Developing Clinical Facilities for BNCT and proton radiotherapy in Birmingham

Stuart Green
University Hospital Birmingham

Particle Physics Group Seminar
Birmingham, November 2010

Overview of techniques and projects

- External beam treatments
  - X-ray therapy
  - Proton and ion beam therapy

localised disease

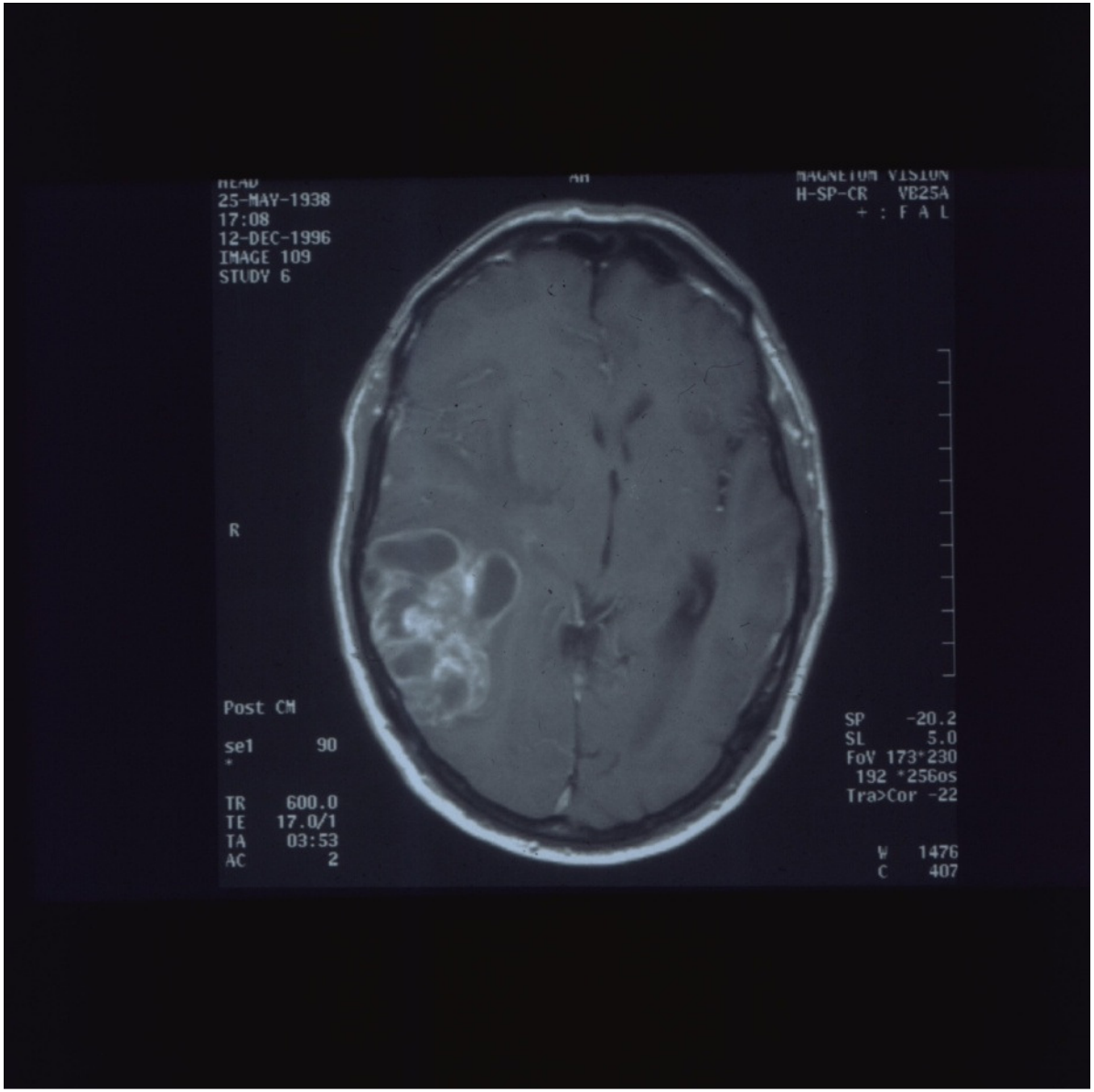
- Binary therapies
  - Boron Neutron Capture Therapy
  - High Z enhanced radiotherapy

locally spread disease

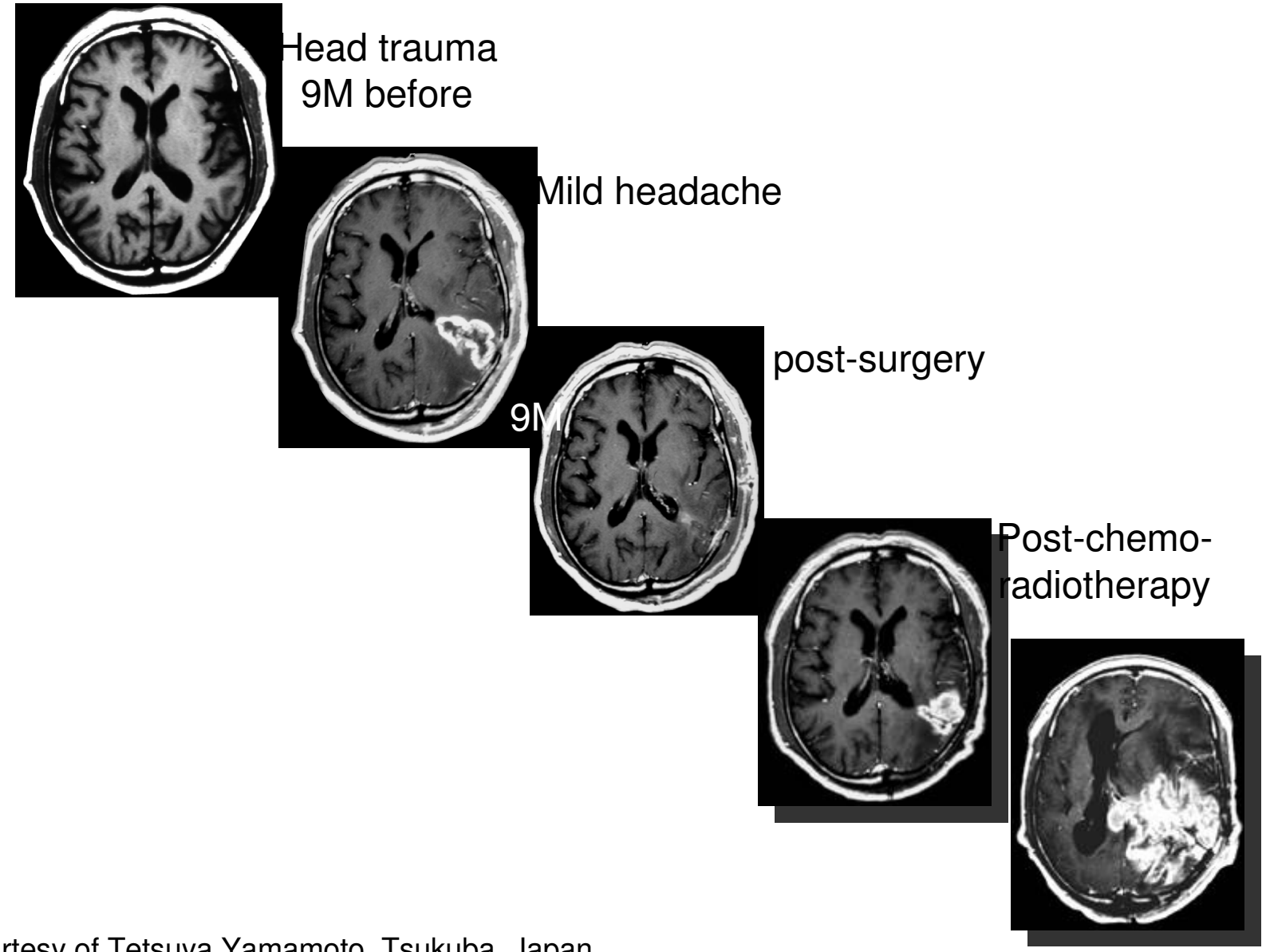
- Systemic treatment
  - Targeted radionuclide therapy
  - chemotherapy

Systemic disease

Glioblastoma

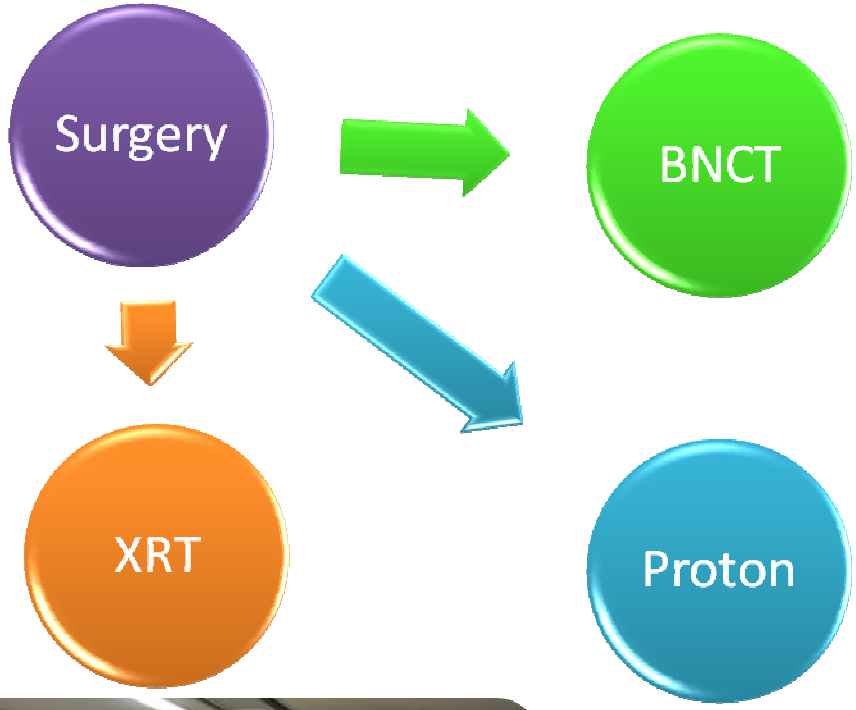


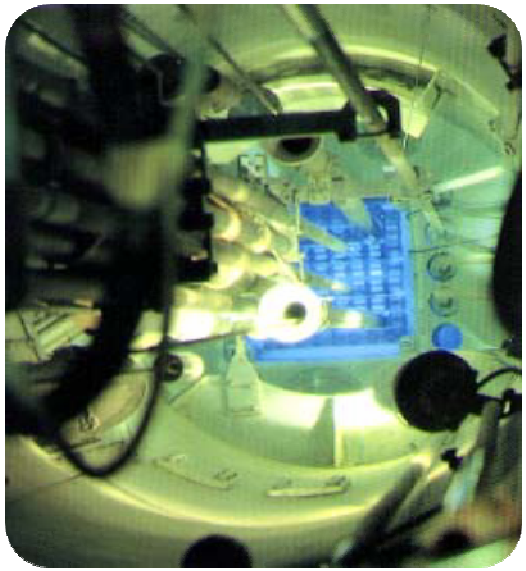
Glioblastoma - clinical course



Courtesy of Tetsuya Yamamoto, Tsukuba, Japan

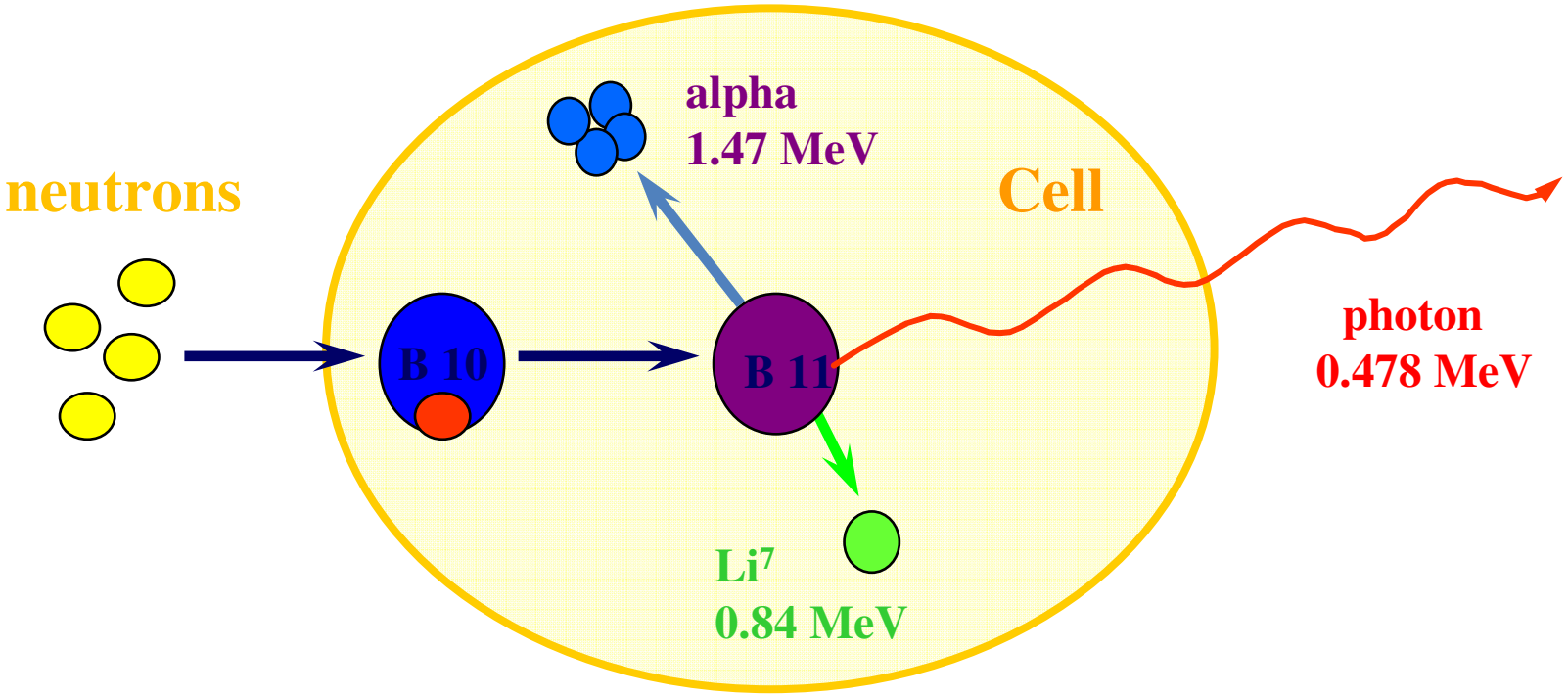
The Tsukuba approach





Courtesy of Tetsuya Yamamoto, Tsukuba, Japan

Boron Neutron Capture Therapy



Ion combined range ~ 8-9μm . Cell diameter ~ 10 μm.

=> radiation damage mostly within cell

BNCT as a binary therapy

2 key steps

- Delivery of ^{10}B selectively to tumour cells and with a sufficiently high concentration
- Delivery of a thermal neutron fluence to the tumour cells, while delivering a non-toxic radiation dose to healthy cells

BPA-formulation – the problem

- Maximum concentration BPA-fructose ~30 mg/ml
- Clinical experience ranges 450 mg/kg/2 hours to 900 mg/kg/6 hours

  → 70 kg adult infusion volume 1.2 to 2.1 litres
- Target BPA dose 1050 mg/kg/2 hours → BPA-fructose volume 2.45 l
- Fructose not allowed for infusion in the UK

- **In order to avoid any limitation imposed by tolerable fluid volume and regulatory authorities, a new BPA formulation was required**.

BPA formulation – the solution?

- A range of excipients were tested for solubility and stability
  - fructose
  - glucose
  - mannitol
- The chosen product: BPA 100mg/ml in 110mg/ml mannitol
- pH of 8±0.2
- Osmotic pressure 1353 mOsm
- Thus BPA-mannitol concentration >3-fold BPA-fructose
- Avoids possible serious adverse reactions from hereditary fructose intolerance

Clinical optimisation of uptake parameters of Boronophenylalanine (BPA) for use in trials of Boron Neutron Capture Therapy (BNCT)

D. Ngoga, S Green, A. Detta, N.D James, C Wojnecki, J Doran, F. Lowe, Z. Ghani, G Halbert, M Elliot , S Ford, R Braithwaite, TMT Sheehan, J Vickerman, N Lockyer, G. Croswell, R Sugar, A. Boddy, A. King, G. Cruickshank.

ICNCT 14.
29th October 2010
Buenos Aires,
Argentina

UNIVERSITY OF BIRMINGHAM

The University of Manchester
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Trial Design

Stage 1: Route of delivery

- a) Using single dose BPA (350mg/kg over 2h) via central venous or intra-carotid artery
- b) With and without rapid (30s) Mannitol infusion (300ml 20%)

Stage 2: Dose escalation

- a) Single 750mg/kg dose over 2h
- b) Single 1050mg/kg dose over 2h

Study Plan

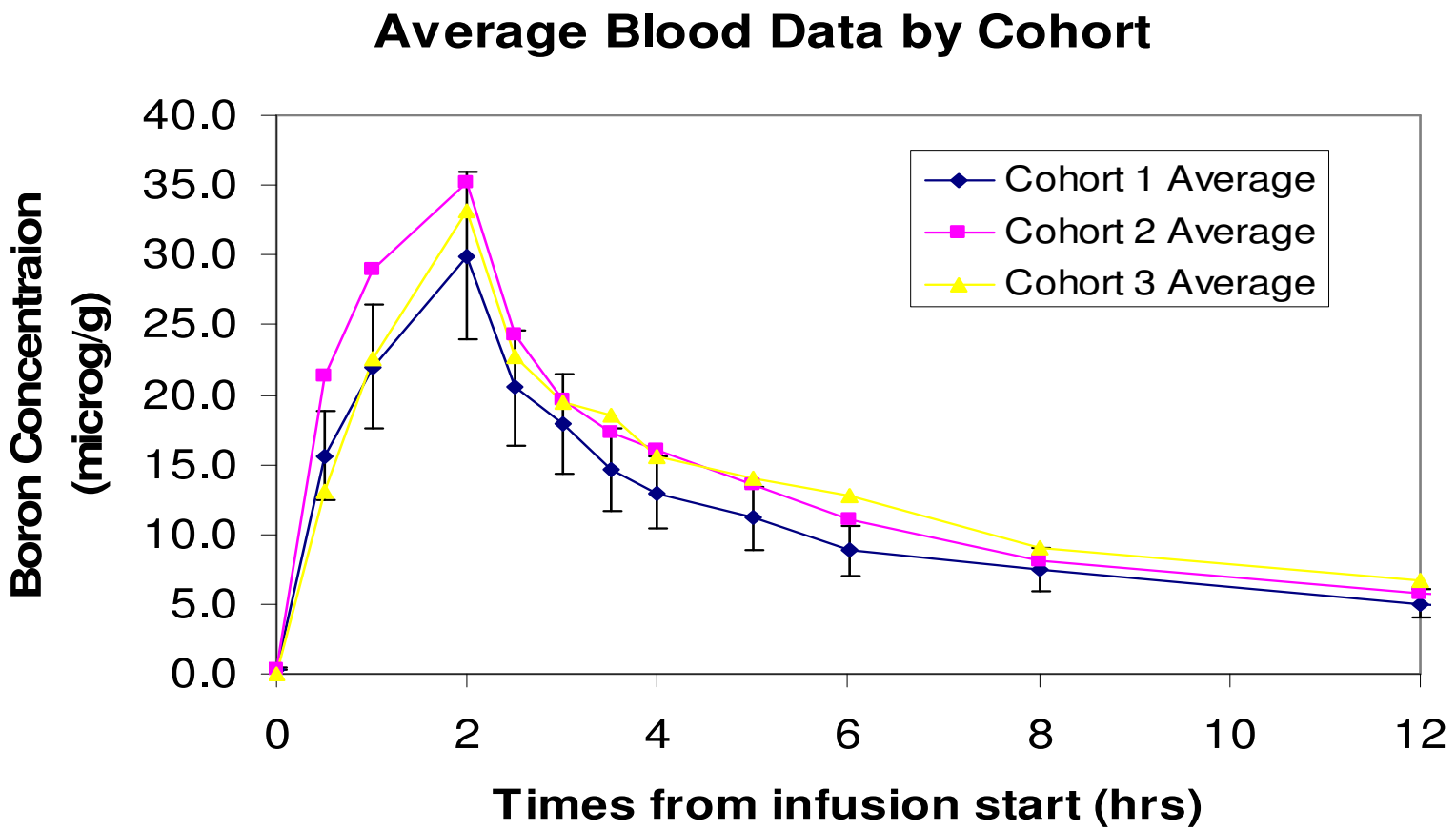
		BPA route	Mannitol BBB	Status
Cohort 1	**3 Patients**	**IV**	**No**	**Completed**
Cohort 2	**3 Patients**	**IV**	**Yes**	**Completed**
Cohort 3	**3 Patients**	**IA**	**No**	**Completed**
Cohort4	**3 Patients**	**IA**	**Yes**	**Open - Nov 2010**

This to be followed by dose escalation study on a further 6 patients

Sampling

- Blood for ^{10}B PK assay (-0.5h to +48h post start of Infusion)
- Brain biopsies for pathology & ^{10}B assays (3h, 3.5 and 4h post infusion)
- CSF for ^{10}B assay (at time of biopsies if accessible)
- ECF (Via Brain microdialysis) for ^{10}B assay (0h to +48h)
- Urine for ^{10}B for assay (-0.5h to +48h)

Results: Blood



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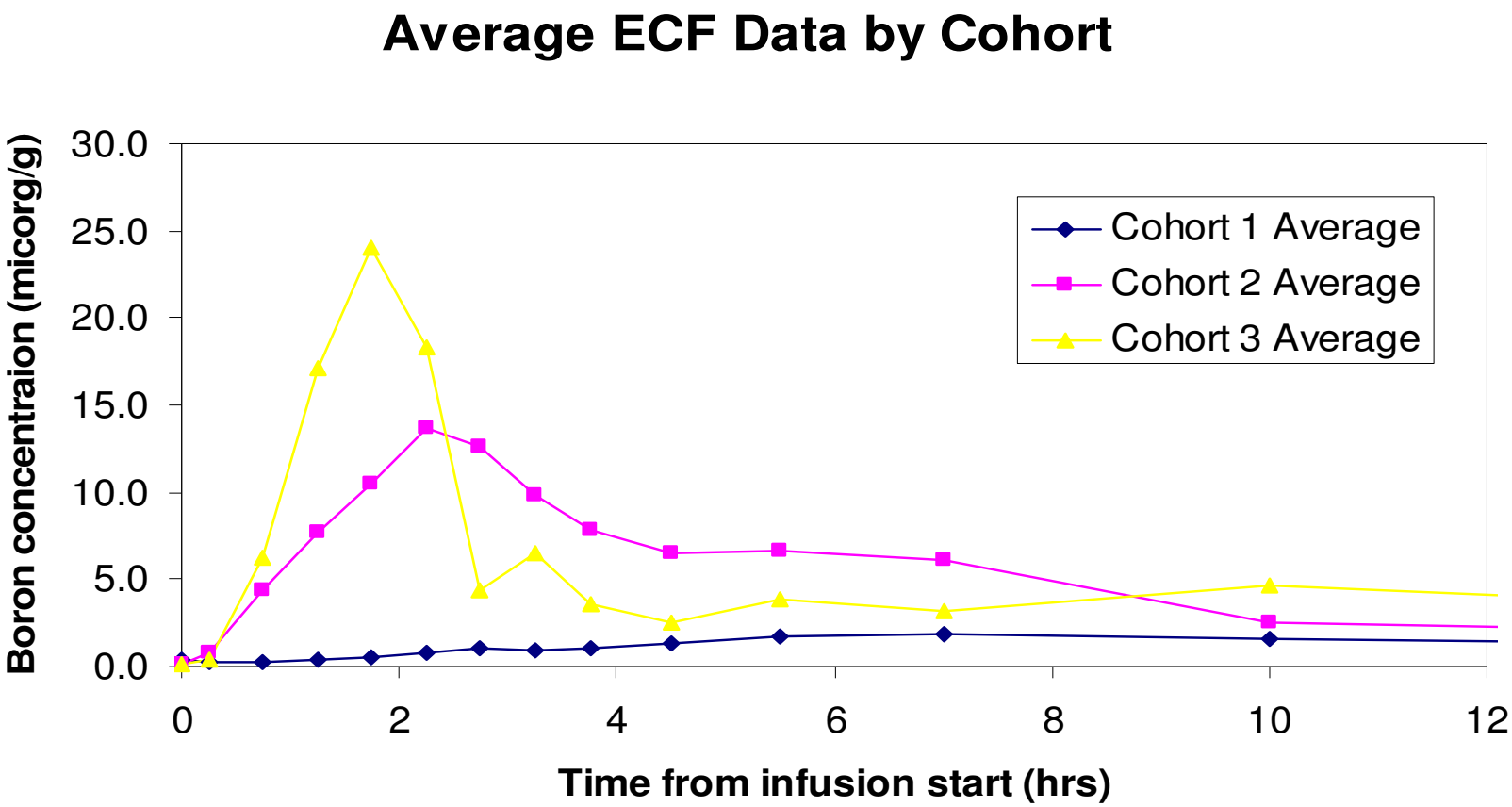
Results: ECF



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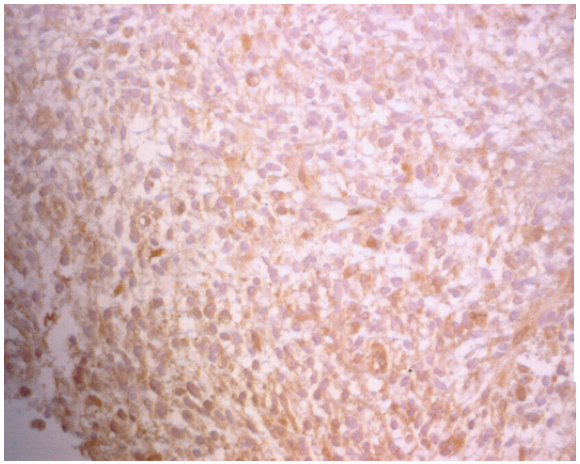
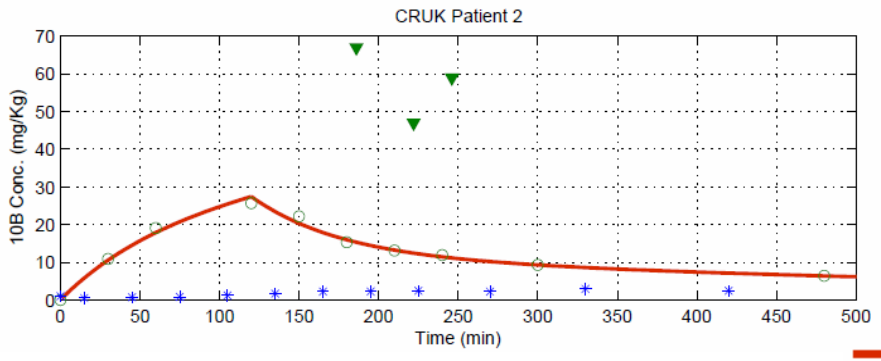
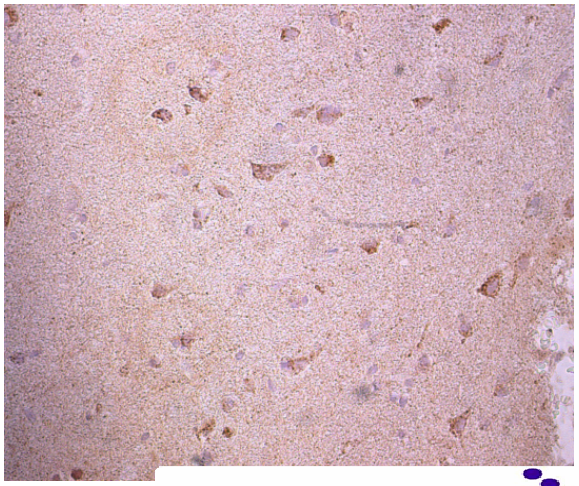
Tumour cellularity

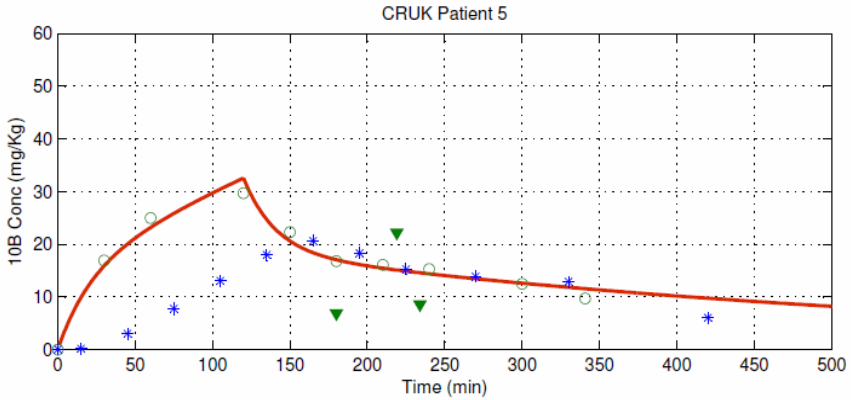
Patient 2 tumour biopsy





Patient 5 tumour biopsy





Fitted blood data

Blood

Biopsy / Debulk

ECF

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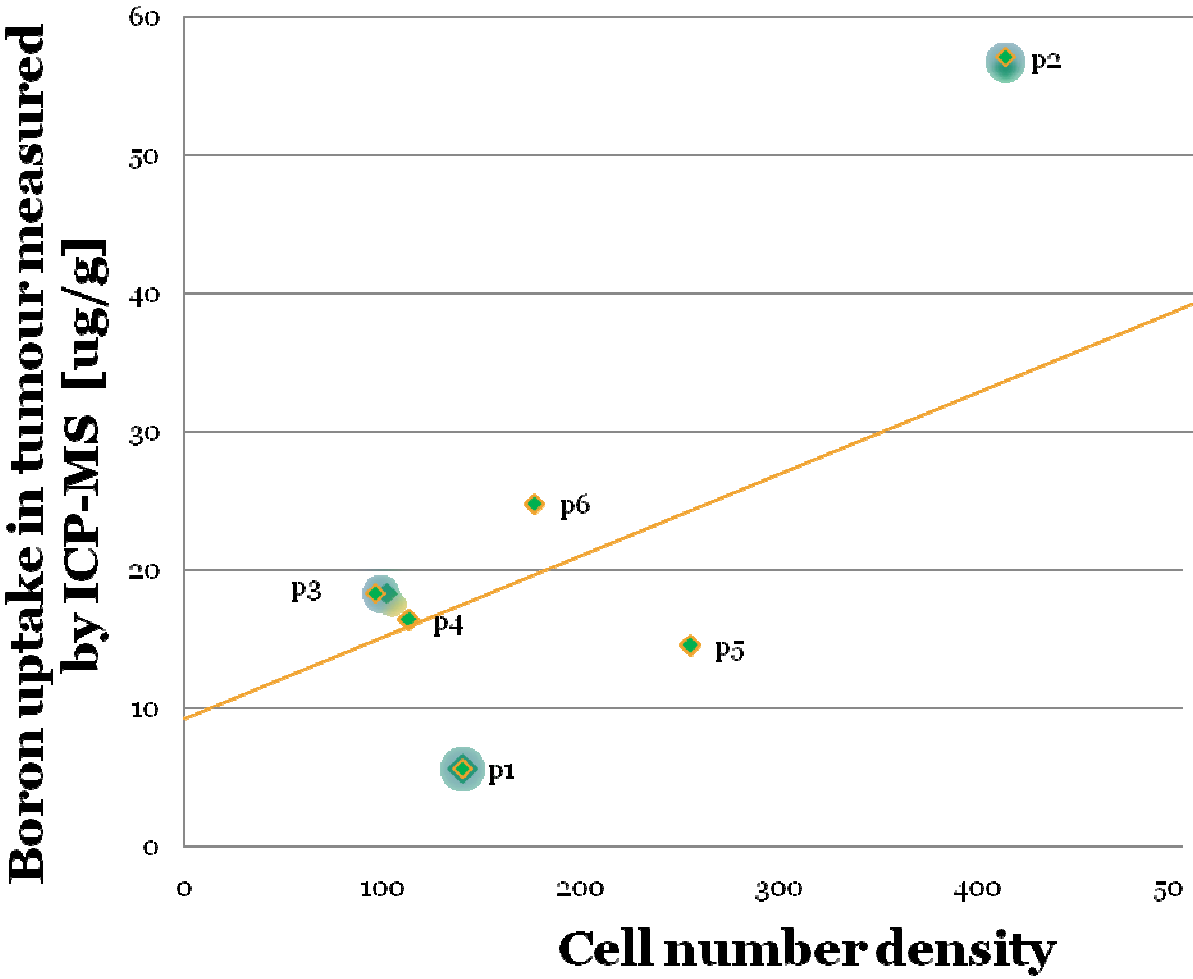
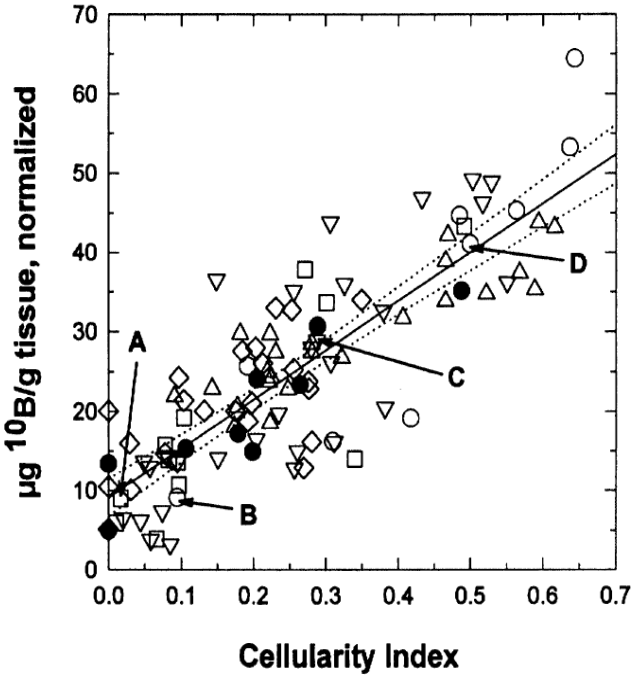
Correlation between boron uptake and Tumour cell number density





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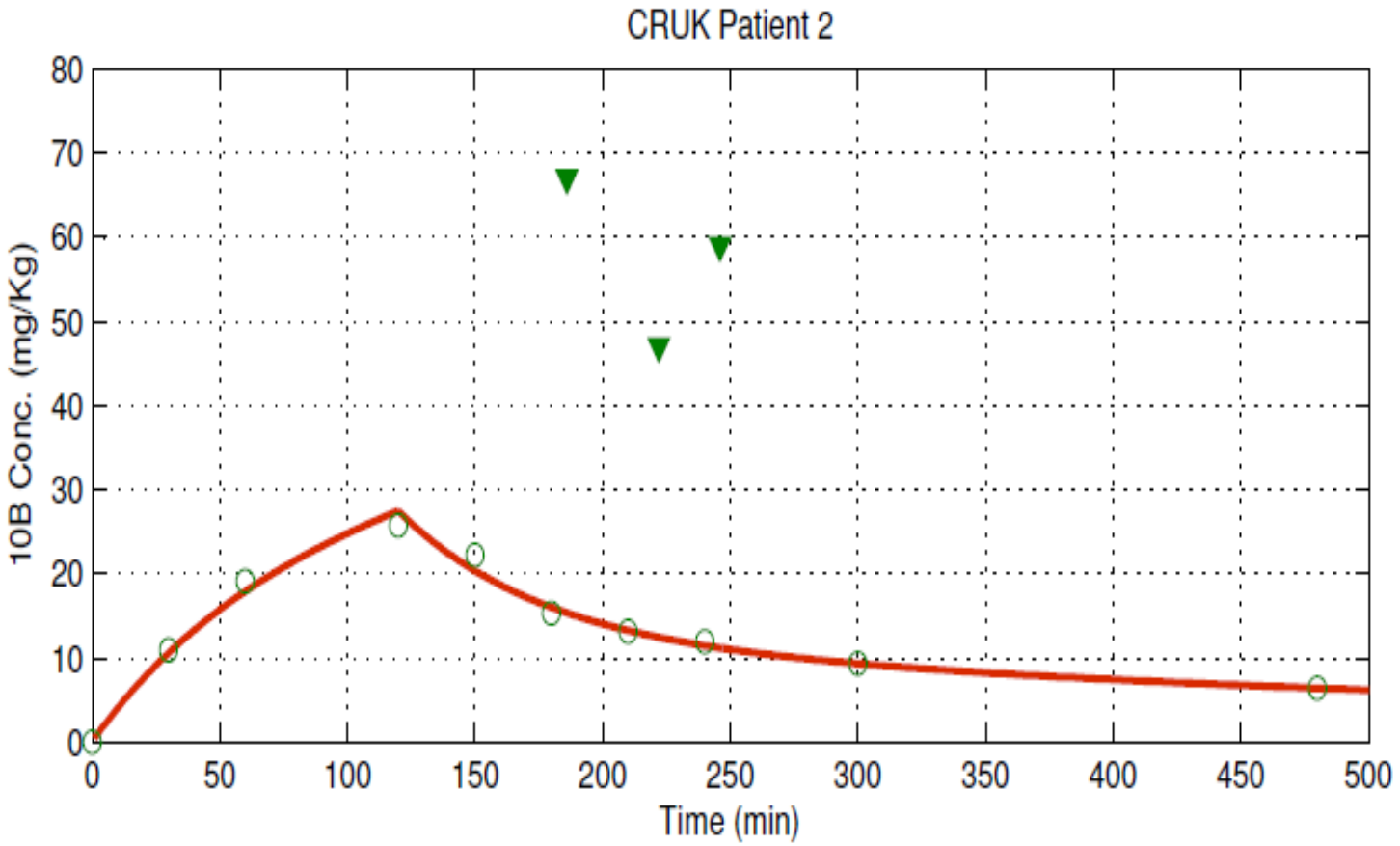
Results: adjusted for cellularity



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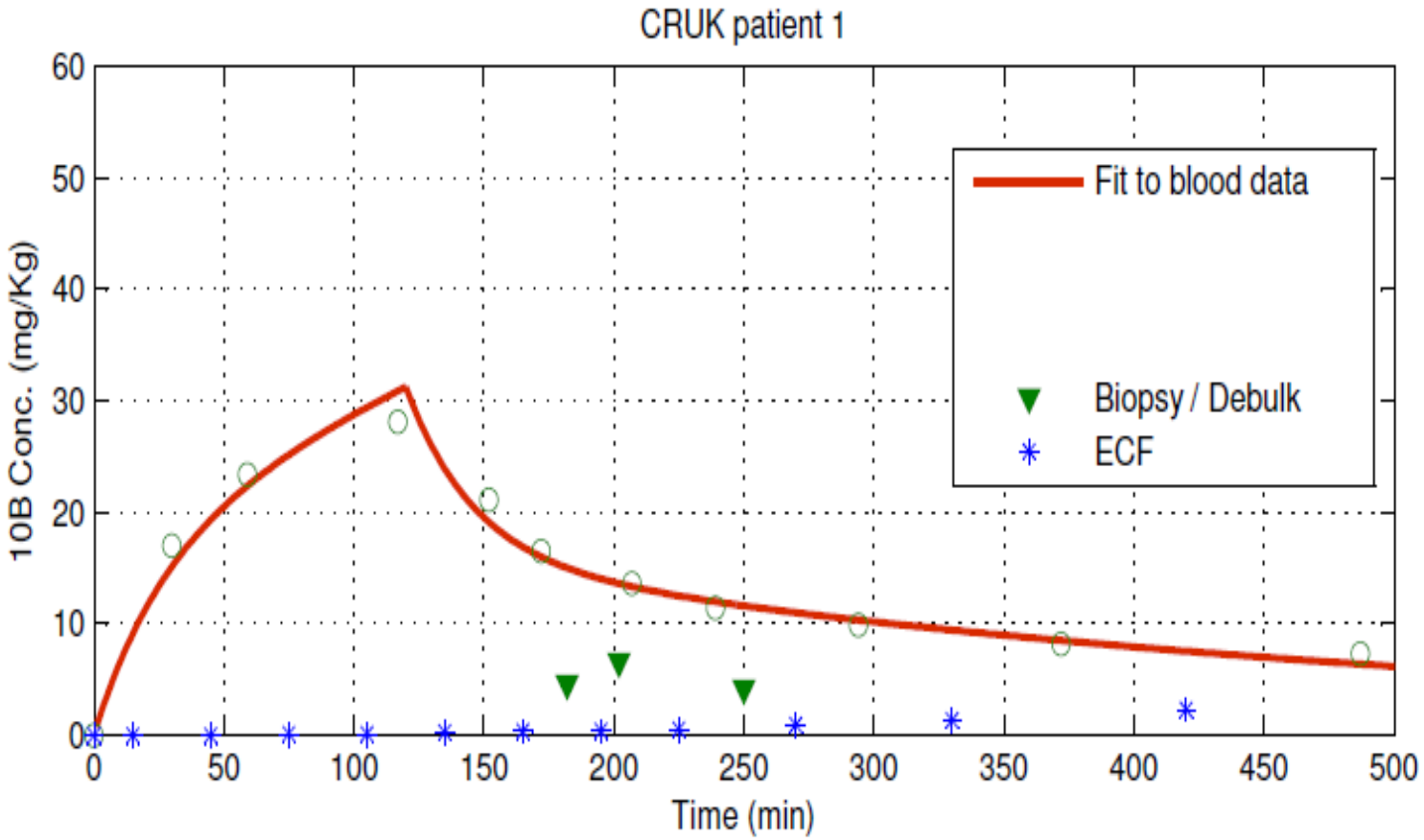

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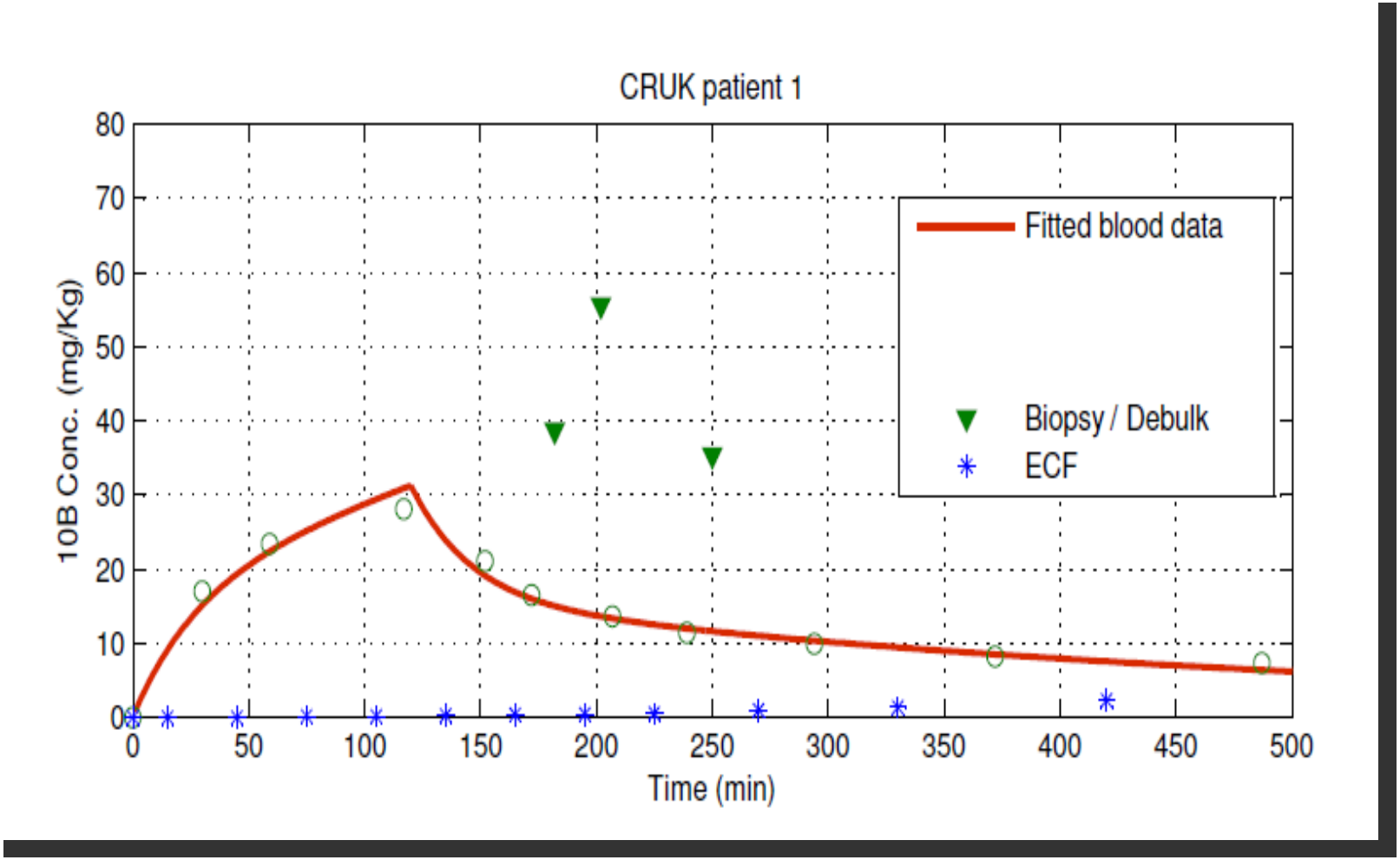

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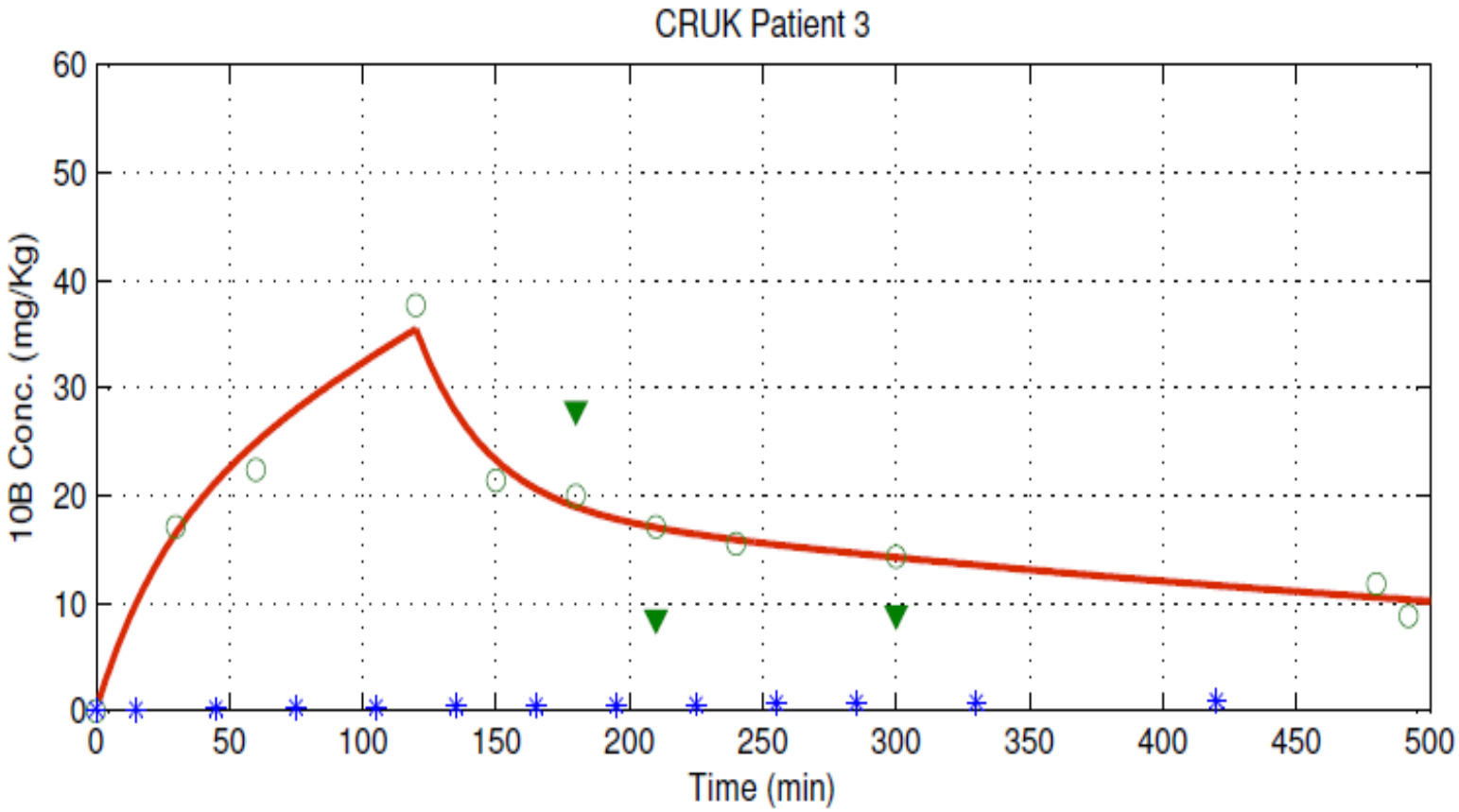

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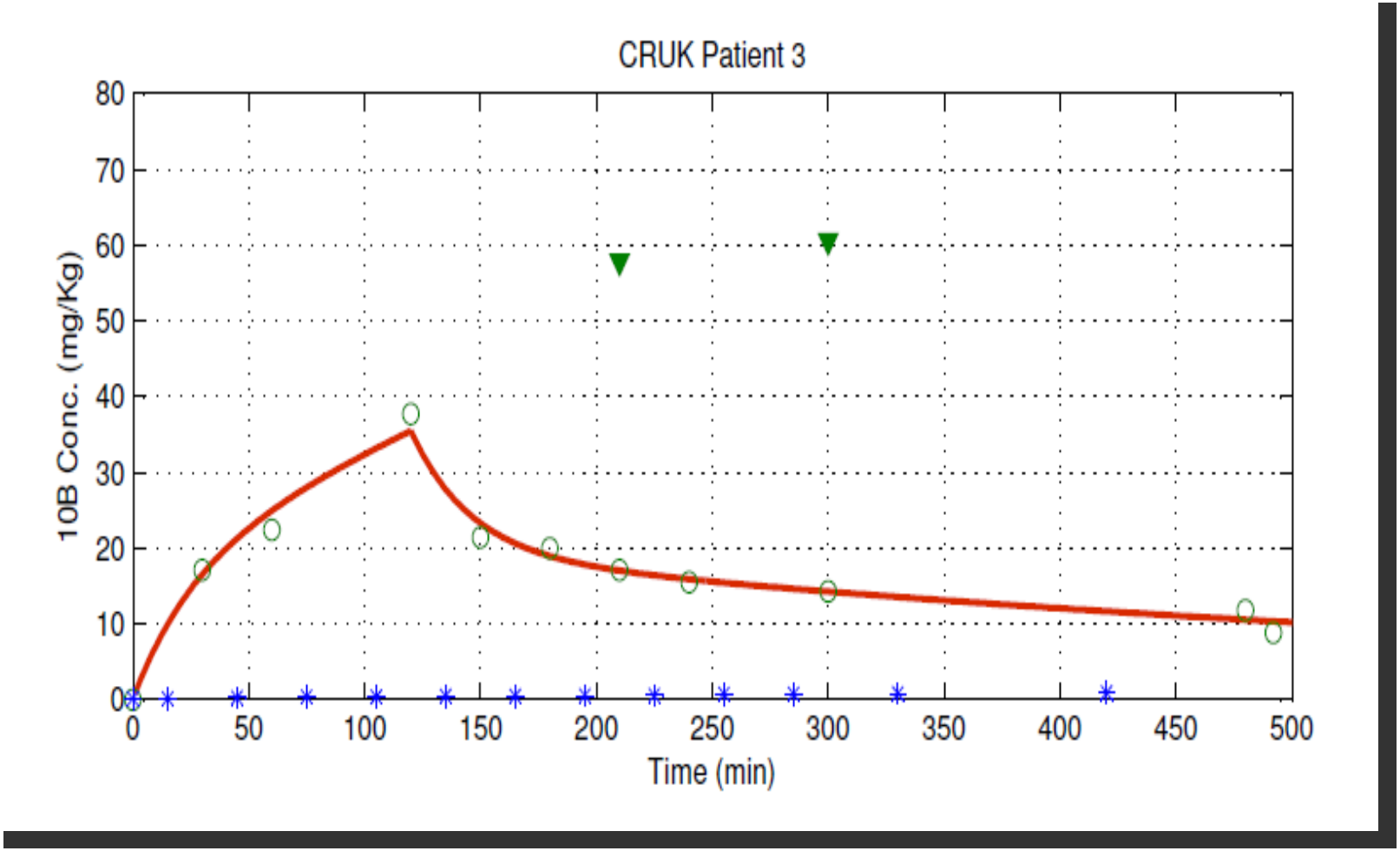

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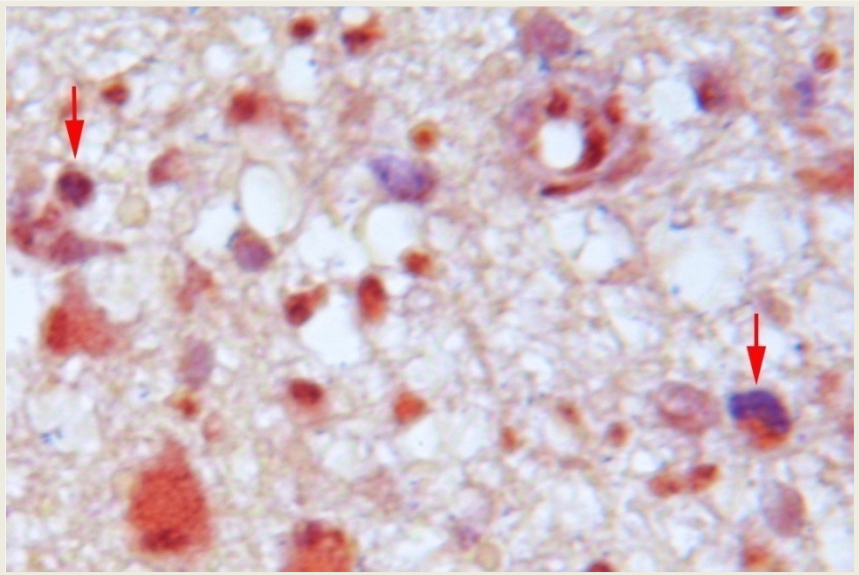
Phenylalanine transport mechanism

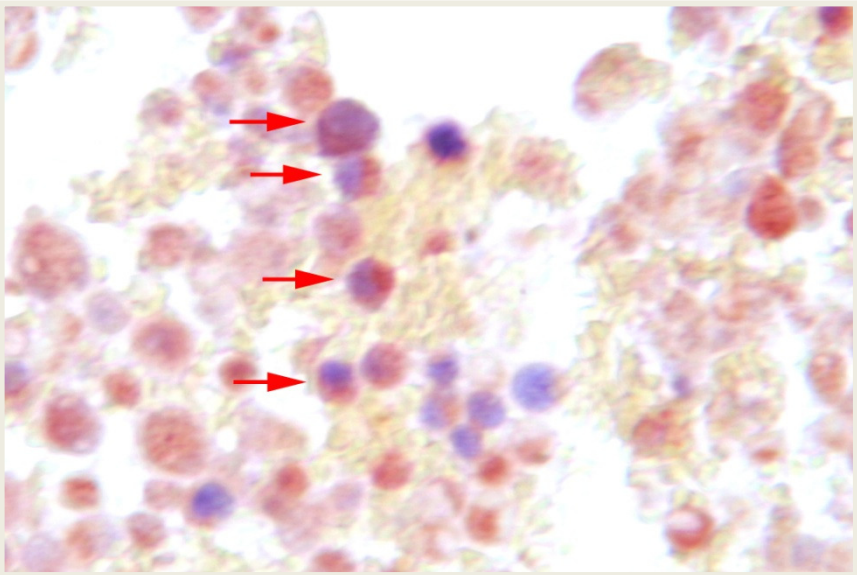
- Selectively transported across the blood brain barrier, endothelial cells and astrocytic cells by a common LAT-1 transporter system.
- LAT-1 is upregulated in tumour cells and might be expected to enhance the concentration of L amino acids particularly in tumour cells.
- Increased uptake may be dependent on:
  - Strongly dependent on duration of exposure,
  - Less strongly dependent on concentration of BPA
  - Strongly dependent on relative expression of LAT-1

LAT-1 expression in GBMs

A



B



Photomicrographs of tumour cells in GBM (A) and a metastatic tumour (B) showing the LAT-1 cells as red, PCNA (proliferating) cells as blue and the LAT-1+PCNA cells as red-blue (arrows)

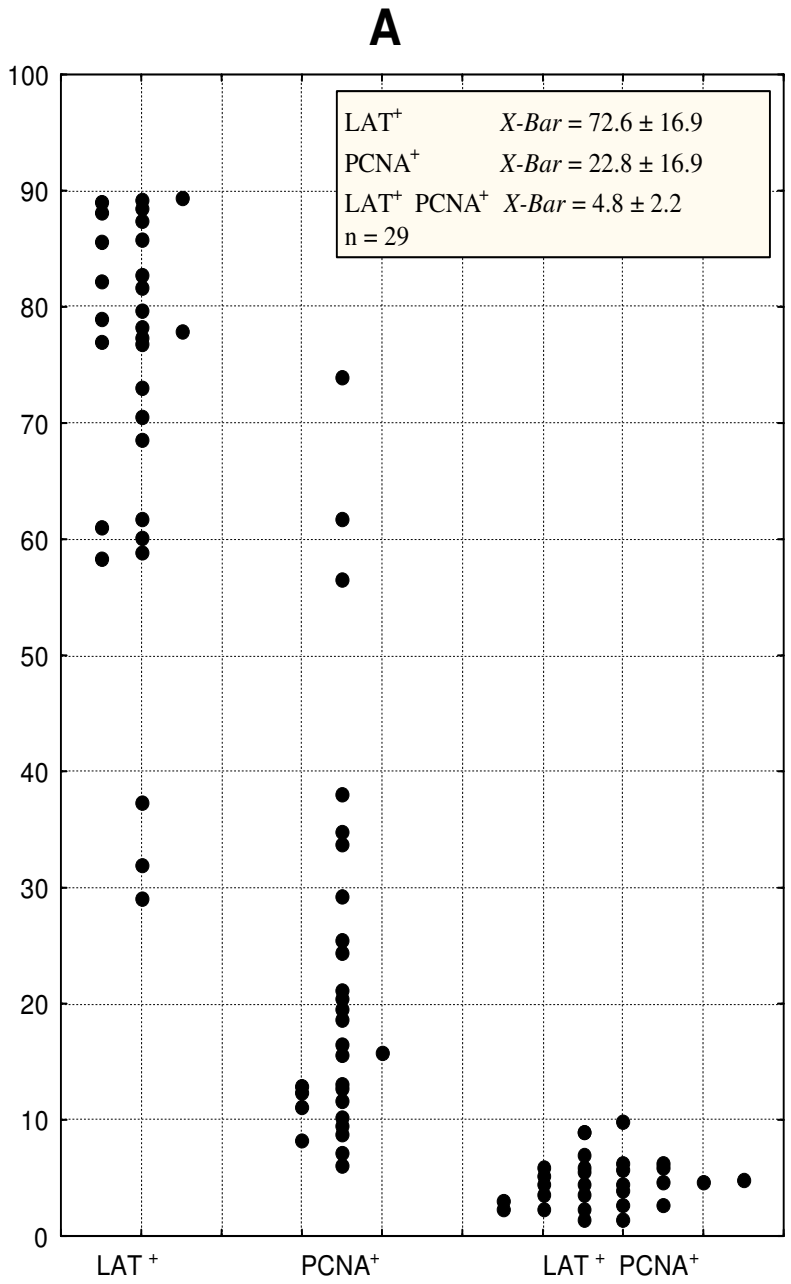
Slide courtesy of A Detta

Results for counted stained cell populations in GBMs

60-90 % of tumour cells express LAT-1

A much lower proportion are proliferating

Detta and Cruickshank, Cancer Res 2009



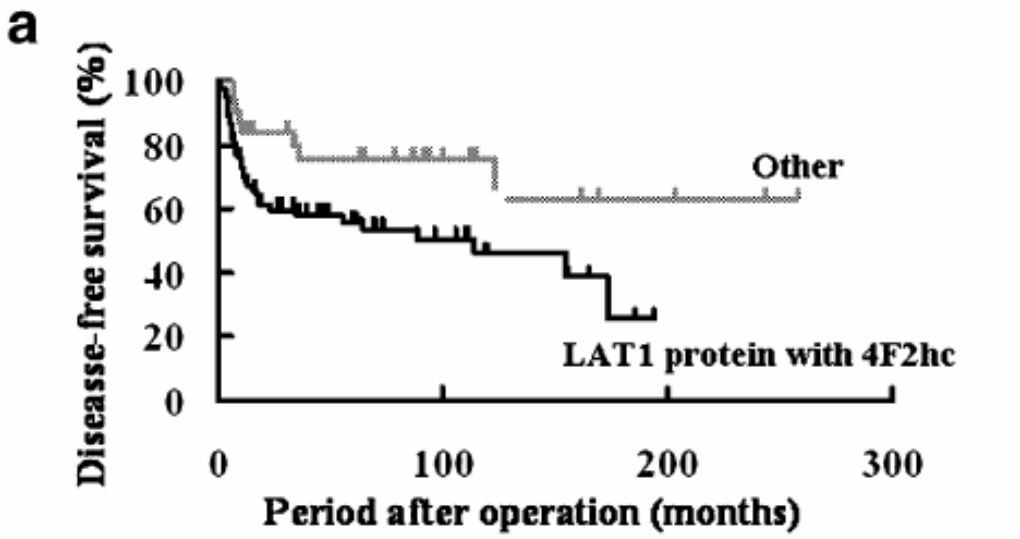
New findings on LAT-1

Virchows Arch (2007) 451:681–690
DOI 10.1007/s00428-007-0457-9

ORIGINAL ARTICLE

Expression of LAT1 predicts risk of progression of transitional cell carcinoma of the upper urinary tract

Kuniaki Nakanishi · Sho Ogata · Hirotaka Matsuo · Yoshikatsu Kanai · Hitoshi Endou · Sadayuki Hiroi · Susumu Tominaga · Shinsuke Aida · Hiroyasu Kasamatsu · Toshiaki Kawai



The conventional research paradigm compared with BNCT

Conventional wisdom

- Find something (protein, pathway, signal etc) that is unique to the tumour
- Block this and the tumour stops growing
  - Problem is that tumours adapt

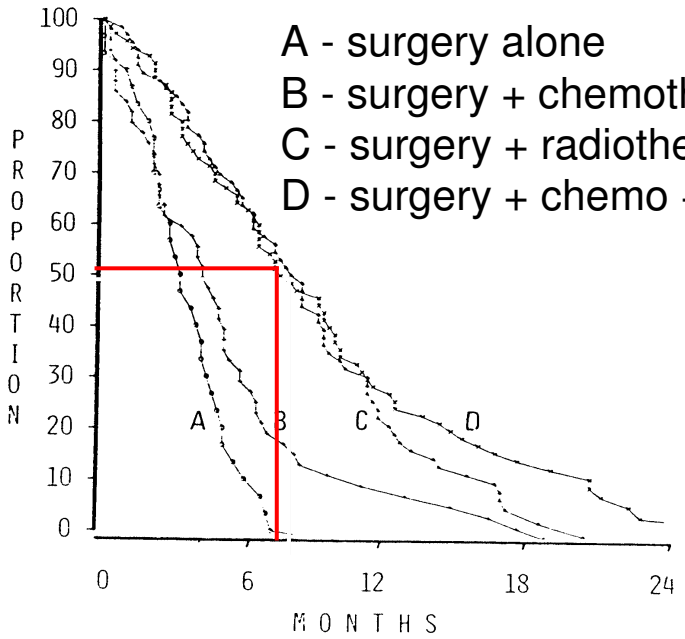
BNCT with BPA

- find something that the tumour is doing (LAT-1 over expression)
- Exploit this to kill the tumour
- The more the tumour does this, the better BNCT will work

Glioblastoma Multiforme
Prognosis improvement in the last 30 years

Walker et al. J Neurosurg 49 (1978) **333-343**

luation of treatment of gliomas



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Stupp et al., N Eng J Med 352 (2005) 987-996

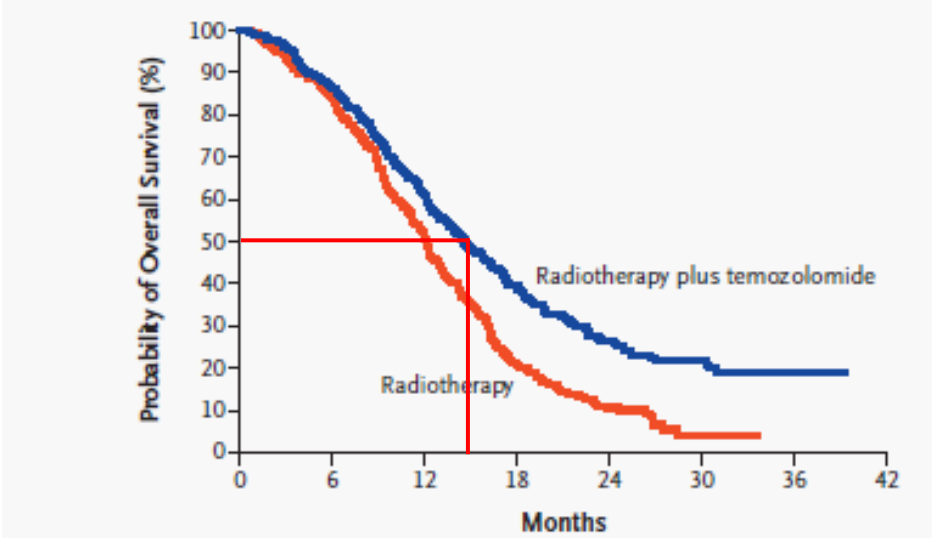
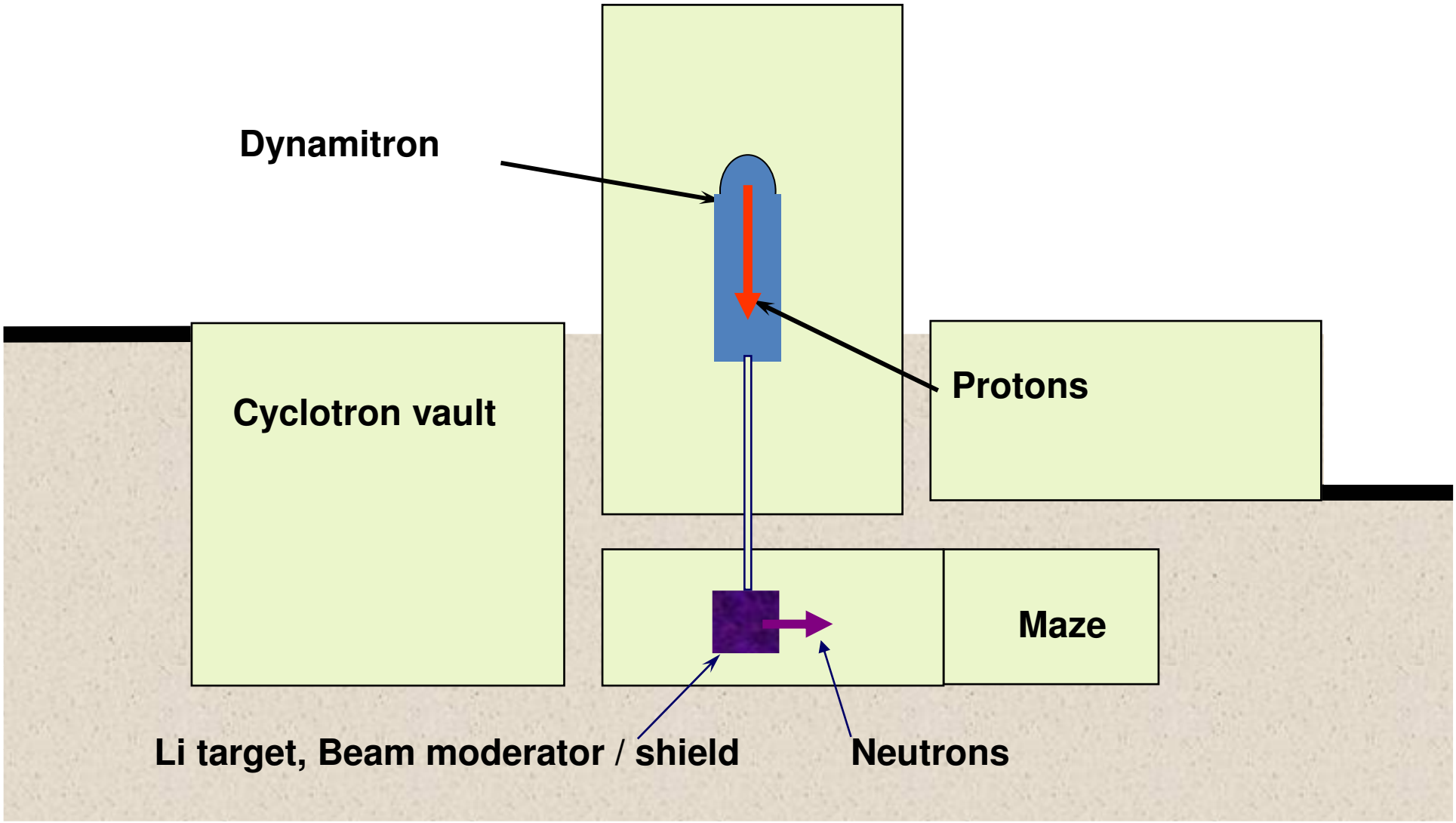


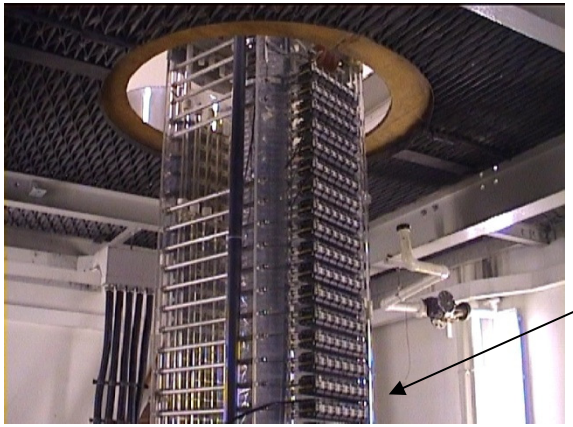
Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

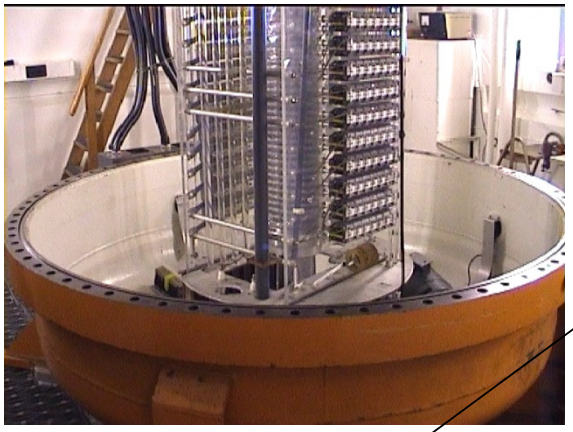
The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

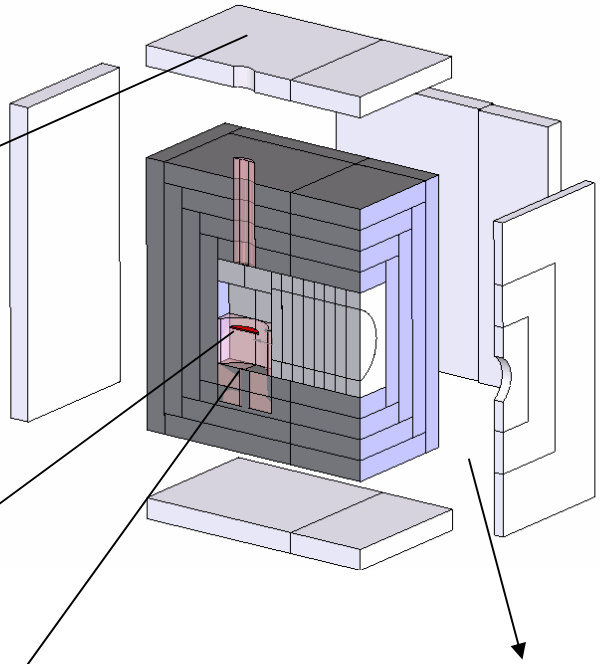
Disease progression or recurrence through lack of local control

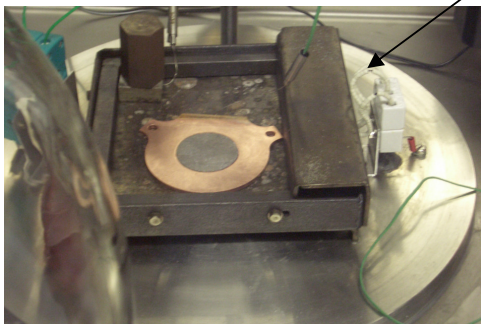
Medical Physics Building

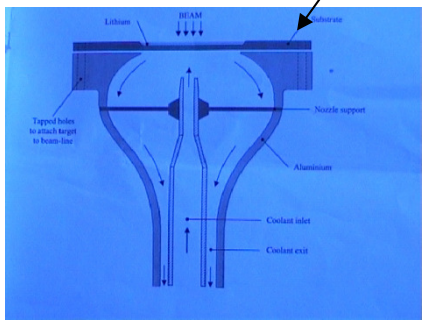


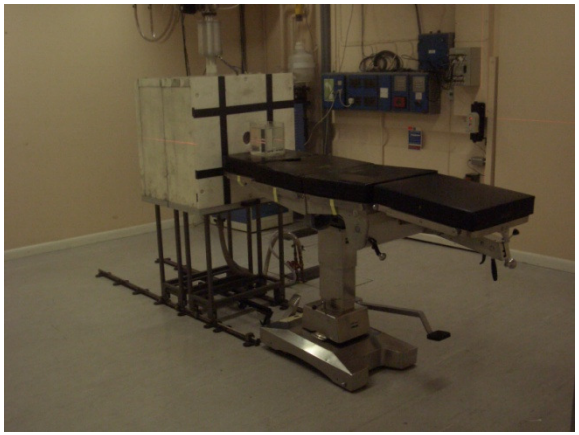








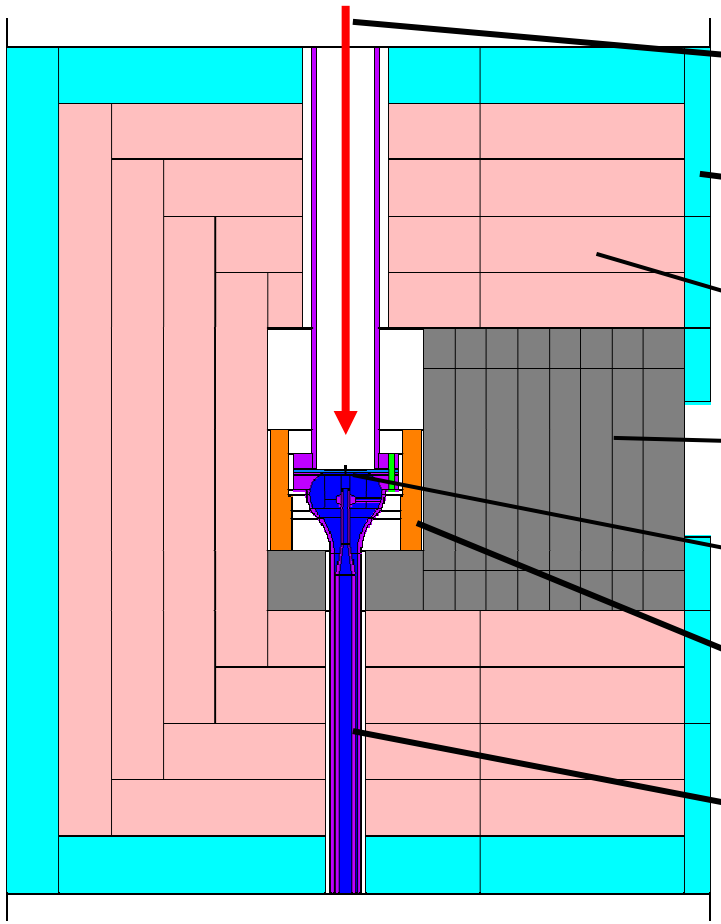




Neutron source is > 1 x 10^{12} s^{-1}
(1 mA proton current at 2.8 MeV)

For 40 minute treatment time, need 5 mA proton current and suitable target

Neutron generation and moderation



scanned proton beam

shield

graphite reflector

FLUENTAL moderator / shifter

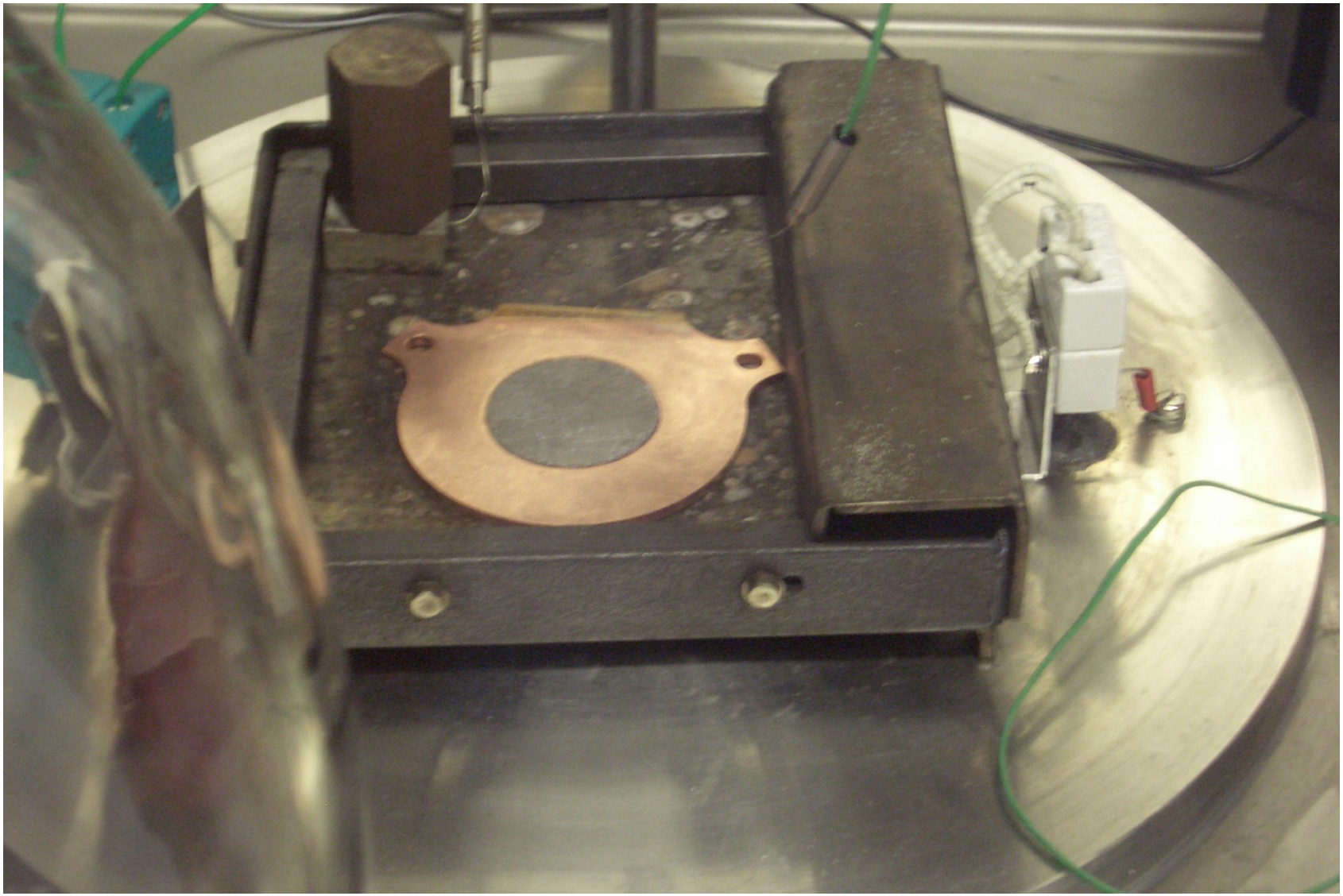
Li target

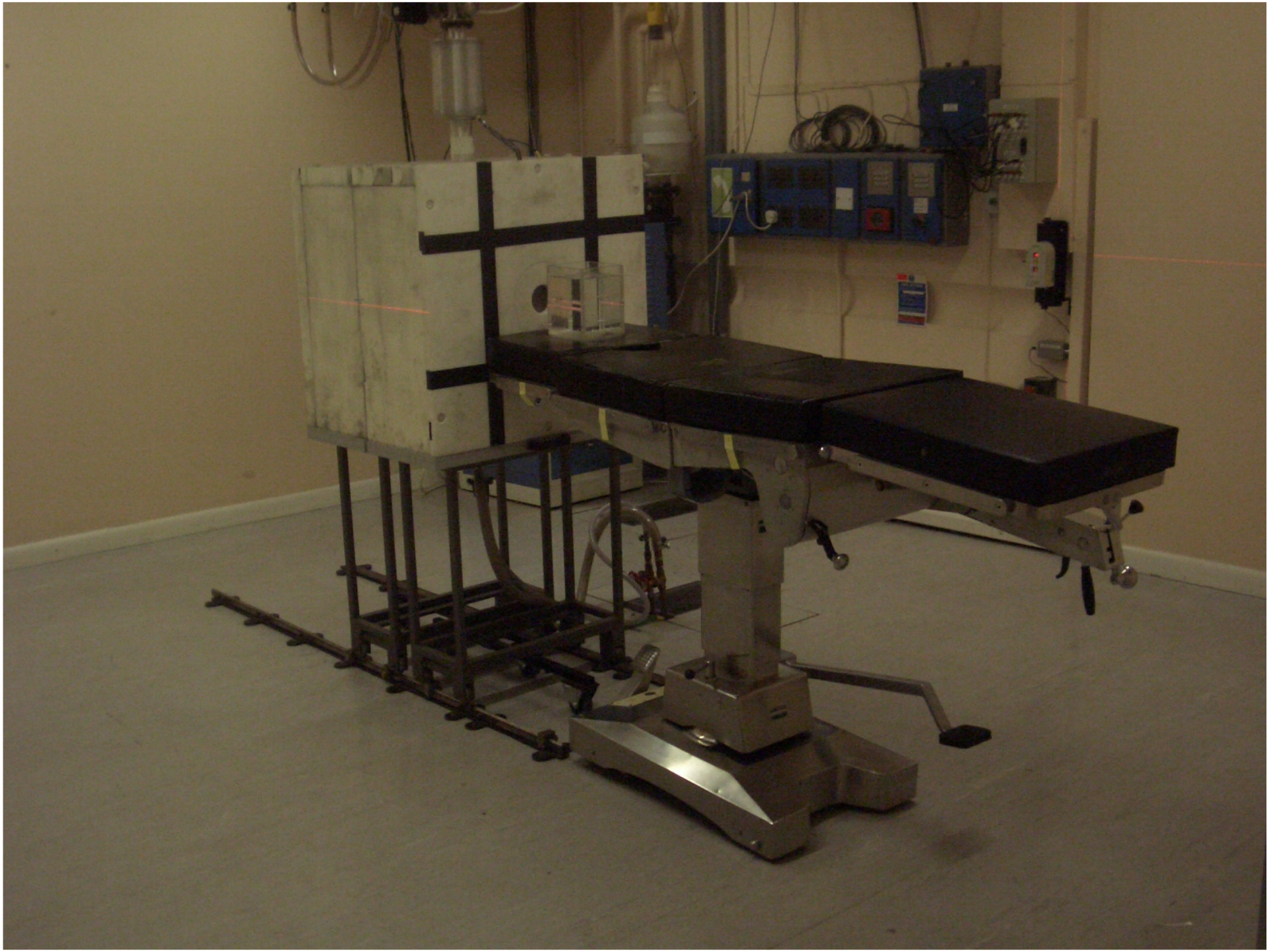
lead filter

heavy water cooling circuit

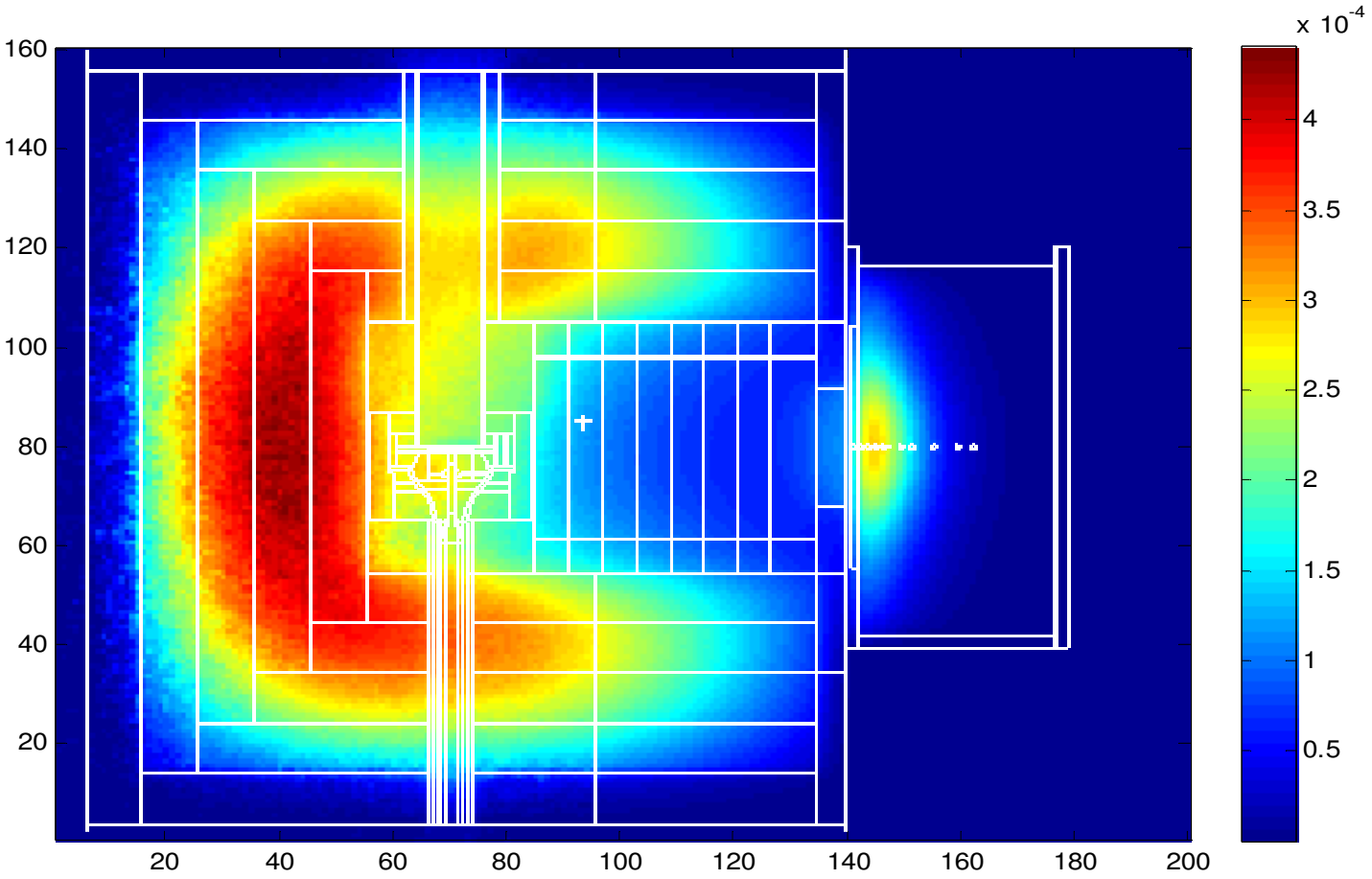
Neutron source is > 1 x 10^{12} s^{-1}

Li target during fabrication

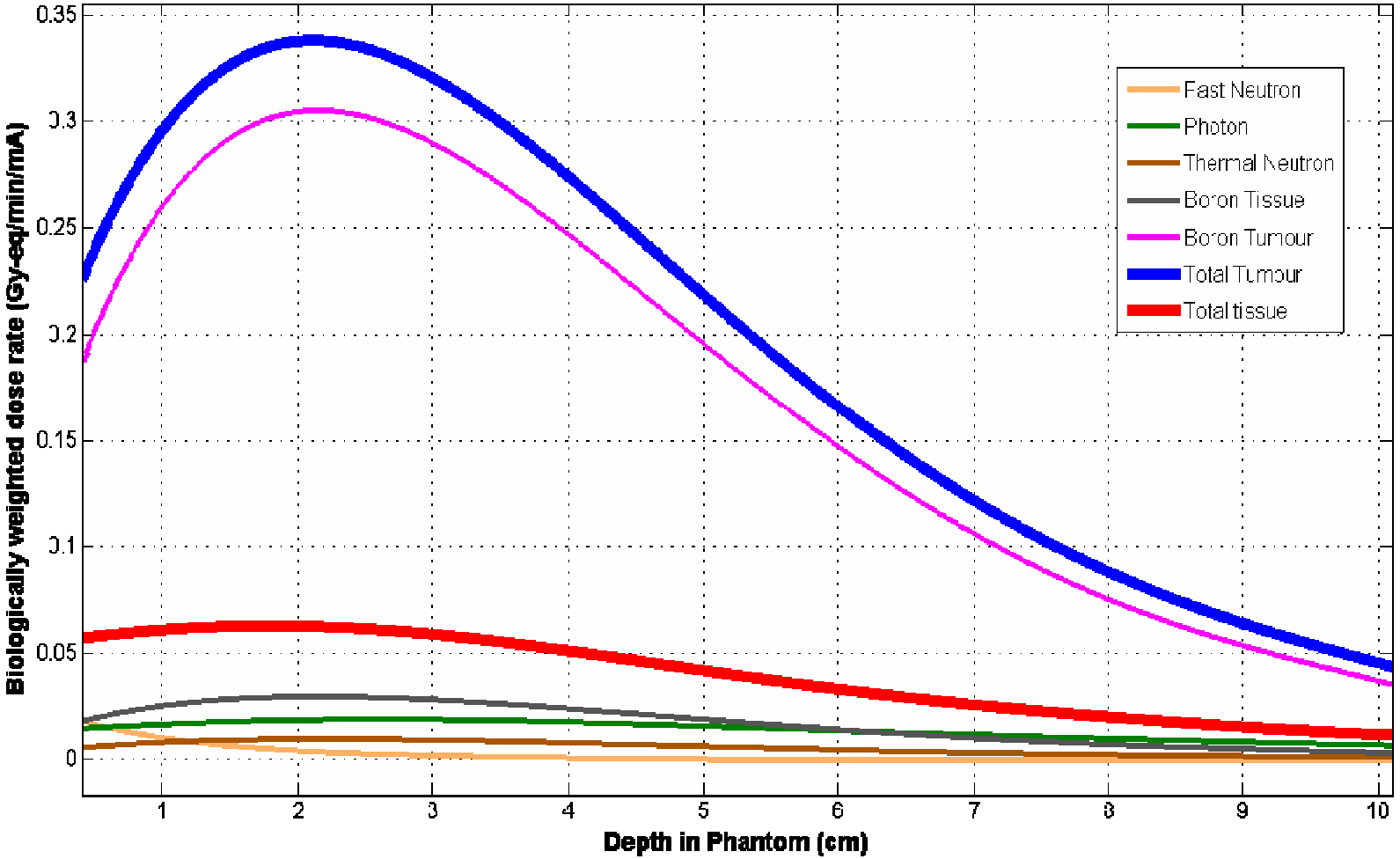




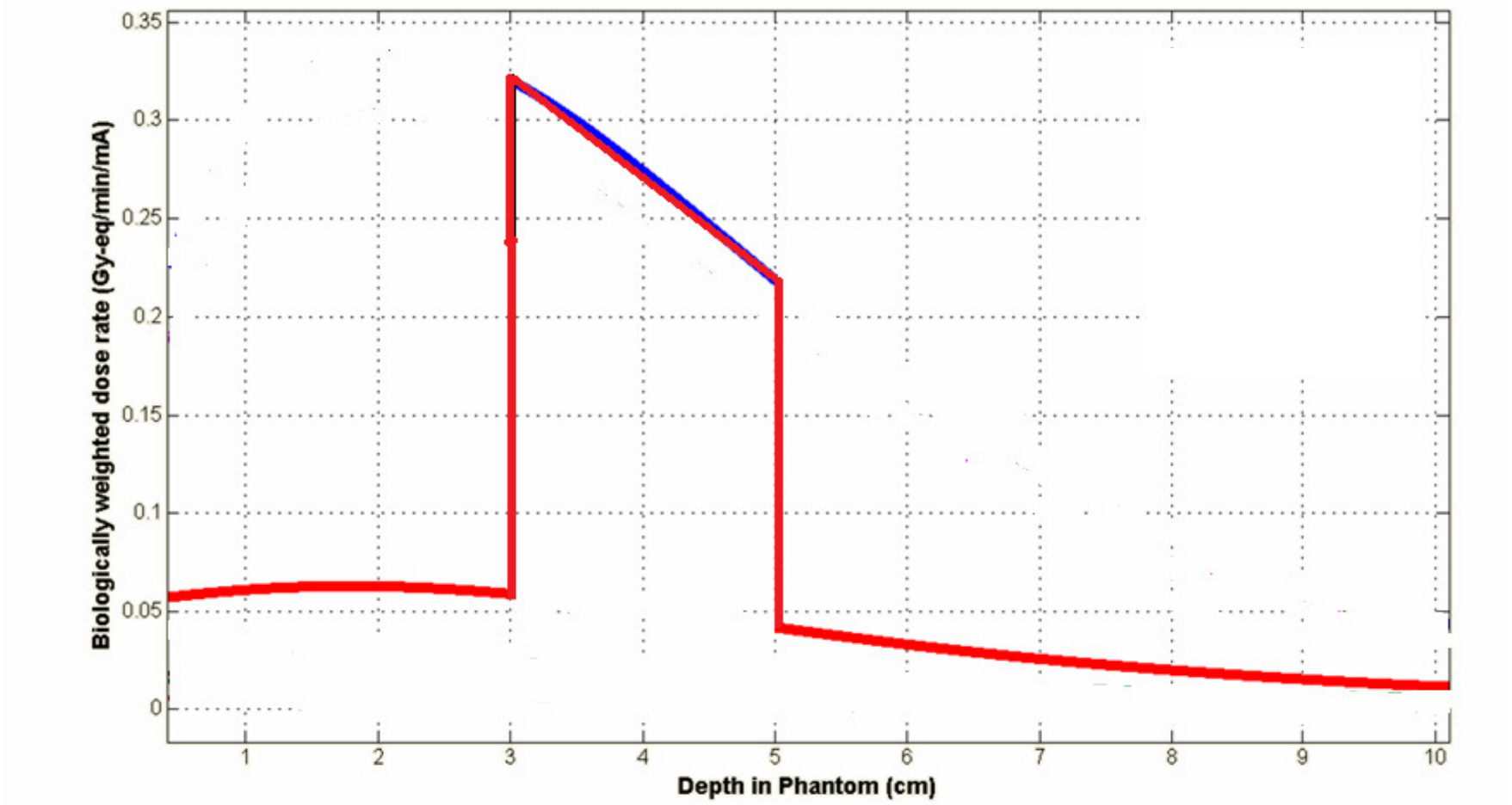
Thermal neutron intensity map



Doses to Tumour and normal cells



Dose to Tumour cells

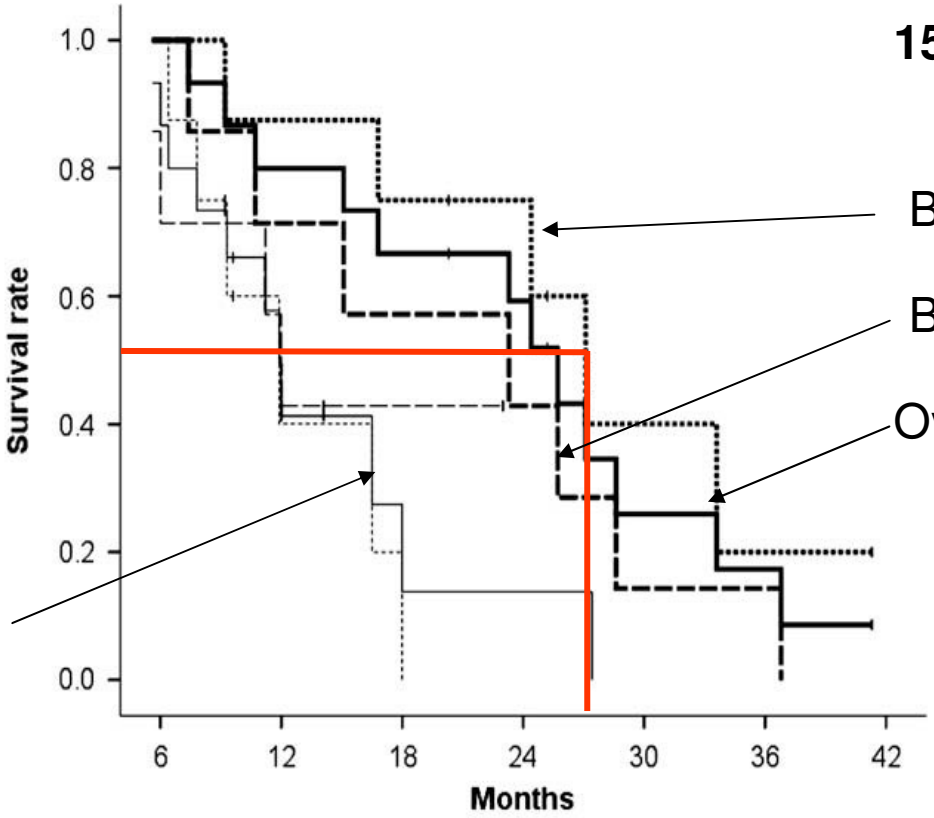


Clinical Experience (Approx data to 2008)

Facility	Approx. patients (compound)	Tumours treated
Japan (various)	>300 (BSH / BPA)	Mainly GBM
Brookhaven, NY	54 (BPA)	GBM
MIT, Boston	28 (BPA)	GBM, melanoma (extremity and brain)
Espoo, Finland	>200 (BPA)	GBM, Head and Neck
Studsvik, Sweden	52 (BPA)	GBM
Pavia, Italy	2 (BPA)	Metastases in liver (ex -vivo)
Petten, Netherlands	34 (BSH)	GBM, melanoma mets in brain
Rez, Czech Republic	5 (BSH)	GBM
Barriloche, Argentina	7 (BPA)	Melanoma of skin

BNCT Clinical Results from Tsukuba

15 patients only



BNCT + XRT

BNCT alone

Overall Survival Time

Time to progression

BNCT for glioblastoma

Boron neutron capture therapy for newly diagnosed glioblastoma

Tetsuya Yamamoto [a,*], Kei Nakai [a], Teruyoshi Kageji [b], Hiroaki Kumada [c], Kiyoshi Endo [a], Masahide Matsuda [a], Yasushi Shibata [a], Akira Matsumura [a]

[a] *Department of Neurosurgery, University of Tsukuba, Tsukuba City, Japan*
[b] *Department of Neurosurgery, Tokushima University, Japan*
[c] *Department of Research Reactor and Tandem Accelerator, Japan Atomic Energy Agency, Japan*

Radiotherapy and Oncology 91 (2009) 80–84

Glioblastoma Multiforme
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Walker et al. J Neurosurg 49 (1978) **333-343**

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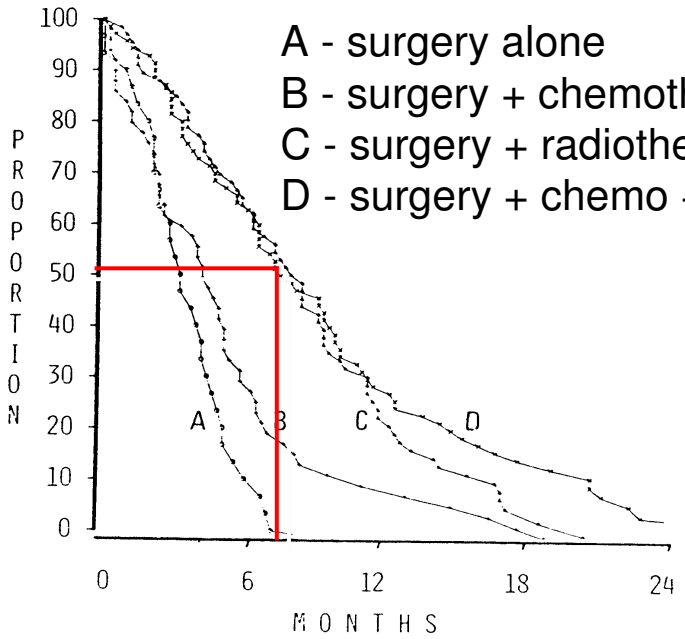

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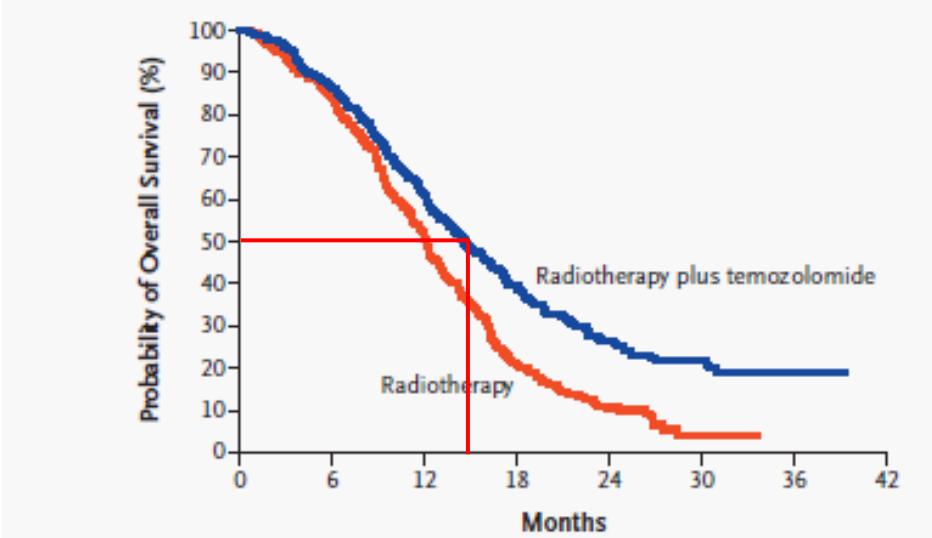

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Collaborations and Acknowledgements

UHB Trust: Prof Alun Beddoe, Drs Cecile Wojnecki and Richard Hugtenburg (now Swansea Uni), Dr Spyros Manolopoulos (ex STFC)

University of Birmingham: Profs David Parker and Garth Cruickshank, Drs Monty Charles and Andy Mill

University of Oxford: Dr Mark Hill, Prof Bleddyn Jones

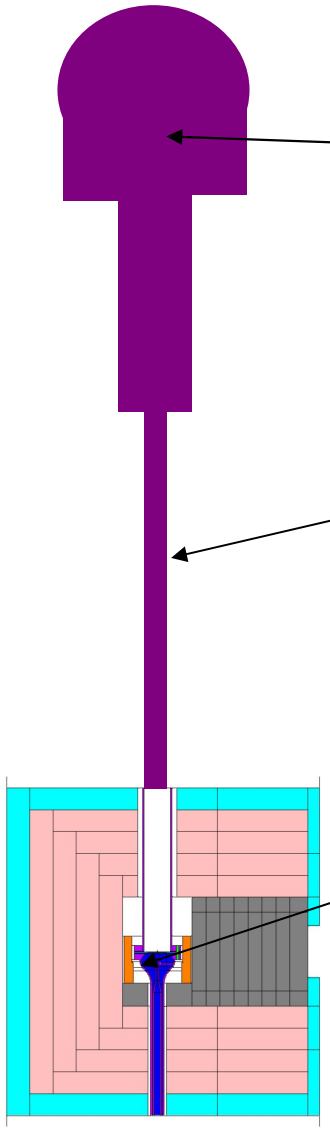
PhD students: Zamir Ghani, Ben Phoenix

Funding bodies, EPSRC, CR-UK, UHB Charities

Critical steps in developing a clinical facility

- Complete P-K study and demonstrate a good understanding of BPA uptake mechanisms
- Improve the power and reliability of our neutron source (STR+FC CLASP proposal)
- Finalise the safety-case for MHRA and respond to queries as appropriate (approx 2 years)
- Funder and legal approvals for clinical trial
- Information paper for UHB Chief Exec in preparation (submission in Spring 2011)
- Formal partnership between UB and UHB?

Proposed Developments



Ion Source: Upgrade power supplies and diagnostics. Re-tune to be a better source of mass-1 protons

Refine beam transport system to minimise proton losses on apertures etc

Improve target cooling system via binary ice approach

Final thoughts (on BNCT)

- Binary therapies such as BNCT are aimed specifically at tumours which exhibit a high degree of infiltration into the surrounding healthy tissues
- BNCT is still at a very early stage of development (patient numbers < 1000)
- They require input from a wide range of scientific disciplines
- BNCT with BPA appears to offer potential as a therapeutic modality for glioblastoma
- New data may identify high LAT-1 expression as a marker of a resistant sub-group of tumours

- BNCT is ripe for investment and provides a great opportunity for the UK to take a lead
- Can we afford to miss this opportunity ? (as we did with particle therapy)

The Birmingham BNCT team

UHB Trust

- Profs Alun Beddoe and Bleddyn Jones (now Oxford), Drs Cecile Wojnecki and Richard Hugtenburg (now Swansea Uni), Dr Allah Detta.

University of Birmingham

- Profs David Parker and Garth Cruickshank, Drs Monty Charles and Andy Mill

University of Oxford

- Dr Mark Hill (Prof John Hopewell)

CR-UK Pharmacokinetic Study

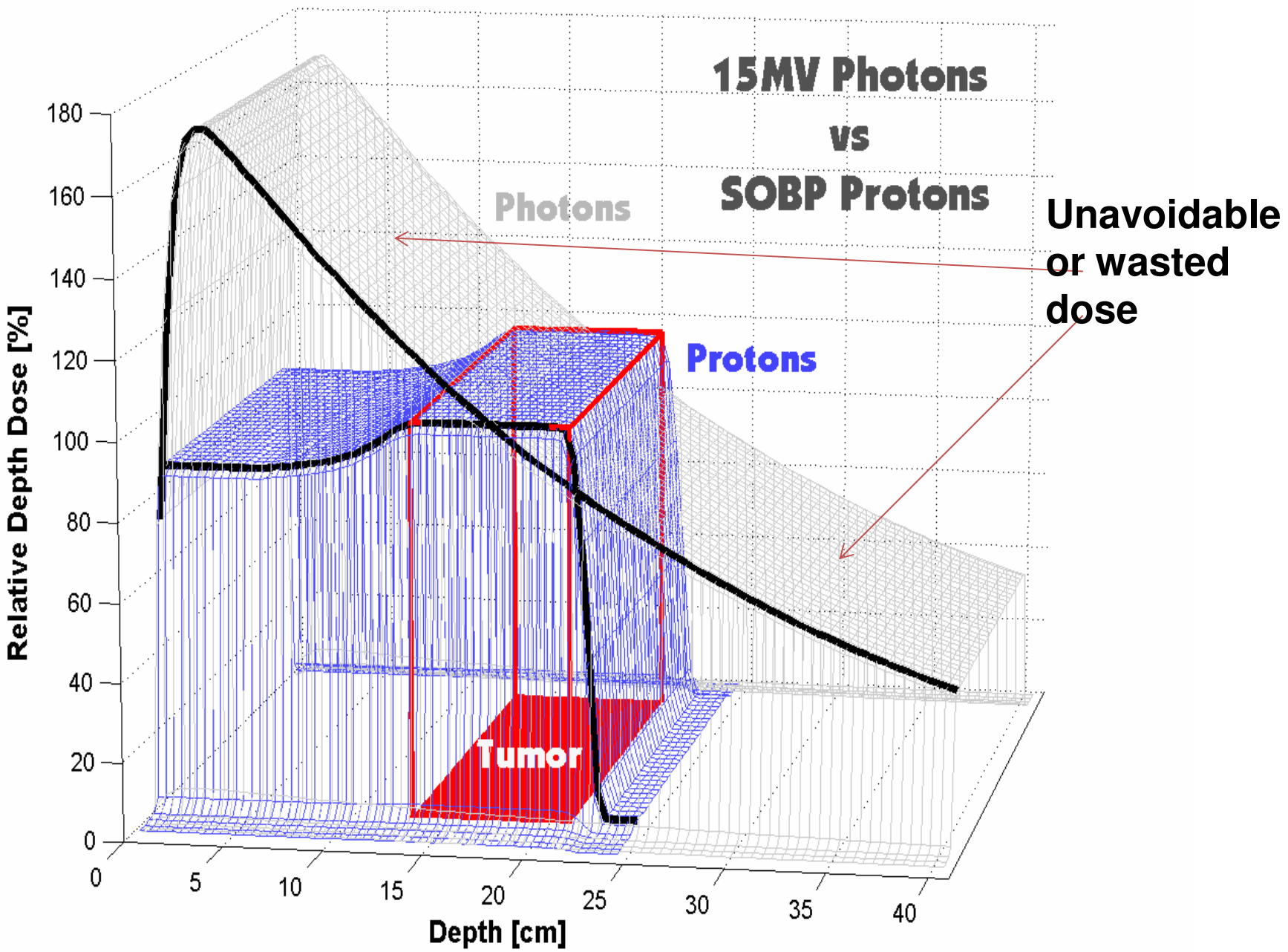
- Contributions from Strathclyde, Newcastle, Manchester and CR-UK

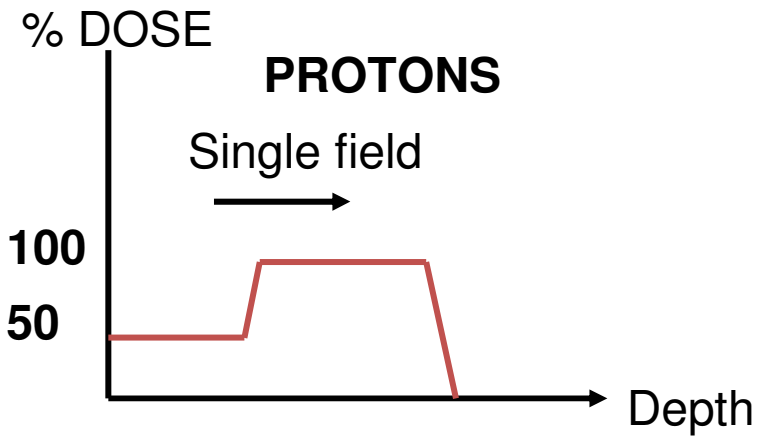
PhD students

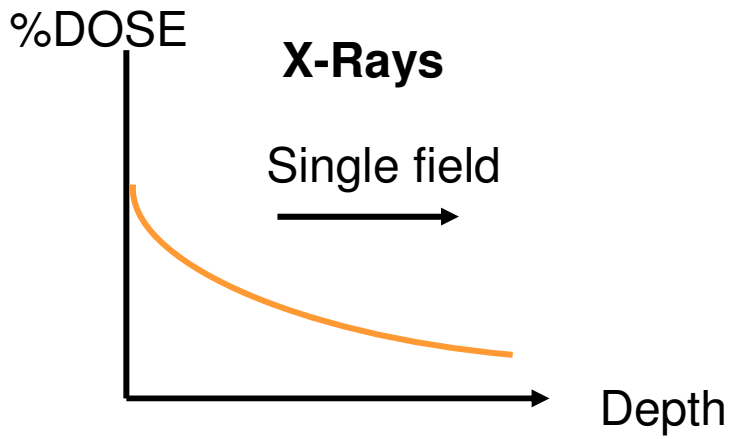
- Zamir Ghani and Ben Phoenix (plus approx 10 previous PhDs)

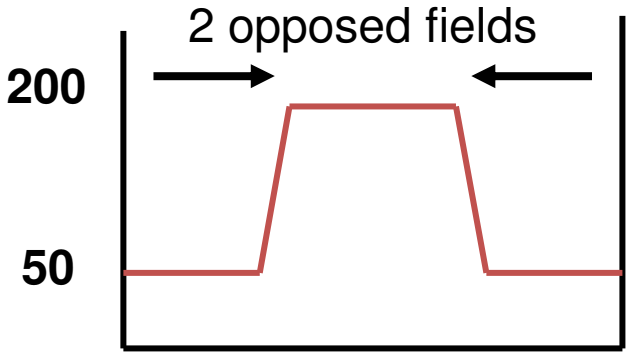
Protons Birmingham

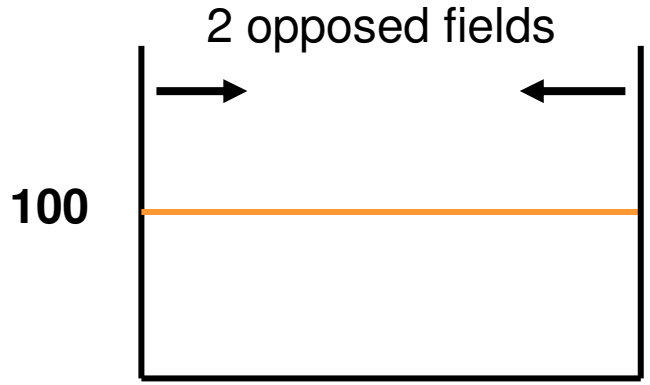
Care is best at the centre

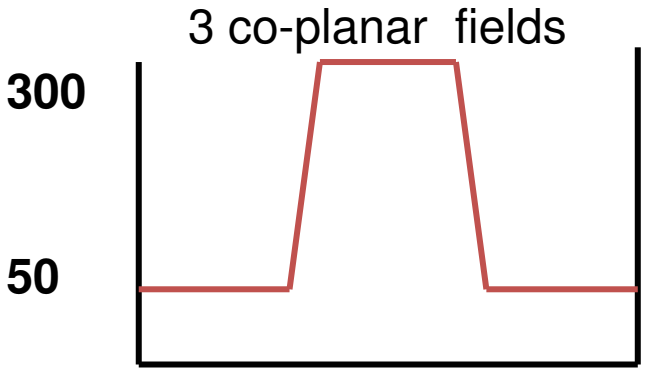

15MV Photons
vs
SOBP Protons
Photons
Protons
Tumor
Unavoidable or wasted dose
Relative Depth Dose [%]
Depth [cm]
0
20
40
60
80
100
120
140
160
180
0
5
10
15
20
25
30
35
40

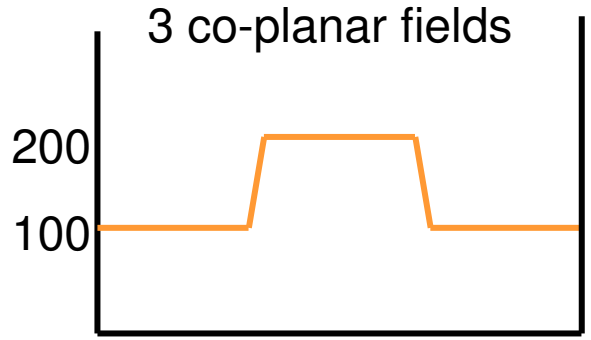






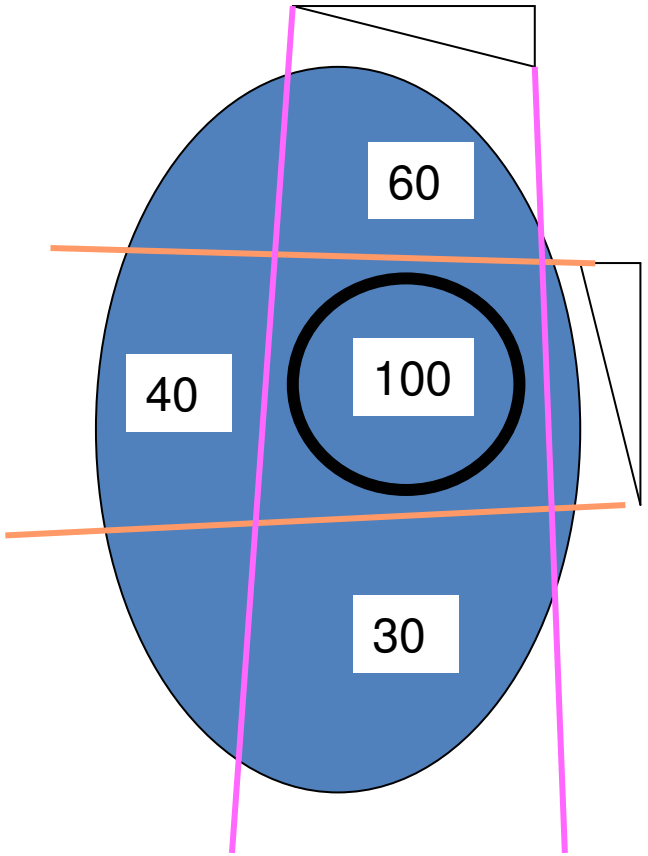




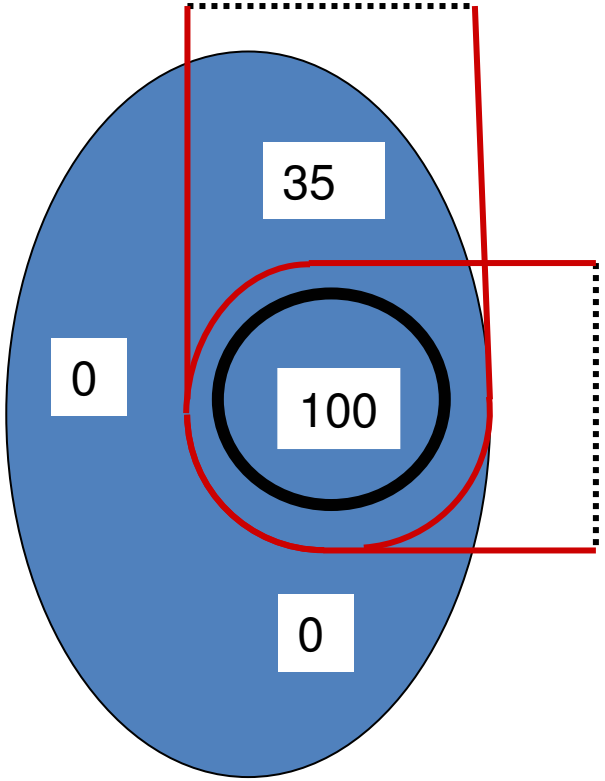


Slide Courtesy of Prof Bleddyn Jones

X-Rays



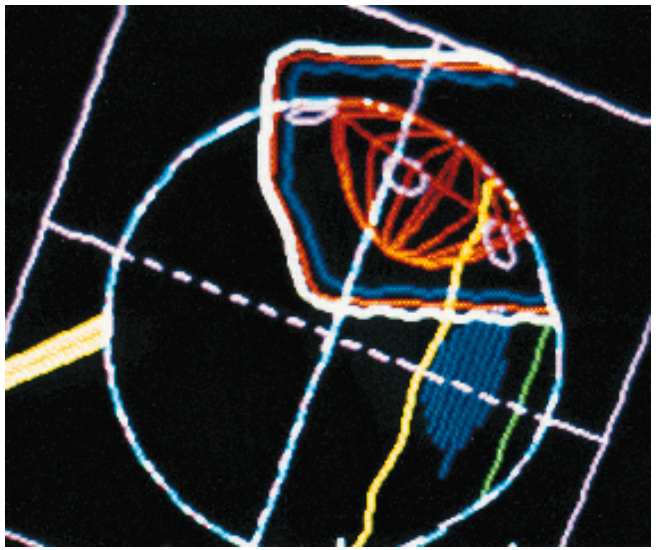
Protons/Ions



Slide Courtesy of Prof Bleddyn Jones

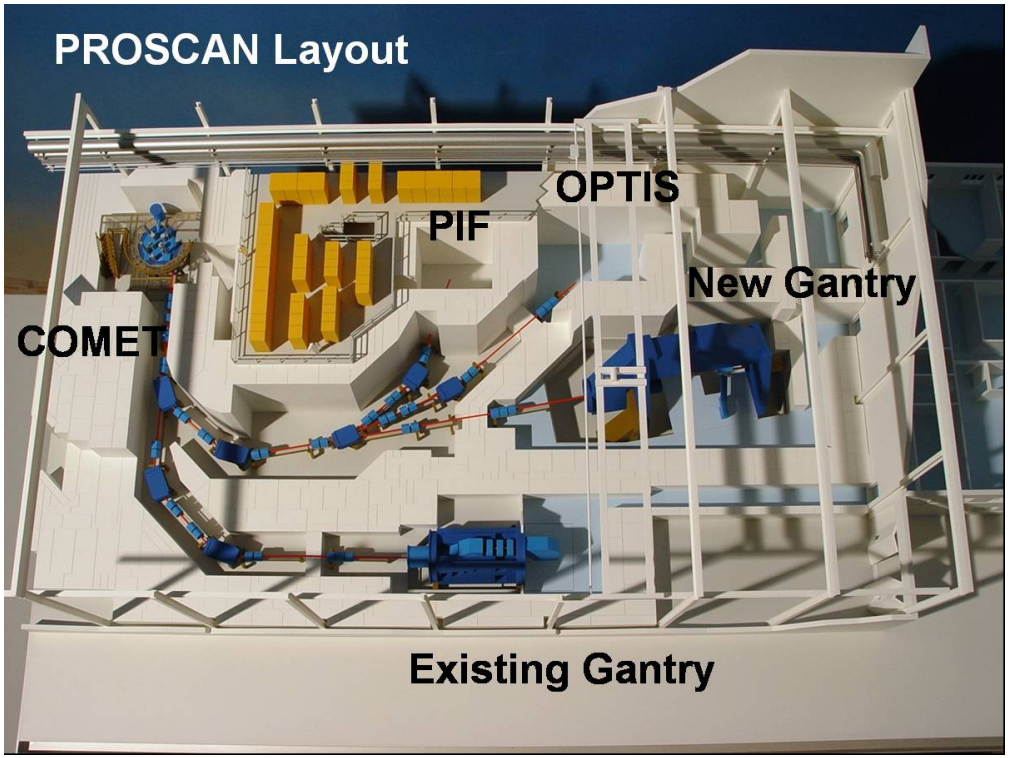
Proton therapy in UK: we already have it!

- World First: hospital based proton therapy at Clatterbridge, Liverpool, [converted fast neutron therapy facility].
- >1400 patients with ocular melanoma; local control >98%.
- First example of 3D treatment planning in UK
- Unsung success story of British Oncology.
- 62 MeV protons so eye tumours only

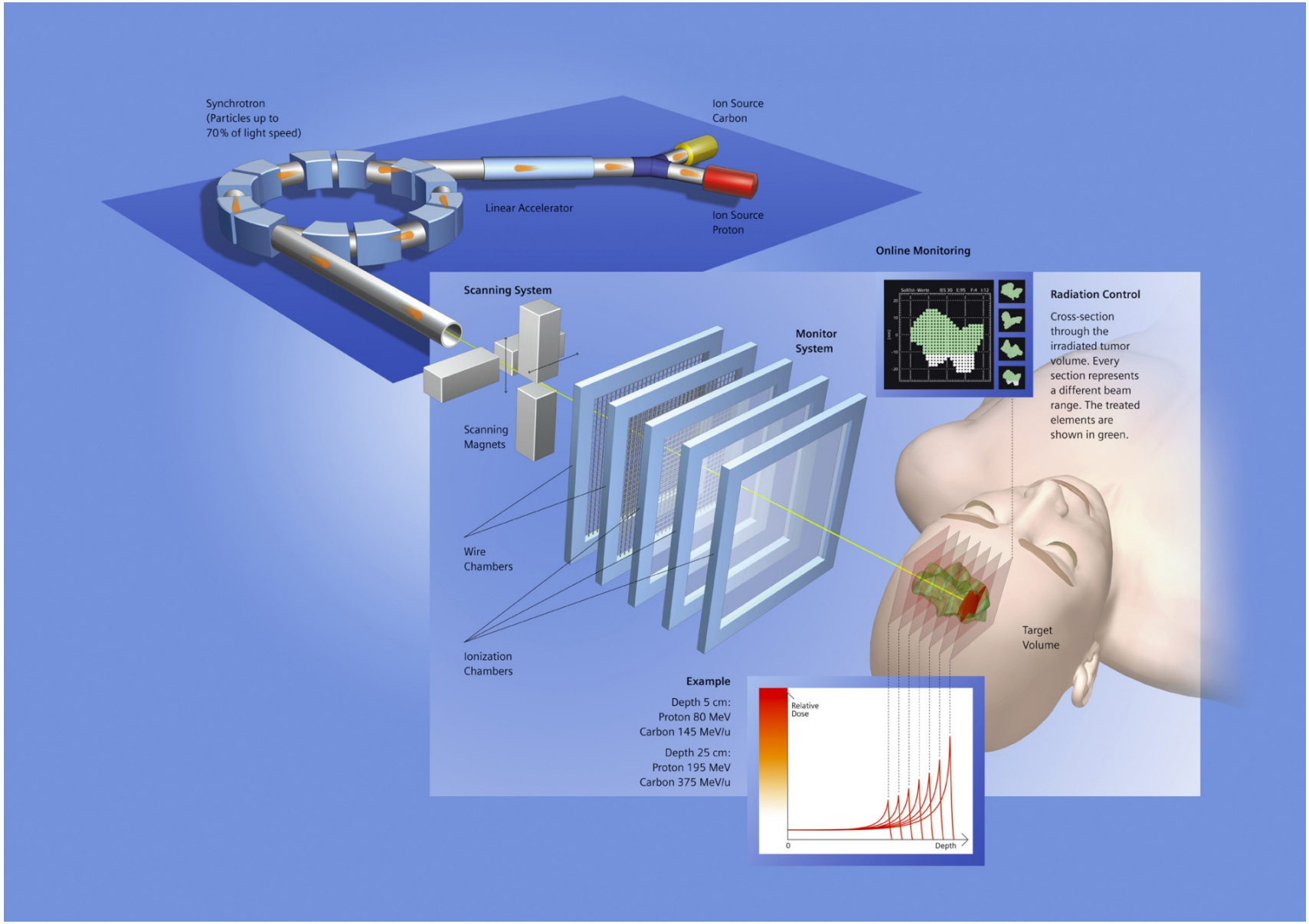


Paul Scherrer Institute

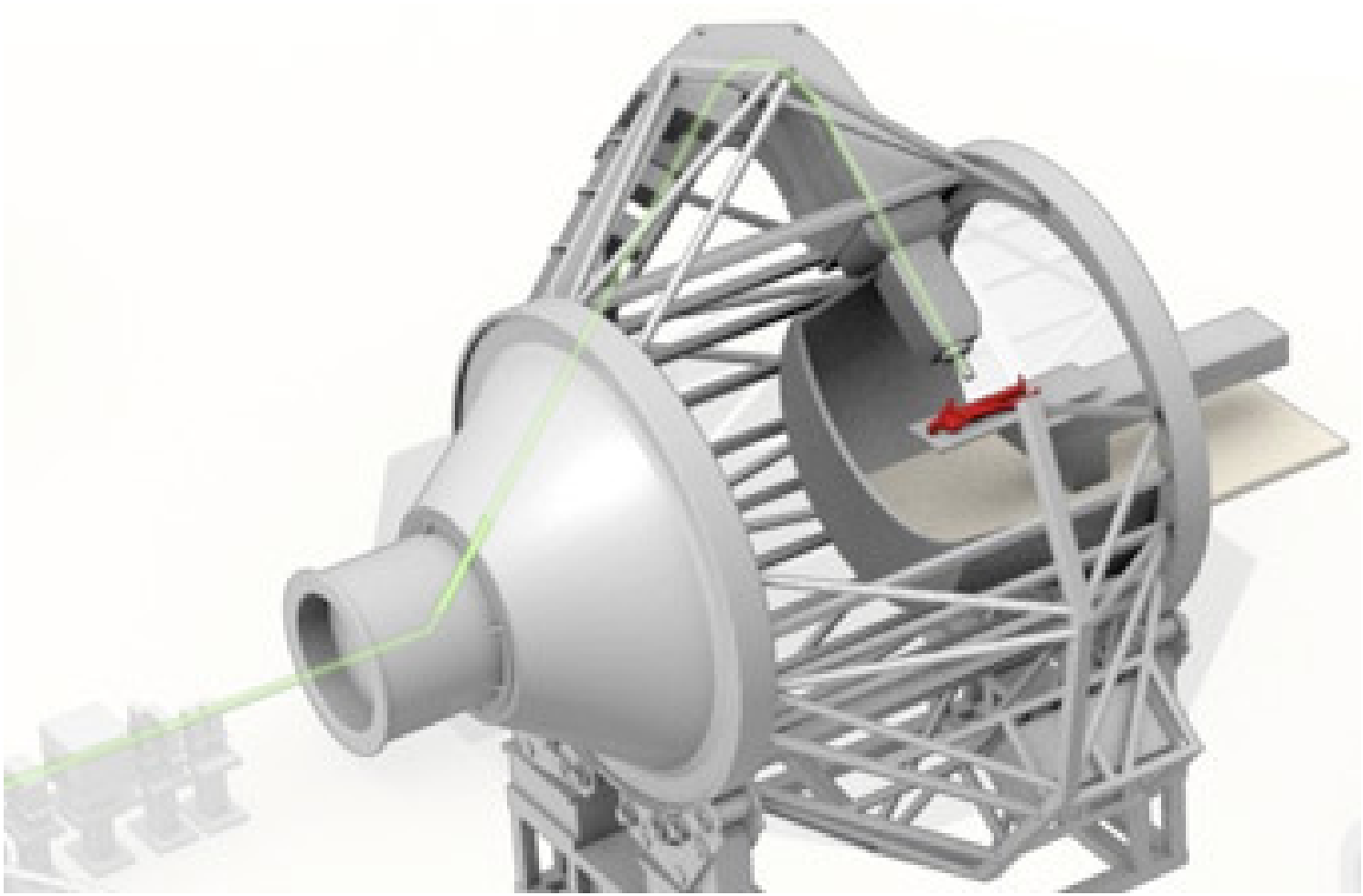
- Swiss National Research Lab
- Long-standing investment in proton therapy
- Major expansion in progress, with new cyclotron (250 MeV) and new treatment room

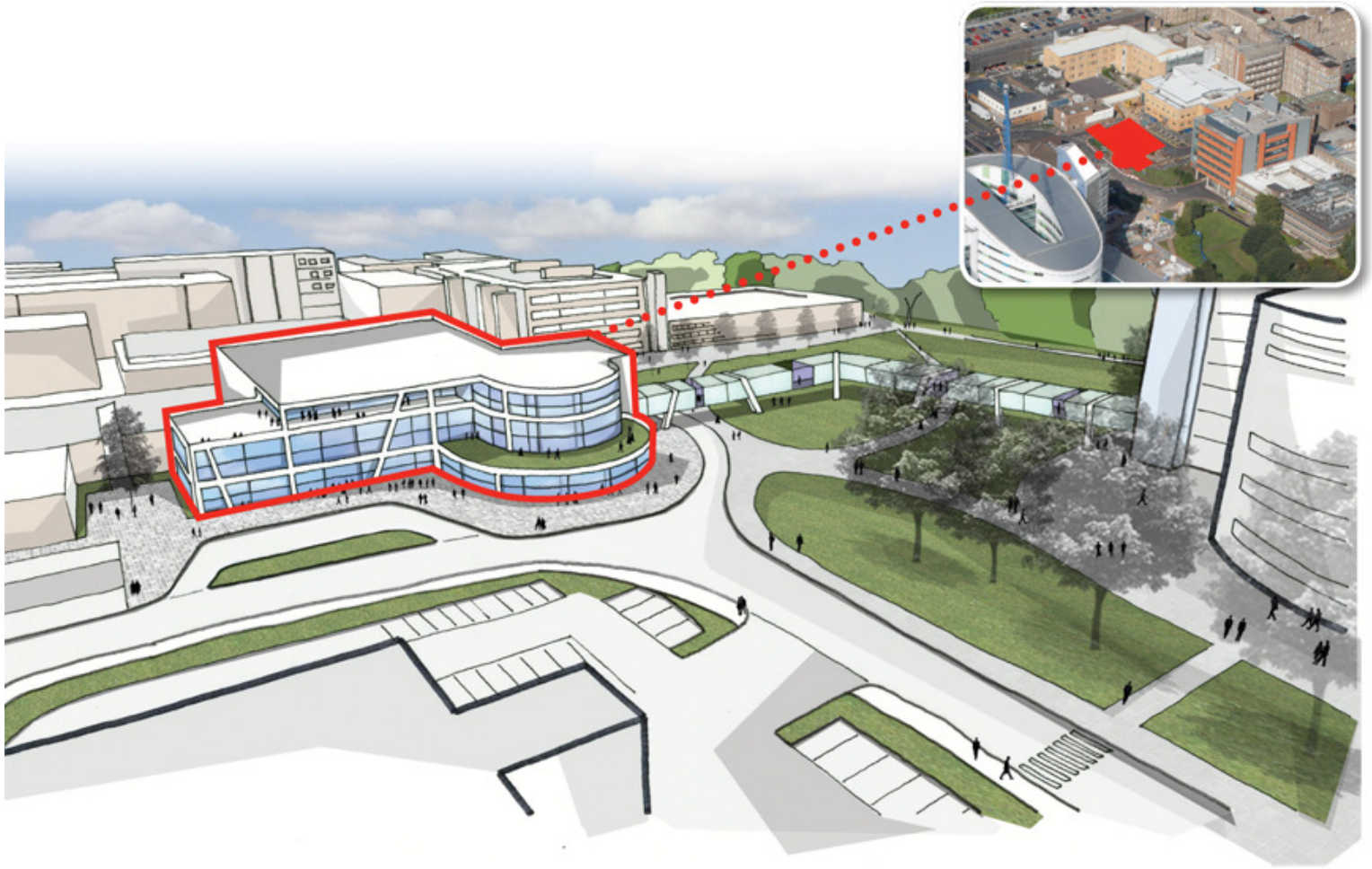


The Siemens synchrotron system



Proton Gantry – scale of a person





Queen Elizabeth Hospital Birmingham NHS
Part of University Hospitals Birmingham NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

The Royal Orthopaedic Hospital NHS
NHS Foundation Trust

Birmingham Children's Hospital NHS
NHS Foundation Trust

Protons Birmingham
Care is best at the centre

Optimal environment … continues to evolve

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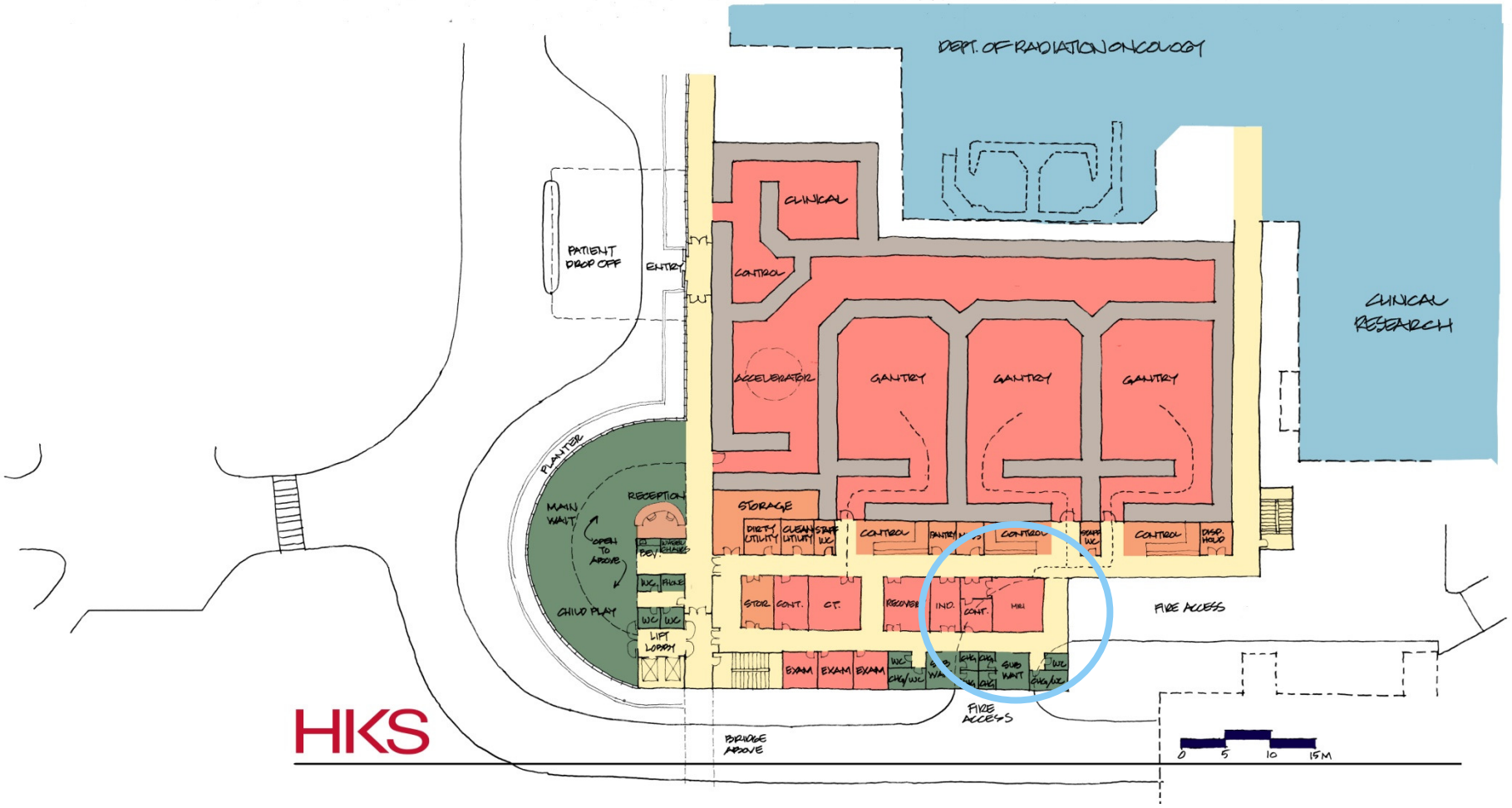
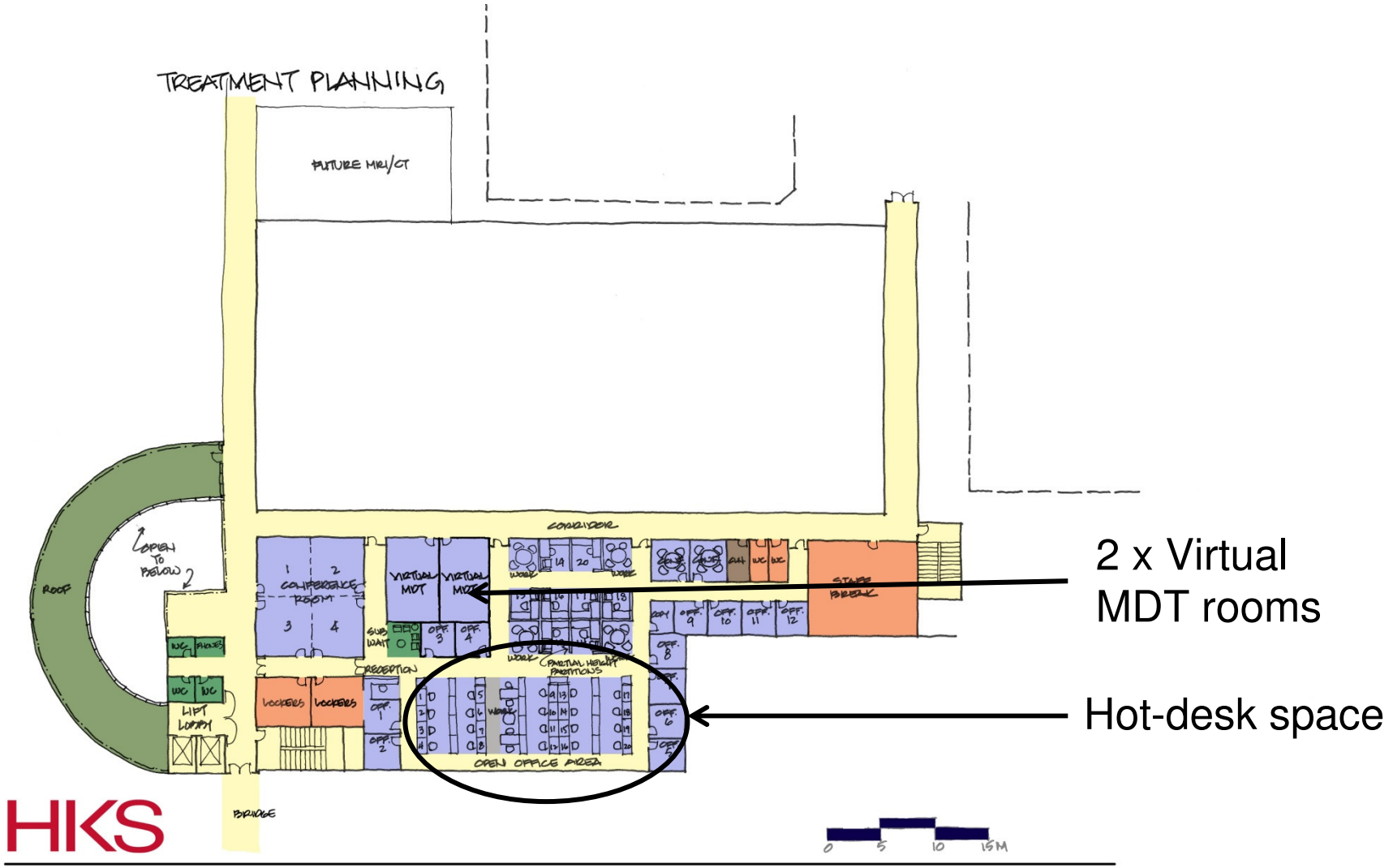
Proposed facility: Treatment Floor



One possible Configuration: First Floor



Second Floor

Paediatric Unit, managed by BCH

HKS

UK scene – latest news..

- 3 Trusts (UCLH, Christie and Birmingham) are “helping the DH with the development of their outline business case for the spending review”
- The choice appears to be between 2 or 3 centres.
- For patients and pathways, 3 is very much better than 2
- If there are 2, they will be London and Manchester
- If there is a 3rd, it will be in Birmingham

Protons Birmingham

Care is best at the centre