A dose response analysis of the patients treated with Boron Neutron Capture Therapy (BNCT) in Finland in 1999 to 2011

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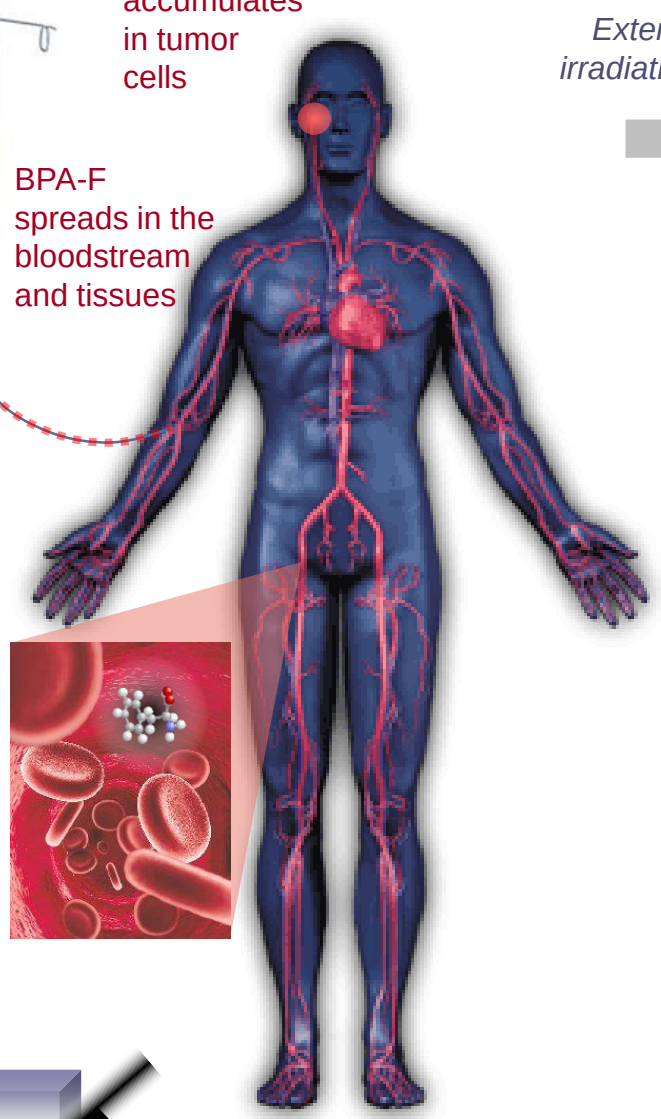
BORON NEUTRON CAPTURE THERAPY (BNCT) IN PRACTICE

^{10}B carrier BPA-F infusion

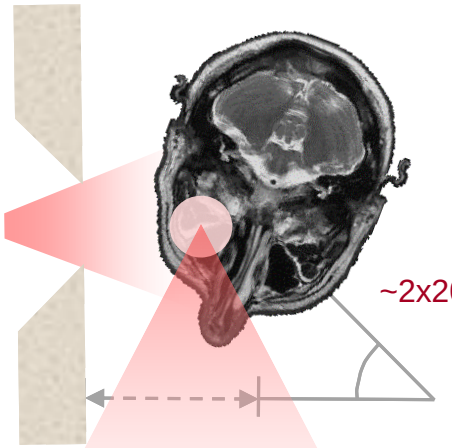
~2h

^{10}B accumulates in tumor cells

BPA-F spreads in the bloodstream and tissues

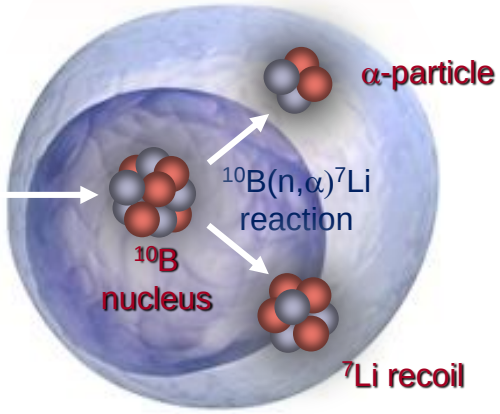


External neutron irradiation $E_n \approx 10$ keV



~2x20min

Thermal neutron



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

WHY BNCT?

1. Biologically targeted radiotherapy

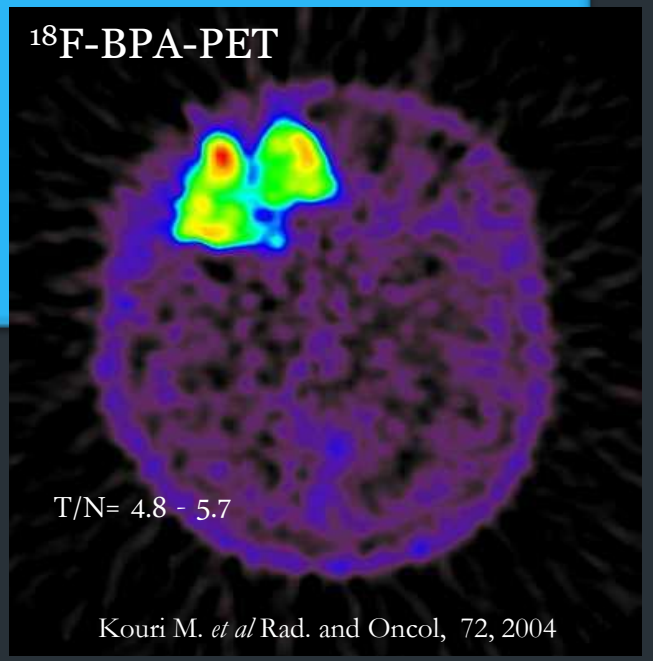
- High dose gradient between tumor and healthy tissue
  1. ^{10}B carrier uptaken by tumor more than normal tissues
  2. Cancerous tissue is more sensitive to BNCT
     - RBE for brain 1.3
     - RBE for brain cancer 3.8

Can be administered

- After high-dose radiotherapy
- Near or within radiosensitive tissues

2. High LET radiotherapy

- Effective againts radioresistant cancers



BNCT LET_{ave}

α-particle ~163 keV/μm

^{7}Li nucleus ~200 keV/μm

LET at clinical energies

Electrons ~ 10 keV/μm

Protons ~90 keV/μm

^{12}C ions ~ 150 keV/μm

Clinical BNCT in Finland

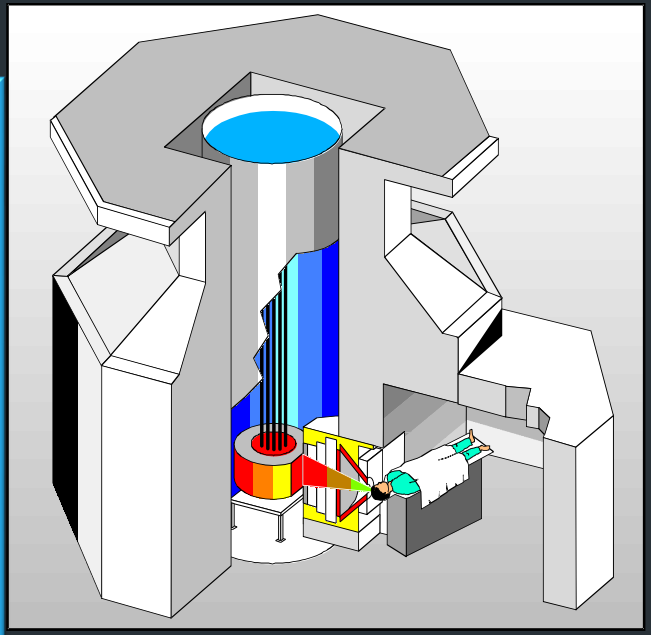
- In 1999 – 2012
  - 249 patients, >300 BNCT treatments
  - Four registered prospective clinical trials
    1. First line GBM
    2. Recurrent GBM
    3. Recurrent inoperable head and neck cancer
    4. Recurrent head and neck BNCT combined with antibody therapy

  + compassionate case patients, who were not eligible for the trials, but were considered to benefit from BNCT
  - Patients from Finland, Sweden, Norway, Estonia, Italy, Monaco, Japan and Australia

- Boronophenylalanine (BPA) as the ^{10}B carrier
  - 2 hours i.v. infusion
  - Dose escalation studied 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



BNCT patients treated in Finland

- rHN cancer in clinical trials n = 47 (30+17)
- rHN cancer, compassionate cases n = 72
- rHN cancer with metastasis n = 16
- First line HN cancer n = 4

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- Primary postoperative glioblastoma (trial) n = 39
- Recurrent malignant glioma n = 58
- Lymphoma n = 1
- Melanoma n = 3
- Meningioma n = 7
- Basocellular carcinoma n = 1

BPA uptake verified with ^{18}F-BPA-PET in Turku PET Center

BNCT DOSE RESPONSE ANALYSIS

1. Glioblastoma multiforme (GBM)
   - Newly diagnosed GBM (n=39)
   - GBM recurrent after radiotherapy (n=43)
     - BNCT given once
     - BPA dose escalation from 290–500 mg/kg
     - Tumor and PTV doses compared with survival time
     - RBE and Photon Isoeffective dose calculation
     - Recurrent GBM data compared with published re-irradiation studies

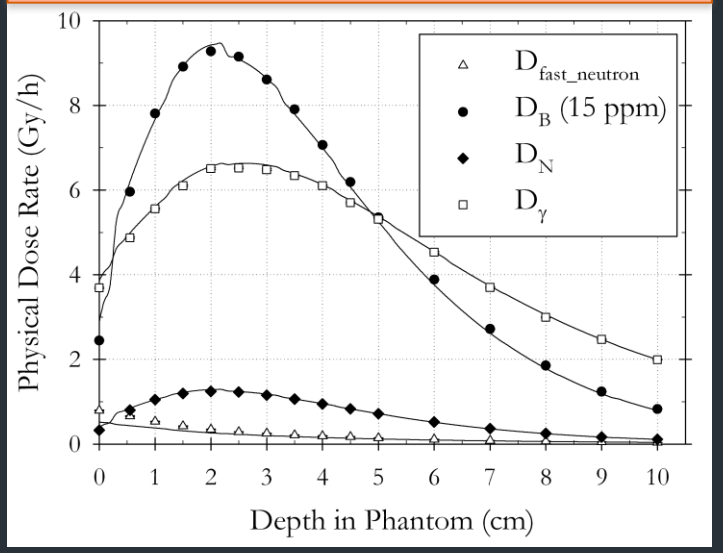
2. Recurrent inoperable head and neck cancer (n=28)
   - BPA dose 400 mg/kg
   - BNCT once or twice
   - Tumor and PTV doses compared with the tumor response
     - Only RBE doses calculated due to lack of cell survival data

BNCT DOSE COMPONENTS

Thermal neutron induced dose components in tissue

1. D_B – Boron dose from $^{10}B(n,\alpha)^7Li$
   - ^{10}B concentration measured from blood
   - Tissue-to-blood concentration estimated based on literature
2. D_N – Proton dose from nitrogen neutron capture reaction in tissue
3. D_γ – Photon dose mainly from $^1H(n,\gamma)^2H$
   - E_γ=2.2 MeV

FiR 1 - 14 cm diameter circular field – depth doses in a phantom assuming homogenus ^{10}B distribution



ppm=part per million, μg/g

Beam quality related dose components

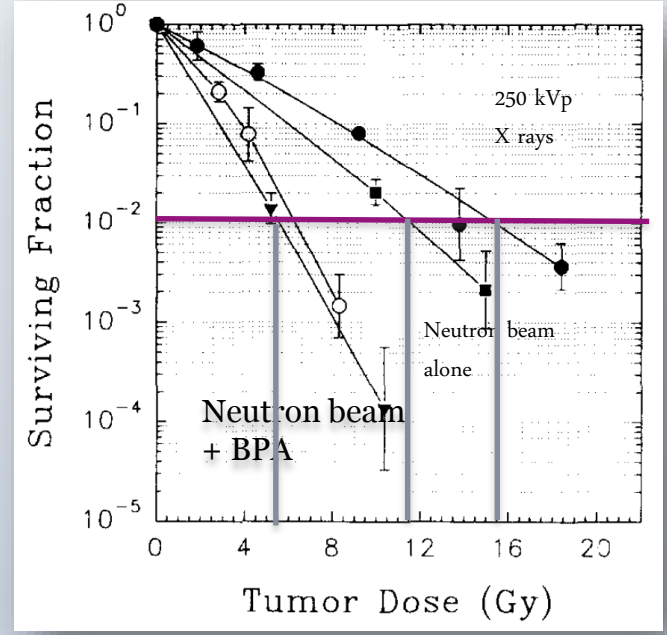
1. D_{n_fast} – "fast neutron" or "proton recoil" dose from $^1H(n, n')p$ in tissue
2. D_γ – "Primary" photons from the neutron interactions in materials around neutron source

"Photon dose equivalent" RBE dose – traditional approach

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

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% cell survival level

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

PROBLEMS

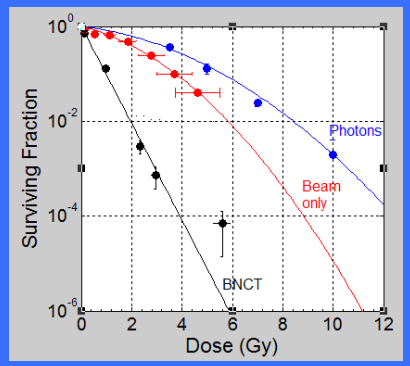
- Radiobiological effect depends on the dose rate and ratio of the dose components
  - → Biological effect should be derived for each irradiation condition individually
- RBE's derived for given cell type and certain end point

Photon-isoeffective doses in BNCT: parameters of the model

González and Santa Cruz, Rad Res. 178, 2012

Takes into account the dose rate of each dose component and cumulative dose

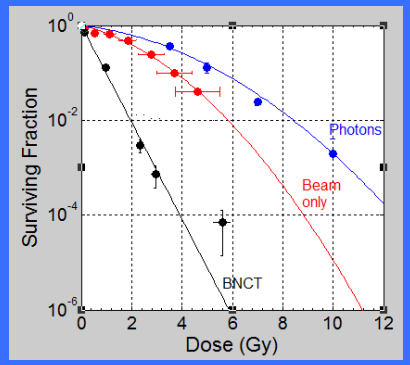
1) Determination of the photon radiation parameters α_R ,β_R (2 param.):



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

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

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

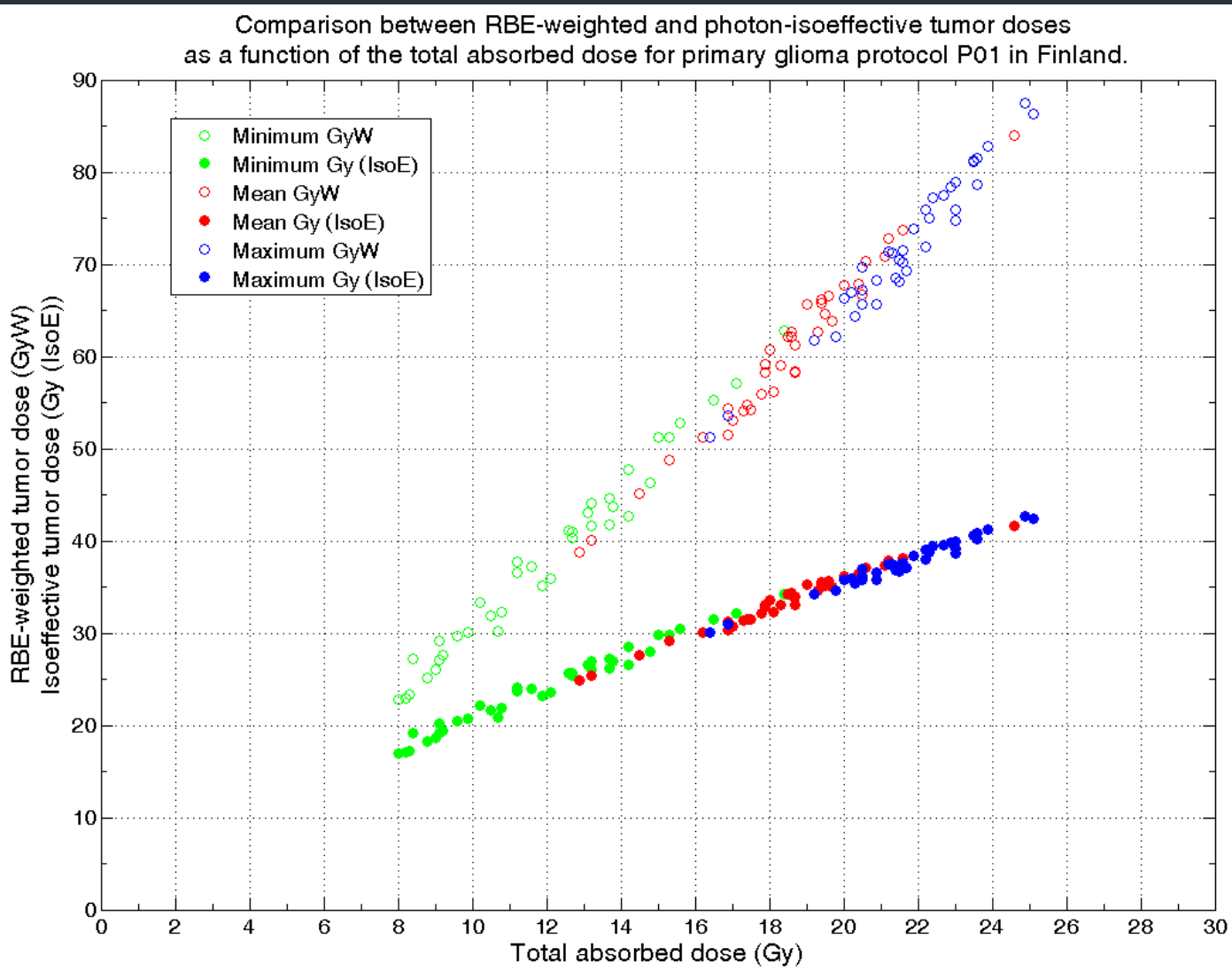


$$-\ln\left(S(D_1,\ldots,D_4)\right) = \sum_{i=1}^{4}\alpha_i D_i + \sum_{i=1}^{4}\sum_{j=1}^{4} G_{ij}(\theta)\sqrt{\beta_i\beta_j}D_i D_j\,.$$

Four-parameter survival model

Survival model + n Beam only & n+^{10}B-BPA data:

parameters are simultaneously obtained explicitly including the dependence of the irradiation time (G factor) .

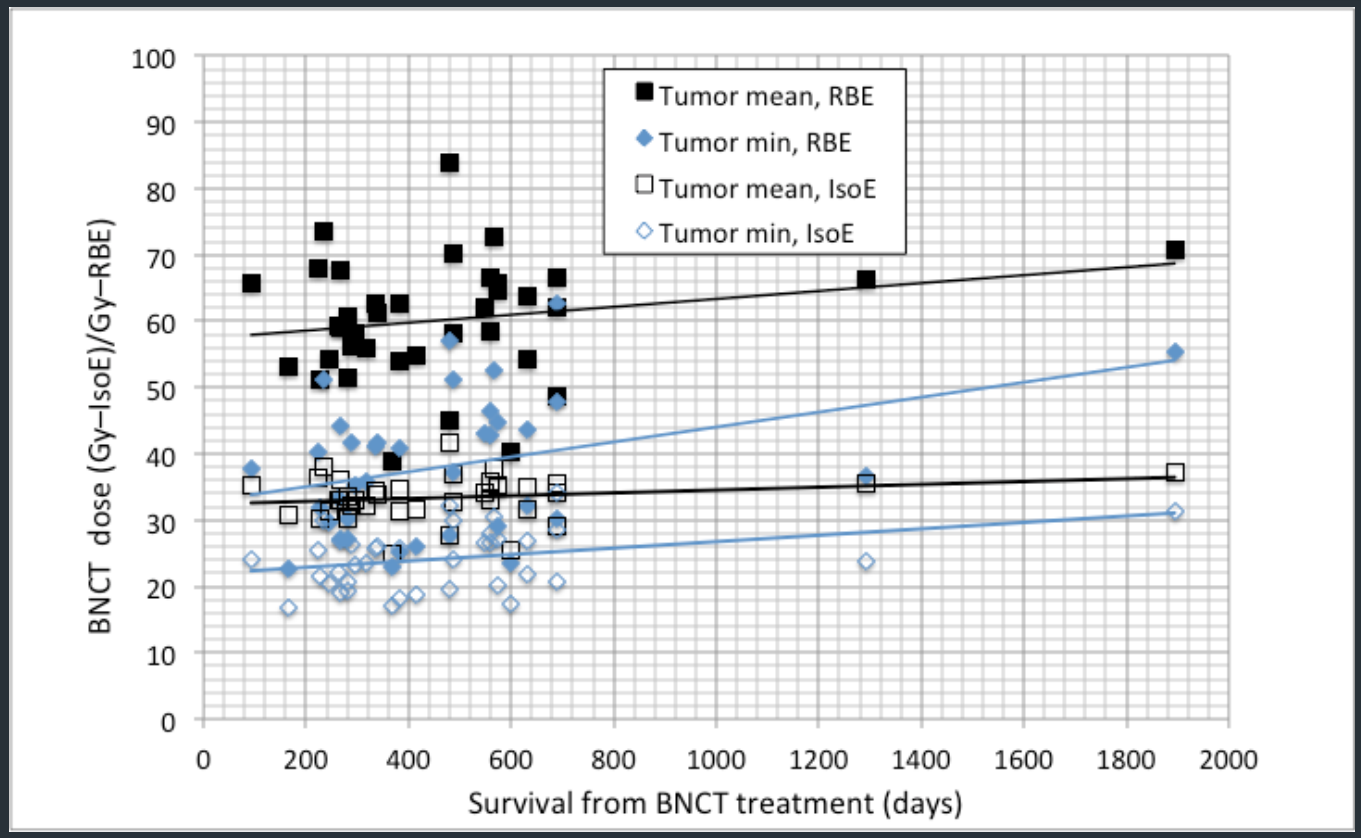


IsoE doses are lower than RBE doses

- For small total doses, difference ~16%
- For high total doses, up to ~50%

NEWLY DIAGNOSED GBM

Normal brain dose:
- D_{ave} = 3 – 6 Gy (W),
- D_{max}= 8 – 14 Gy(W)



- Higher mean and minimum tumor doses may correlate with longer OAS
- Median OAS 487 days (16 months) (range, 416 – 1894 days) from BNCT
  - Stupp *et al.* N Engl J Med 2005:
    RT + temozolomide at median follow-up of 28 months median OAS 14.6 m

ELSEVIER

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

0360-3016/$–see front matter

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
  - Median OAS 7.3 months from BNCT
  - ≥290 mg/kg BPA dose and mean PTV dose of ≥34 Gy(W) improved survival

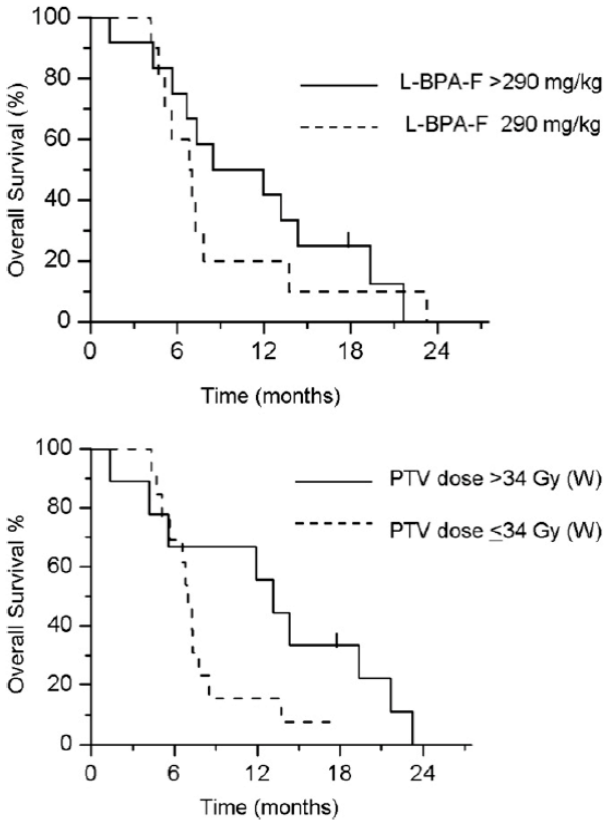
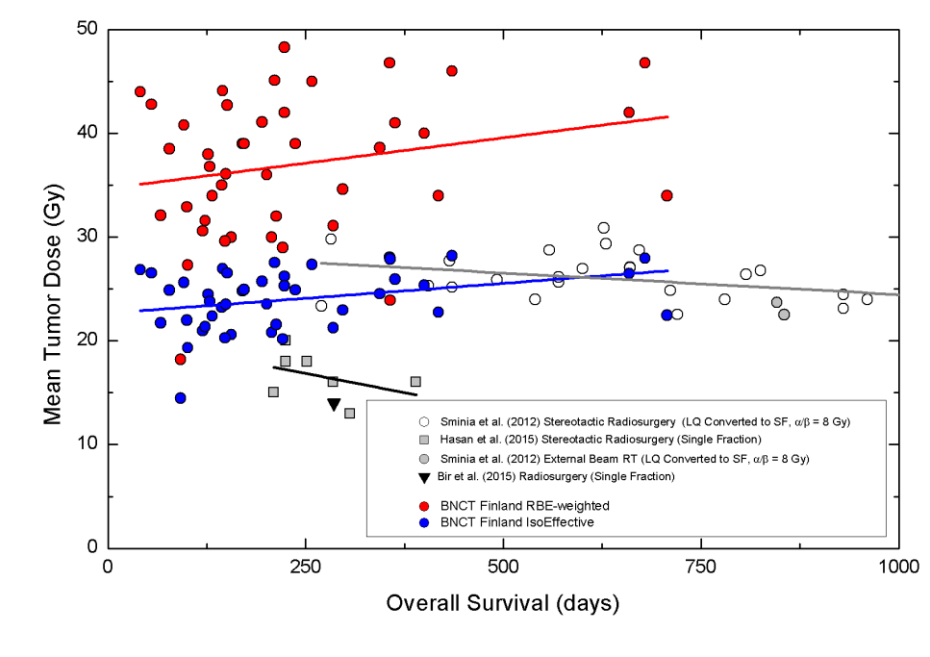


Fig. 2. Exploratory survival analyses based on the L-BPA-F dose delivered (A) and the estimated median planning target volume (PTV) dose administered (B). A patient alive at the time of the analysis is shown with a bar.

Recurrent GBM:
BNCT comparison with conventional radiotherapy



Sminia *et al.* Cancers 4, 2012
- An overview of six trial
- 4 –23 fractions
- OAS 187 – 7.9 mo

Hasan *et al.* Front. in Oncology, 2015
- SRT; OAS 5.3 months
- CTV volume 0.9–152 cm^3

Bir *et al.* Neurosurg Rev, 2015
- Median OAS 7.9 mo;
- Ave tumor volume 11 cm^3

Normal brain BNCT dose
D_{ave} = 2 – 4 Gy (W)
D_{max}= 6 – 8 Gy(W)

Tumor volumes in BNCT
Median 62 cm^3 (7 – 340 cm^3)

Recurrent head and neck cancer: Tumor response analysis

PR = Partial response SD = Stable disease CR = Complete response	Patients with PR or SD response (n=15)	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, mean (Gy(W))	32	35	0.59
PTV min dose, mean (Gy(W))	12	15	0.061
PTV ave dose, mean (Gy(W))	21	23	0.249
Tumor max dose, mean (Gy(W))	31	33	0.626
Tumor min dose, mean (Gy(W))	**15**	**19**	**0.015**
Tumor ave dose, mean (Gy(W))	22	25	0.427

- Mucosal membrane D_{max} = 4–6 Gy ≈ 10–14 Gy(W)
- Spinal Cord D_{max} = 3–4 Gy(W)

CONCLUSION

- Photon-Isoeffective dose calculation formalism predicts lower delivered doses for GBM patients than conventional RBE based formulism
- Higher minimum and average BNCT dose to tumor (GBM) calculated with RBE or Isoeffective model may correlate with longer survival time
  - Survival time after photon radiotherapy and BNCT on newly diagnosed and recurrent GBM is very similar
- >19 Gy(W) minimum RBE-dose to head and neck tumor correlate with complete tumor response
  - Head and neck cell survival study ongoing with University of Pavia group

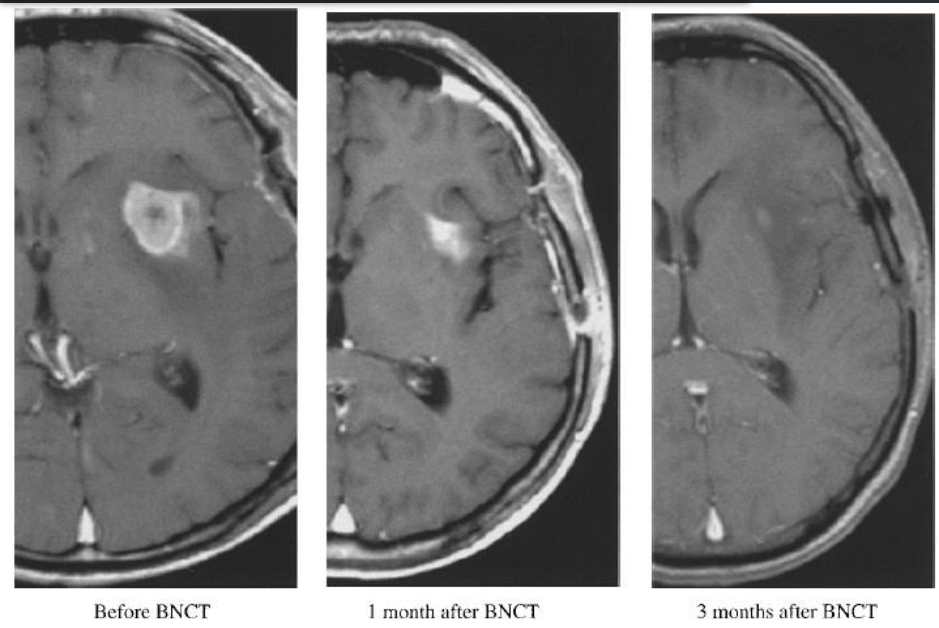
- RBE– and Photon Isoeffective doses in BNCT correlate with clinical outcome
- RBE–doses maybe overestimated, not really photon dose equivalent doses

FUTURE ASPECTS

- Clinical outcome of BNCT maybe improved
  - Dynamic ^{18}F-BPA-PET to find out optimal irradiation window before BNCT
  - Boron-capture gamma SPECT to detect boron distribution in the patient during the treatment
  - Better tumor targeting boron carriers: under investigation

- Accelerator based neutron sources developed/under development
  - Sumitomo Heavy Industries: 30 MeV protons+Be target (Kyoto and Fukushima Prefecture)
  - Hitachi & CICS: 2.5 MeV protons+Li target (National Cancer Center, Tokyo
  - IBA: 2.5 MeV protons+Li target
  - Mitsubishi Heavy Industries: 7 MeV protons+Be target (Tokai Mura, Japan)
  - Neutron Therapeutics: 2.6 MeV protons+Li target

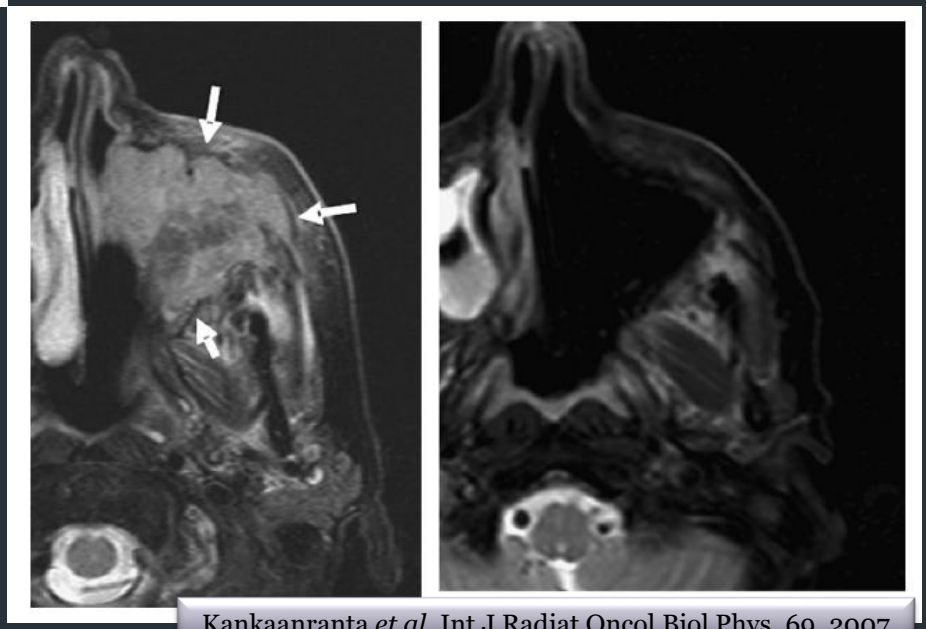
Newly diagnosed glioblastoma multiforme
Joensuu *et al.* J of Neuro-Oncology 62, 2003



Thank you! Merci!

Before BNCT

After 2xBNCT: CR



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