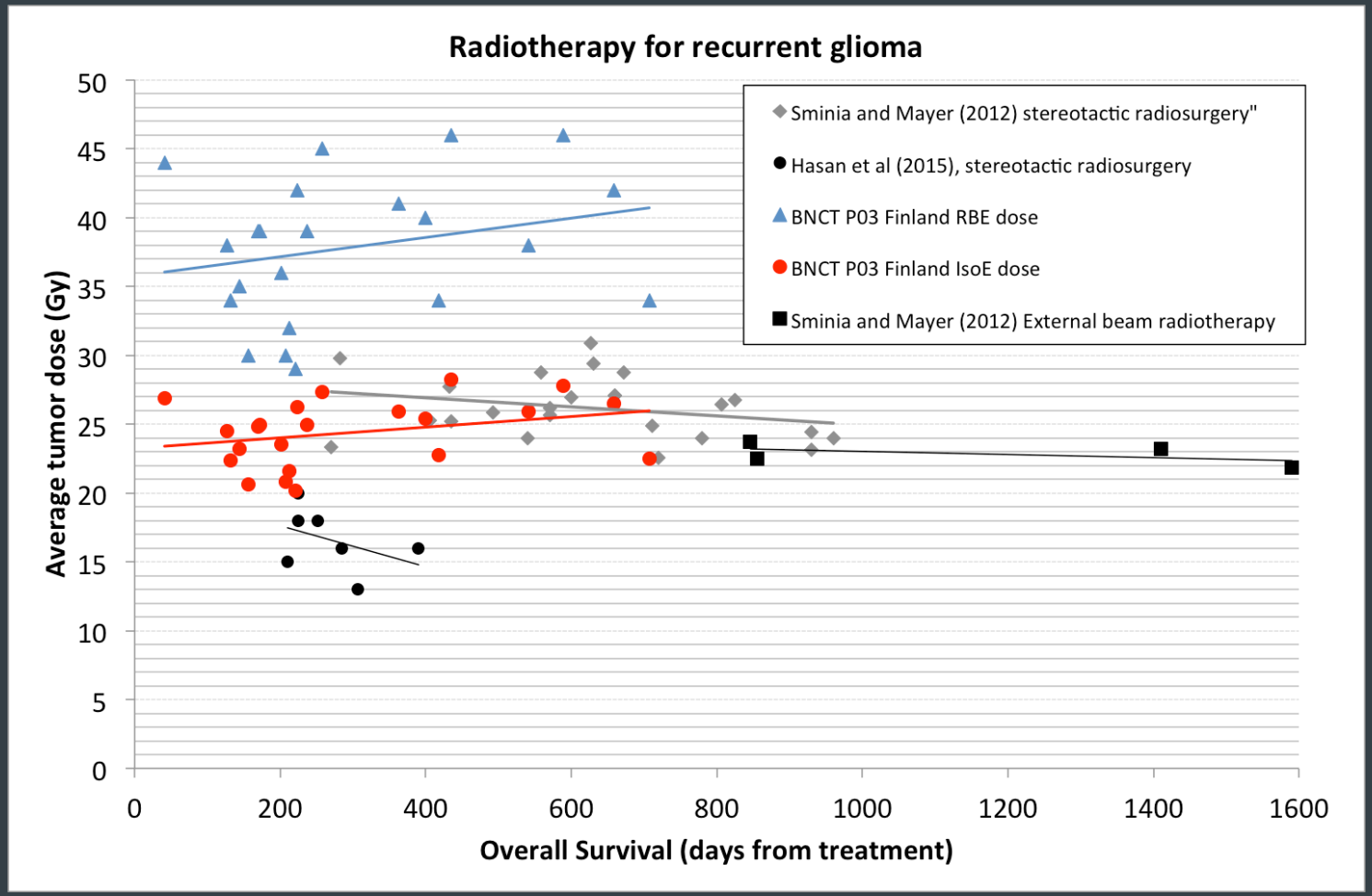
Doses compared to overall survival –preliminary analysis





- Increase in PTV or tumor dose seem to correlate with longer overall survival time
  - Physical absorbed boron dose, but not other dose components
  - Total RBE dose and Photon isoeffective dose

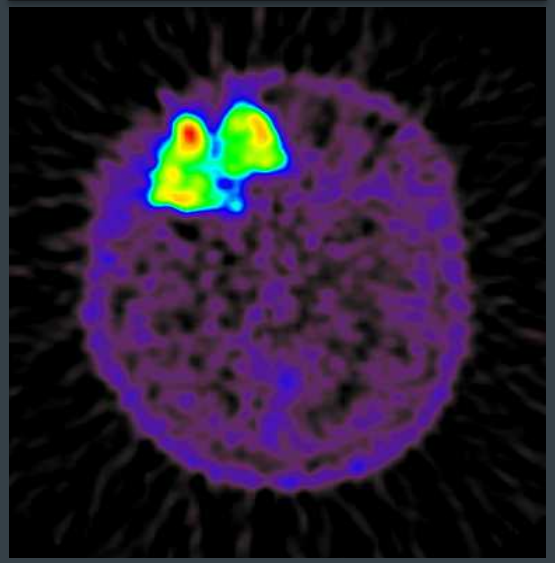
Comparison with conventional radiotherapy

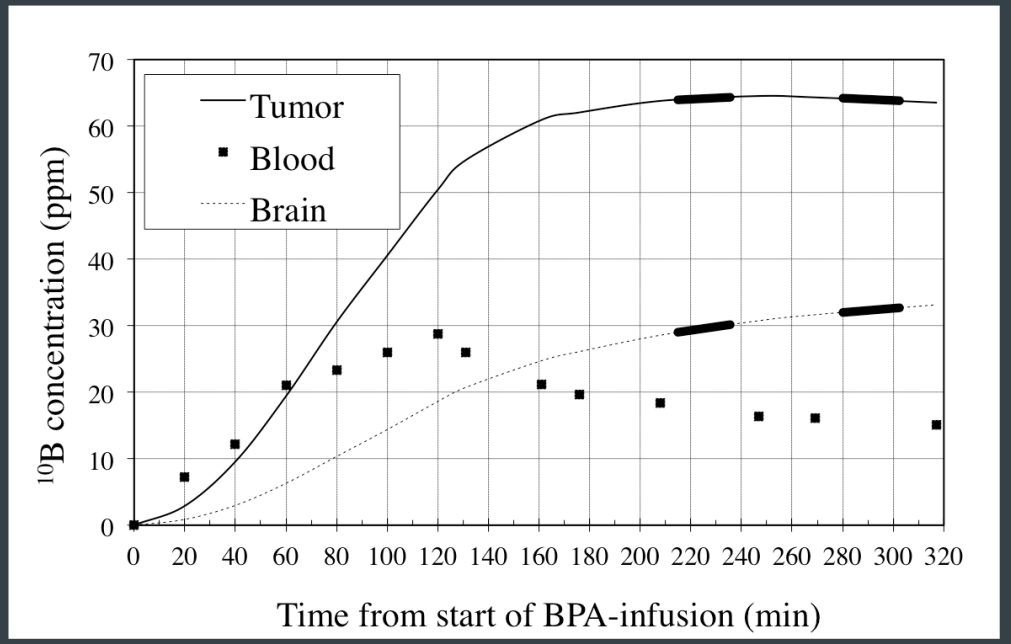


Correlation between tumor doses and survival in BNCT!?

Preliminary results of BPA kinetics based on dynamic ^{18}F-BPA-PET

Kouri M. *et al* Rad. and Oncol, 72, 2004



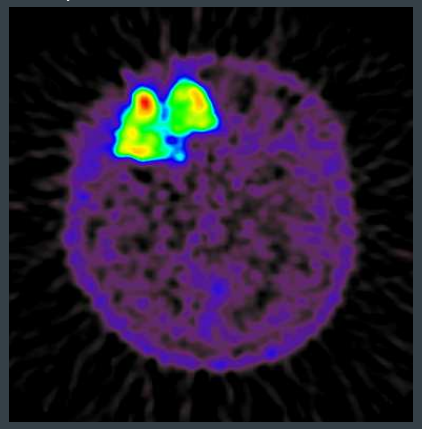


- Preliminary results from a study on BPA pharmacokinetics in patients with high grade glioma in Birmingham (Cruickshank 2009, Ngoga *et al* 2010):
  - Slow ^{10}B uptake in the brain, extra-cellular fluid and tumor observed
  - ^{10}B concentrations peaked as late as 4 to 6 hours after a 2-hour BPA-mannitol infusion
  - ^{10}B concentration remained high until the end of the analysis, up to 6 hours from the end of the infusion

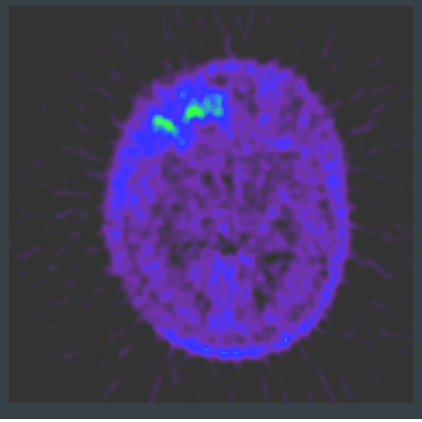
Head and neck (HN) cancer
BNCT in Finland

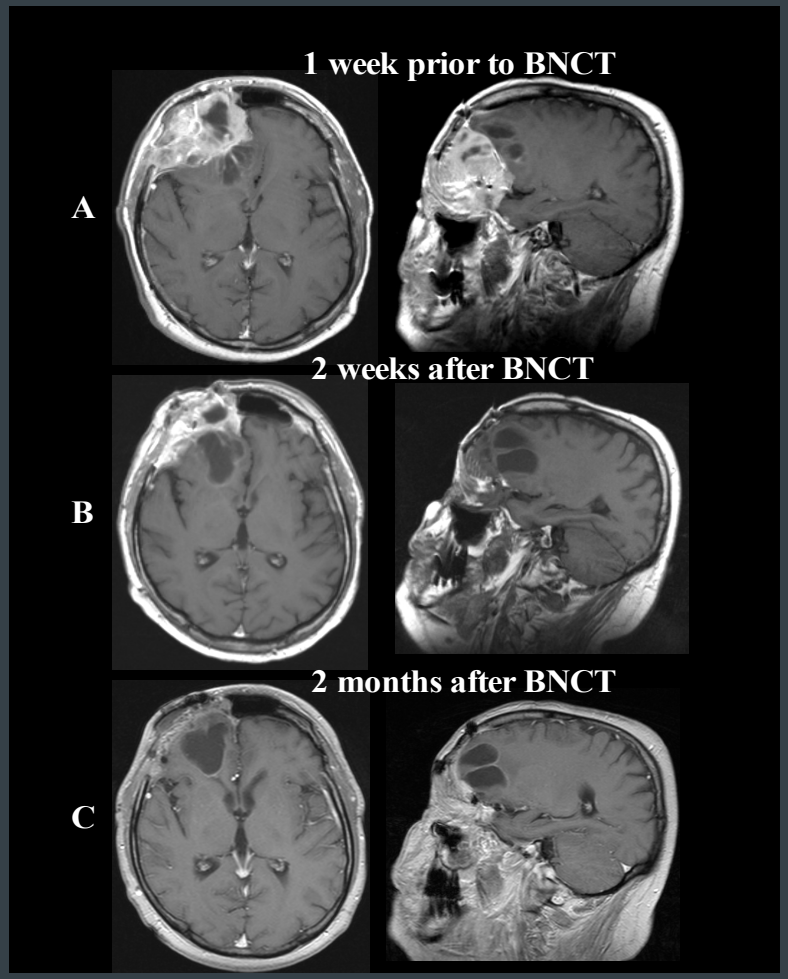
Undifferentiated sinonasal carcinoma may respond to single-fraction boron neutron capture therapy

^{18}F-BPA-PET
before BNCT
T/N= 4.8 - 5.7



2 weeks after
BNCT
T/N= 1.9 - 2.5





Kouri M. *et al* Radiotherapy and Oncology, 72 (2004)

Head and neck (HN) cancer BNCT in Finland

- Histologically verified locally recurred inoperable head-and-neck cancer
  - Two clinical trials
  1. Boronophenylalanine (BPA)-Based Boron Neutron Capture Therapy (BNCT) in the Treatment of Inoperable and Irradiated Head and Neck Tumors: A Feasibility Study
  2. Boronophenylalanine (BPA)-Based Boron Neutron Capture Therapy (BNCT) Combined With Anti-erbB1 Antibody Therapy in the Treatment of Locally Recurred Head and Neck Cancer: A Phase I/II Study.
- Later on, also newly diagnosed HN cancers (Kankaanranta *et al* 2011)
- ^{18}F-BPA-PET when available
- Typically 1 or 2 BNCT treatments 4-12 weeks apart
- 350-400 mg/kg of BPA-fructose (BPA-F)

Treatment of Inoperable and Irradiated Head and Neck Tumors

Kankaanranta *et al.* Int J Radiat Oncol Biol Phys. 69, 2007 & 82, 2012

- To investigate the efficacy and safety of BNCT in the treatment of inoperable head-and-neck (HN) cancers that recur locally after conventional photon radiation therapy
- 30 patients: 29 carcinomas and 1 sarcoma
- 2 BNCT treatments at 3 to 5-week intervals (26/30)
- 400 mg/kg of L-BPA-F i.v. in 2 hours
- Tumors were large:
  - PTV **88-987** cm^3 **(**ave 257 cm^3) and **GTV 13-517** cm^3 **(ave 99** cm^3)

- Dose limiting factors
  - Mucosal membrane absorbed physical dose
    - ≤6 Gy for each BNCT
  - Spinal cord dose
    - ≤4 Gy (W) for each BNCT
    - Previous photon irradiation + BNCT ≤ 50 Gy

Treatment of Inoperable and Irradiated Head and Neck Tumors

Kankaanranta *et al.* Int J Radiat Oncol Biol Phys. 69, 2007 & 82, 2012

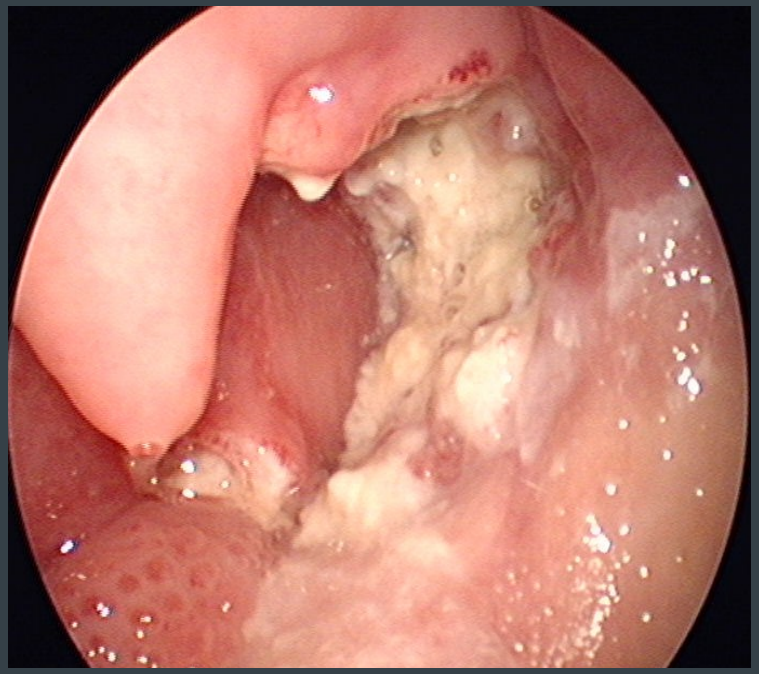
Results

- 22 (76%) responded to BNCT
- 6 (21%) had tumor growth stabilization for 5.1 and 20.3 months
- 1 (3%) progressed
- 27 % of the patients survived for 2 years without locoregional recurrence
- The 4-year locoregional recurrence–free survival rate was 16%, indicating that some of the responses were durable

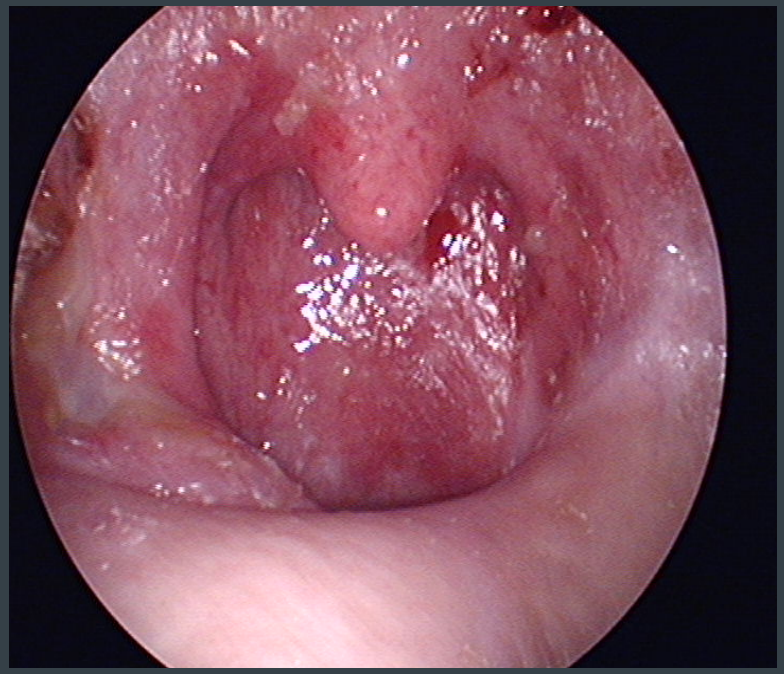
Most common adverse effects

- 54% Mucositis and oral pain (Grade 3) (acute, reversible)
- 33% Fatigue (Grade 3)
- 7% osteoradionecrosis (Grade 3, late effect)
- 20% xerostomia (Grade 1-3, late effect)
- 3% life-threatening soft-tissue necrosis (Grade 4)

Kankaanranta *et al*. Int J Radiat Oncol Biol Phys. 69, 2007 & 82, 2012

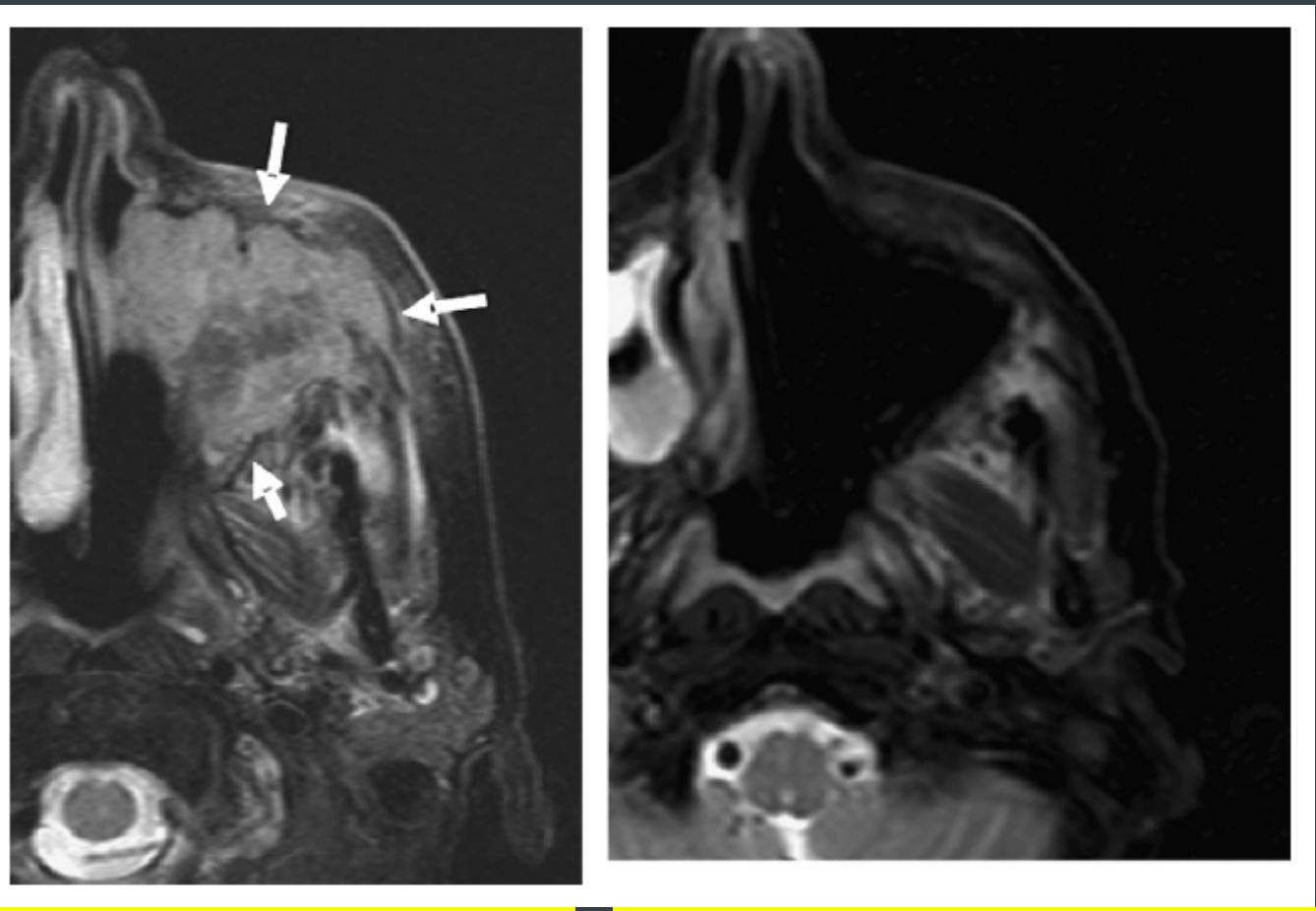


Recurrent cancer of the tongue that grows in the left oropharynx and hypopharynx before BNCT



Complete tumor response 10 months after BNCT. The patient is alive without recurrence 19 months after administering BNCT

Kankaanranta *et al*. Int J Radiat Oncol Biol Phys. 69, 2007



A MRI showing recurrent transitional cell carcinoma in the maxillary sinus with subcutaneous infliltration and growth into the left orbita (patient 9)

Complete tumor response after BNCT:

- 2 treatments 76 days between
- Mean tumor doses 23 Gy(W) and 20 Gy(W)

Kankaanranta *et al.* IJROBP. 69, 2007 & 82, 2012

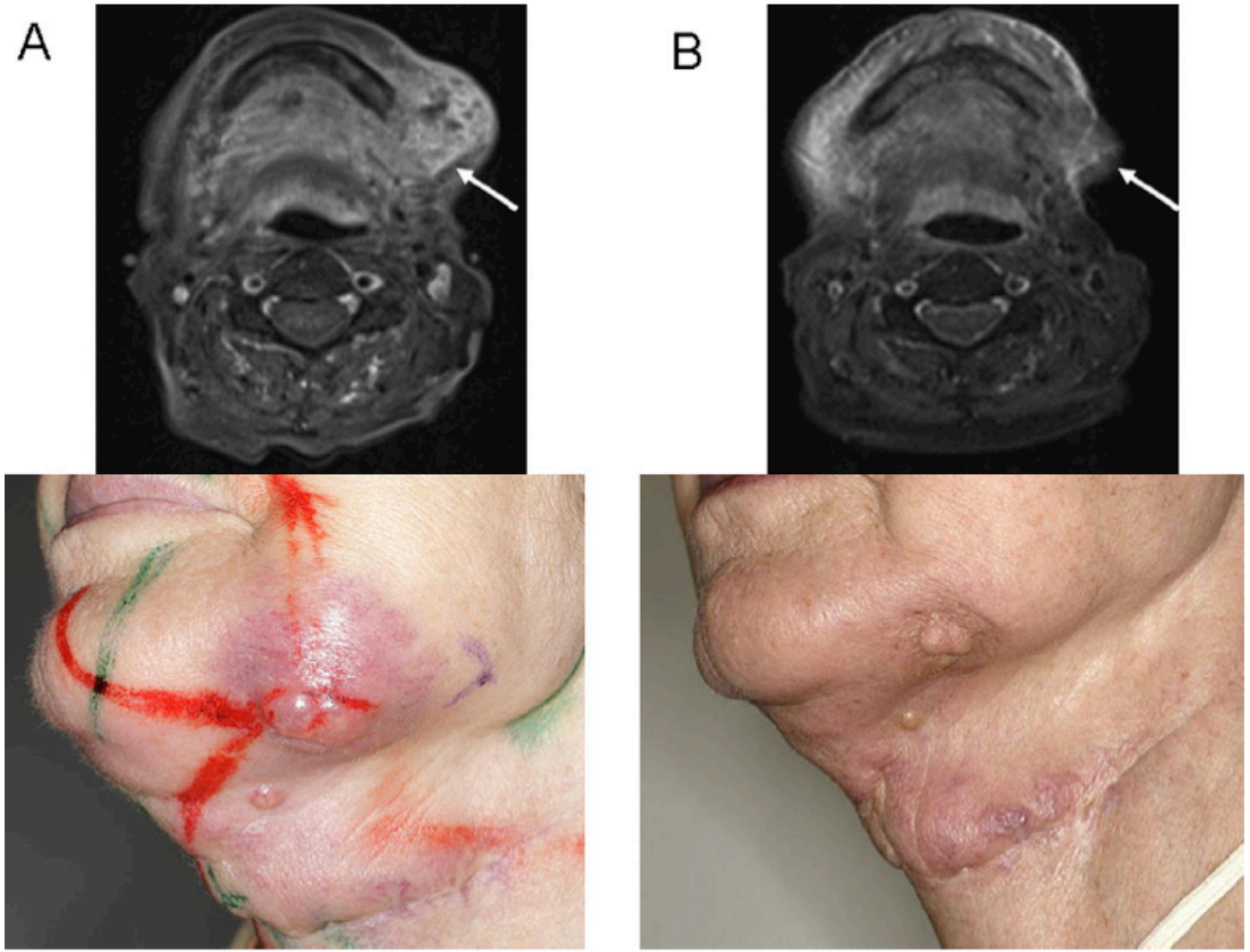


Fig. 3. Recurrent squamous cell carcinoma of jaw. (A) Before BNCT. (B) Partial response after BNCT. The arrows point at the tumor.

Kankaanranta *et al.* IJROBP. 69, 2007 & 82, 2012

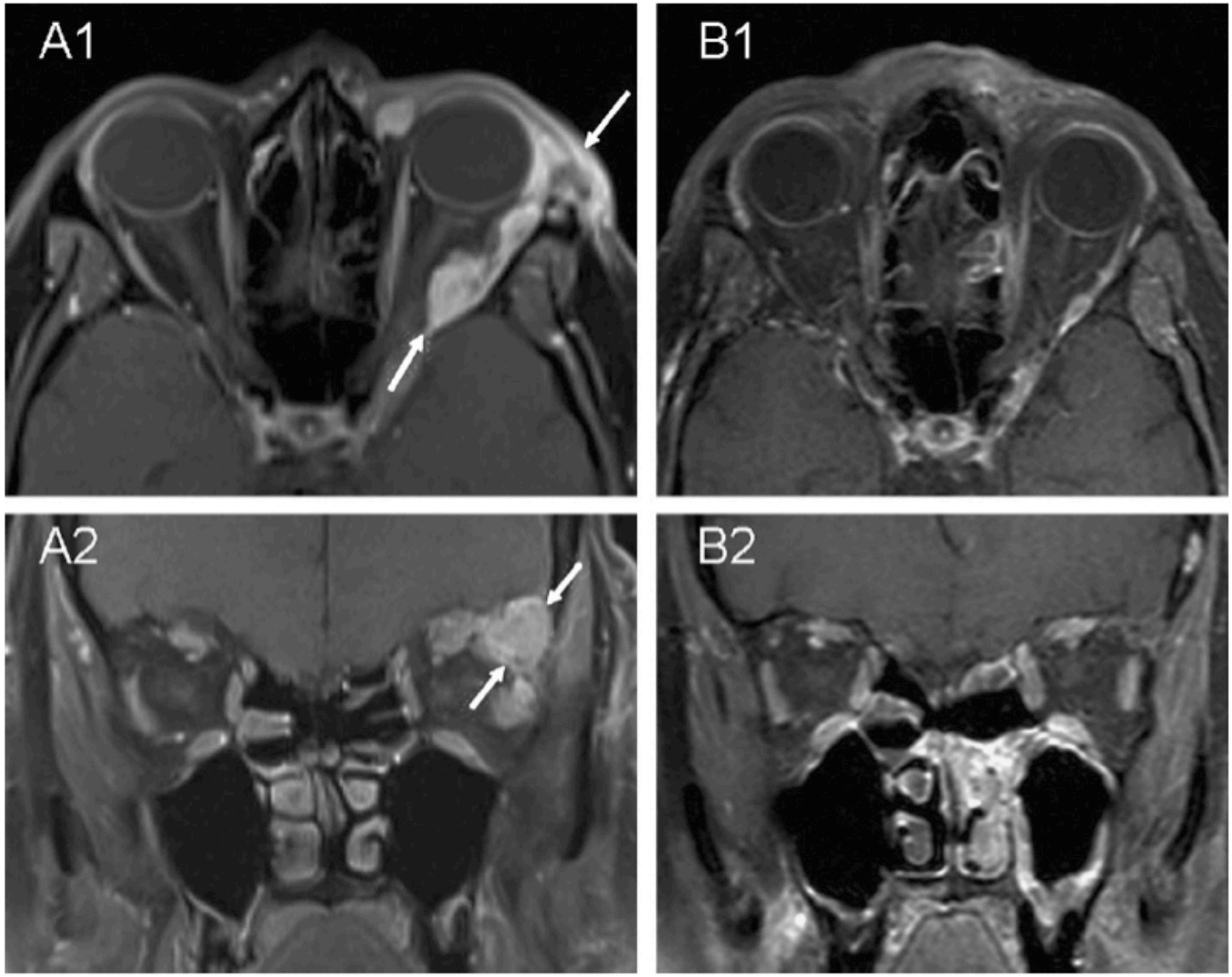


Fig. 2. (A) Recurrent adenoid cystic carcinoma of lacrimal gland before BNCT shown in transverse (A1) and frontal (A2) MRI views. (B) Partial response after BNCT in transverse (B1) and frontal (B2) views. The arrows point at the tumor.

Dose response analysis:
Recurrent head and neck trial

	Patients with PR or SD response (n=13)	Patients with CR response (n=13)	P value Kruskal-Wallis Test
PTV (cm3)	**320**	**177**	**0.015**
GTV (cm3)	**135**	**55**	**0.006**
PTV max dose (Gy(W))	65	66	0.59
PTV min dose (Gy(W))	23	28	0.061
PTV ave dose (Gy(W))	42	45	0.249
GTV max dose (Gy(W))	63	63	0.626
GTV min dose (Gy(W))	**29**	**35**	**0.015**
GTV ave dose (Gy(W))	45	47	0.427

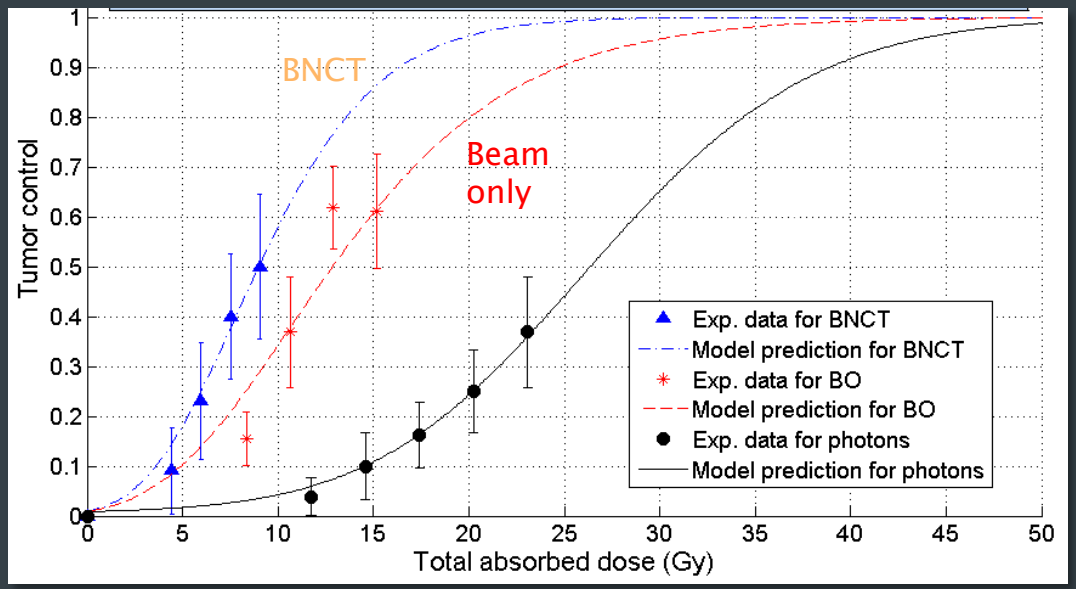
Photon Isoeffective Model parameters from in-vivo oral cancer dose-response data.

In collaboration with Dr. A. Schwint and collab. (CNEA radiobiology group)

Based on the **in-vivo oral cancer model in the hamster check pouch**, they have determined dose-tumor control data for:

1)the photon reference radiation (^{60}Co photons),
2)the neutron beam only (BO, RA3 reactor), and
3)the neutron beam in the presence of the boron compound BPA-F (BNCT, RA3 reactor).

Preliminary results: > 400 tumors, different volumes

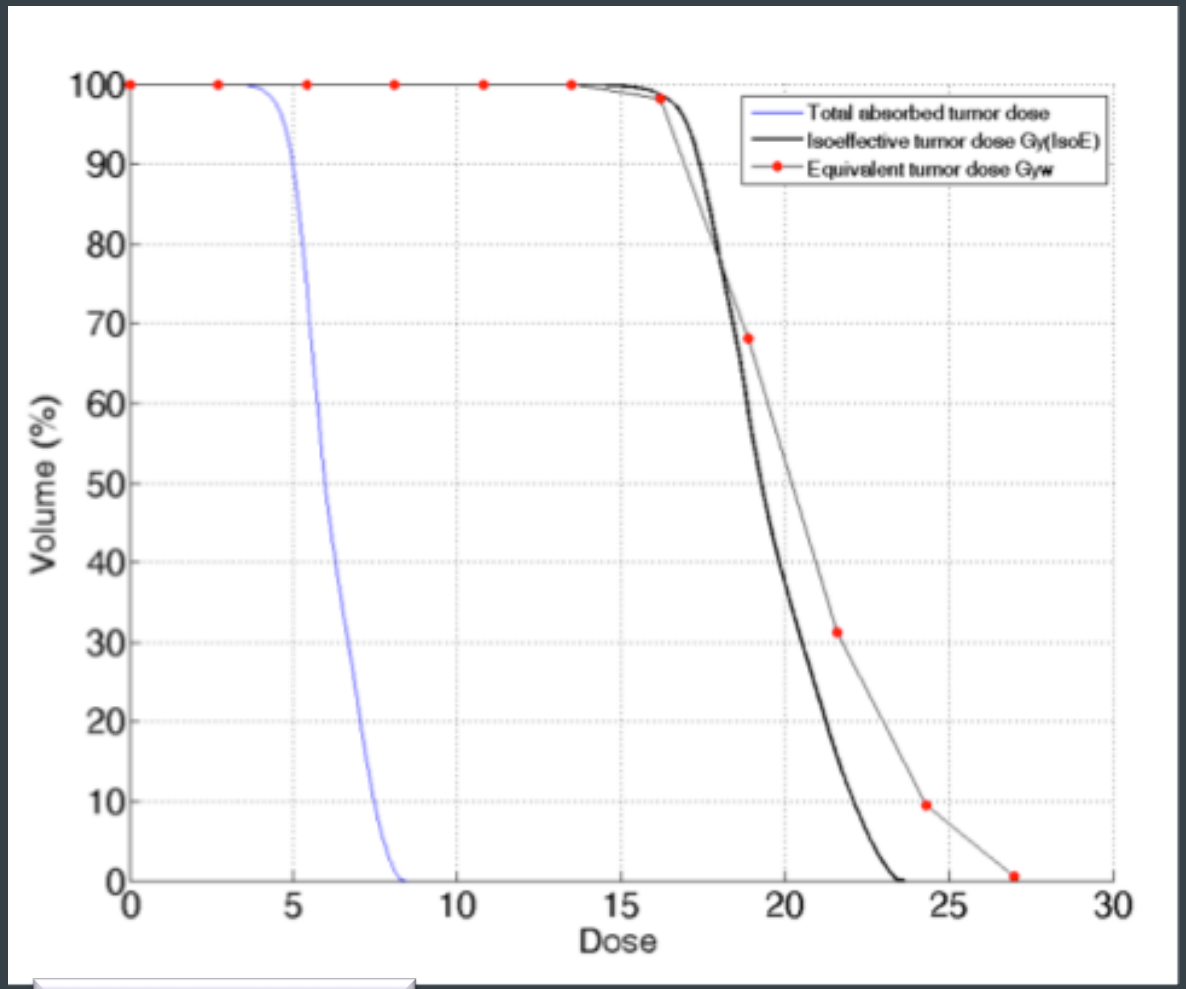


Photon-isoeffective model
+
parameters derived from the in-vivo oral model

Estimation of doses in BNCT for tumors in the oral cavity or head & neck.

BNCT Terapia por Captura Neutronica en Boro
Comision Nacional de Energia Atomica

Preliminary result: Isoeffective doses for H&N cancer in Finland



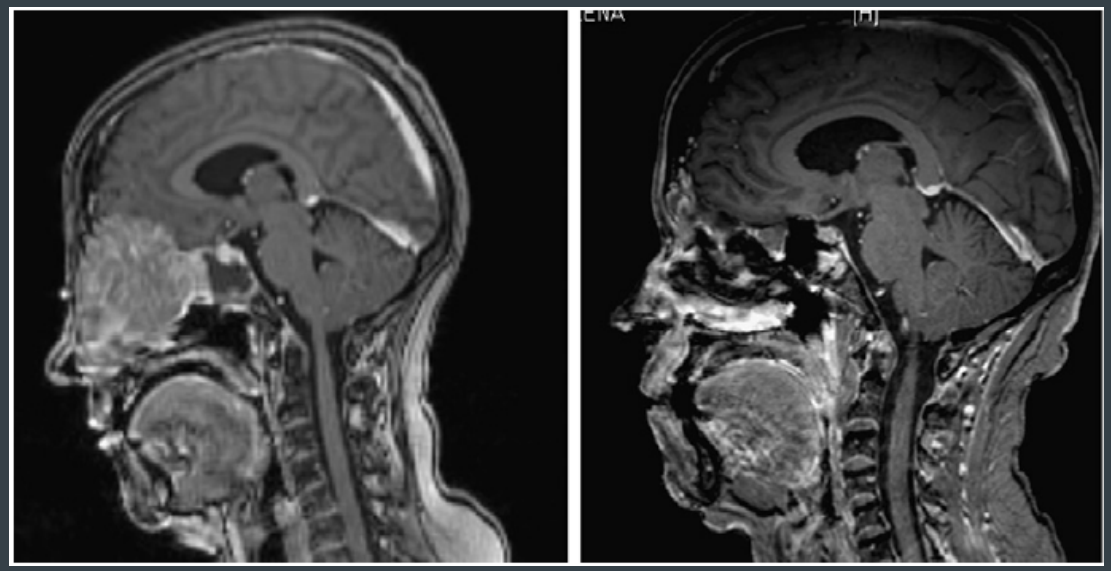
Preliminary result!

Case study
BNCT + chemoradiotherapy as primary treatment for inoperable HN cancer

Kankaanranta *et al.* Radiother Oncol. 99, 2011

- BNCT as first-line therapy of a patient diagnosed with large, inoperable head and neck carcinoma
  - Tumor was adjacent to both optic nerves making it challenging to achieve a cure at a low risk of severe organ damage with conventional radiotherapy
  - BNCT causes only little dose to the optic nerves, due to low uptake of L-BPA

February, 2010
before BNCT



August, 2010
after BNCT followed by 50 Gy of intensity modulated chemoradiotherapy

Today, patient is alive and tumor free

Unpublished clinical trial

Boronophenylalanine (BPA)-Based BNCT Combined With Anti-erbB1 Antibody Therapy in the Treatment of Locally Recurred Head and Neck Cancer: A Phase I/II Study

- To investigate efficacy and safety of BNCT administered in combination with cetuximab in the treatment of HN cancer that has recurred locally following conventional cancer treatment (surgery and radiation therapy)
- **Cetuximab** is an antibody directed against epidermal growth factor receptors found on cancer cell surface
  - Cetuximab may or may not improve treatment efficacy, when administered immediately after BNCT
- BNCT was given once, cetuximab 1-3 times one week apart
- 17 patients treated

All BNCT patients treated in Finland

primary postoperative malignant glioma	n= 39
recurred glioblastoma	n= 58
rHNC in metastatic setting	**n= 16**
rHNC in protocols	**n= 47** (30+ 17 cetuximab)
rHNC	**n= 67**
first line HNC	**n= 4**
lymphoma	n= 1
melanoma	n= 3
meningioma	n= 7
basocellular carcinoma	n= 1

- approx. 5 out of 300 treatments were interrupted for patient, other logistics or technical reasons

Future plans

- Further evaluation of the patient dose reponses
  - Ongoing co-operation with Sara González and Gustavo Santa Cruz, CNEA, Buenos Aires, Argentina
- Comparison of the BNCT treatment planing systems
  - Ongoing co-operation with Hiroaki Kumada, Tsukuba, Japan
- Boron capture gamma detector studies for determining the ^{10}B concentration and distribution in a patient with Alexander Winkler, Helsinki University

Continuing clinical BNCT with an accelerator based neutron source at our hospital within 2 years





Thank you!

Merci!