Clinical Proton Beam Therapy:

A look into the future

Richard A. Amos

Associate Professor of Proton Therapy
Translational Proton Therapy Physics Lead
Department of Medical Physics and Biomedical Engineering
University College London

r.amos@ucl.ac.uk

UK Accelerator Institutes Seminar Series

February 2nd, 2023

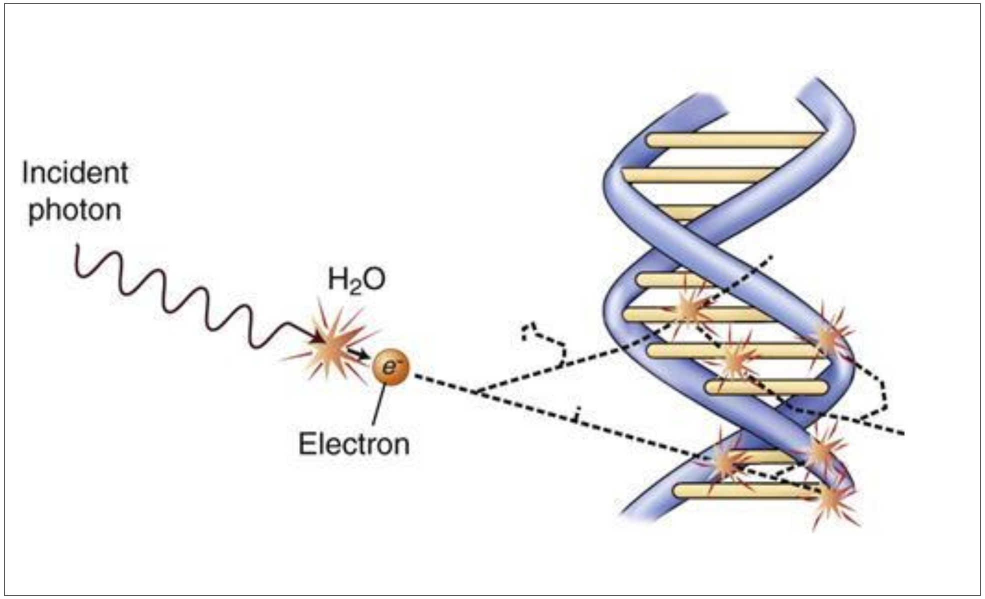
Significance of radiotherapy

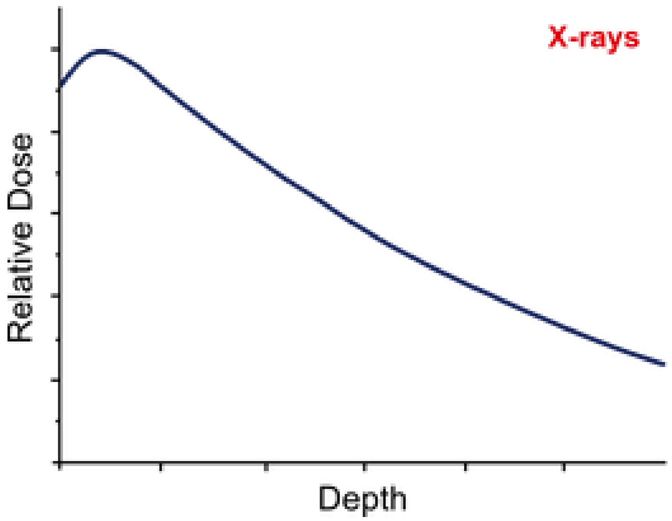
The Royal College of Radiologists (RCR) estimates that, of those cancer patients who are cured:

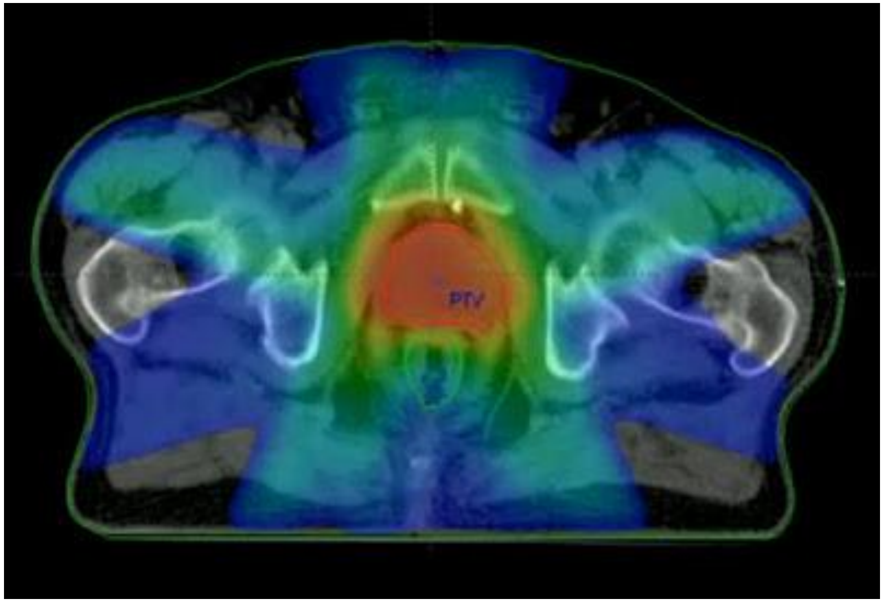
⇨ 49% are cured by surgery

⇨ 40% are cured by radiotherapy

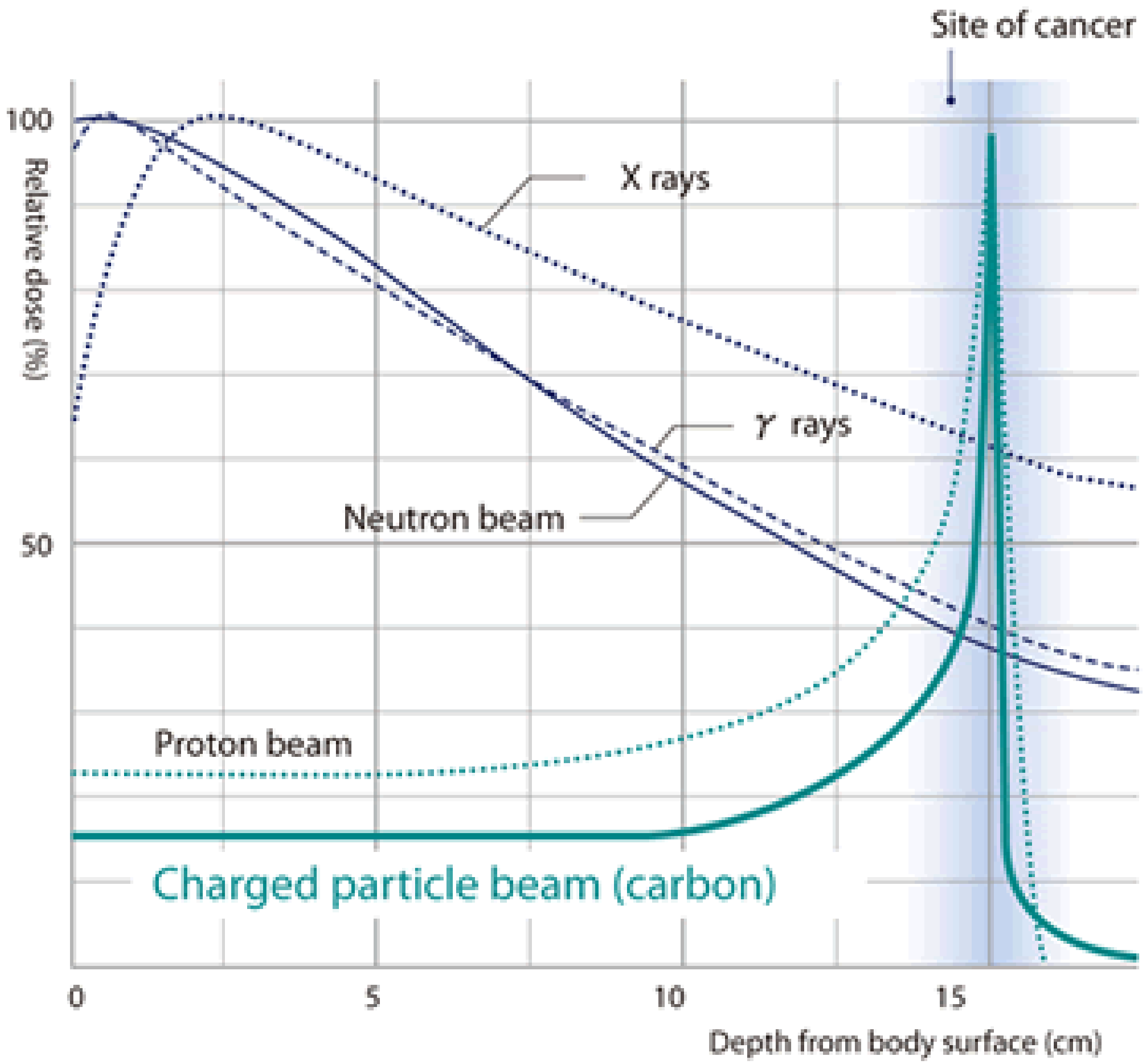
⇨ 11% are cured by chemotherapy

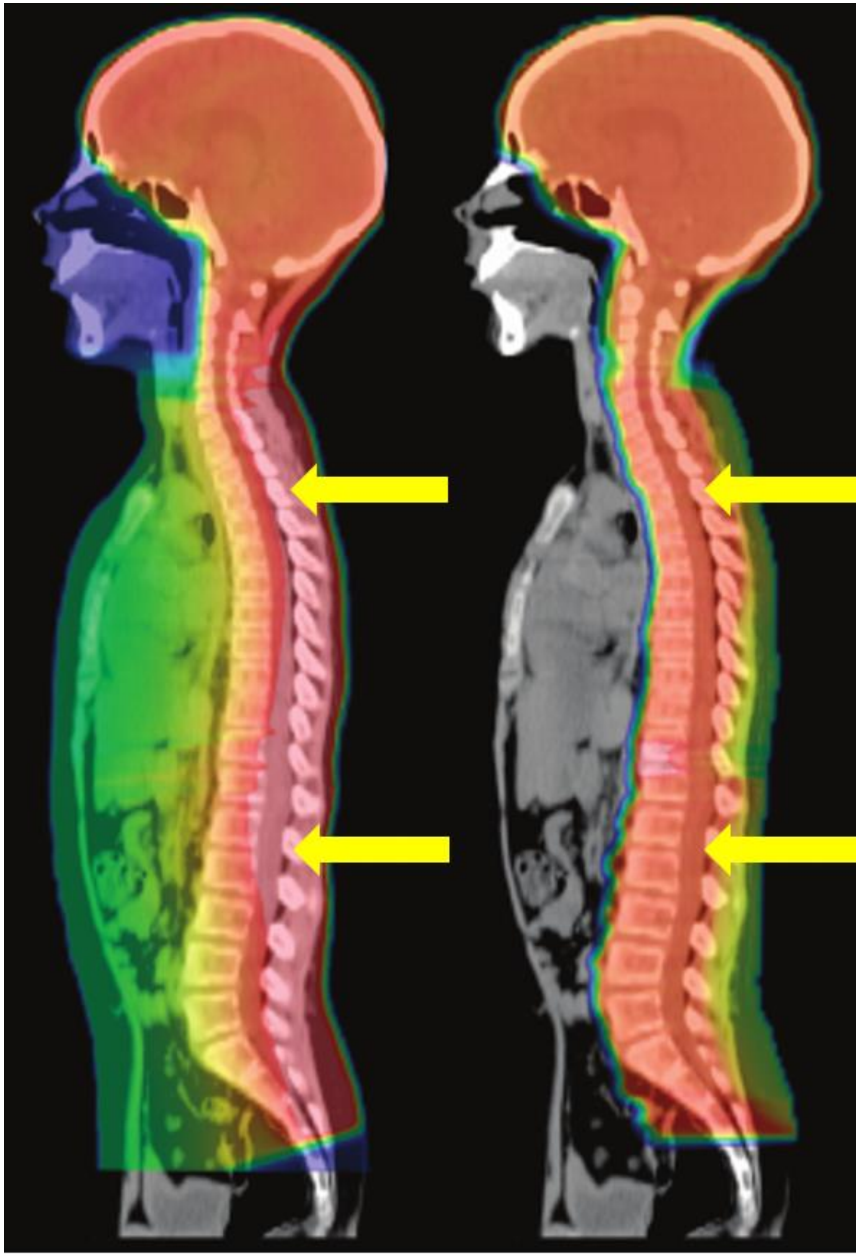

Incident photon
H_2O
e^-
Electron


X-rays
Relative Dose
Depth


PTV

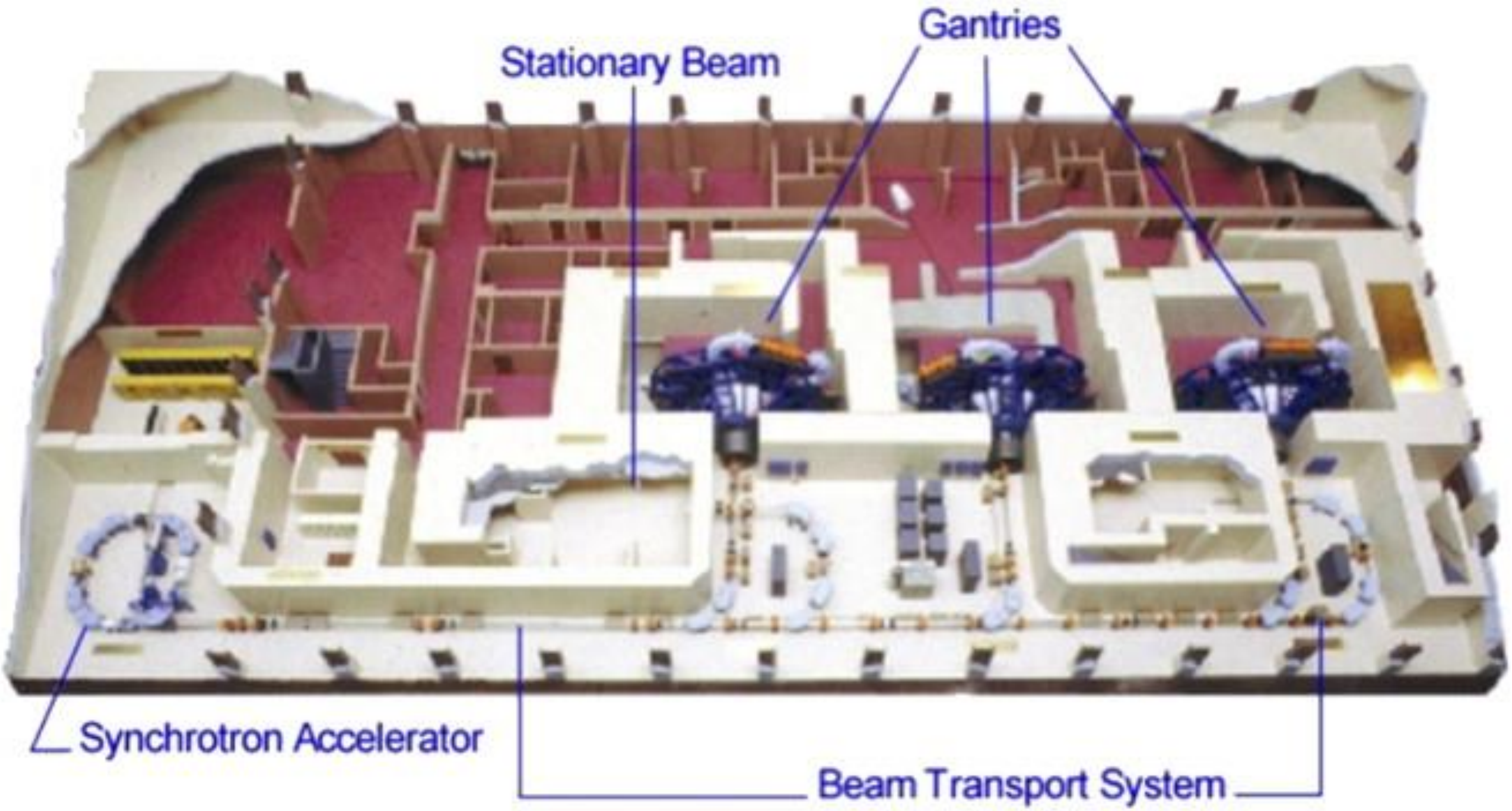
Rationale for proton beam radiotherapy





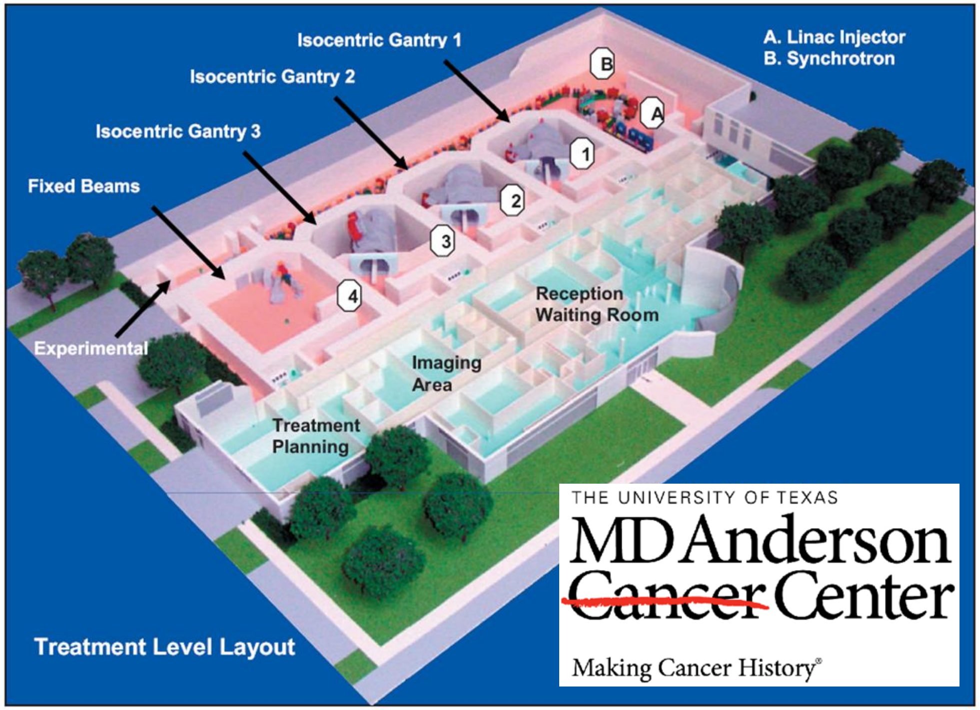
Photons

Protons



- **250 MeV synchrotron** developed in collaboration with Fermi National Accelerator Laboratory
- 3 gantries (**passive scattering**)
- 1 fixed clinical beamline (passive scattering)
- 1 fixed ocular beamline (passive scattering)
- 1 fixed experimental beamline (passive scattering)

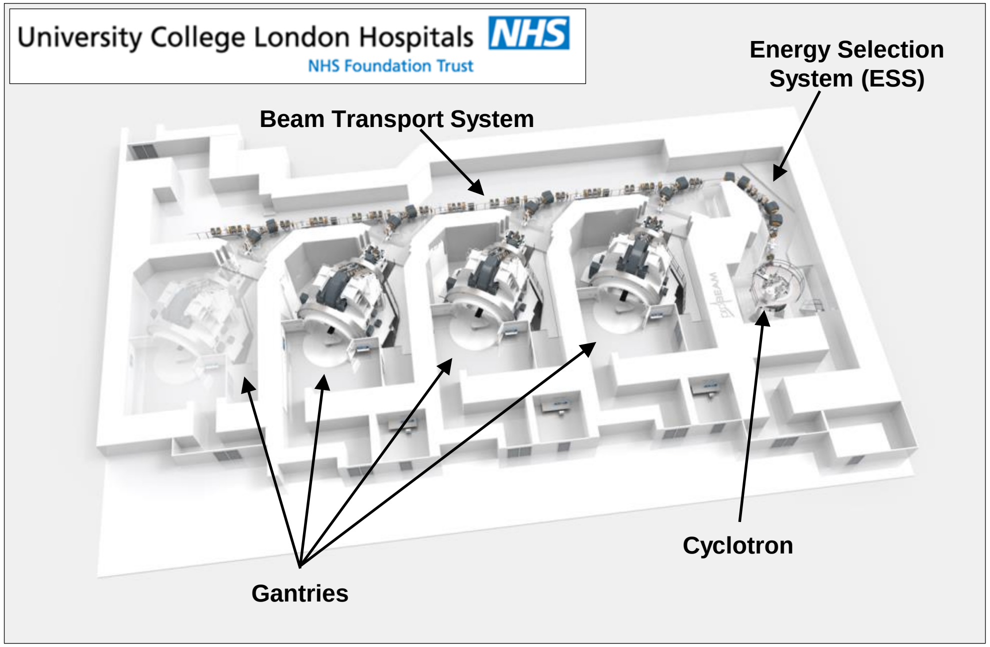
World's first hospital-based proton therapy facility - clinically operational since 1990



250 MeV synchrotron (Hitachi PROBEAT system)

- 3 gantries (2 **passive scattering** + 1 ***pencil beam scanning***)
- 1 fixed clinical beamline (passive scattering)
- *1 fixed ocular beamline (passive scattering)*
- *1 fixed experimental beamline (passive scattering)*

Clinically operational since 2006



250 MeV Cyclotron (Varian ProBeam system)

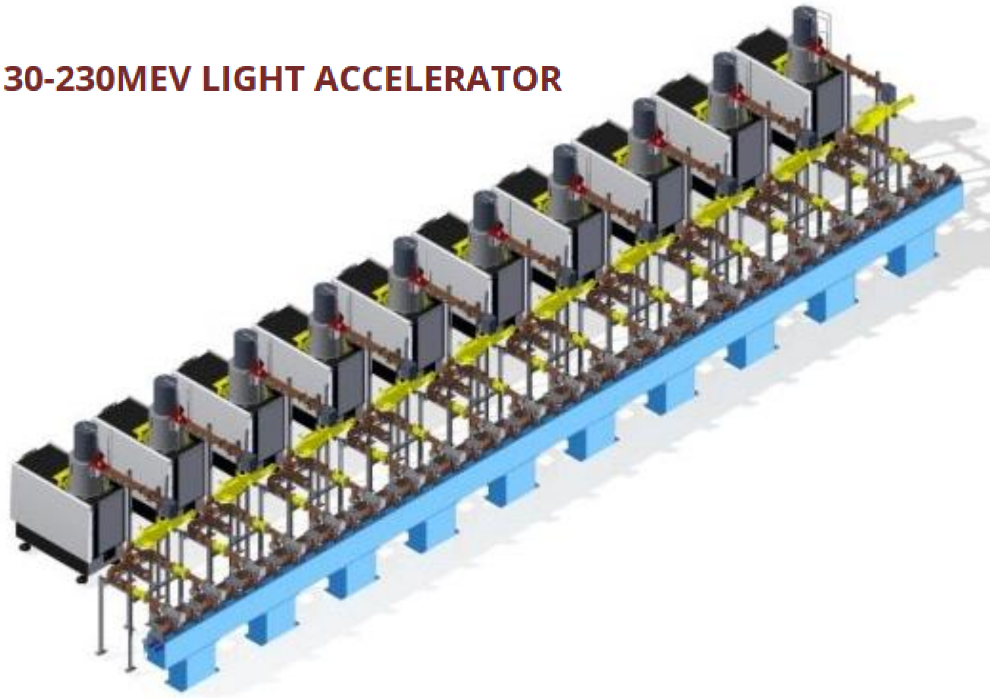
- 4 gantries (***pencil beam scanning***)

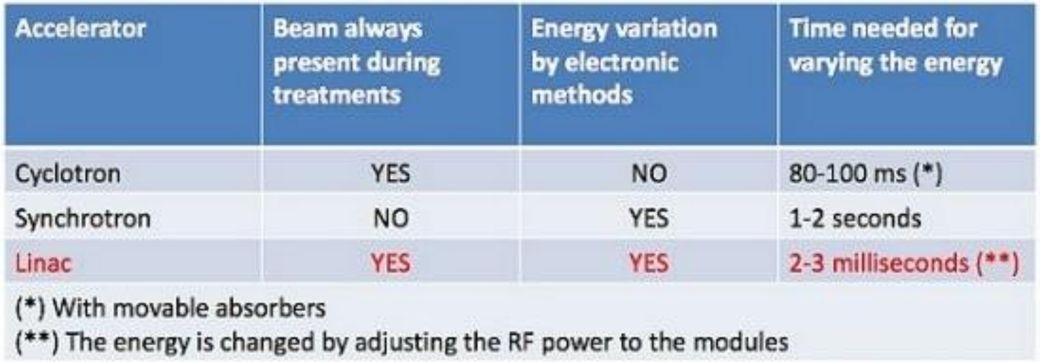
Clinically operational since 2021

Single-room proton therapy system:

Gantry-mounted 250 MeV synchrocyclotron

30-230MEV LIGHT ACCELERATOR





Accelerator	Beam always present during treatments	Energy variation by electronic methods	Time needed for varying the energy
Cyclotron	YES	NO	80-100 ms (*)
Synchrotron	NO	YES	1-2 seconds
Linac	YES	YES	2-3 milliseconds (**)

(*) With movable absorbers
(**) The energy is changed by adjusting the RF power to the modules

Capital cost:

- Increased access to proton therapy for patients
  - More clinical data
- Increased availability of research facilities
  - Detector development
  - Radiobiological data
  - ….

Compact/modularity:

- Construction and installation
- Ease of maintenance

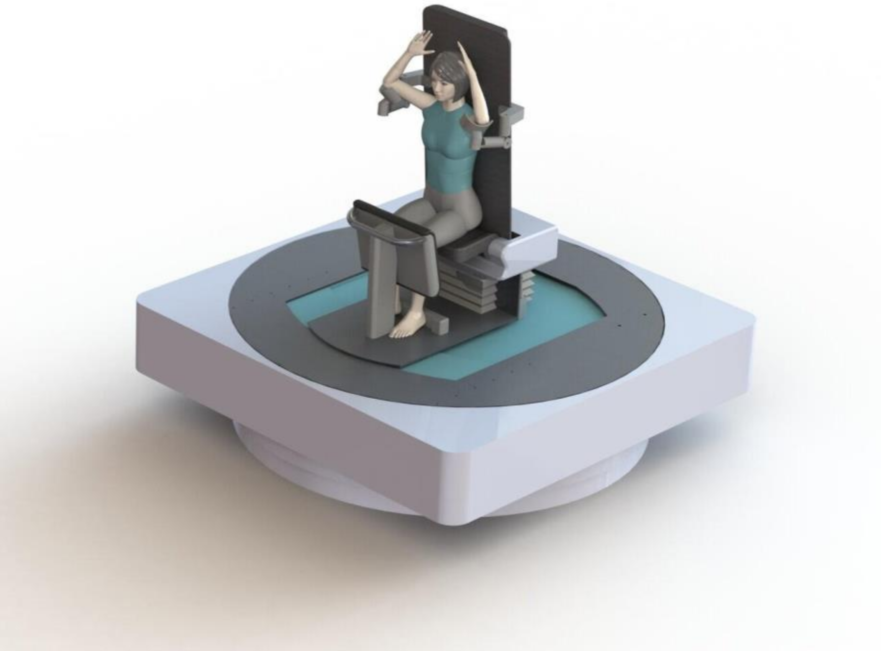
Reduced shielding:

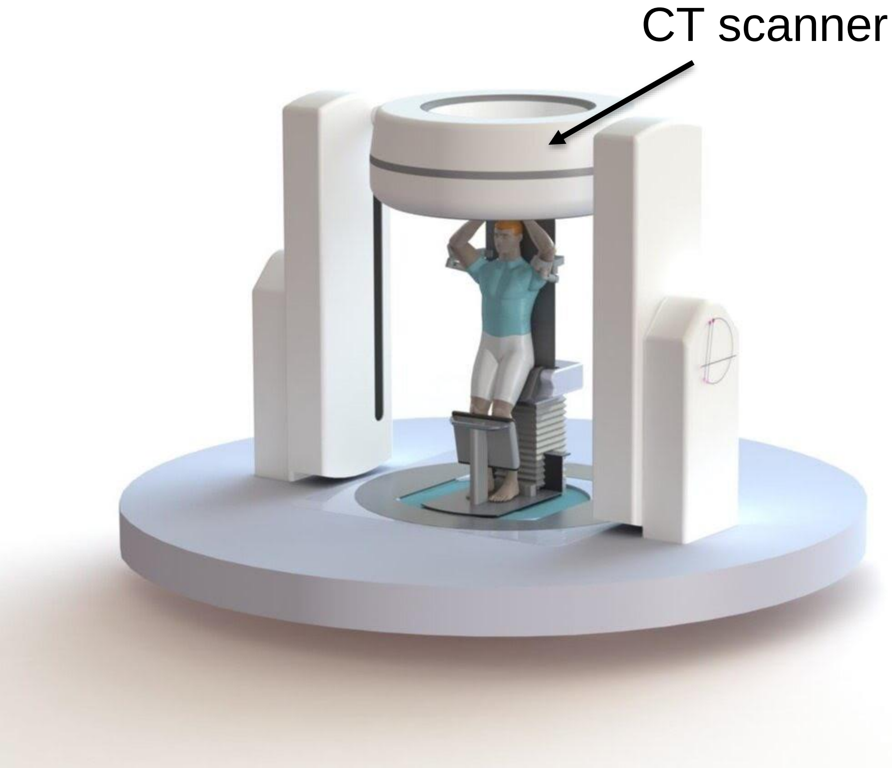
- Space and cost

Performance characteristics:

- Motion mitigation techniques
- Fast adaptive delivery
- …..

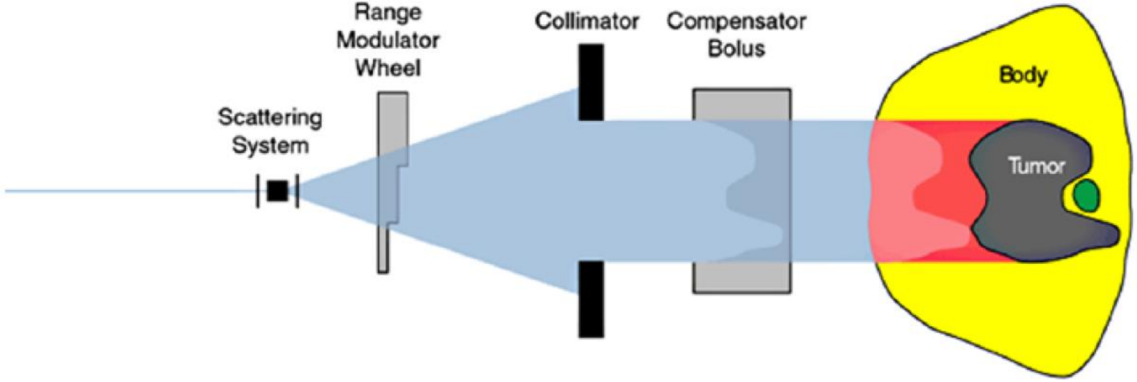
Patient treatment in seated position?



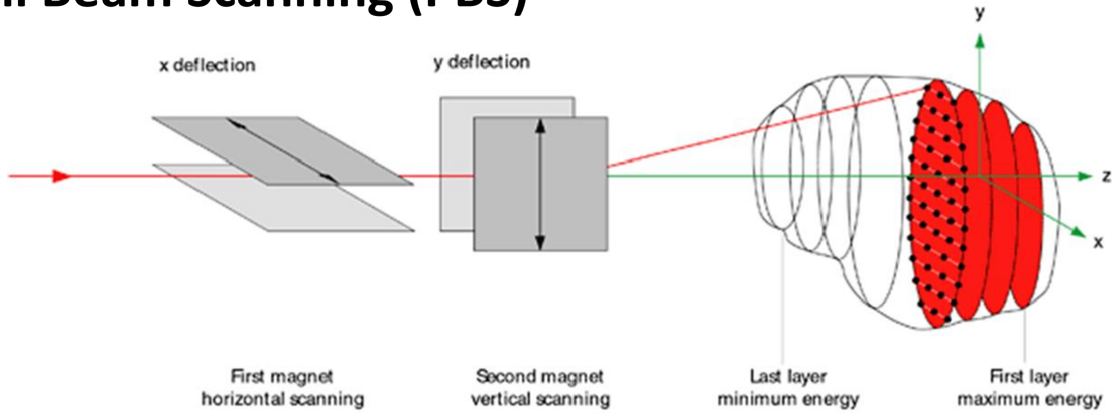


Beam Delivery System

Passive Scattering



Pencil Beam Scanning (PBS)



Advantages of scanned beam delivery

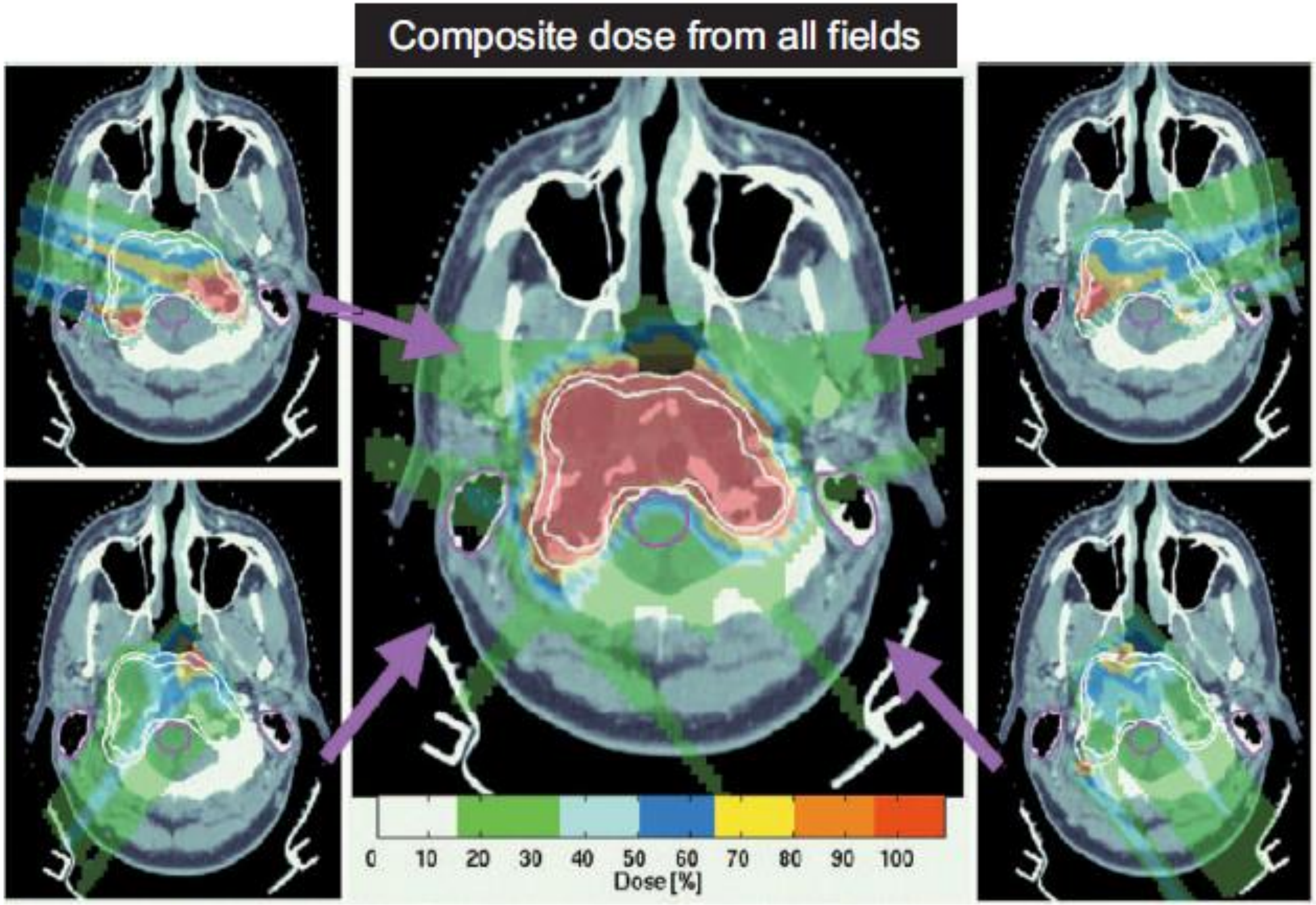
1. Can "paint" any physically possible dose distribution.
2. Uses protons very efficiently as compared to passive scattering in which more than 50% of protons have to be "thrown away".
3. Generally, requires no patient-specific hardware.
4. The neutron background is substantially reduced as a result of points (2) and (3).
5. Allows the implementation of IMRT with protons – termed *intensity-modulated proton therapy (IMPT)*

Disadvantages of scanned beam delivery

1. The need to overcome *"interplay effects"* (Bortfeld, 2002)* induced by organ motion.

**Bortfeld T et al. (2002) Effects of intra-fraction motion on IMRT dose delivery: Statistical analysis and simulation. Phys Med Biol 47:2203-2220*

Intensity Modulated Proton Therapy (IMPT)

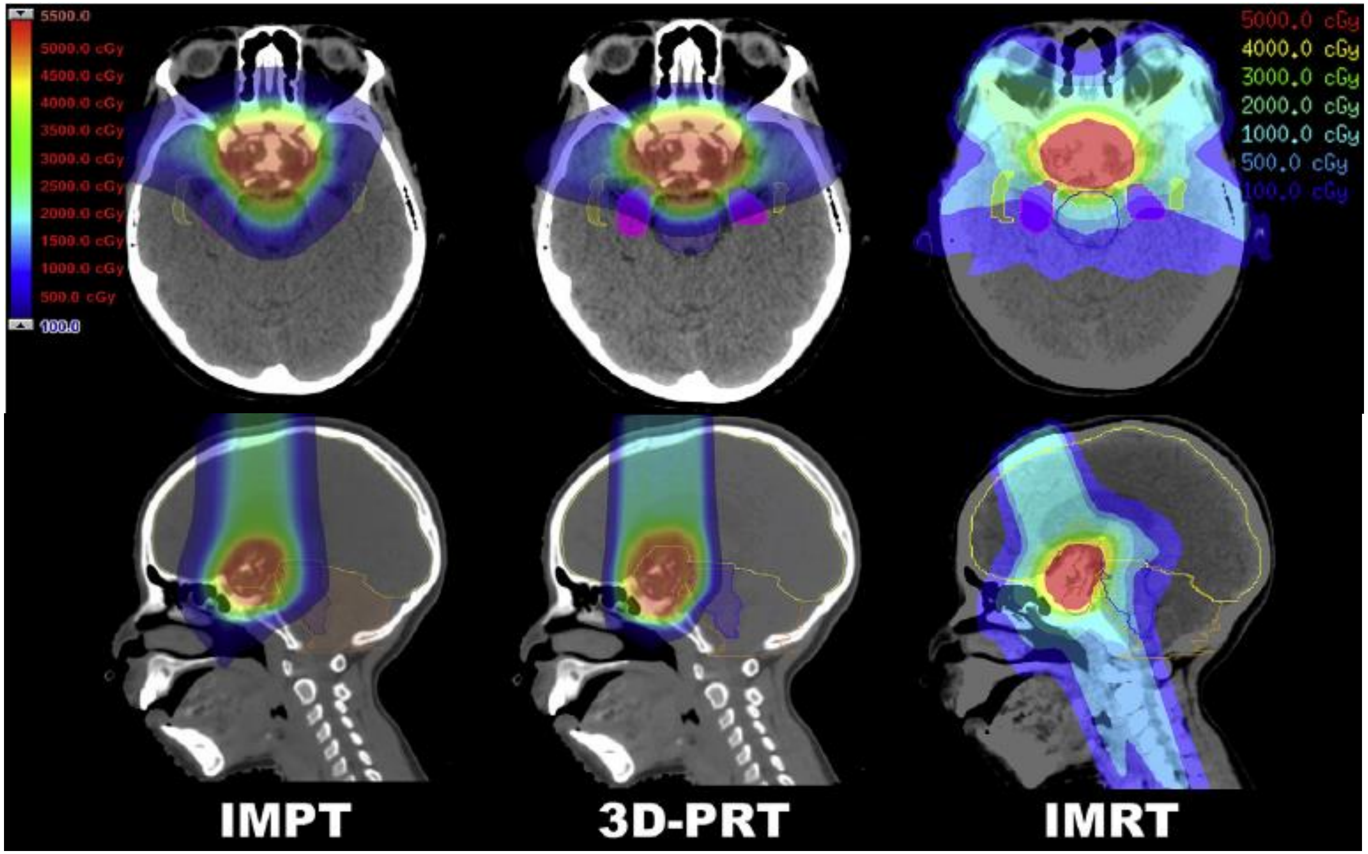


CLINICAL INVESTIGATION **Pediatric Cancer**

DOSIMETRIC COMPARISON OF THREE-DIMENSIONAL CONFORMAL PROTON RADIOTHERAPY, INTENSITY-MODULATED PROTON THERAPY, AND INTENSITY-MODULATED RADIOTHERAPY FOR TREATMENT OF PEDIATRIC CRANIOPHARYNGIOMAS

Nicholas S. Boehling, B.A.,* David R. Grosshans, M.D., Ph.D.,* Jaques B. Bluett, C.M.D., M.S.,†
Matthew T. Palmer, C.M.D., M.B.A.,* Xiaofei Song, Ph.D.,† Richard A. Amos, M.Sc.,†
Narayan Sahoo, Ph.D.,† Jeffrey J. Meyer, M.D.,* Anita Mahajan, M.D.,* and Shiao Y. Woo, M.D.*

Departments of *Radiation Oncology and †Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX



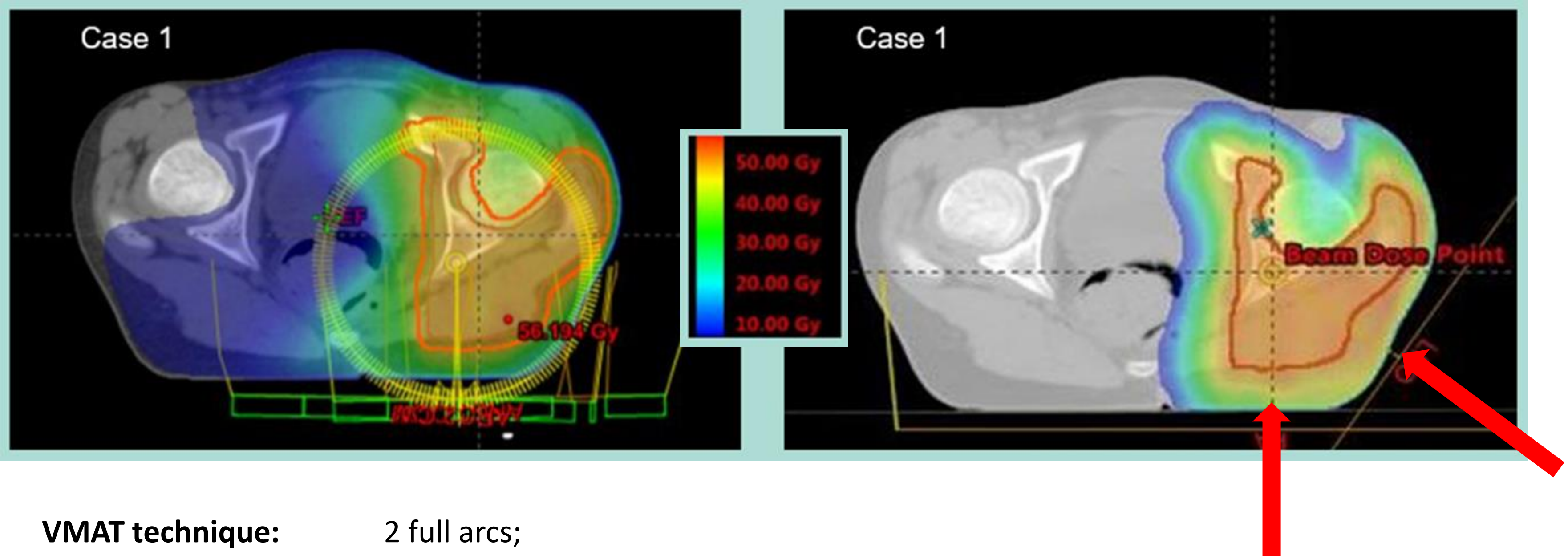
Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 643–652, 2012

Dosimetric comparison of intensity-modulated proton therapy (IMPT) and volumetric-modulated arc therapy (VMAT) treatment plans for Ewing sarcoma of the pelvis.

Franél le Grange[1], Richard A. Amos[2], Rachel Bodey[2] and Beatrice Seddon[1]
Departments of [1]Oncology and [2]Radiotherapy Physics, University College London Hospitals NHS Foundation Trust, London, UK.

Proceedings 55th International Conference of the Particle Therapy Co-Operative Group. *Int J Particle Ther*. Summer 2016, **3**(1), 231

VMAT **IMPT**



VMAT technique: 2 full arcs;
5mm PTV expansion from CTV.

IMPT technique: Multi-field optimization (MFO) with 2 pencil beam scanning fields;
positional uncertainty of 5mm & range uncertainty of 3% to robustly cover CTV.

Advantages of scanned beam delivery

1. Can “paint” any physically possible dose distribution.
2. Uses protons very efficiently as compared to passive scattering in which more than 50% of protons have to be “thrown away”.
3. Generally, requires no patient-specific hardware.
4. The neutron background is substantially reduced as a result of points (2) and (3).
5. Allows the implementation of IMRT with protons – termed *intensity-modulated proton therapy (IMPT)*

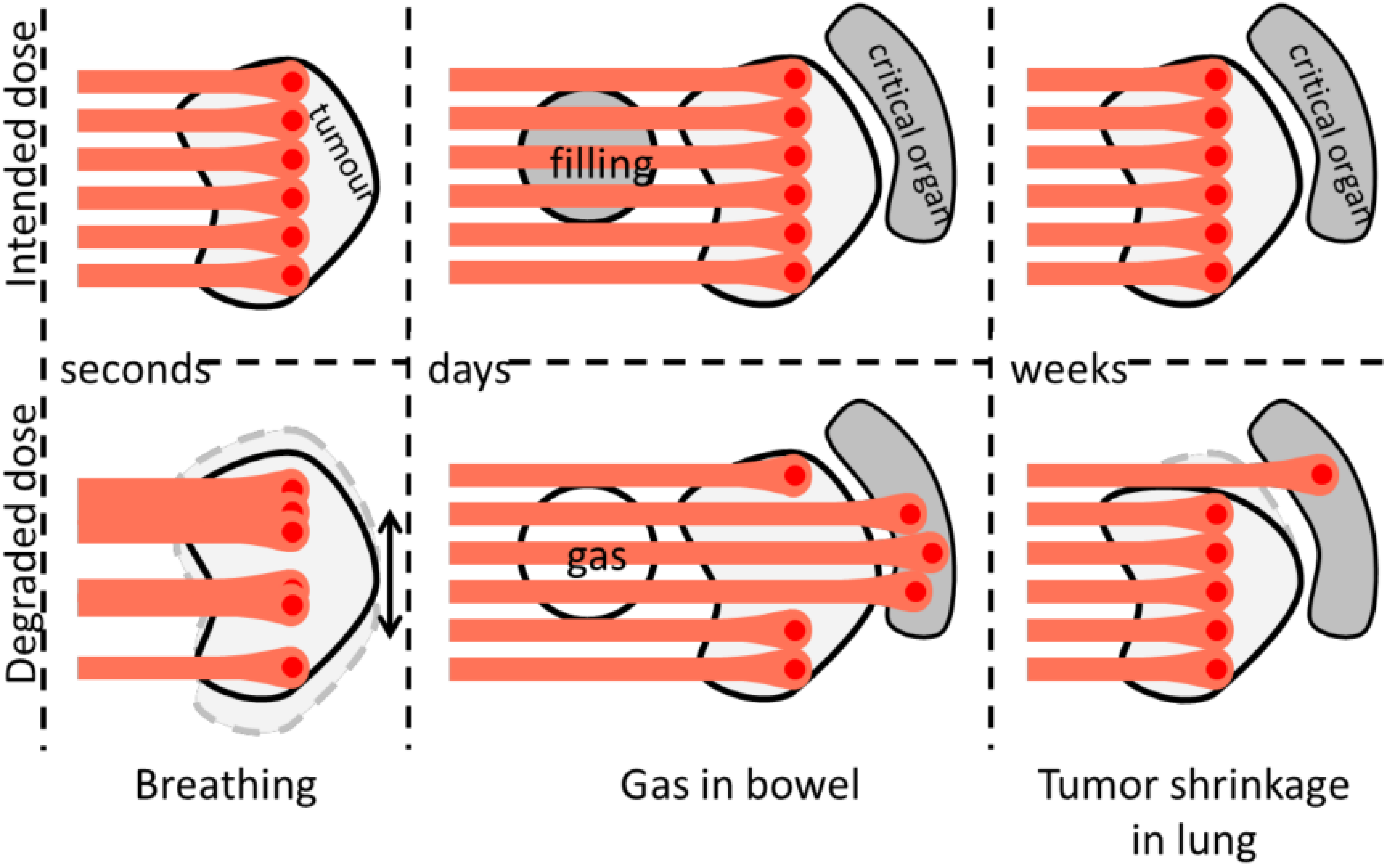
Disadvantages of scanned beam delivery

1. The need to overcome *“interplay effects”* (Bortfeld, 2002)[*] induced by organ motion.

---

[*] *Bortfeld T et al. (2002) Effects of intra-fraction motion on IMRT dose delivery: Statistical analysis and simulation. Phys Med Biol 47:2203-2220*

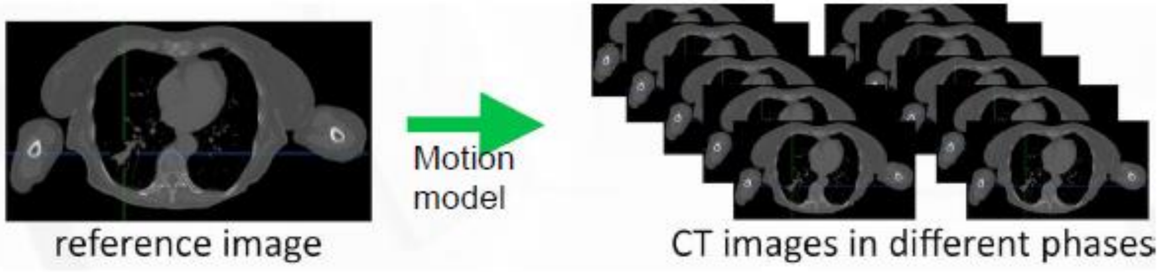
Positional uncertainty and anatomical variation over course of treatment



Study of Dosimetric Impact of Scanning Beam Delivery Parameters and Interplay Mitigation Strategies for Proton Therapy for Lung Cancer

Ho Lok Man[1], Richard A. Amos[1,2] & Jamie McClelland[1,3]
[1]Department of Medical Physics and Biomedical Engineering, University College London
[2]Department of Radiotherapy Physics, University College London Hospitals NHS Foundation Trust
[3]Centre for Medical Imaging Computing, University College London

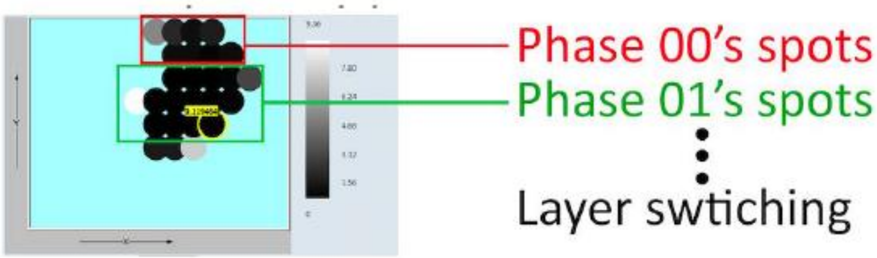
PTCOG 56, 2017



reference image

Motion model

CT images in different phases

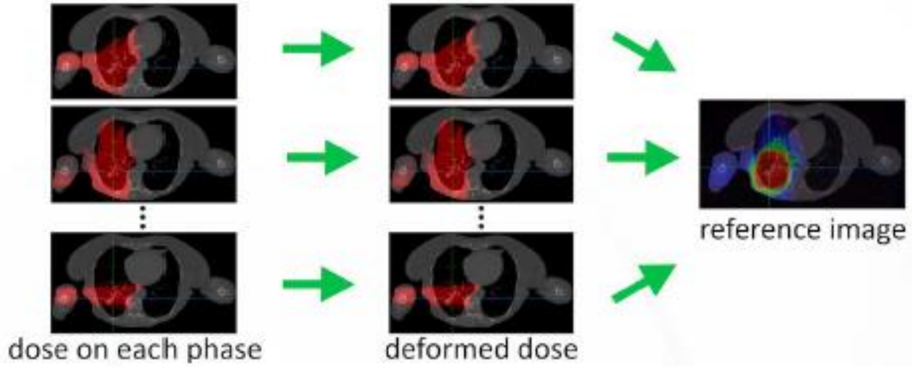


Phase 00's spots

Phase 01's spots

⋮

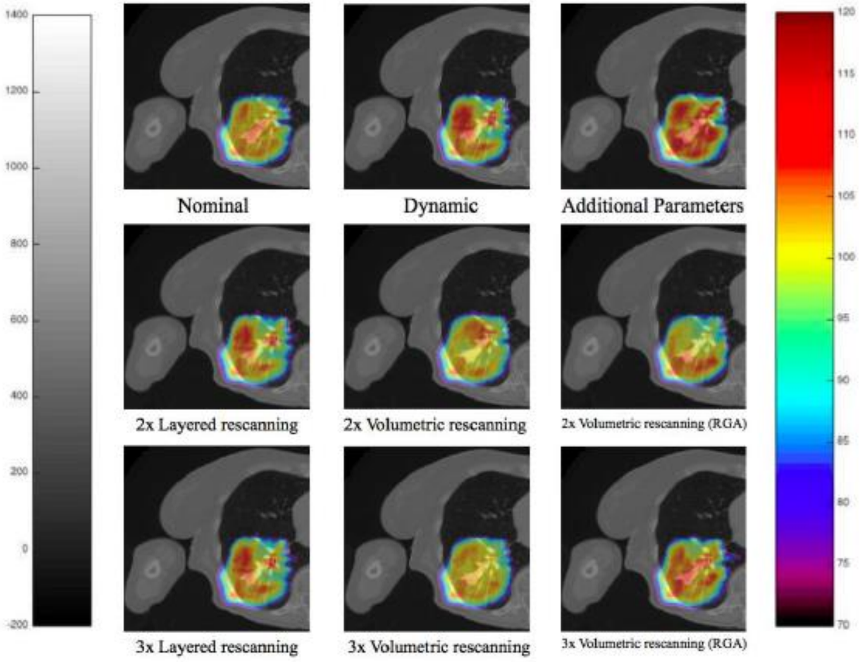
Layer swtiching



dose on each phase

deformed dose

reference image



Nominal | Dynamic | Additional Parameters

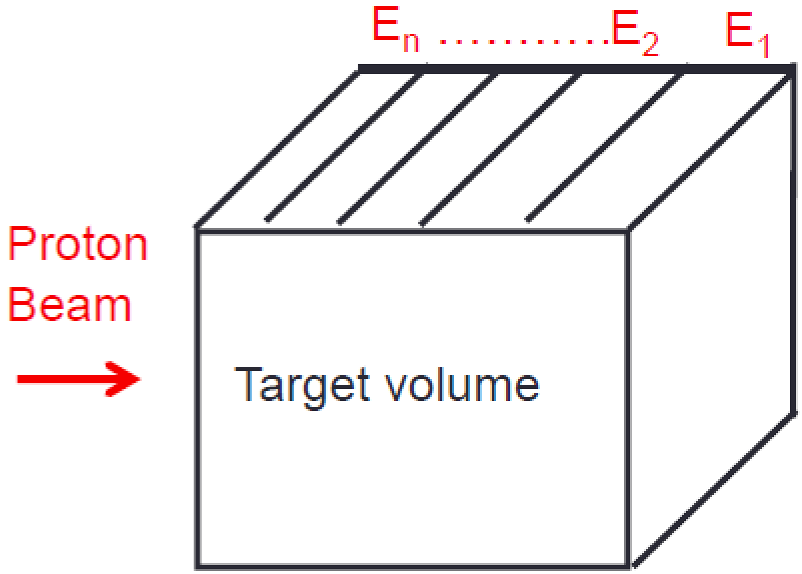
2x Layered rescanning | 2x Volumetric rescanning | 2x Volumetric rescanning (RGA)

3x Layered rescanning | 3x Volumetric rescanning | 3x Volumetric rescanning (RGA)

Repainting

Zenklusen *et al*. PMB 2010

- Iso-layer repainting (within each energy)
  - Not necessary helpful – repainting could complete within a short time relative to breathing cycle
- Volumetric repainting (visit all energies, then repeat)
  - To simulate passive scattering beam delivery
  - The total irradiation time would increase considerably
  - Energy change needs to be fast
  - typically ~ 1 to 2 sec; PSI ~ 80 ms



- Require large number of repainting
- Scanning motion and target motion are uncorrelated.

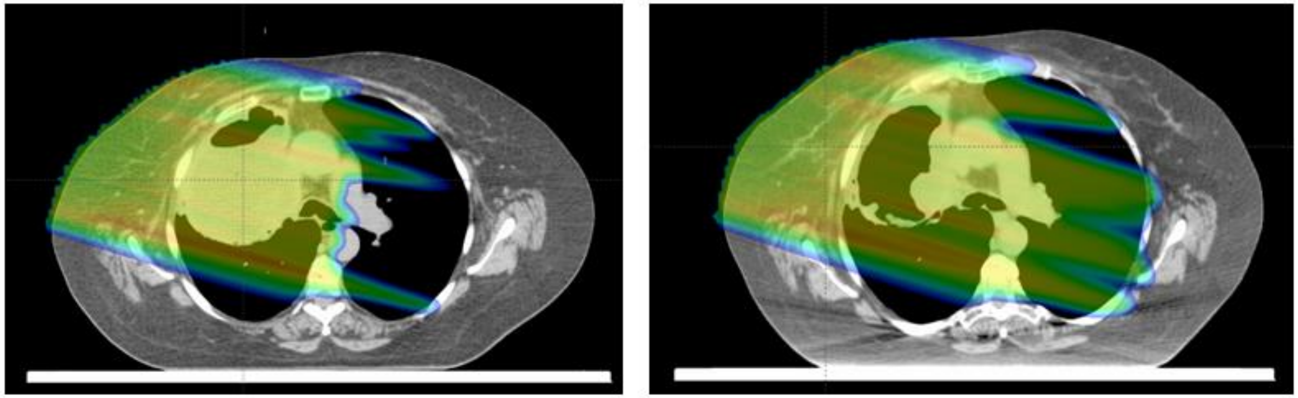


Fig.2 Comparison of dose distribution from single RAO field before and after tumor shrinkage as detected during third week of treatment. (This patient experienced the most dramatic tumor shrinkage).

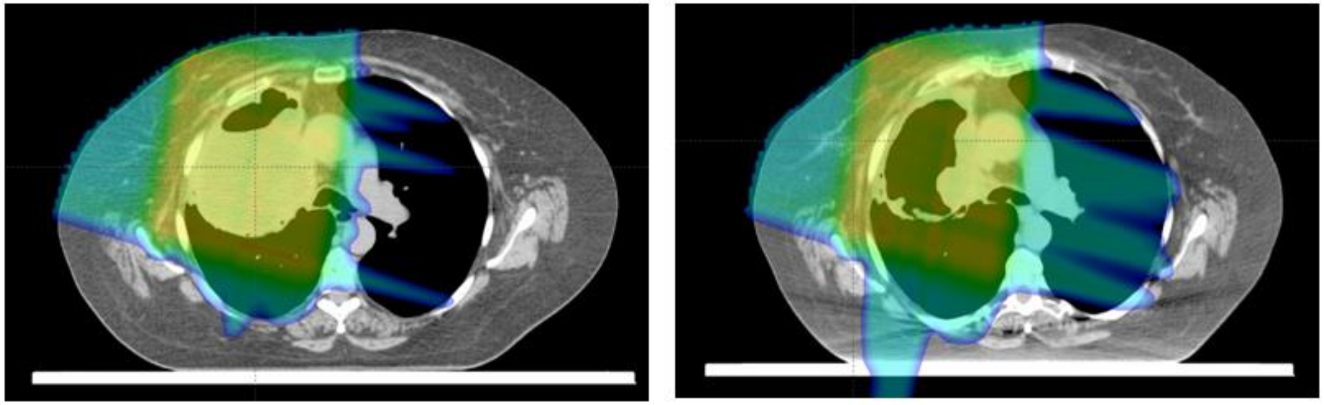


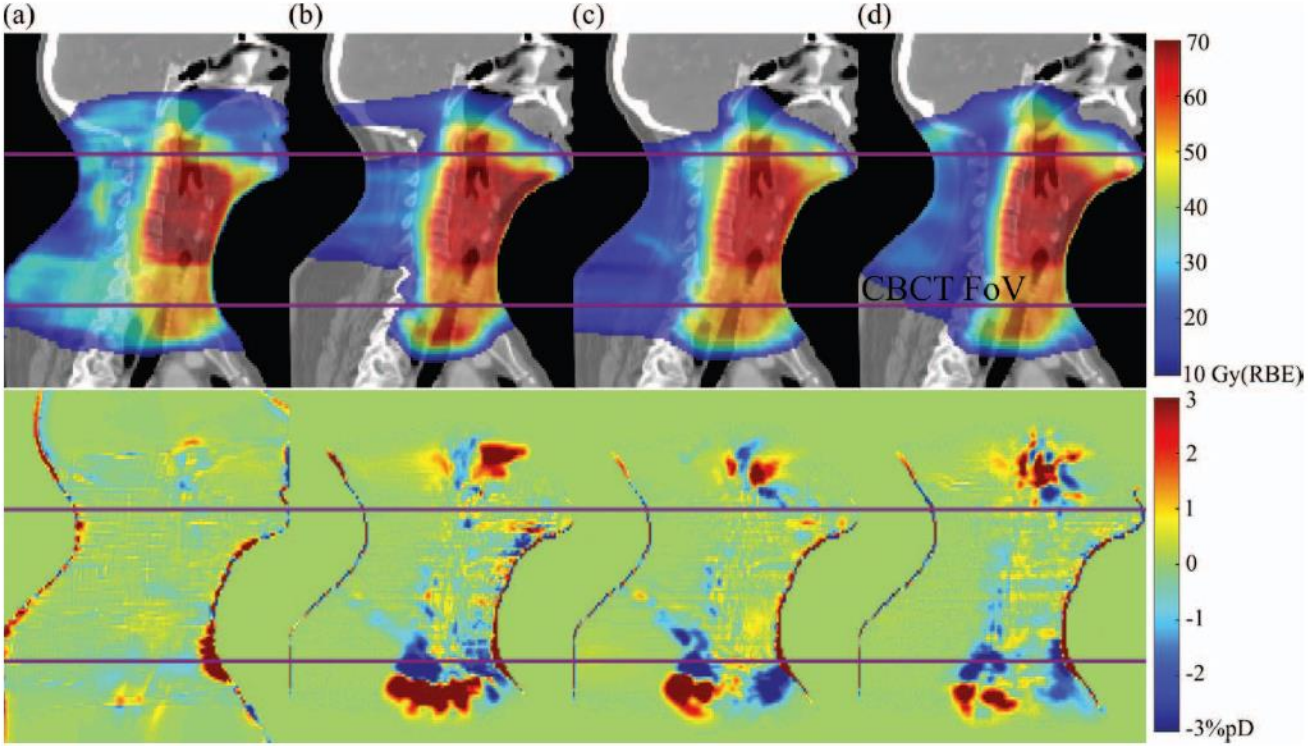
Fig.3 Comparison of total dose distribution before and after tumor shrinkage. (Same patient as Fig.2)

Amos R, *et al.* Variation in dose distribution with tumor shrinkage for proton therapy of lung cancer. Proceedings of PTCOG 46, Zibo, Shandong, China, 2007

Cone-Beam Computed Tomography and Deformable Registration-Based “Dose of the Day” Calculations for Adaptive Proton Therapy

Catarina Veiga, MSc[1]; Jailan Alshaikhi, MSc[1,2]; Richard Amos, MSc[2]; Ana Mónica Lourenço, MSc[1,3]; Marc Modat, PhD[4]; Sebastien Ourselin, PhD[4]; Gary Royle, PhD[1]; Jamie R. McClelland, PhD[4]

Figure 3. Dose color wash overlayed on the replan CT (top row) and difference in dose between replan CT and deformed CT (bottom row) for (A) the IMRT plan, (B) the IMPT$_{3B}$ plan, (C) the SFUD$_{3B}$ plan, and (D) the IMPT$_{5B}$ plan for one of the patients included in this study. The horizontal purple lines indicate the length of the CBCT FoV. Abbreviations: CBCT, cone-beam computed tomography; CT, computed tomography; FoV, field of view; IMPT, intensity-modulated radiation therapy; IMRT, intensity-modulated radiation therapy; SFUD, single-field uniform dose.



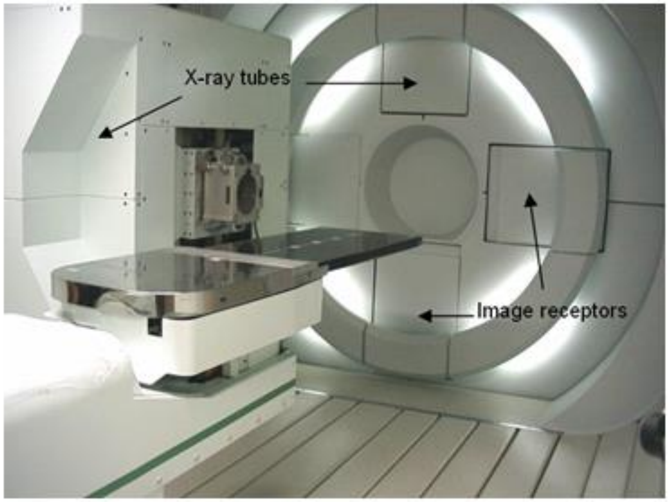
Importance of Volumetric Image-Guidance

Proton therapy

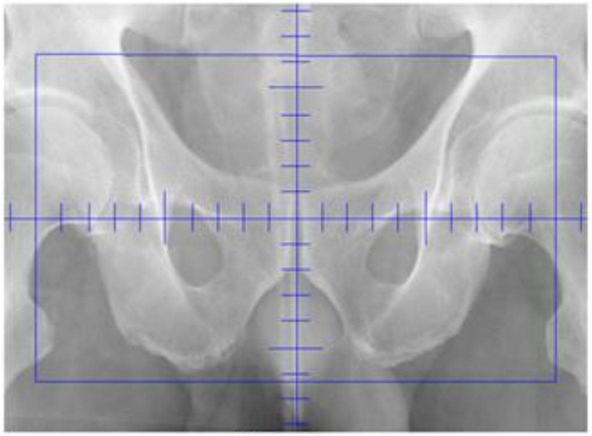
IMRT

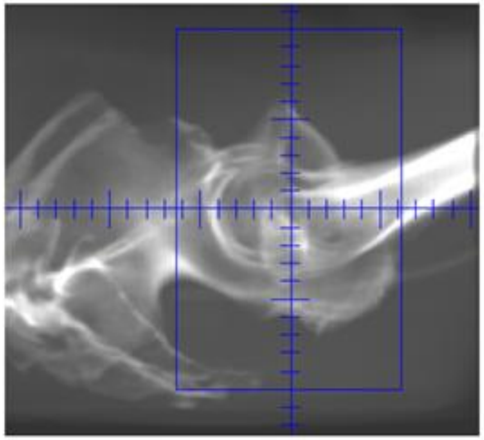
Image-guidance

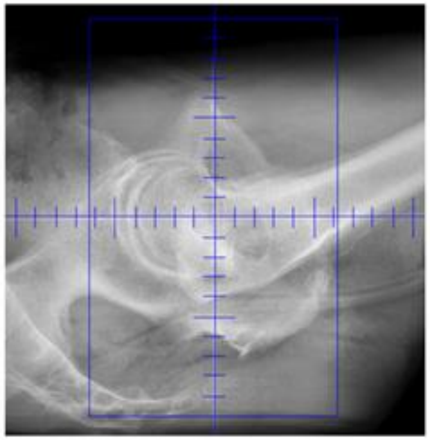
- Daily orthogonal kV x-rays taken to align anatomy with reference DRR's using 2-D matching



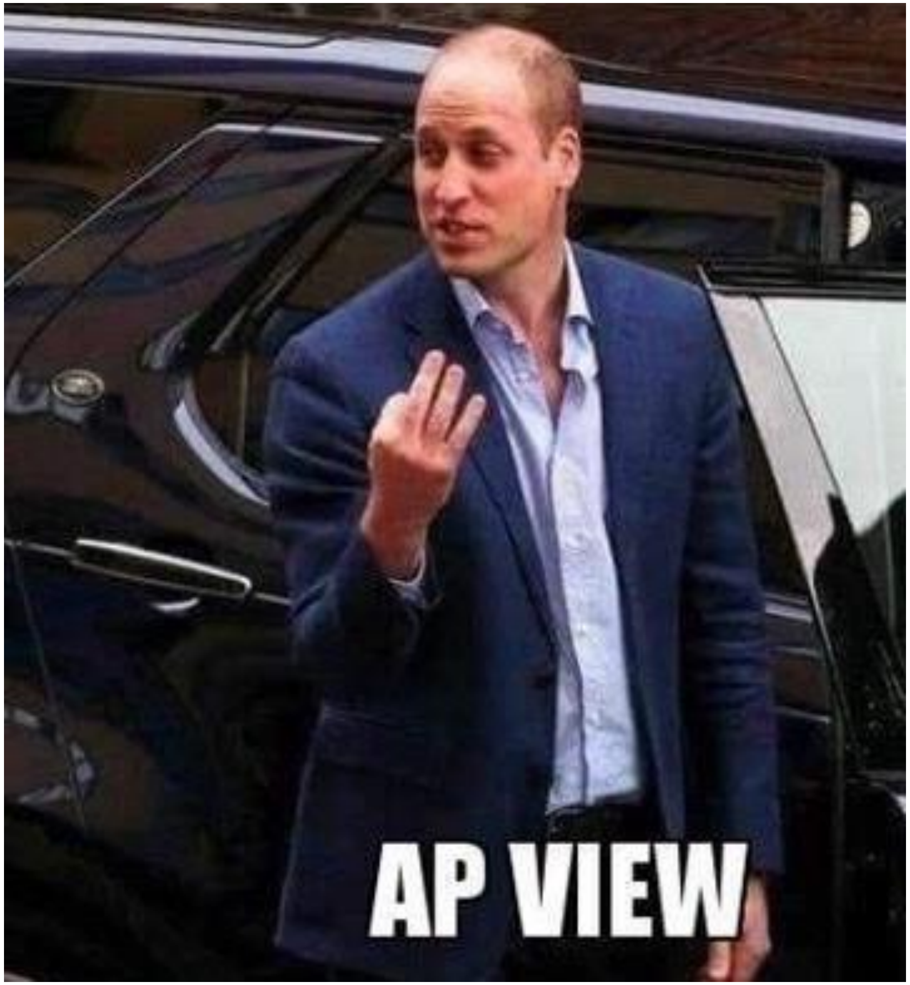

AP DRR


AP x-ray image


Rt Lat DRR


Rt Lat x-ray image

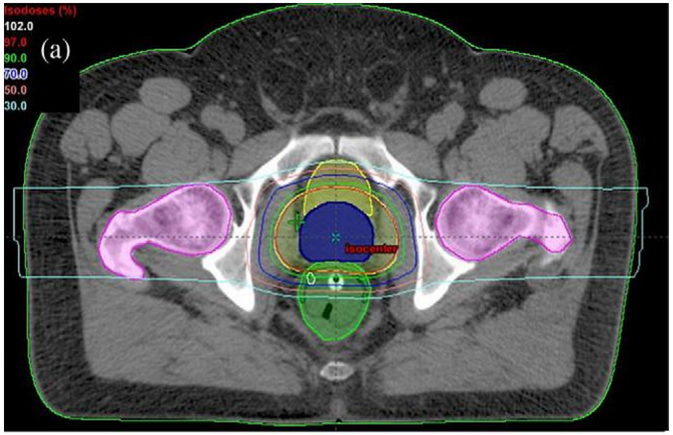

LATERAL VIEW

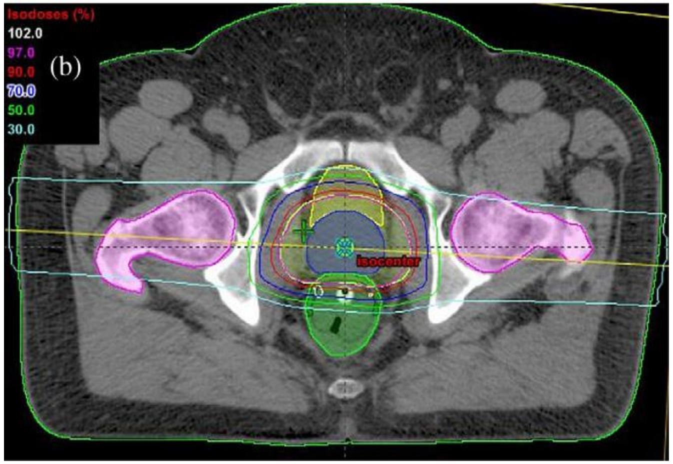

AP VIEW

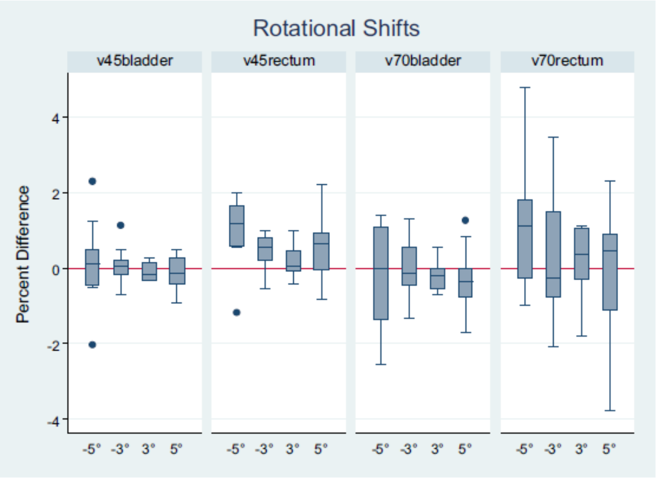
SPOT SCANNING PROTON BEAM THERAPY FOR PROSTATE CANCER: TREATMENT PLANNING TECHNIQUE AND ANALYSIS OF CONSEQUENCES OF ROTATIONAL AND TRANSLATIONAL ALIGNMENT ERRORS

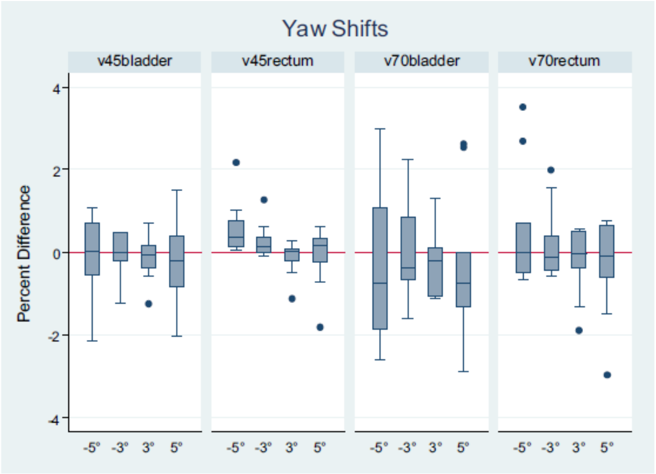
Jeff Meyer, M.D.,* Jaques Bluett, M.S.,* Richard Amos, M.S.,* Larry Levy, M.S.,*
Seungtaek Choi, M.D.,* Quynh-Nhu Nguyen, M.D.,* X. Ron Zhu, Ph.D.,* Michael Gillin, Ph.D.,*
and Andrew Lee, M.D., M.P.H.*

From the *University of Texas-M.D. Anderson Cancer Center, Houston, TX

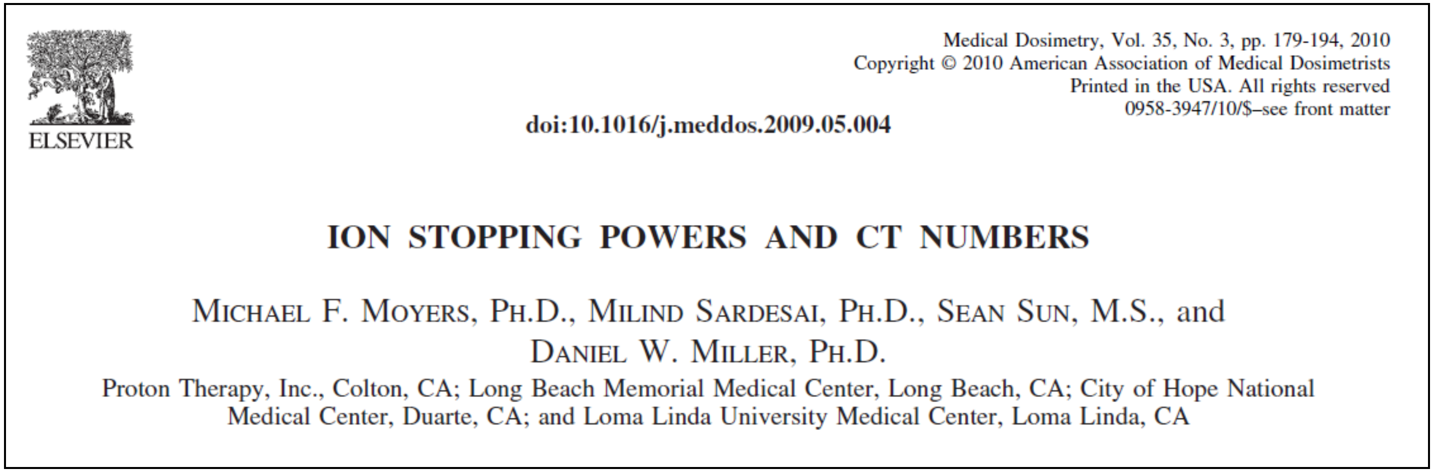








Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 2, pp. 428–434, 2010



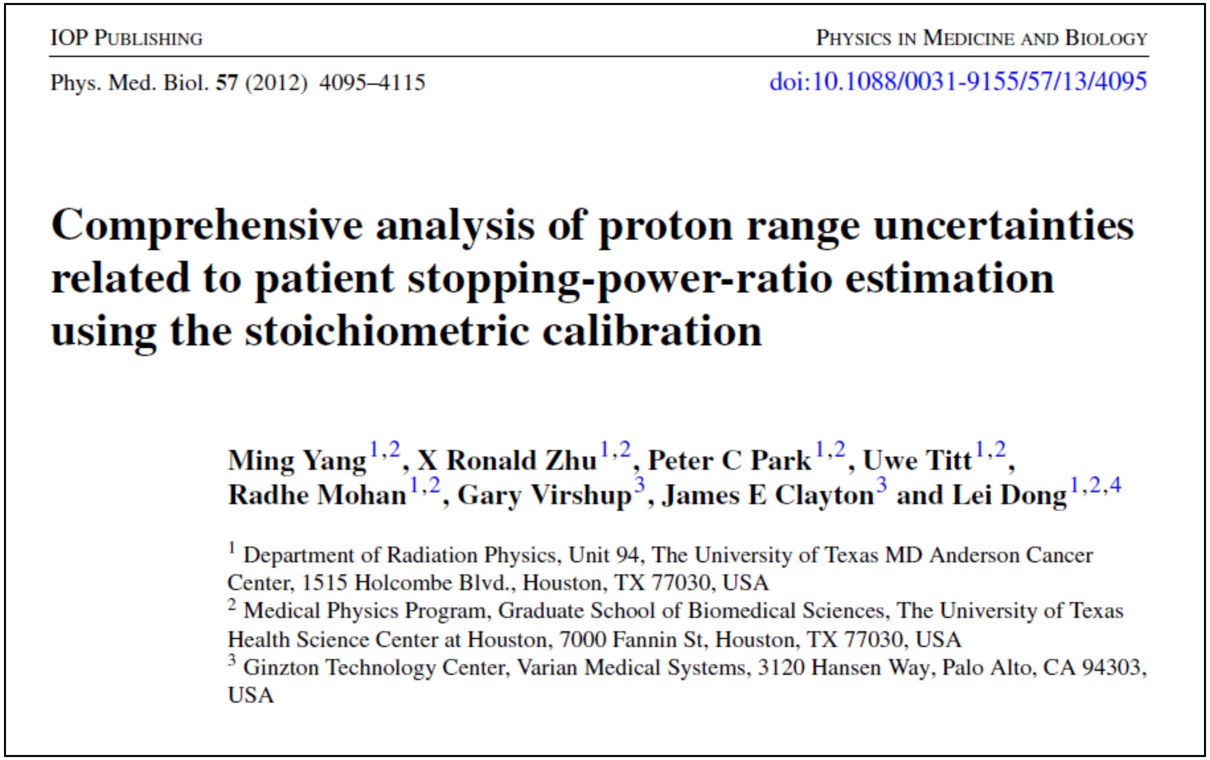
Medical Dosimetry, Vol. 35, No. 3, pp. 179-194, 2010
Copyright © 2010 American Association of Medical Dosimetrists
Printed in the USA. All rights reserved
0958-3947/10/$–see front matter

ELSEVIER

doi:10.1016/j.meddos.2009.05.004

ION STOPPING POWERS AND CT NUMBERS

MICHAEL F. MOYERS, PH.D., MILIND SARDESAI, PH.D., SEAN SUN, M.S., and
DANIEL W. MILLER, PH.D.
Proton Therapy, Inc., Colton, CA; Long Beach Memorial Medical Center, Long Beach, CA; City of Hope National Medical Center, Duarte, CA; and Loma Linda University Medical Center, Loma Linda, CA



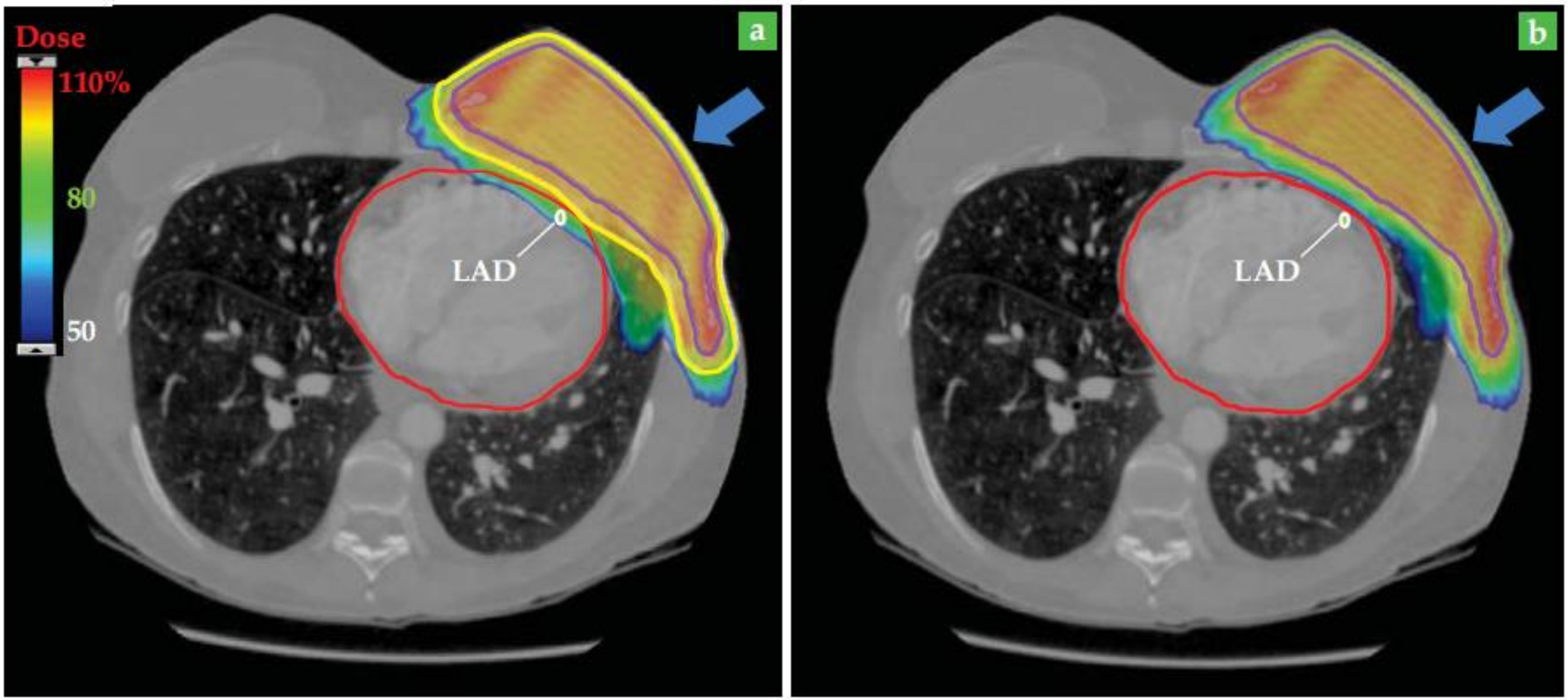
IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. **57** (2012) 4095–4115 doi:10.1088/0031-9155/57/13/4095

Comprehensive analysis of proton range uncertainties related to patient stopping-power-ratio estimation using the stoichiometric calibration

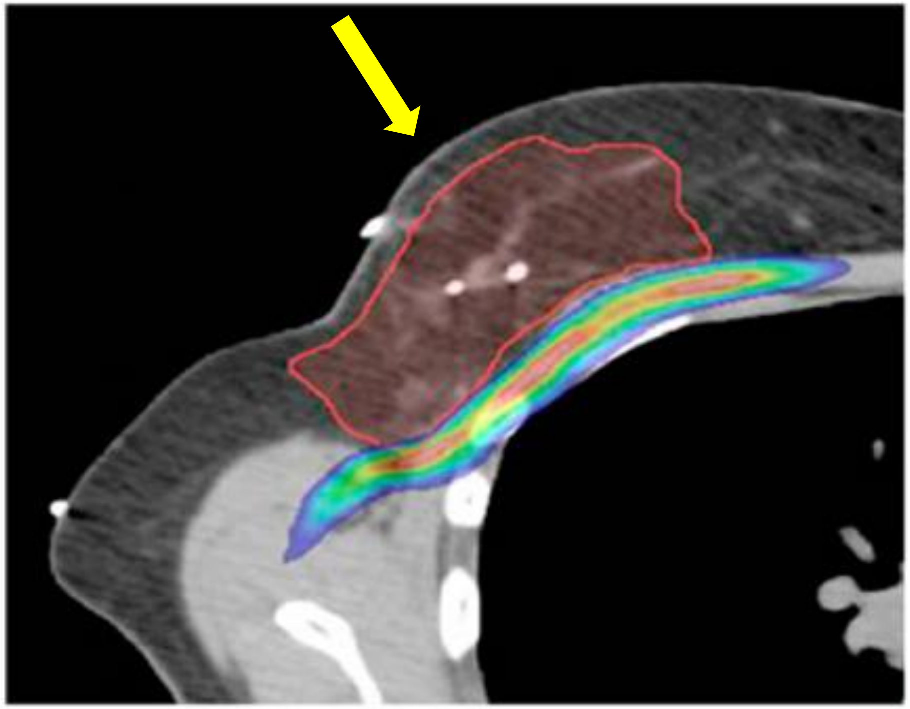
Ming Yang[1,2], X Ronald Zhu[1,2], Peter C Park[1,2], Uwe Titt[1,2], Radhe Mohan[1,2], Gary Virshup[3], James E Clayton[3] and Lei Dong[1,2,4]

[1] Department of Radiation Physics, Unit 94, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA
[2] Medical Physics Program, Graduate School of Biomedical Sciences, The University of Texas Health Science Center at Houston, 7000 Fannin St, Houston, TX 77030, USA
[3] Ginzton Technology Center, Varian Medical Systems, 3120 Hansen Way, Palo Alto, CA 94303, USA

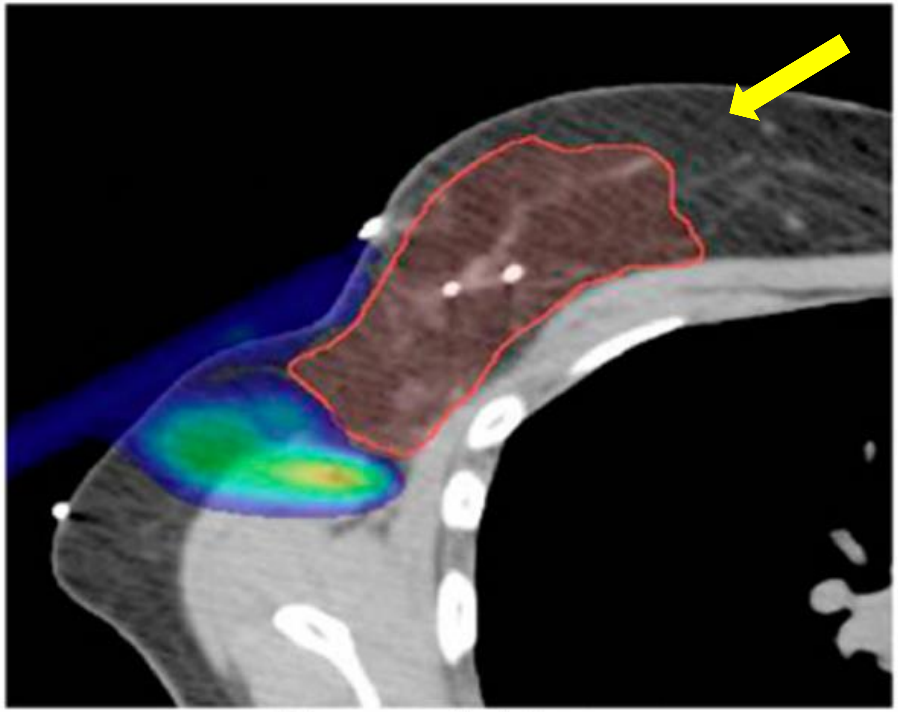


LAD: Left Anterior Descending artery

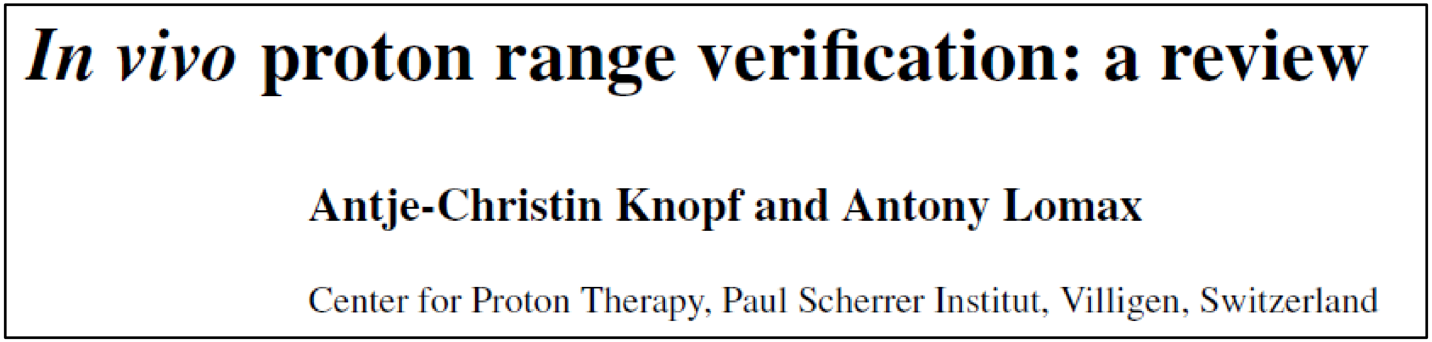
Wang X, Zhang X, Li X, **Amos RA**, Shaitleman SF, Hoffman K, *et al.*
Br J Radiol 2013;86:20130176



En face beam



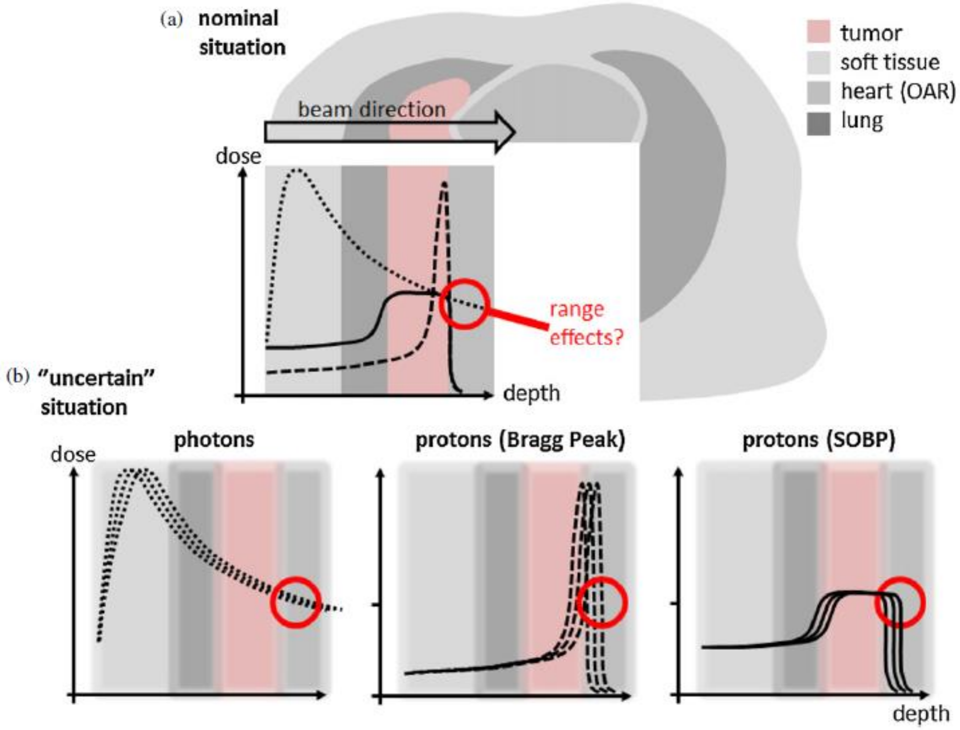
Tangential beam



In vivo proton range verification: a review

Antje-Christin Knopf and Antony Lomax

Center for Proton Therapy, Paul Scherrer Institut, Villigen, Switzerland



Phys. Med. Biol. **58** (2013) R131–R160

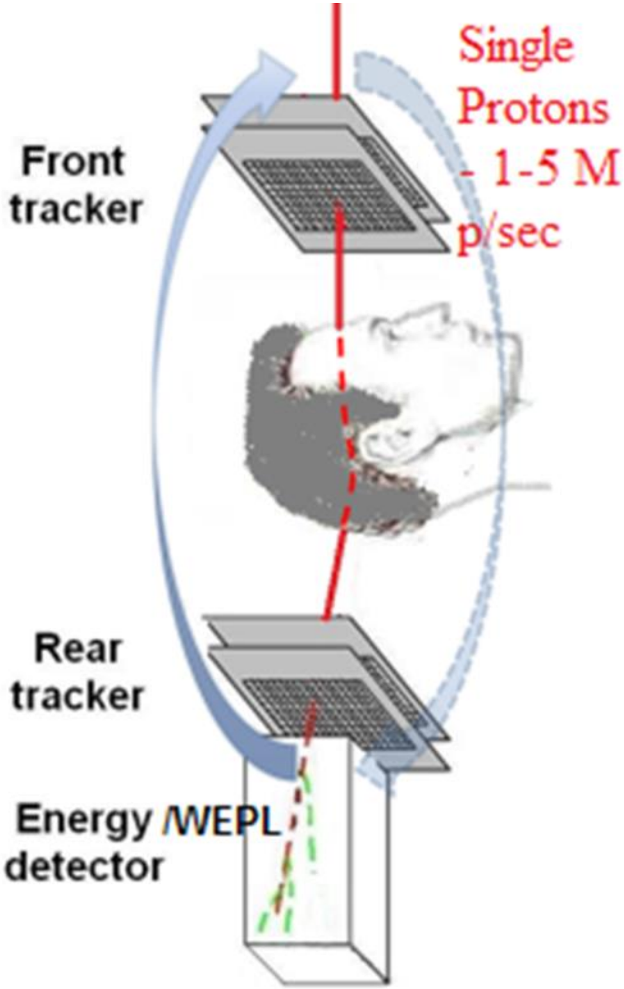
Range probe / proton radiography
- Possible prior, during and after field delivery
- pCT only possible pre- or post-delivery

Prompt gamma
- Prompt γ emission within nanoseconds
- Only applicable for on-line range verification

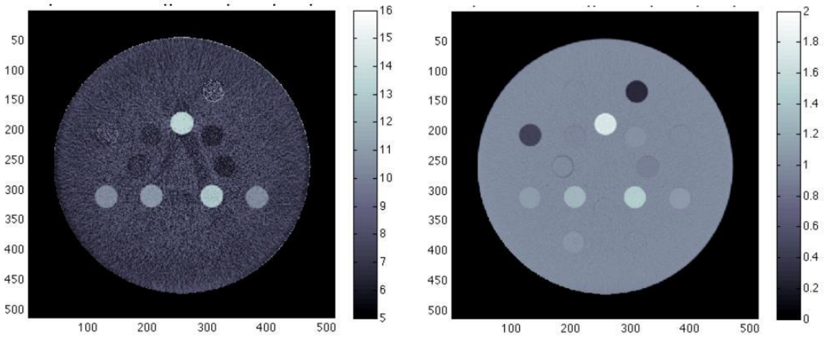
PET
- Possible on-line, or short time after irradiation
- Biological wash-out can be an issue

MRI
- Retrospective range verification as a function of tissue change.

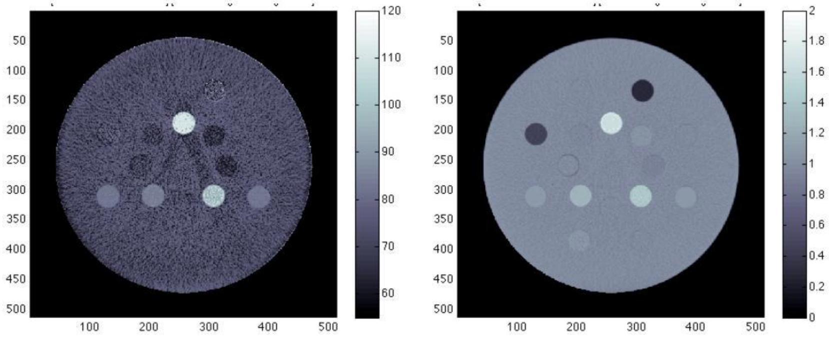
Proton CT (pCT)



Dual Energy CT (DECT)



(a) Effective atomic number (b) Relative electron density

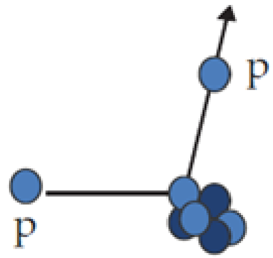


(c) Mean excitation energy (d) Relative proton stopping power

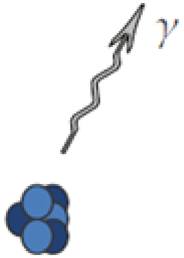
- More information – greater accuracy
- Reduction in CT artifacts

In-vivo verification

Prompt gammas

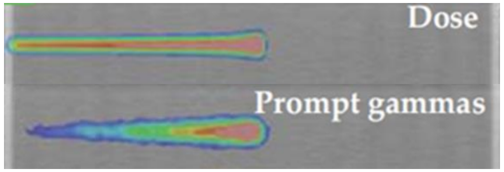


Nuclear scatter promote nuclei to excited states that decay through emission of single gamma

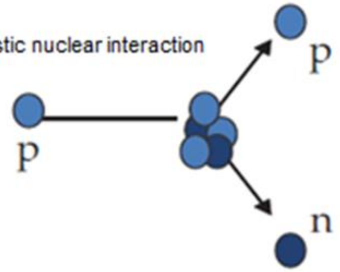


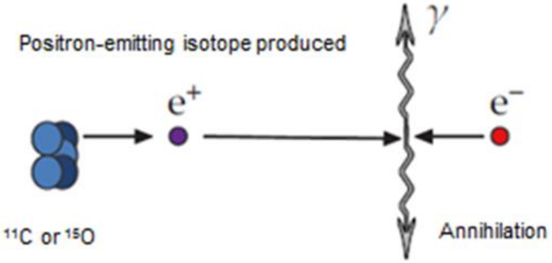
2 – 15 MeV gammas

(Existing imaging systems designed for gamma energies of a few hunded keV)

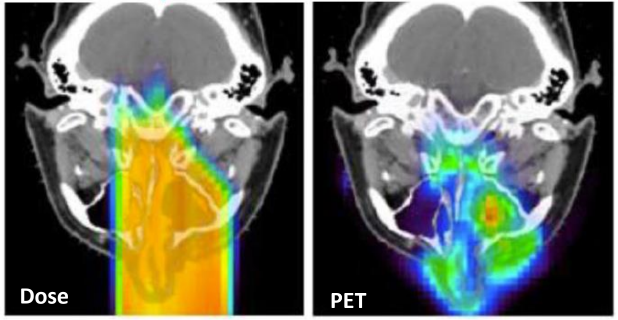


Positron-annihilation gammas

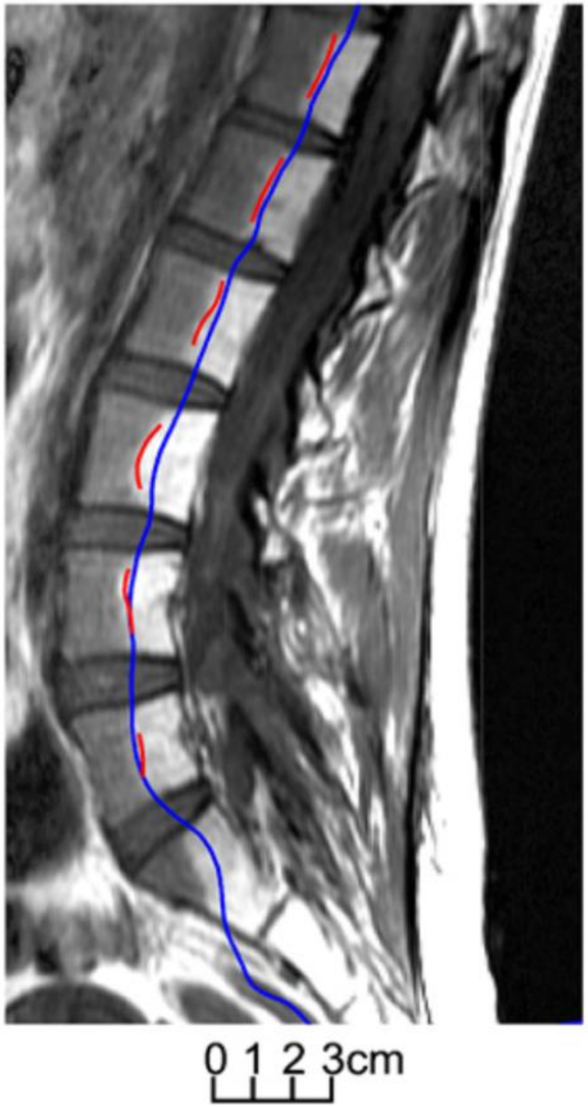

Inelastic nuclear interaction


Positron-emitting isotope produced

511 keV gammas

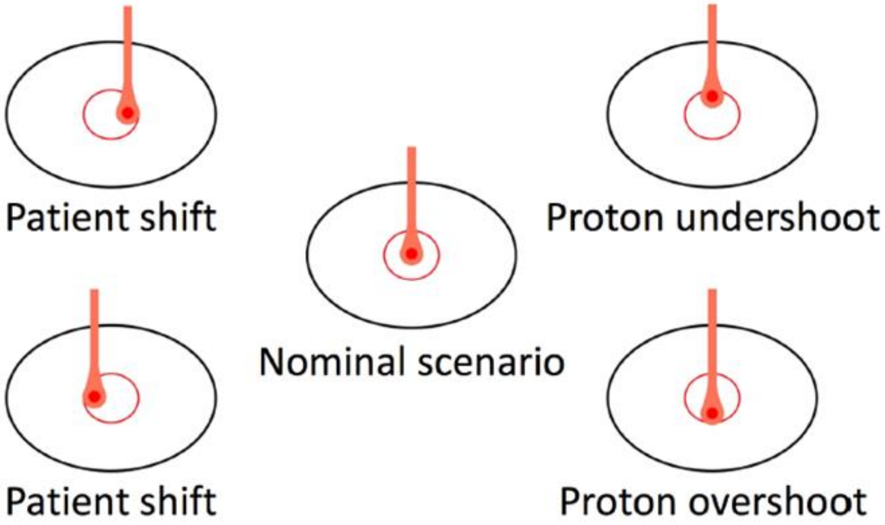


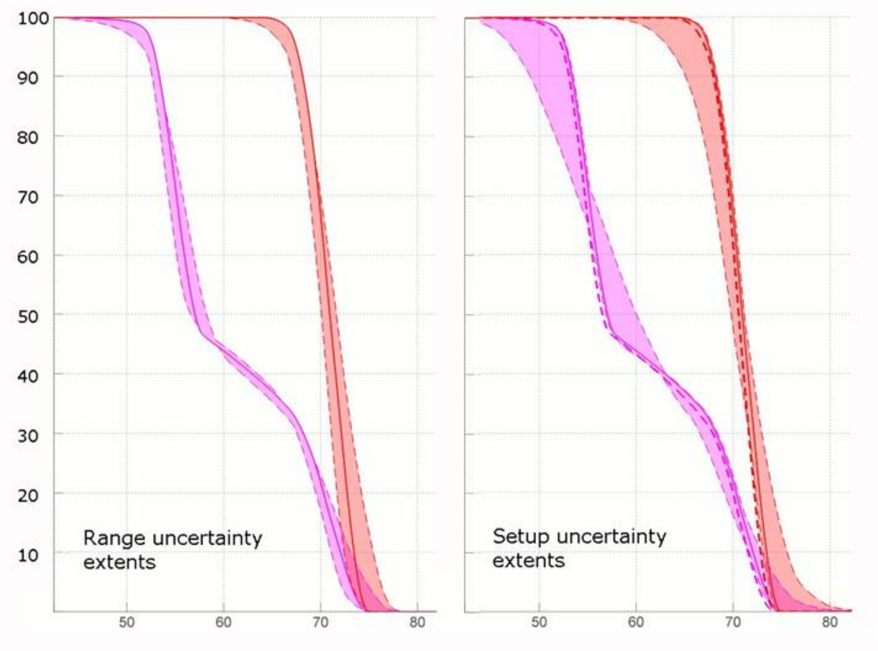
MRI



Pt. 5, 50.4 Gy (RBE)

Plan robust optimization

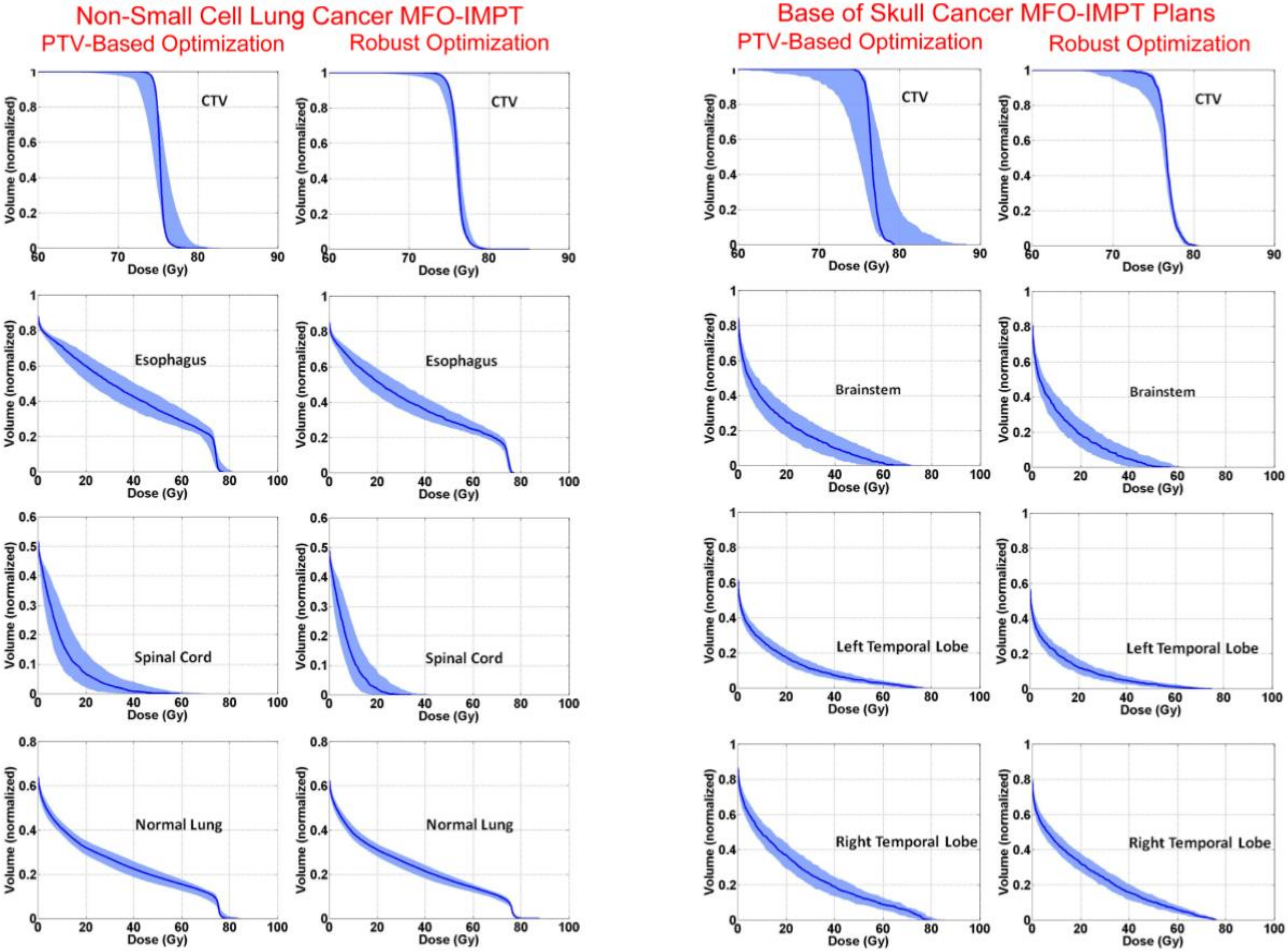




Medical Physics, Vol. 39, No. 2, February 2012

Robust optimization of intensity modulated proton therapy

Wei Liu,[a)] Xiaodong Zhang, Yupeng Li, and Radhe Mohan
Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030



Non-Small Cell Lung Cancer MFO-IMPT

PTV-Based Optimization   Robust Optimization

Base of Skull Cancer MFO-IMPT Plans

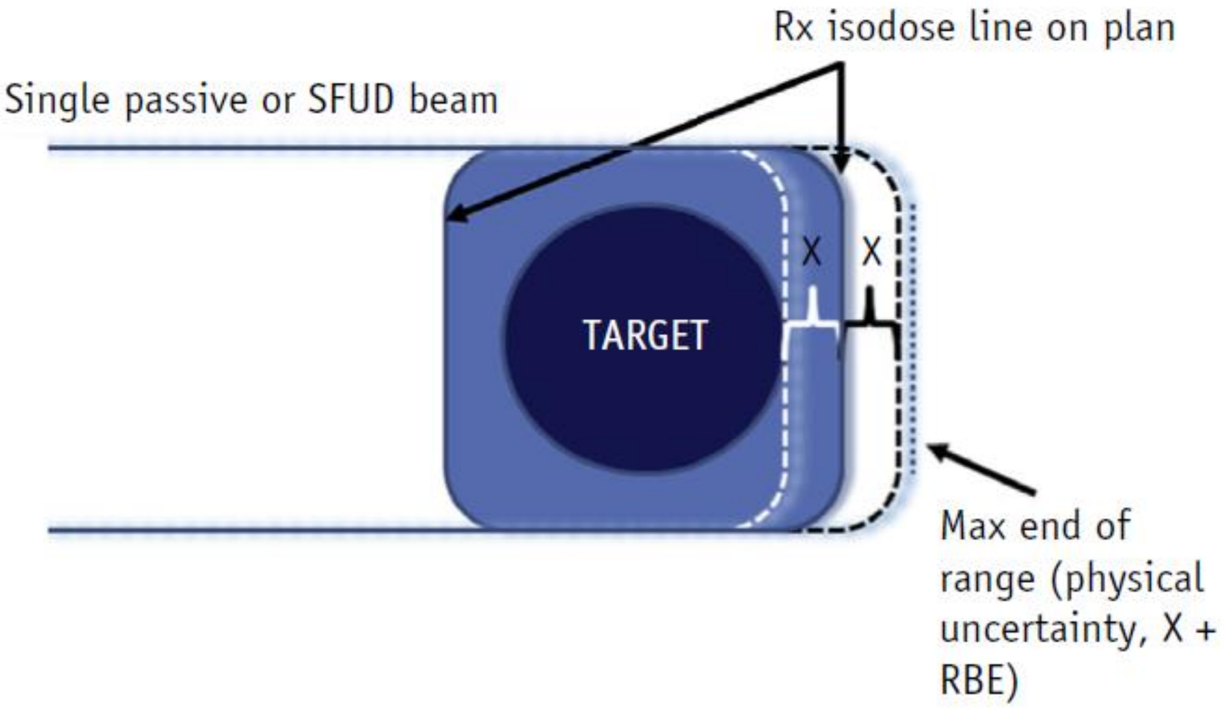
PTV-Based Optimization   Robust Optimization

Int J Radiation Oncol Biol Phys, Vol. 95, No. 1, pp. 59–61, 2016

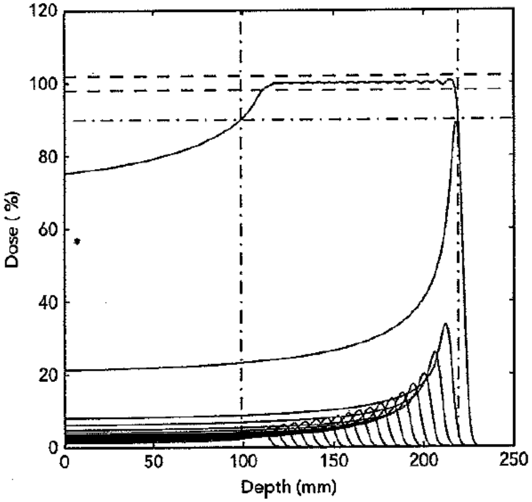
Proton Radiation Biology Considerations for Radiation Oncologists

Wendy A. Woodward, MD, PhD,[*] and Richard A. Amos, MSc, FIPEM[†,‡]

[*]Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; [†]Department of Radiotherapy Physics, University College London Hospitals NHS Foundation Trust, London, United Kingdom; and [‡]Department of Medical Physics and Biomedical Engineering, University College London, London, United Kingdom

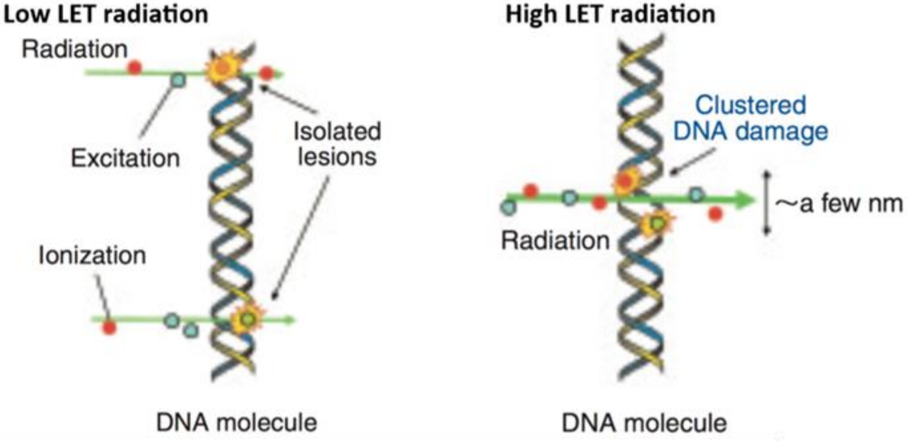


Relative biological effectiveness (RBE) of clinical proton beams



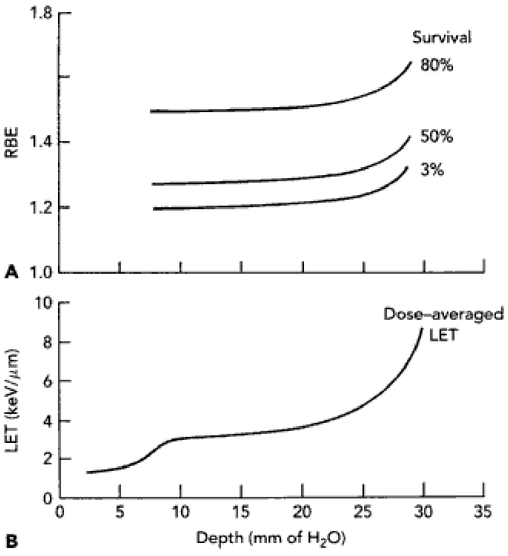
Distal most portion of the SOBP predominantly contains Bragg peak high-LET particles, whereas the most proximal portion of the beam increasingly contains higher-energy, lower-LET particles.

RBE varies throughout the SOBP due to the changing LET.

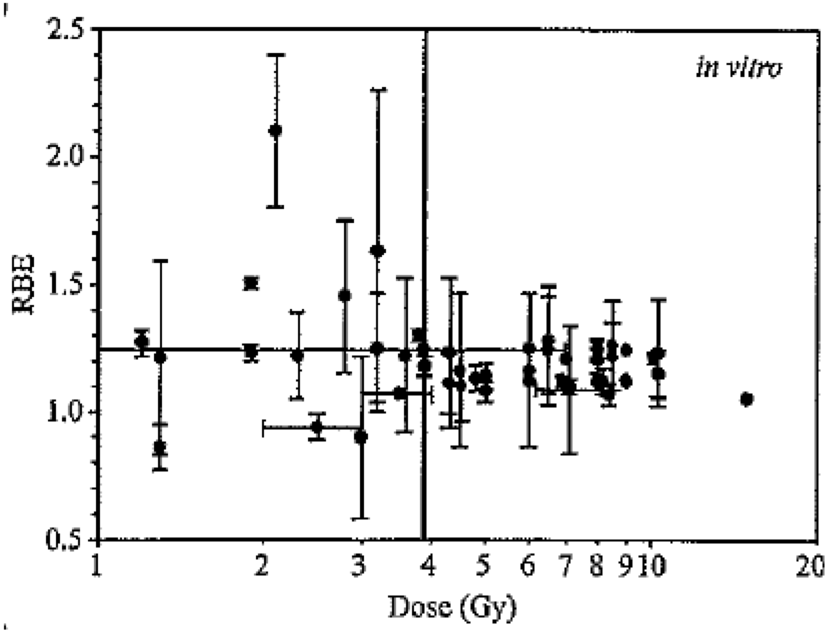


LET and RBE in V79 cells as a function of depth in a 70 MeV proton beam with a 2.5 cm SOBP.

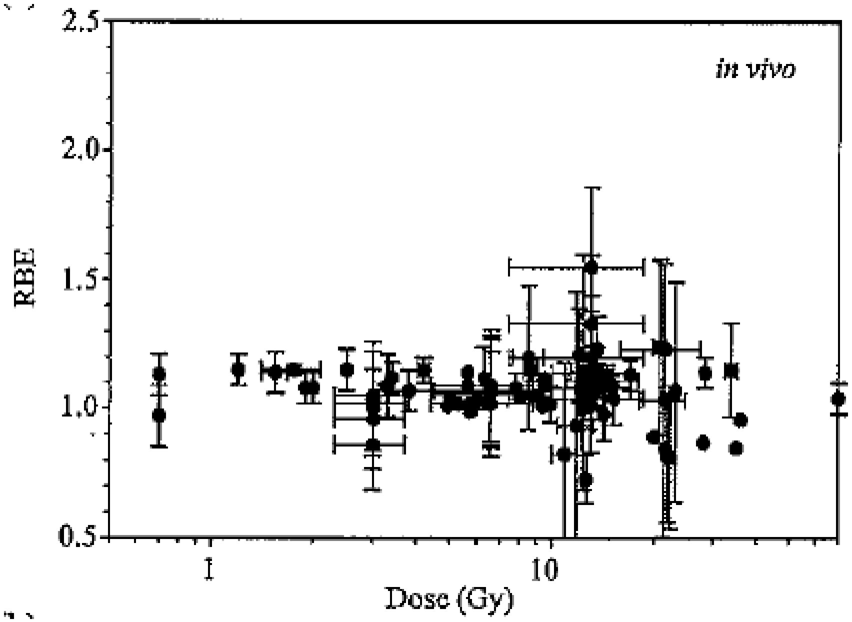
Wouters B. *et al. Radiat Res.* 1996;146:159-170



RBE determined *in vitro* and *in vivo*



All known published RBE values at all dose levels for mammalian cell lines studied *in vitro* in proton beams in the clinical energy range.

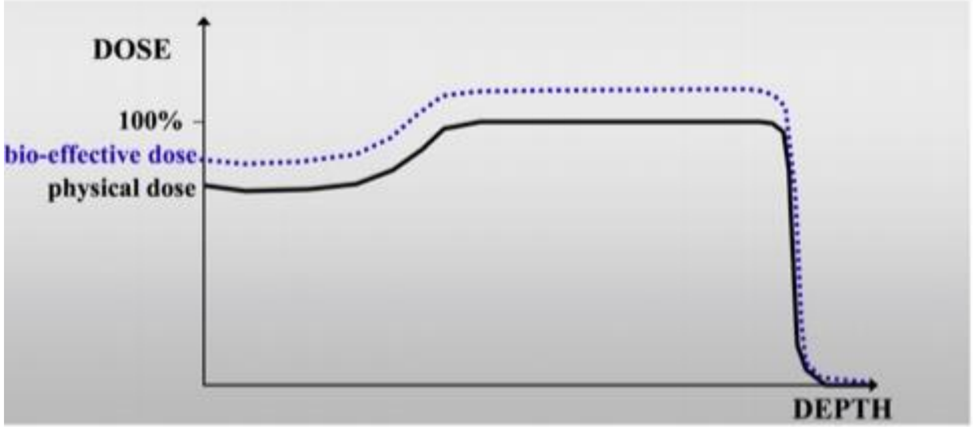


All RBE vs. dose values for acute- and late-reacting experimental animal systems.

Paganetti[1] reviewed and tabulated the data above an determined that the average RBE was 1.1.

[1] Paganetti H. *et al. Int J Radiat Oncol Biol Phys.* 2002;53:407-421

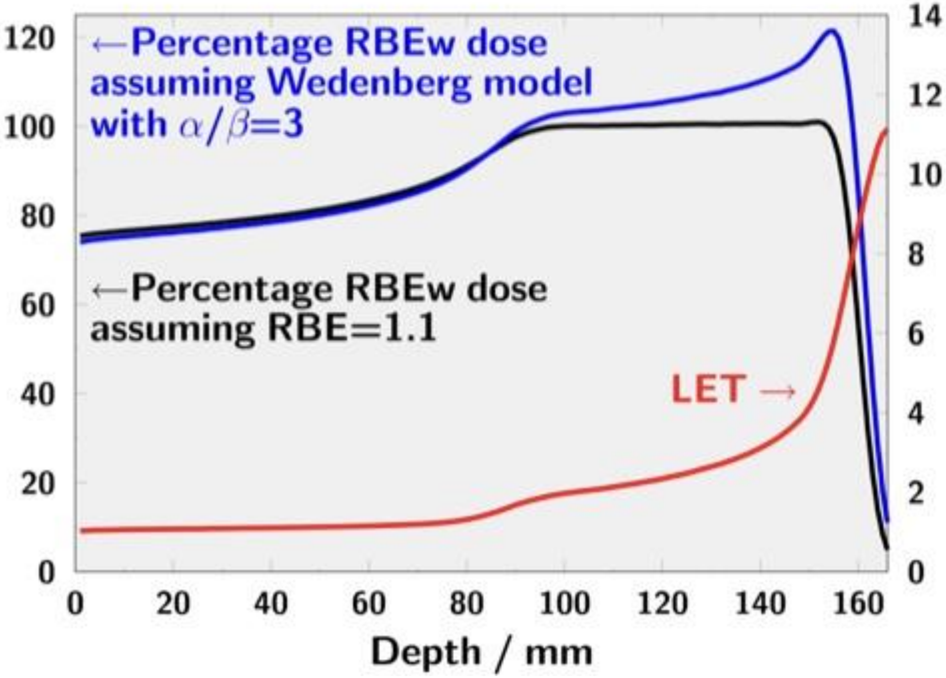
Uncertainty in RBE



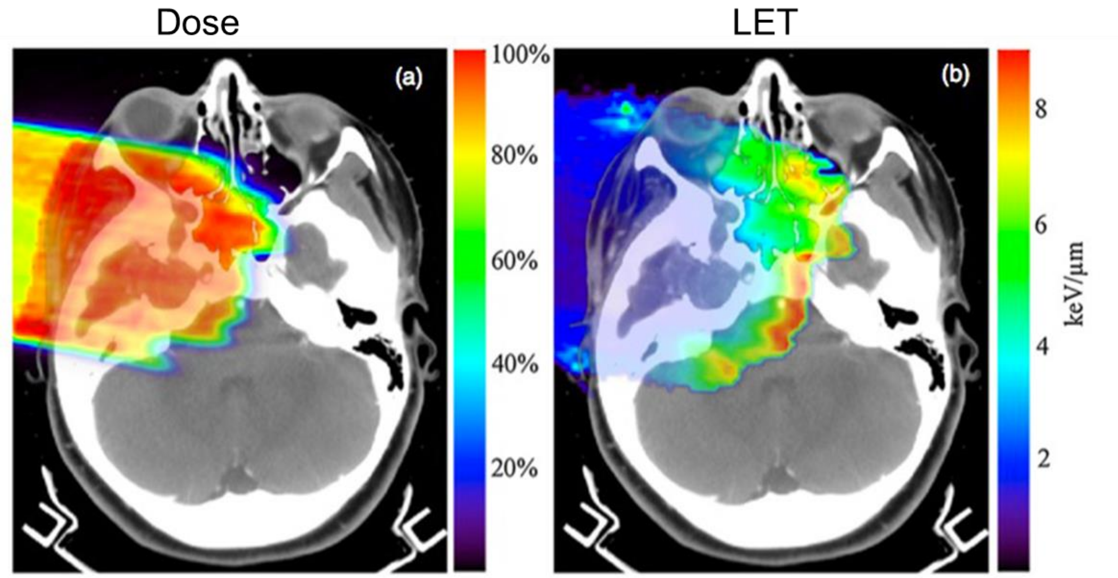
Michael Goitein

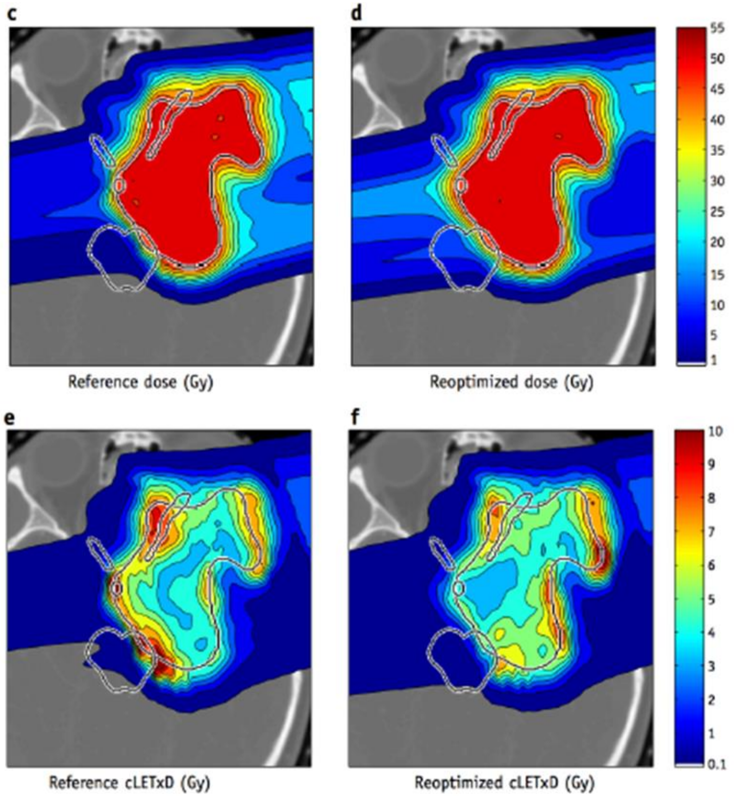
- Clinically, a fixed Relative Biological Effectiveness (RBE) of 1.1 is assumed at all positions along the Spread Out Bragg Peak (SOBP)

- From in-vitro cell experiments, we expect proton RBE to rise across the SOBP, rising rapidly at the end, extending the "biological range" by ~1-2mm



Biological effect: LET based planning





Reference dose (Gy)

Reoptimized dose (Gy)

Reference cLETxD (Gy)

Reoptimized cLETxD (Gy)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

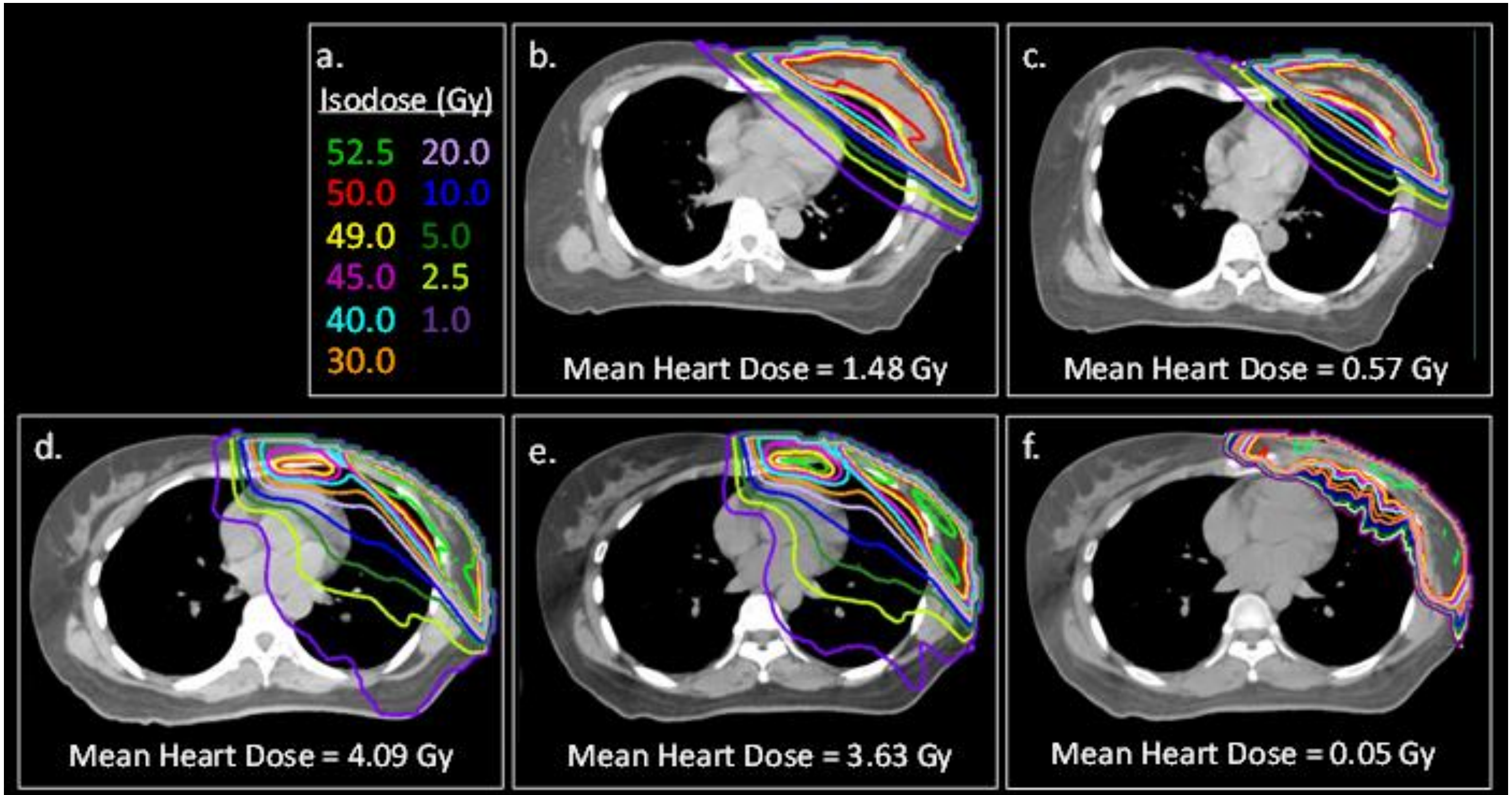
CONCLUSIONS

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. (Funded by Cancer Research UK and others.)

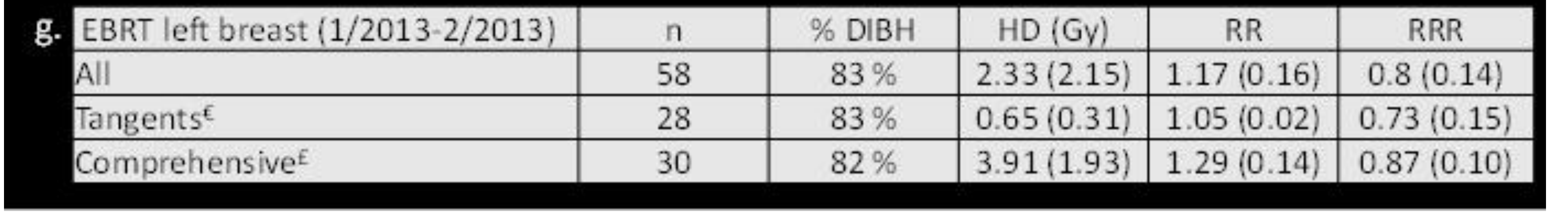
Howell R, Amos R, Kanke J, *et al.*

Predicted risk of cardiac effects with modern cardiac-sparing radiation therapy techniques

Proceedings of PTCOG 53. *Int J Particle Ther*. 2014;**1**(2):617-618



g.



EBRT left breast (1/2013-2/2013)	n	% DIBH	HD (Gy)	RR	RRR
All	58	83 %	2.33 (2.15)	1.17 (0.16)	0.8 (0.14)
Tangents€	28	83 %	0.65 (0.31)	1.05 (0.02)	0.73 (0.15)
Comprehensive£	30	82 %	3.91 (1.93)	1.29 (0.14)	0.87 (0.10)

R. Amos et al. / Clinical Oncology 30 (2018) 280–284

Proton Beam Therapy – the Challenges of Delivering High-quality Evidence of Clinical Benefit

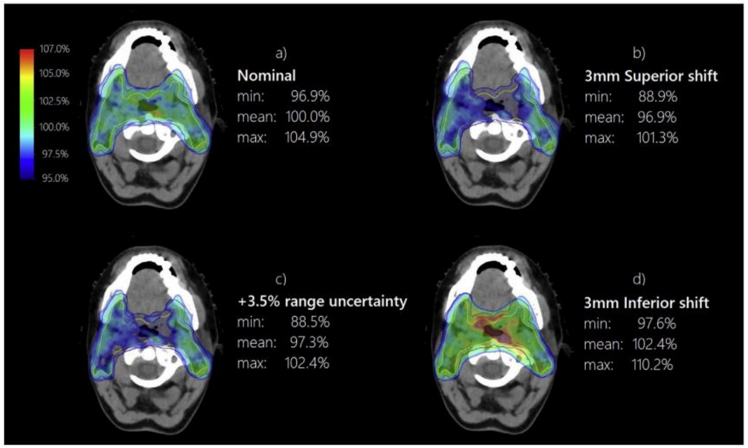
National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group (CTRad) Proton Beam Clinical Trial Strategy Group

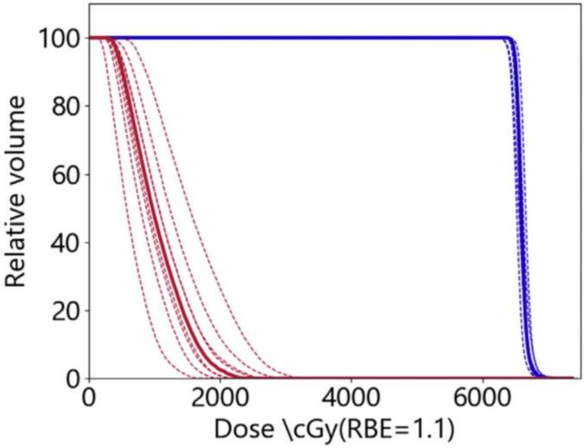
---

M. Lowe et al. / Clinical Oncology 32 (2020) 459–466

Comparing Proton to Photon Radiotherapy Plans: UK Consensus Guidance for Reporting Under Uncertainty for Clinical Trials

M. Lowe[*,†,1], A. Gosling[‡,1], O. Nicholas[§,¶,||], T. Underwood[†], E. Miles[**], Y.-C. Chang[††], R.A. Amos[‡‡], N.G. Burnet[†,§§], C.H. Clark[**], I. Patel[*,†], Y. Tsang[**], N. Sisson[¶¶,2], S. Gulliford[‡,||||,2]





Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

Aims:

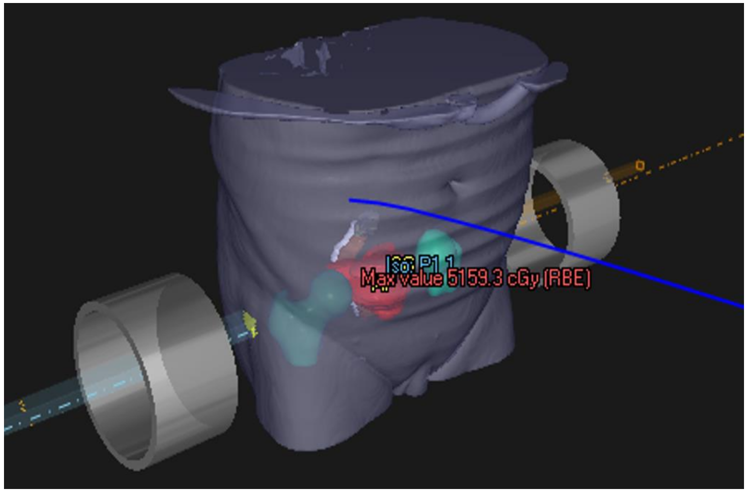
- To re-evaluate the technical requirements for clinical PBT systems.
- To suggest potential solutions for equipment cost-savings with the view to further democratize PBT for RT patients who may benefit.

Methods:

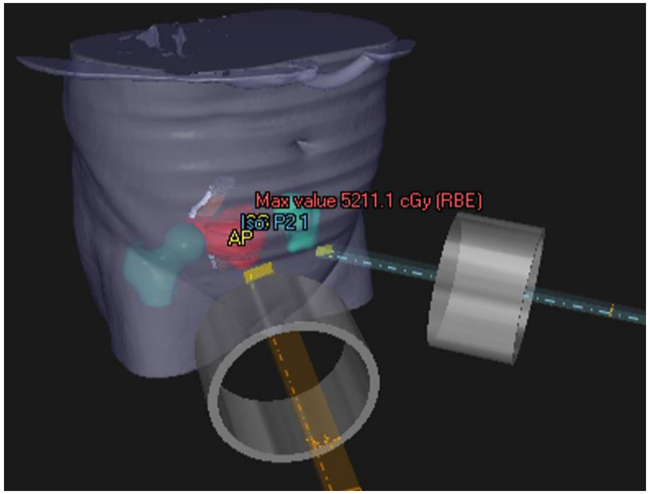
- Survey PBT community to establish baseline parameters for contemporary clinical practice.
- Attempt to re-establish a new baseline by examining:
  - a) Relevant indications for proton irradiation;
  - b) Pencil beam scanning (PBS) treatment techniques for these indications;
  - c) Related proton beam field parameters.
- Initial treatment planning study of two common PBT indications:
  1) Low- to intermediate-risk prostate cancer (*typically requires high-energy beams*).
  2) Cranio-spinal irradiation (CSI).
- LET_d re-distribution methods were applied and considered when evaluating treatment planning techniques.
- Treatment planning was done in research version 11B-IonPG(12.0.130) of RayStation (RaySearch Laboratories AB, Sweden).
- ***Work in progress***

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

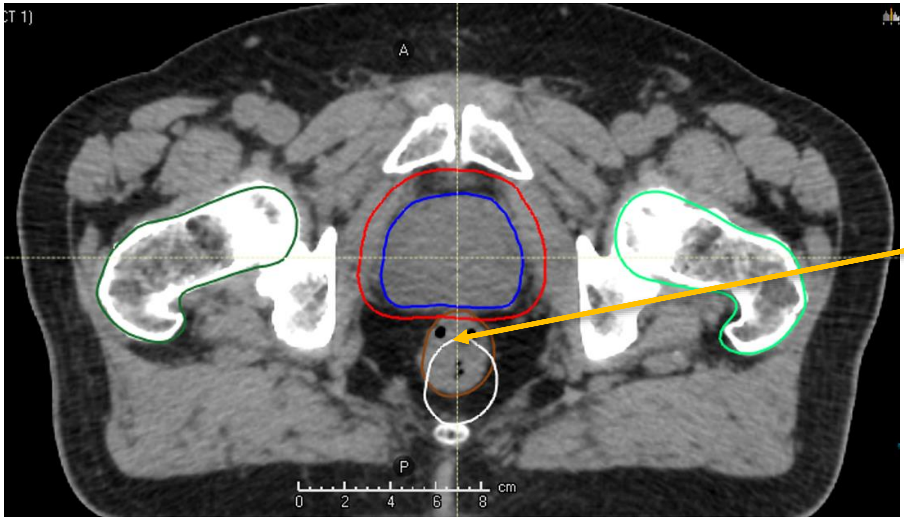
Example 1: Low- to intermediate-risk prostate PBT



Standard parallel-opposed Lats



Lt and Rt Anterior Obliques



Rectal volume displacement to simulate the use of the SpaceOAR™, or similar device, for rectal spacing.

Rectal displacement used: **12.7 mm**[1,2]

[1] Noyes WR, *et al*. Human collagen injections to reduce rectal dose during radiotherapy. *IJROBP* 2012; **82(5)**: 1918-1922

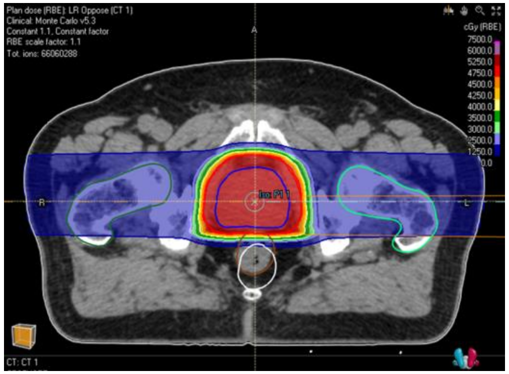
[2] **Amos RA**. Rectal dose reduction through tissue displacement during intensity-modulated proton therapy (IMPT) for prostate cancer. MPEC 2012

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

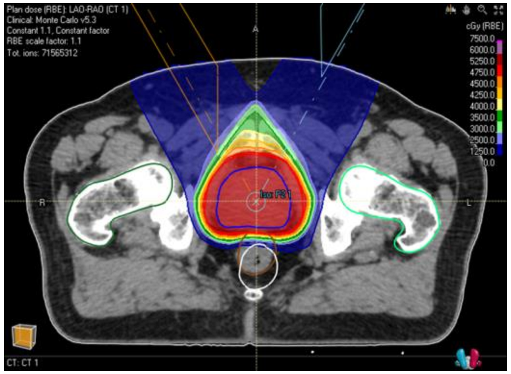
Robustly optimized PBS treatment plans

Standard parallel-opposed Lats

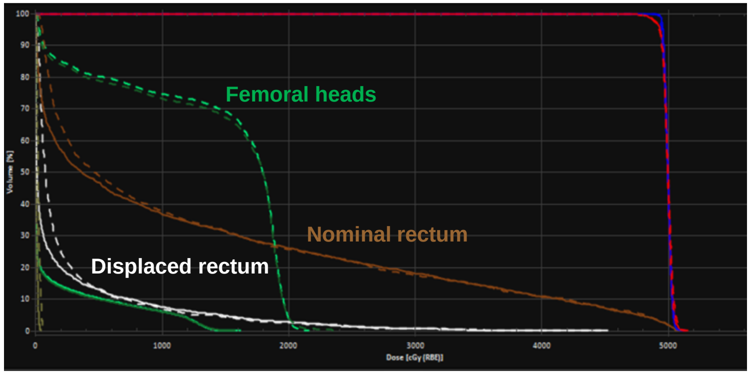
Lt and Rt Anterior Obliques



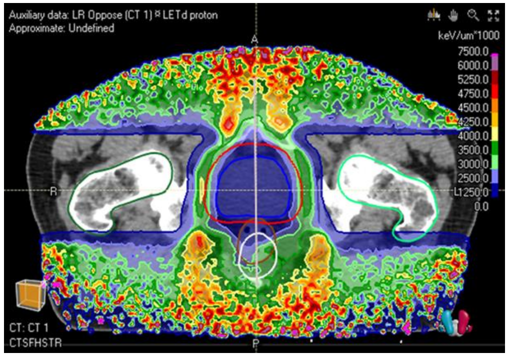
Highest beam energy = **205 MeV**



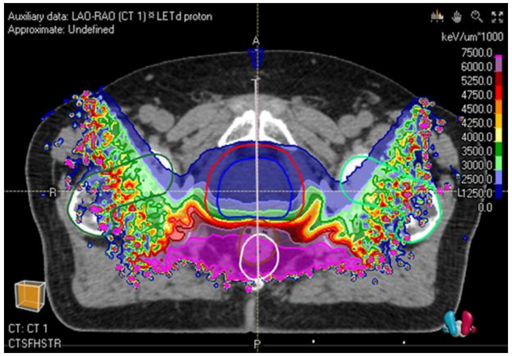
Highest beam energy = **171 MeV**



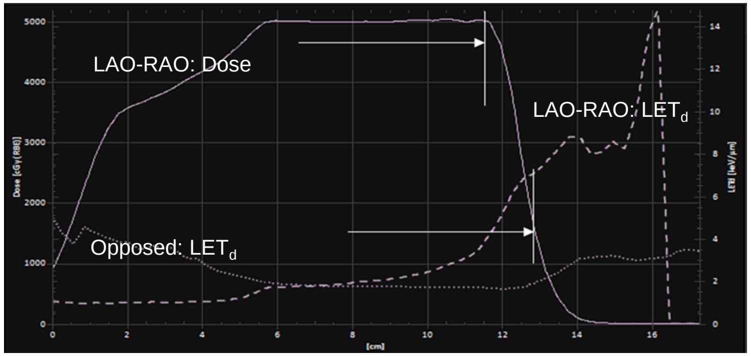
—— LAO-RAO - - - - - Opposed Lats



LET$_d$ distribution



LET$_d$ distribution

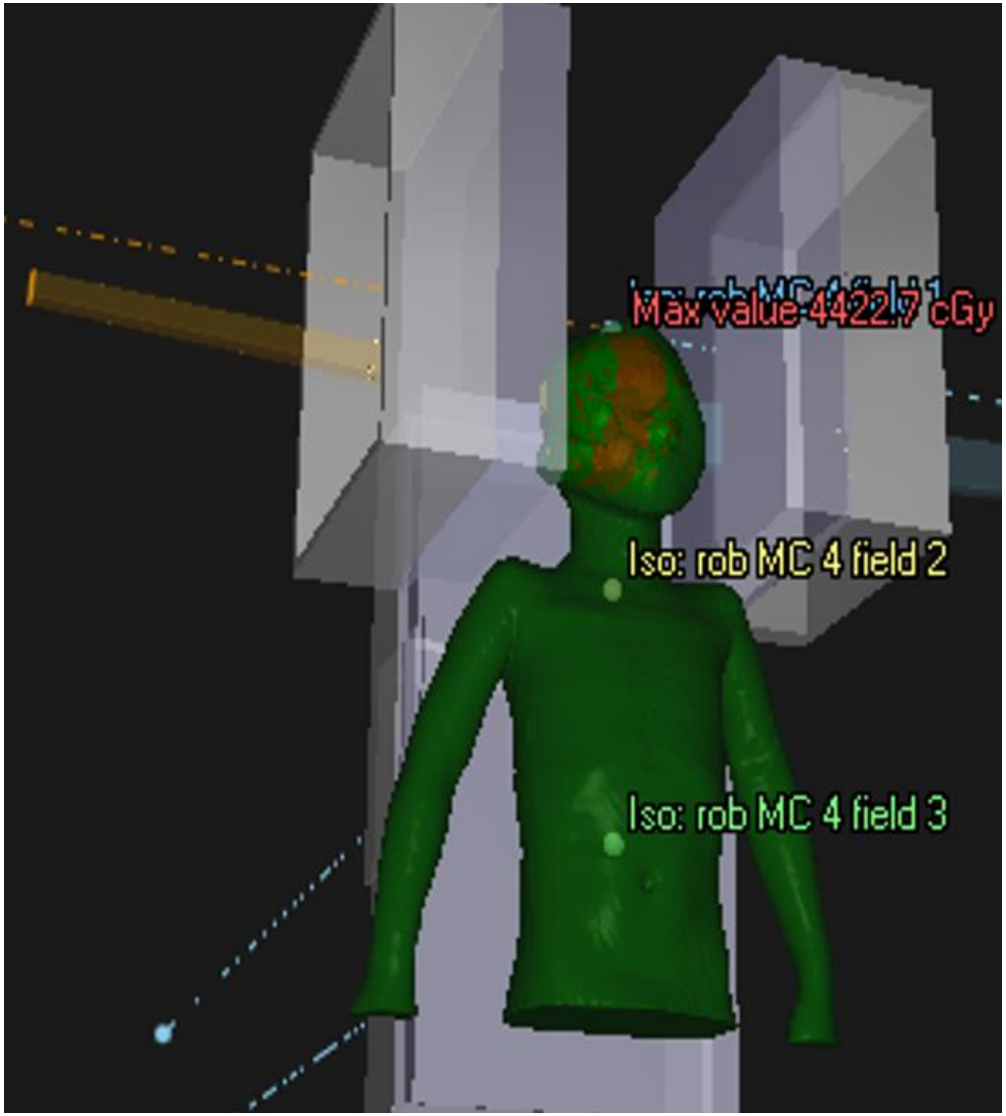


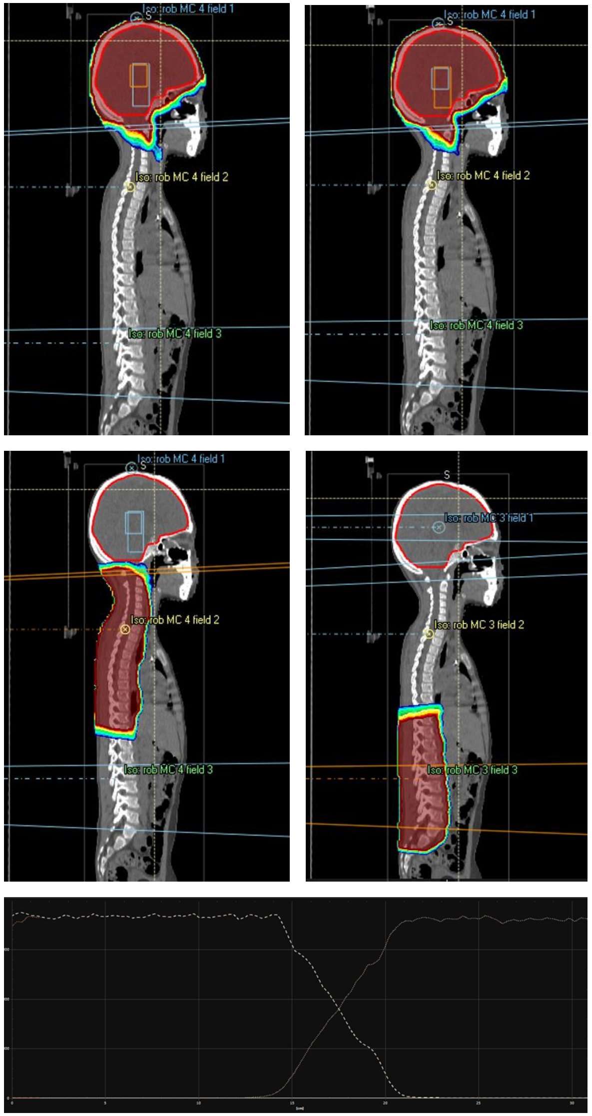
Dose and LET$_d$ data along central AP axis:

- Higher LET$_d$ in rectum for LAO-RAO plan, but at onset of dose fall-off (25% of Rx)

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

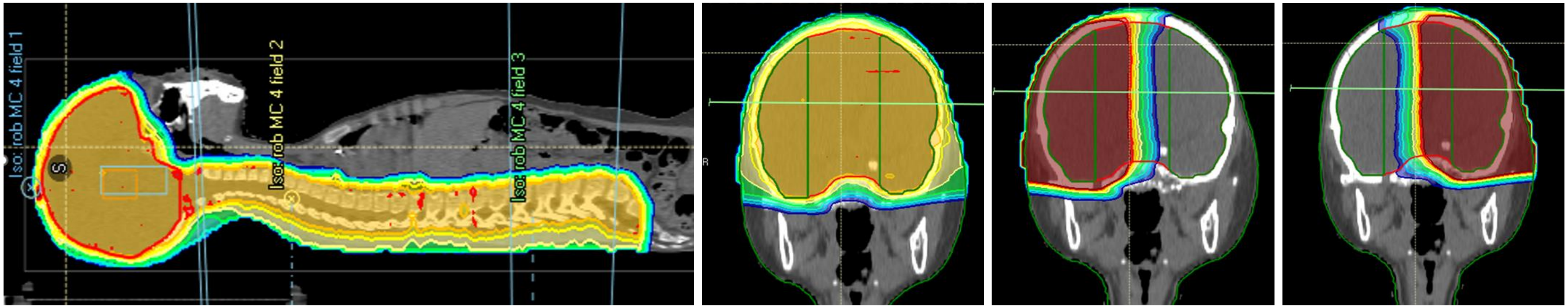
Example 2: Cranio-spinal irradiation (CSI)





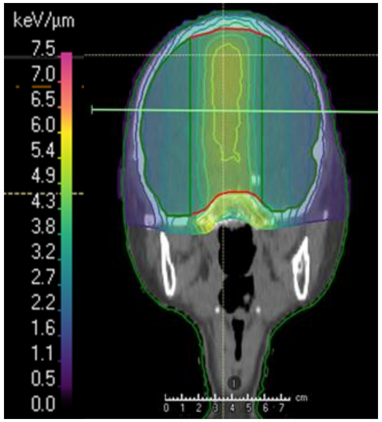
Robustly matched PBS fields

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

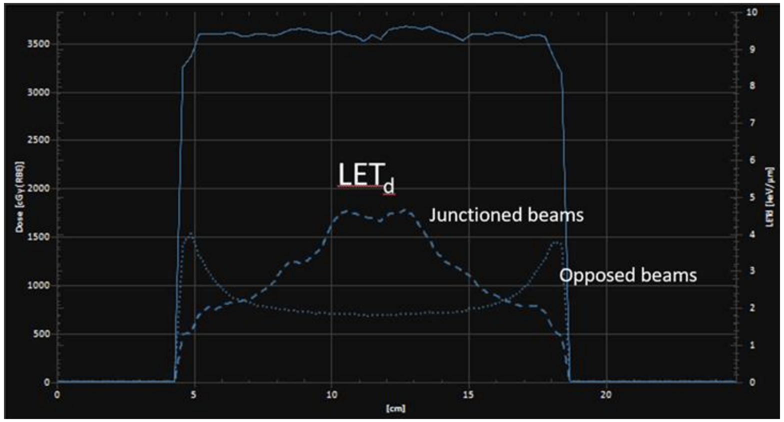


CSI with standard matched PA fields for the spine and Rt and Lt lateral *“junctioned”* fields for the whole brain **using $\mathbf{LET_d}$ penalty functions**. The junctioned fields match distally at mid-plane.

- Max. beam energy: spine fields = **150 MeV**
- Max. beam energy: *junctioned* brain fields = **165 MeV**
- Max. beam energy: standard parallel-opposed brain fields = **187 MeV**



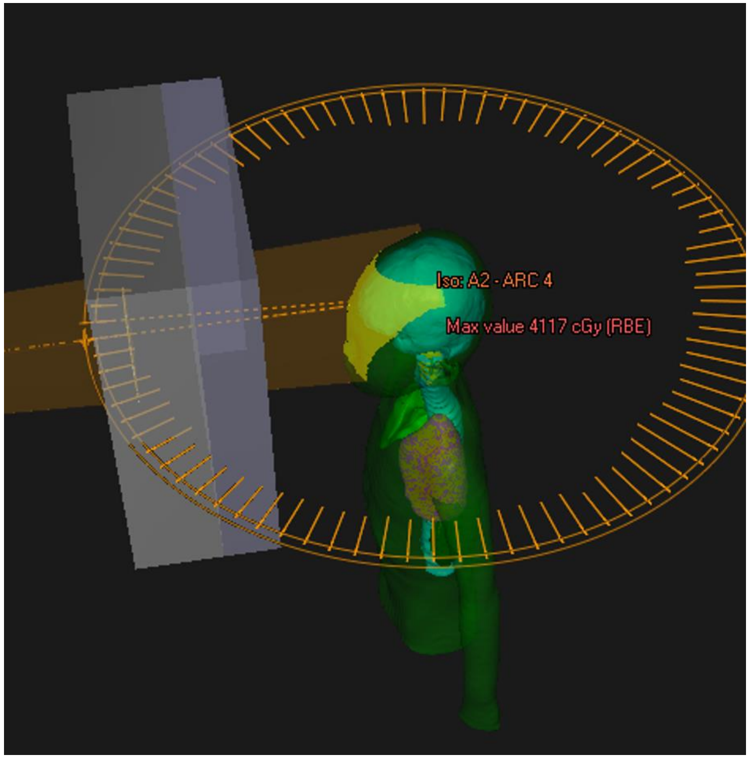
LET_d for *junctioned* fields.



Comparison of LET_d across whole brain for standard parallel-opposed fields and lateral *junctioned* fields.

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

Alternative approach:
Proton arc therapy to whole brain component of CSI



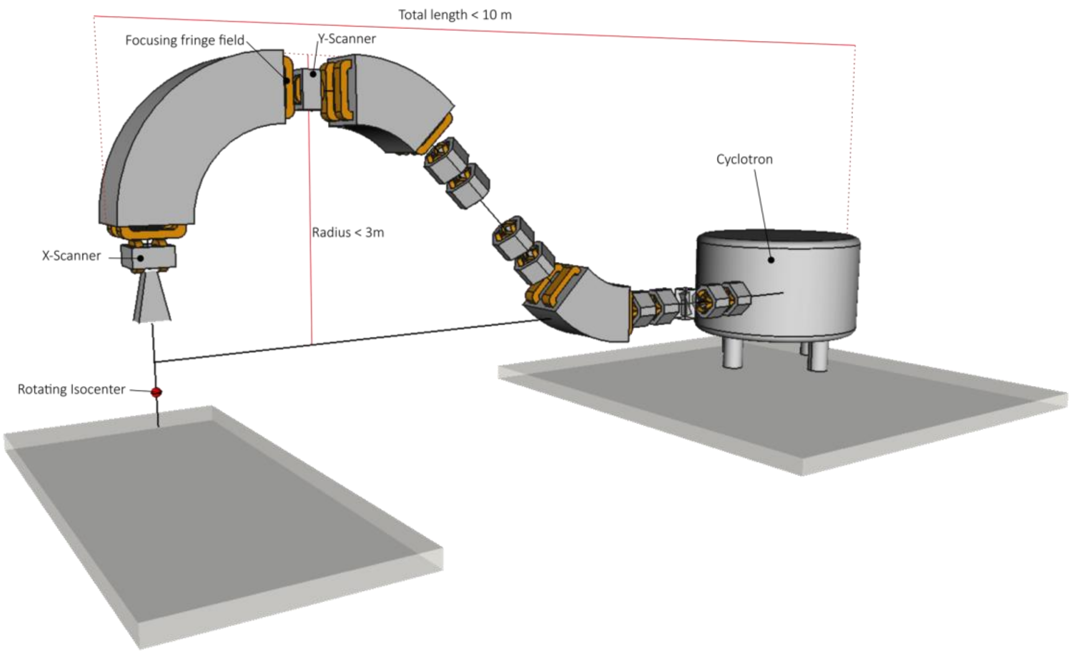
- Single 360º degree arc
- Max. beam energy = **159 MeV** (using a maximum radiological depth limit)
- Homogeneous LET_d

Further consideration of short IMPT spine field delivered while translating patient on couch.

Amos RA, *et al*. Re-evaluation of beam energy and field size limits for clinical proton beam therapy (PBT) and related PBT system requirements. *Physica Medica* **104(S1)**, S52-S53 (2022)

Proposed PBT System Configuration and Specifications (*patent pending*)

- Conventional (*non-superconductive*) cyclotron with beam energy of **180 MeV or less**.
- Degrader without a downstream energy selection system - *not required due to small distal fall-off at maximum energy.*
- Lightweight 360º non-isocentric gantry - *non-isocentricity reducing gantry radius.*
- Scanning system with one scanner before last bending magnet - *reducing gantry radius.*
- Bending magnet with focusing entrance fringe field – *enabling compactness of magnet.*
- Small maximum field size (20x10 or 10x10 cm^2) reducing cost of scanning magnets and power supplies and enabling scanning through the last bending magnet.

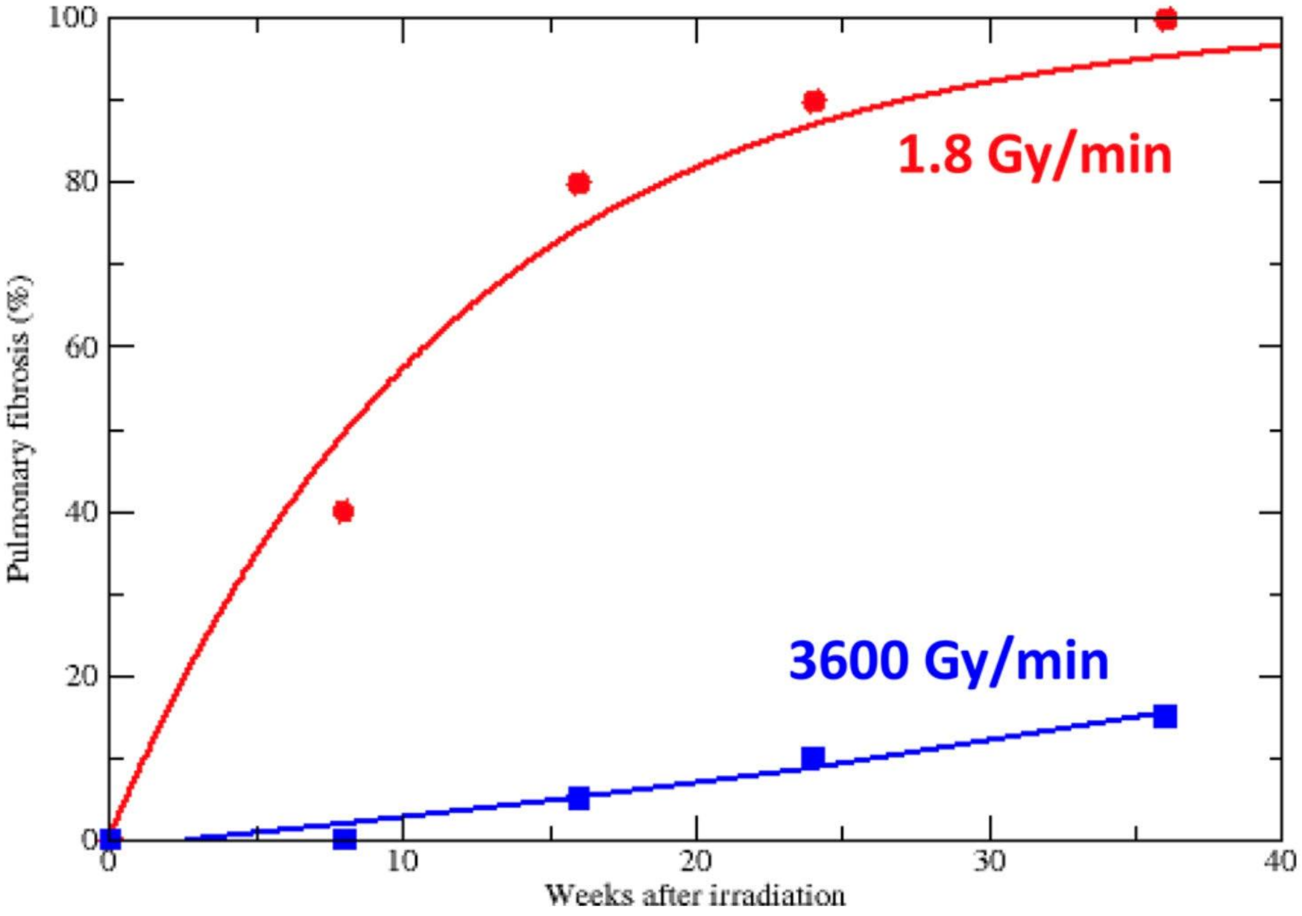


Main Advantages of Proposed System

- Equipment **cost greatly reduced** (estimated to be below $10M) ⇒ **improved accessibility of PBT**
- Gantry radius < 3 m and total length < 10 m ⇒ **significant reduction in building cost**
- Low energy requiring **less shielding** of secondary radiation ⇒ further reduction in building cost
- Possible combination with conventional linacs (*several options of level of integration*) ⇒ combination x-ray/proton therapy for certain indications.
- Low maximum energy enabling high beam currents ⇒ **FLASH compatible**
- **Proton arc compatible**

FLASH-RT: Ultra-high dose rate (UHDR) radiotherapy

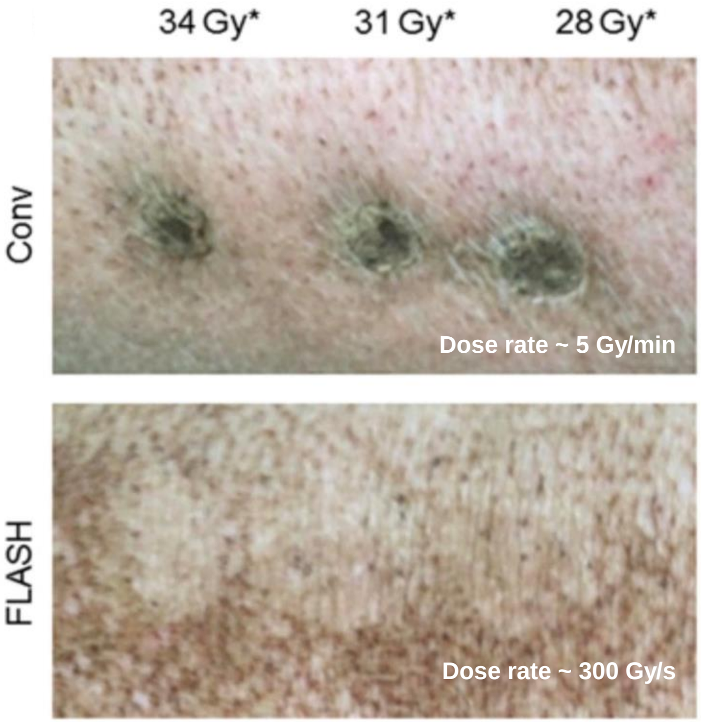
Dose rate >40 Gy s^{-1}



Data from:
Favaudon V, *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med* 2014; 6: 245ra93.

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

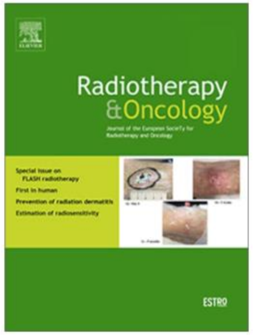


36 weeks post-irradiation of mini-pig skin:

- Conv-irradiation – severe fibronecrotic lesions
- FLASH-irradiation – normal appearance of skin

Conclusions: Our results confirmed the potential advantage of FLASH-RT and provide a strong rationale for further evaluating FLASH-RT in human patients.

FLASH-RT for SCC



First in Human

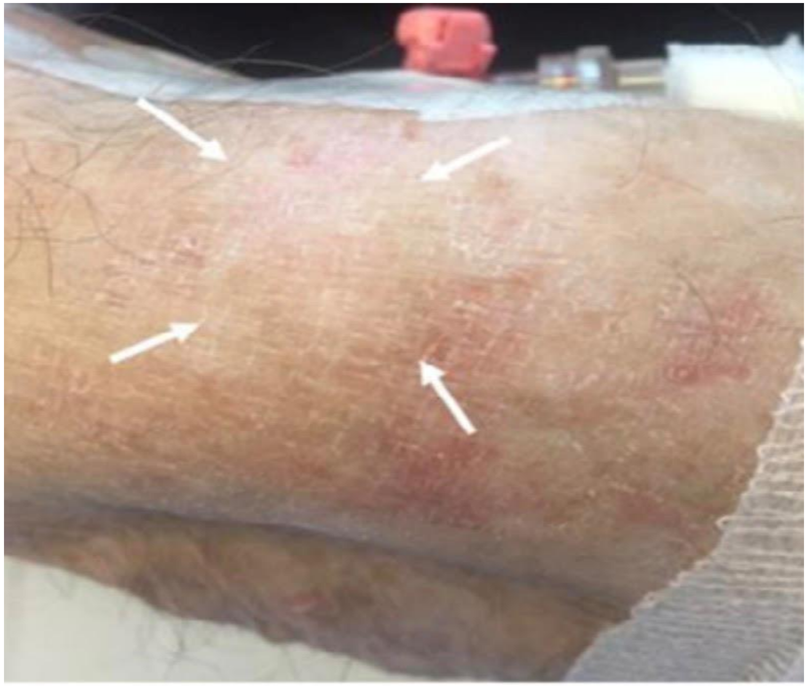
Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

75 yr old patient with multi-resistant CD30+ T-Cell cutaneous lymphoma

FLASH-RT - 15 Gy in 90 ms

Day 0

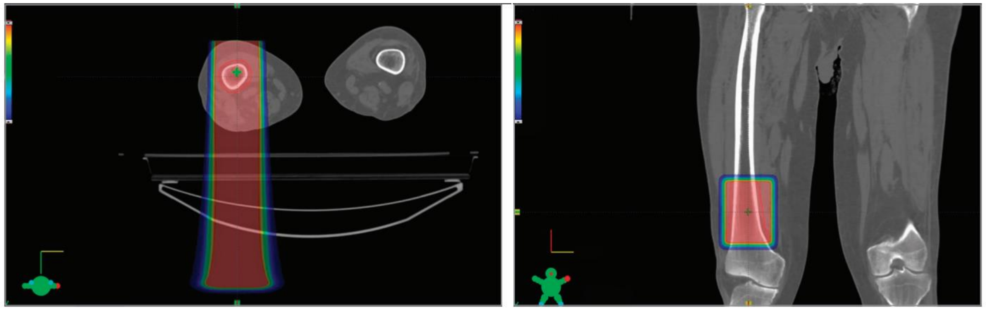


5 Months

JAMA Oncology | **Original Investigation**

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases

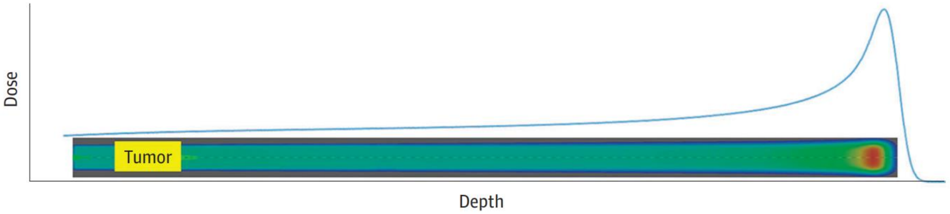
The FAST-01 Nonrandomized Trial



A Axial CT

B Coronal CT

C Radiation dose as a function of depth of penetration

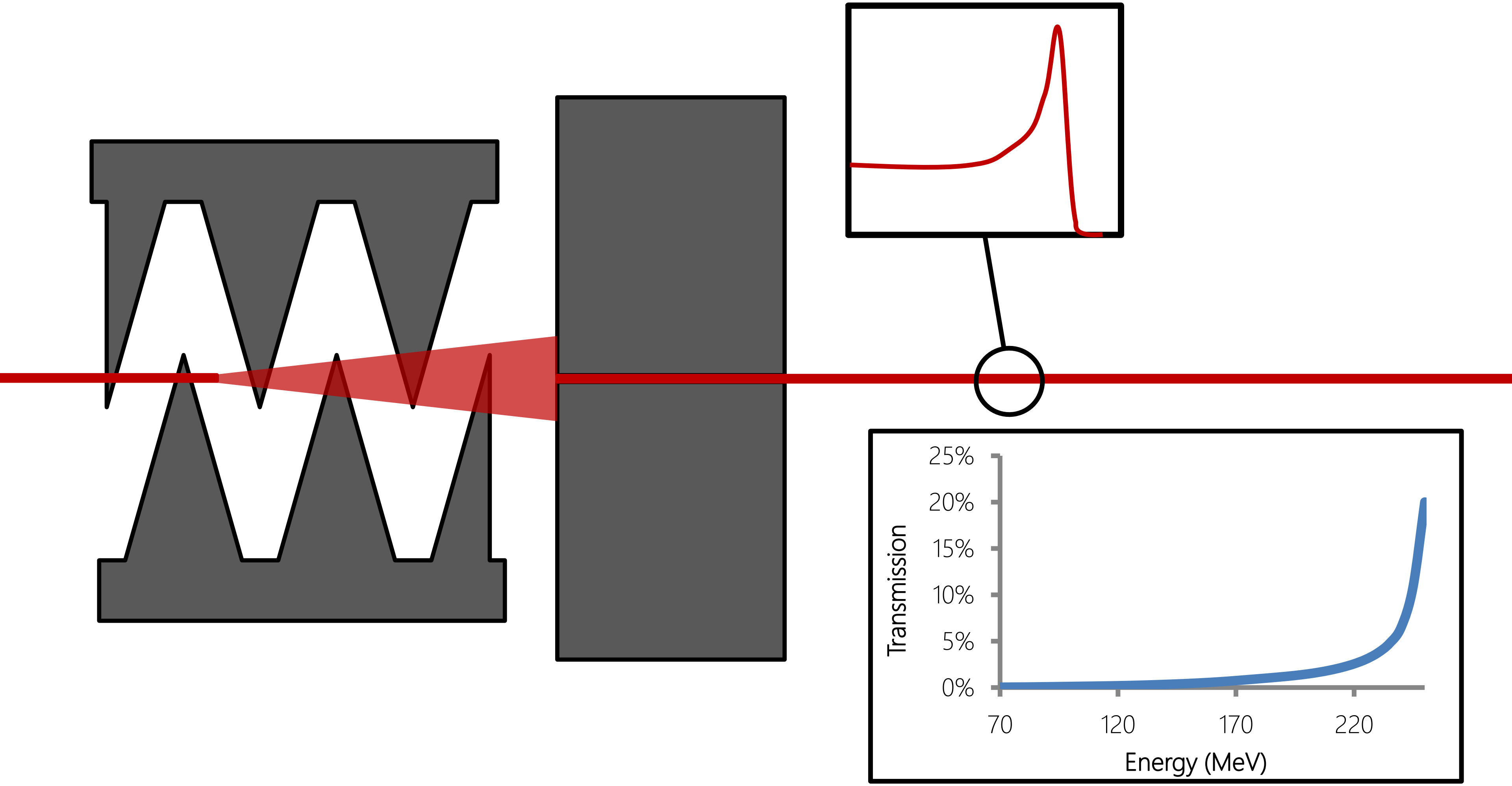


Key Points

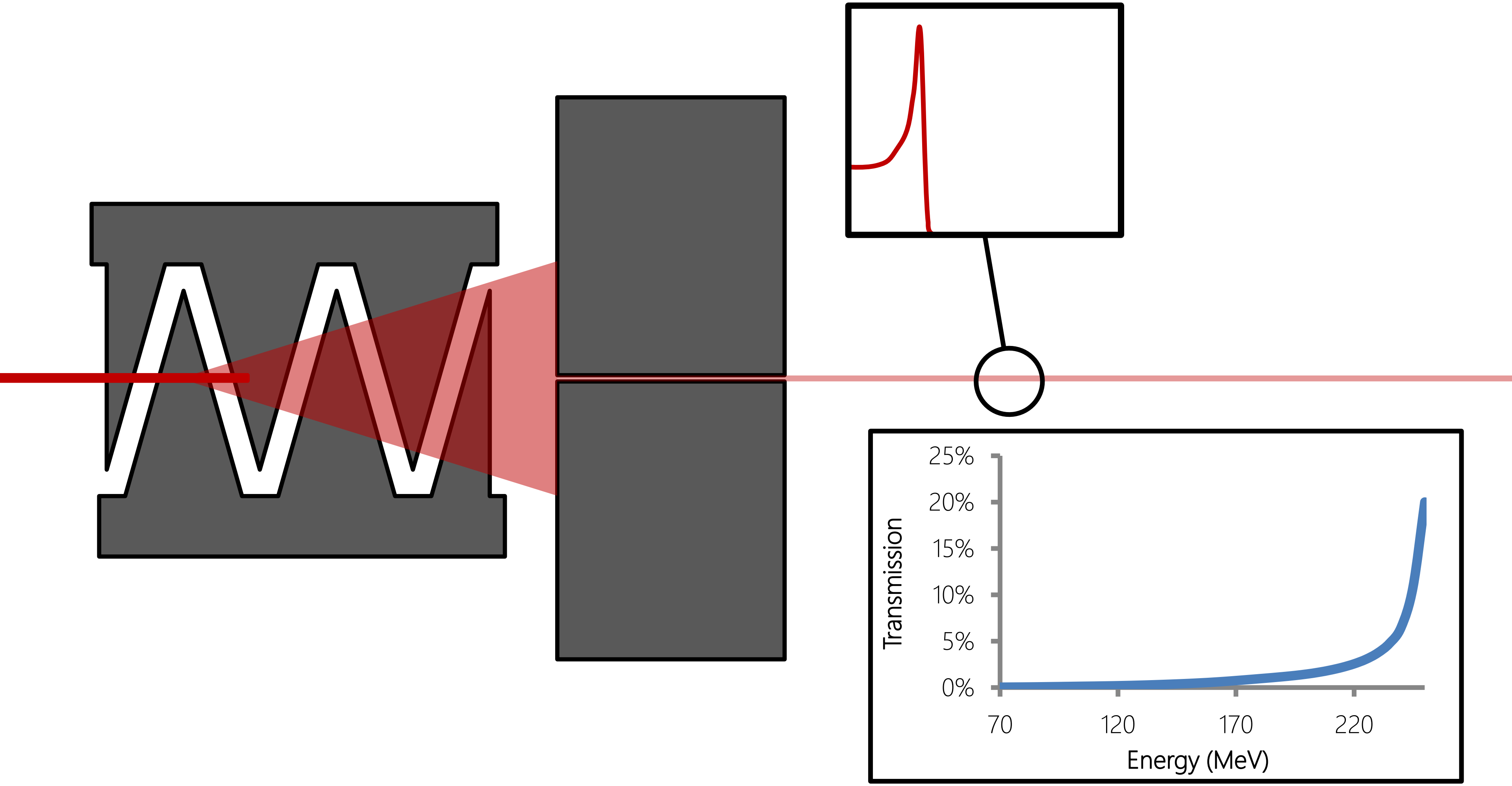
Question Is proton FLASH radiotherapy, delivered at 1000 times the dose rate of conventional-dose-rate photon radiotherapy for its potential normal tissue-sparing effects, feasible for the palliation of painful bone metastases in the extremities?

Findings This nonrandomized trial of 10 patients with bone metastases in the extremities found that proton FLASH was clinically feasible, and its safety was supported by the minimal severity of related adverse events. In this small sample size, the efficacy of FLASH treatment for pain relief appeared to be similar to that of conventional-dose-rate photon radiotherapy.

Meaning The results of this study confirm the workflow feasibility of delivering ultra-high-dose-rate proton FLASH radiation treatment in a routine clinical setting and support the further exploration of proton FLASH radiotherapy.



Courtesy of Matthew Lowe



Courtesy of Matthew Lowe

Practical challenges for the clinical delivery of safe and efficacious proton FLASH

Taking advantage of the Bragg peak:
- Transport lower energies at ultra-high dose rates
- Custom beam shaping devices at end of delivery nozzle
  - eg: “*Hedgehog*” from IBA
- What is the impact of sub-FLASH dose rates at distal fall off for distal OAR?
- …….

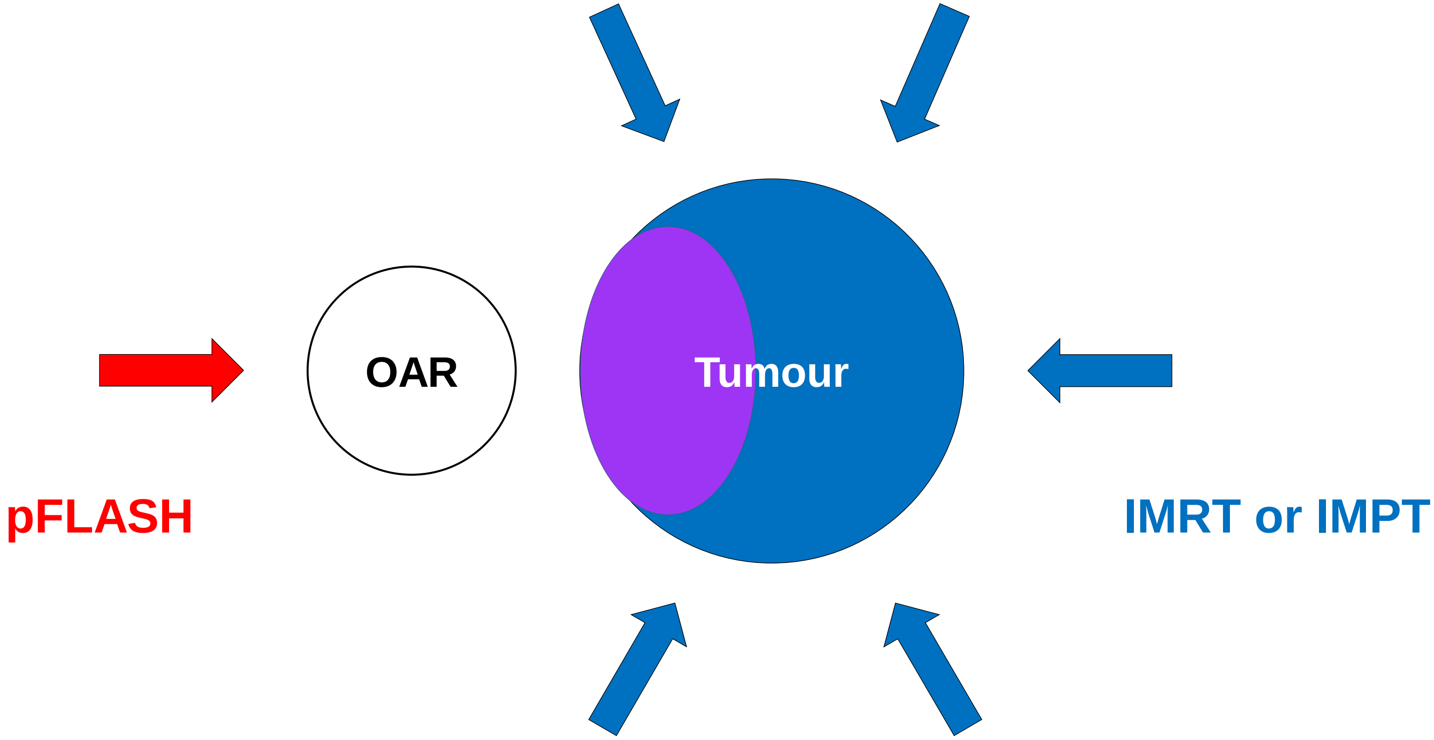
Motion mitigation:
- No motion-related interplay effect
- FLASH delivery requires precise timing to hit a moving target
- …

Accurate absolute and relative dosimetry:
- Dose rate dependency issues with dosimeters
- …

Radiation shielding:
- Higher dose rates
- Different workload
- …

………

Combining pFLASH with conventional dose rate RT to spare OAR?



PTCOG 57

IPEM Code of Practice for proton and ion beam dosimetry: update on work in progress

Stuart Green[1], Richard Amos[2], Francesca Fiorini[3], Frank van den Heuvel[3], Andrzej Kacperek[4], Ana Lourenço[5], Ranald MacKay[6], Hugo Palmans[5], John Pettingell[7], Derek D'Souza[8], Russell Thomas[5]

[1]University Hospital Birmingham, [2]University College London, [3]University of Oxford, [4]Clatterbridge Cancer Centre, [5]National Physical Laboratory, [6]Manchester Cancer Research Centre, [7]Proton Partners International Ltd., [8]University College London Hospitals

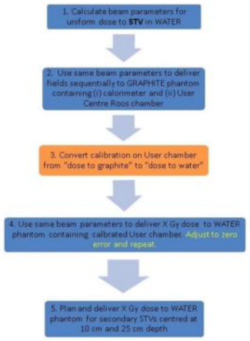
OBJECTIVES

This poster provides an update on the development of a new Code of Practice for reference dosimetry of proton and ion beams, applicable to both scanned and scattered beam configurations.

It is aimed to deliver an uncertainty on reference dose (at 95% CL) for protons of at most ±2%

This is approximately half of the uncertainty estimated for calibrations utilising the framework of TRS-398[1]

It will utilise a primary standard graphite calorimeter that is robust and portable enough to be used in the end-user facility.


1. Calculate beam parameters for uniform dose to **STV** in WATER

2. Use same beam parameters to deliver fields sequentially to GRAPHITE phantom containing (i) calorimeter and (ii) User Centre Roos chamber

3. Convert calibration on User chamber from "dose to graphite" to "dose to water"

4. Use same beam parameters to deliver X Gy dose to WATER phantom containing calbrated User chamber. Adjust to zero error and repeat.

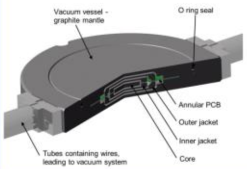
5. Plan and deliver X Gy dose to WATER phantom for secondary STVs centred at 10 cm and 25 cm depth

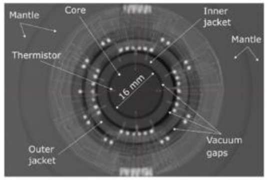
METHODS – Portable Graphite calorimeter

Main effort will focus on the approach for scanned beams, but will also make recommendations for passively scattered beams

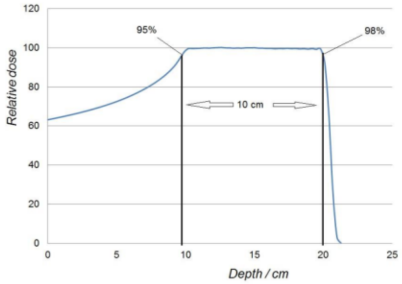
For scattered beams the recommendations will follow those of TRS 398 with modification only where required to incorporate use of the NPL calorimeter in the user beams

Definitive dose calibration will be performed in a Standard Test Volume (STV) of dose which can be considered as a Plan Class Specific Reference Field[2]





Definition of the STV(s) and issues with ripple



There will be a degree of "ripple" in the "flat" region of dose in which measurements are made. This should be within normal clinical tolerances (less than 1% peak-to-peak) but where a Roos-design chamber is used, unless this is mitigated in some way it will contribute to uncertainties in the dose calibration. Experimental approaches to mitigate this effect will be necessary

There will be supplementary STVs defined to be centred at 10cm and 25 cm deep which will also be utilised

Detailed description of proposed steps

Step 1:

Define primary STV as 10 x 10 x 10 cm centred at 15 cm depth in water. Use the TPS to plan a uniform prescribed dose to the primary STV, with the centre of the STV positioned at the beam isocentre.

Step 2:

(i) Use the derived beam parameters to deliver this treatment to the graphite phantom with the calorimeter core at the centre of the reference STV, and the core positioned at the beam isocentre.

(ii) Deliver the same beams to the graphite phantom with the users secondary standard Roos chamber at the position of the calorimeter core.

Step 3:

Use generic simulations and other required measurements to derive the conversion factor between dose-to-graphite and dose-to-water for this STV and apply this to the user secondary standard reference chamber. This step is the responsibility of the NPL team and the derivation of the conversion factors will be done only once.

Step 4:

Deliver the field(s) as planned in Step 1 to a water phantom with the user secondary standard Roos chamber positioned at the centre of the reference STV and at the beam isocentre. Note the ratio (averaged over a number of deliveries) of the planned and delivered dose. Adjust beam calibration as necessary and repeat.

Step 5:

Repeat for the STV dose volumes at reduced and increased depth and note results as above in Step 4.

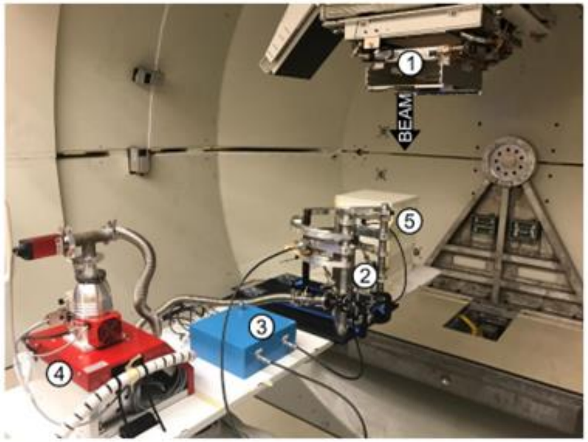
References

1. TRS398. *Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry based on Standards of Absorbed Dose to Water, Chapters 10 and 11,* IAEA, 2000
2. Alphonso R, Andreo P, Capote R, Huq SM, Kilby W, Kjall P, Mackie TR, Palmans H, Rosser K, Seuntjens J, Ullrich W, Vatnitsky S. *A new formalism for reference dosimetry of small and non-standard fields*, Med Phys **53**, 5179-5186 (2008).

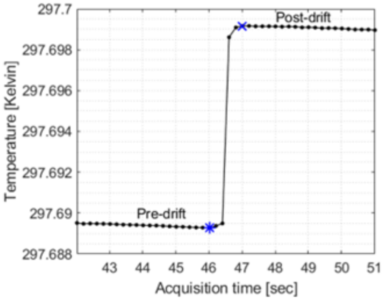
Absolute dosimetry for FLASH proton pencil beam scanning radiotherapy

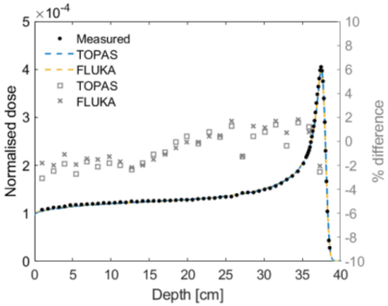
Ana Lourenço[1,2*], Anna Subiel[1], Nigel Lee[1], Sam Flynn[1,3], John Cotterill[1], David Shipley[1], Francesco Romano[4], Joe Speth[5,6], Eunsin Lee[5,6], Yongbin Zhang[5,6], Zhiyan Xiao[5,6], Anthony Mascia[5,6], Richard A. Amos[2], Hugo Palmans[1,7] and Russell Thomas[1,8]

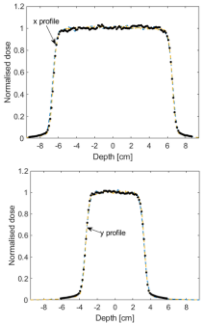
(Accepted for publication in ***Nature Scientific Reports***)

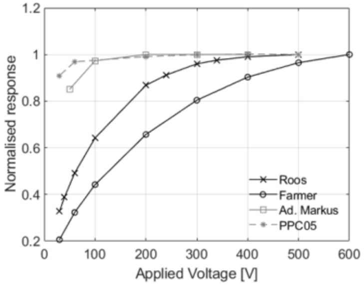


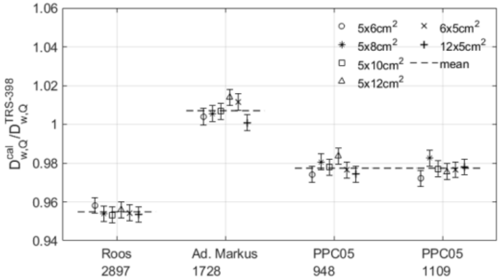
1. gantry
2. NPL primary-standard proton calorimeter (PSPC)
3. instrumentation for the NPL PSPC
4. vacuum pump
5. ion chamber setup











Calorimetry measurements were performed, and necessary correction factors established for absolute dosimetry of FLASH proton pencil beam scanning. This enabled the safe and accurate implementation in the clinic of this new treatment modality. The NPL PSPC accurately measures the dose delivered with an uncertainty two times smaller than the dose derived from ionisation chambers. The response of the calorimeter is dose-rate independent, as opposed to the response of ionisation chambers which need to be very well characterised at FLASH dose-rates since large ion recombination effects occur. The overall uncertainty on the dose measured with the NPL PSPC is 0.9% (1σ) which is in line with recommendations[33,34] for reference dosimetry for effective radiotherapy treatments.

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

Med Phys. 2022;49:6171–6182.

Ultrahigh dose rate pencil beam scanning proton dosimetry using ion chambers and a calorimeter in support of first in-human FLASH clinical trial

Eunsin Lee[1,2] | **Ana Mónica Lourenço**[3,4] | **Joseph Speth**[5] | **Nigel Lee**[3] | **Anna Subiel**[3] | **Francesco Romano**[6] | **Russell Thomas**[3,7] | **Richard A. Amos**[4] | **Yongbin Zhang**[1,2] | **Zhiyan Xiao**[1,2] | **Anthony Mascia**[1,2]

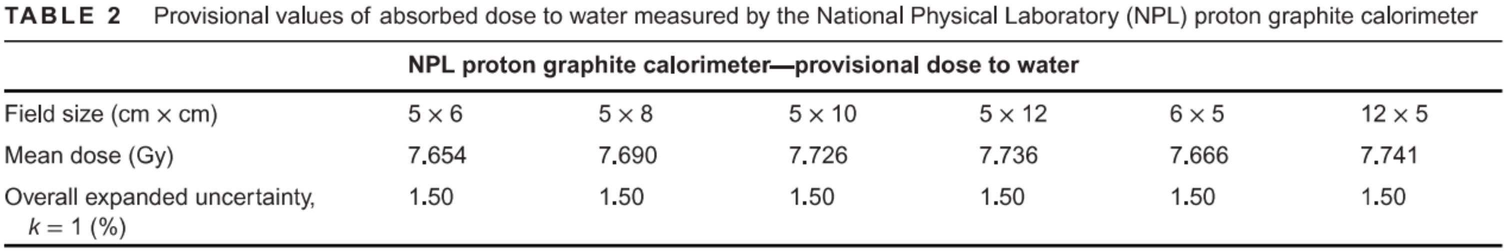


TABLE 2 Provisional values of absorbed dose to water measured by the National Physical Laboratory (NPL) proton graphite calorimeter

	NPL proton graphite calorimeter—provisional dose to water					
Field size (cm × cm)	5 × 6	5 × 8	5 × 10	5 × 12	6 × 5	12 × 5
Mean dose (Gy)	7.654	7.690	7.726	7.736	7.666	7.741
Overall expanded uncertainty, $k = 1$ (%)	1.50	1.50	1.50	1.50	1.50	1.50

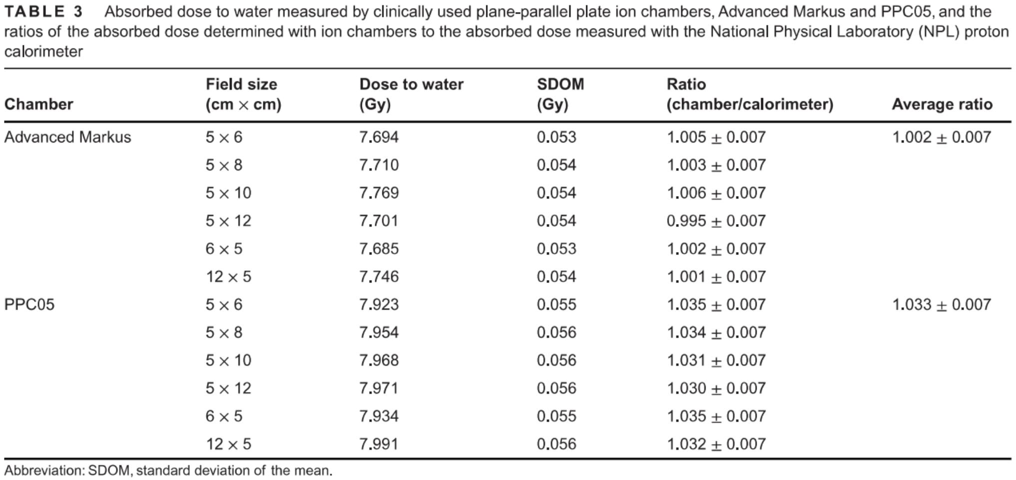
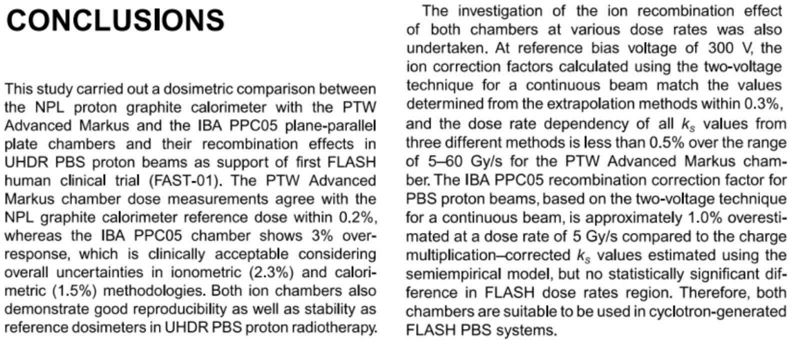


TABLE 3 Absorbed dose to water measured by clinically used plane-parallel plate ion chambers, Advanced Markus and PPC05, and the ratios of the absorbed dose determined with ion chambers to the absorbed dose measured with the National Physical Laboratory (NPL) proton calorimeter

Chamber	Field size (cm × cm)	Dose to water (Gy)	SDOM (Gy)	Ratio (chamber/calorimeter)	Average ratio
Advanced Markus	5 × 6	7.694	0.053	1.005 ± 0.007	1.002 ± 0.007
	5 × 8	7.710	0.054	1.003 ± 0.007	
	5 × 10	7.769	0.054	1.006 ± 0.007	
	5 × 12	7.701	0.054	0.995 ± 0.007	
	6 × 5	7.685	0.053	1.002 ± 0.007	
	12 × 5	7.746	0.054	1.001 ± 0.007	
PPC05	5 × 6	7.923	0.055	1.035 ± 0.007	1.033 ± 0.007
	5 × 8	7.954	0.056	1.034 ± 0.007	
	5 × 10	7.968	0.056	1.031 ± 0.007	
	5 × 12	7.971	0.056	1.030 ± 0.007	
	6 × 5	7.934	0.055	1.035 ± 0.007	
	12 × 5	7.991	0.056	1.032 ± 0.007	

Abbreviation: SDOM, standard deviation of the mean.



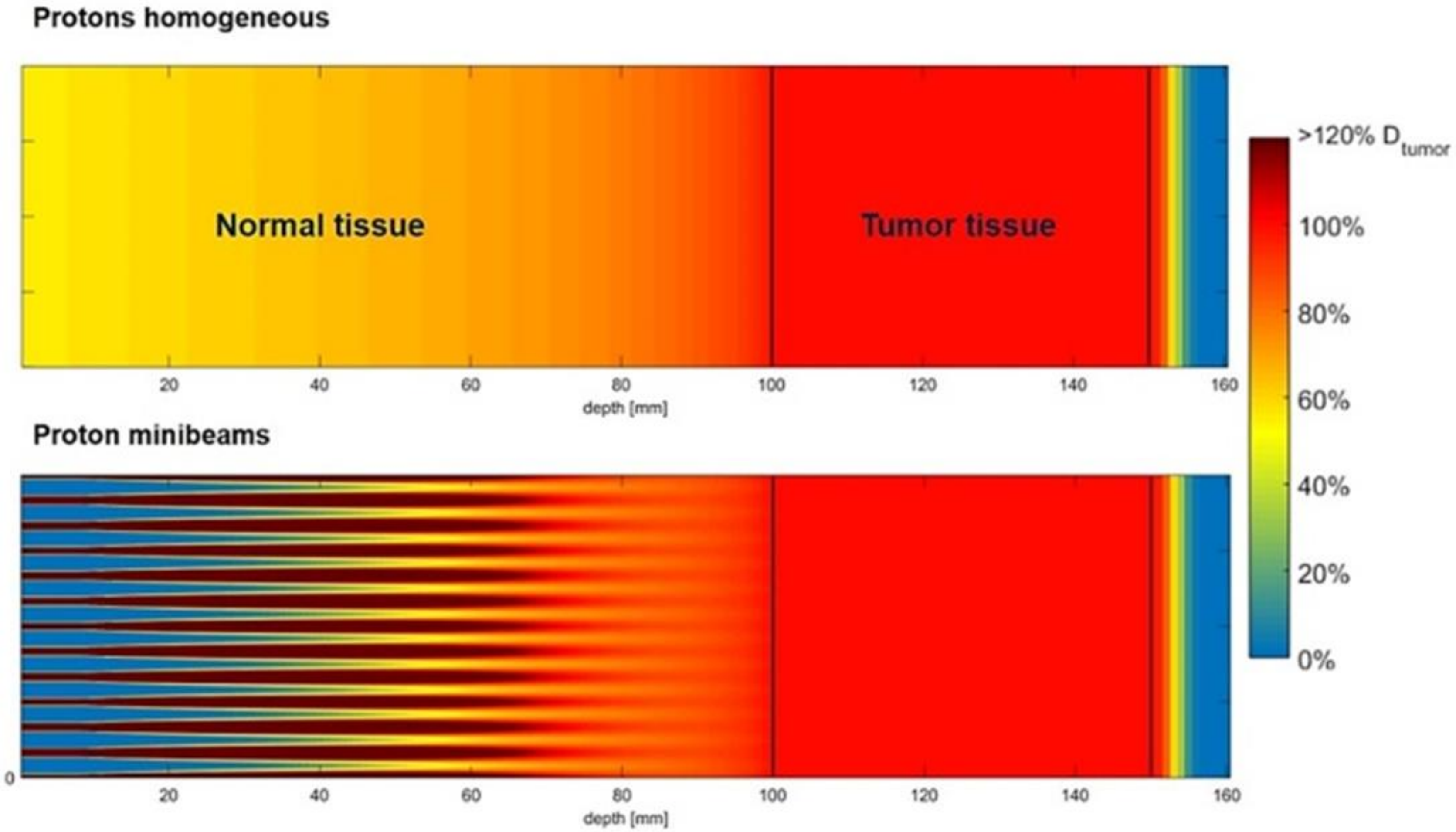
CONCLUSIONS

This study carried out a dosimetric comparison between the NPL proton graphite calorimeter with the PTW Advanced Markus and the IBA PPC05 plane-parallel plate chambers and their recombination effects in UHDR PBS proton beams as support of first FLASH human clinical trial (FAST-01). The PTW Advanced Markus chamber dose measurements agree with the NPL graphite calorimeter reference dose within 0.2%, whereas the IBA PPC05 chamber shows 3% over-response, which is clinically acceptable considering overall uncertainties in ionometric (2.3%) and calorimetric (1.5%) methodologies. Both ion chambers also demonstrate good reproducibility as well as stability as reference dosimeters in UHDR PBS proton radiotherapy.

The investigation of the ion recombination effect of both chambers at various dose rates was also undertaken. At reference bias voltage of 300 V, the ion correction factors calculated using the two-voltage technique for a continuous beam match the values determined from the extrapolation methods within 0.3%, and the dose rate dependency of all k_s values from three different methods is less than 0.5% over the range of 5–60 Gy/s for the PTW Advanced Markus chamber. The IBA PPC05 recombination correction factor for PBS proton beams, based on the two-voltage technique for a continuous beam, is approximately 1.0% overestimated at a dose rate of 5 Gy/s compared to the charge multiplication–corrected k_s values estimated using the semiempirical model, but no statistically significant difference in FLASH dose rates region. Therefore, both chambers are suitable to be used in cyclotron-generated FLASH PBS systems.

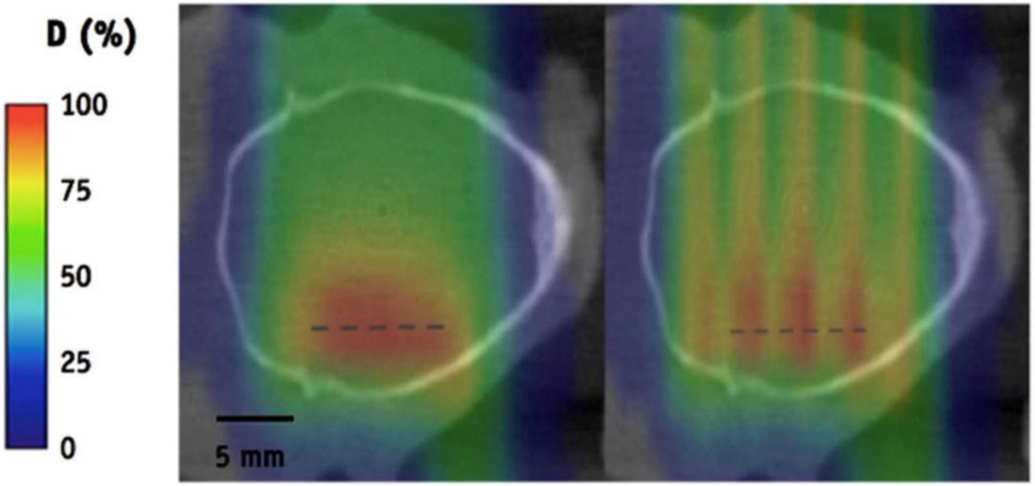
Proton Minibeam Radiation Therapy (pMBRT)

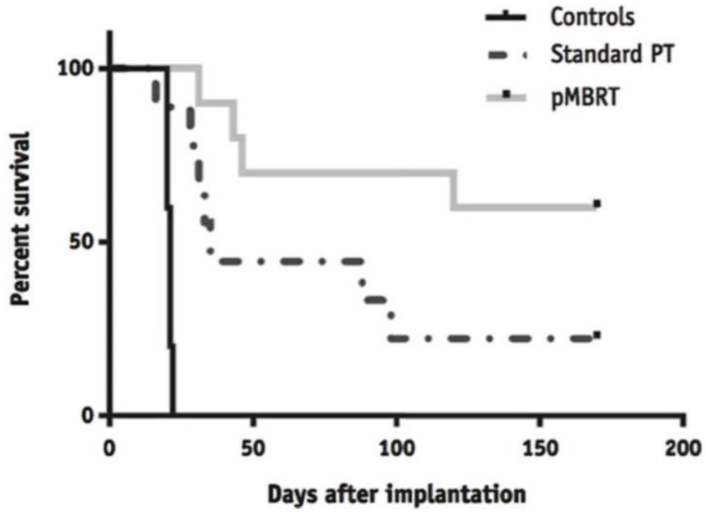
- Spatially fractionated proton beams – spares proximal normal tissue.
- Minibeam FWHM approx. 1 – 2mm.
- Minibeams created with either PBS or PSPT system with slit collimation.



International Journal of
Radiation Oncology
biology • physics

Tumor Control in RG2 Glioma-Bearing Rats: A Comparison Between Proton Minibeam Therapy and Standard Proton Therapy

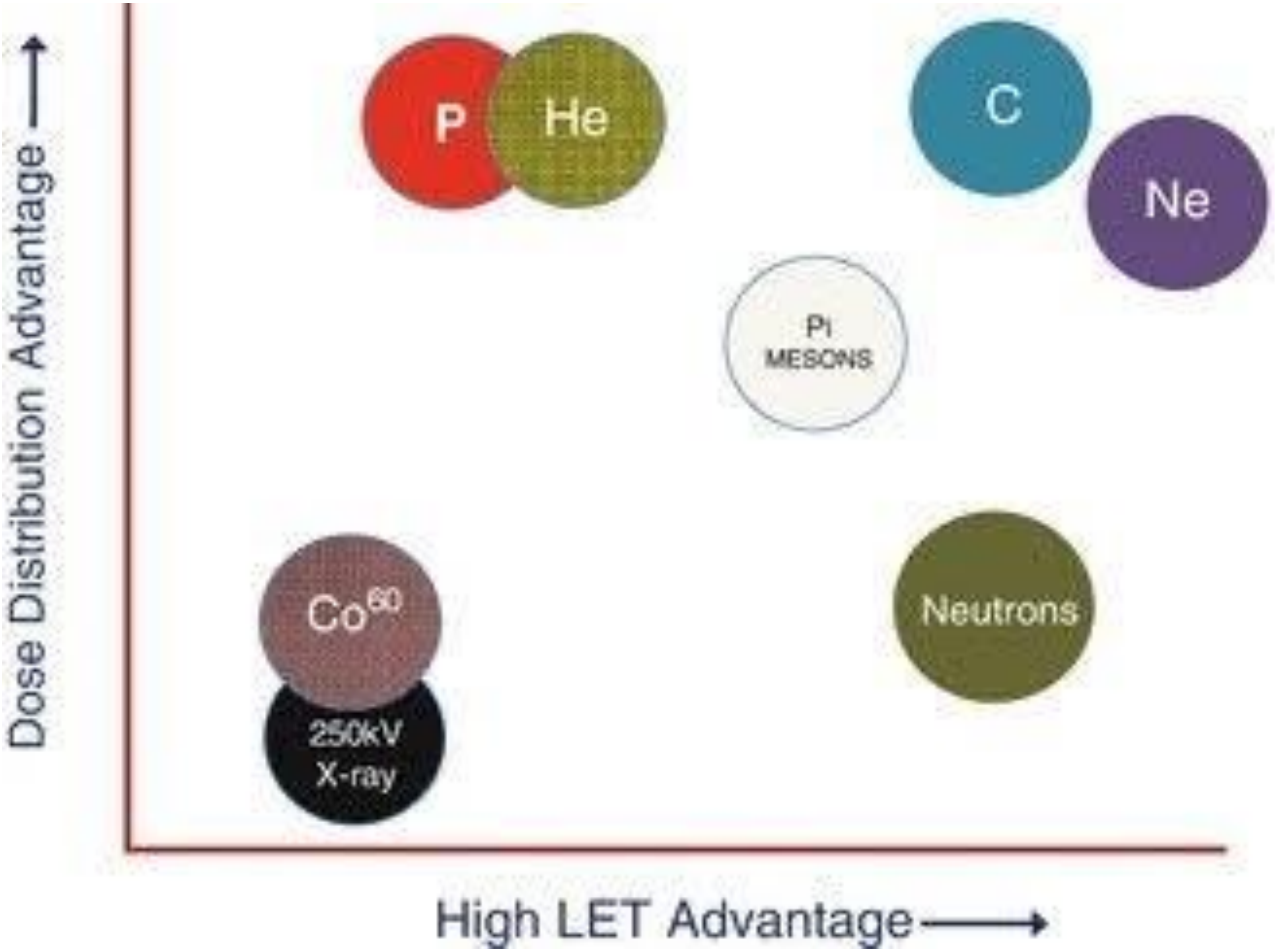




Results: Tumor control was achieved in the 2 irradiated series, with superior survival in the pMBRT group compared with the standard proton therapy group. Long-term (>170 days) survival rates of 22% and 67% were obtained in the standard proton therapy and pMBRT groups, respectively. No tumor was observed in the histopathological analysis. Although animals with long-term survival in the standard radiation therapy exhibit substantial brain damage, including marked radionecrosis, less severe toxicity was observed in the pMBRT group.

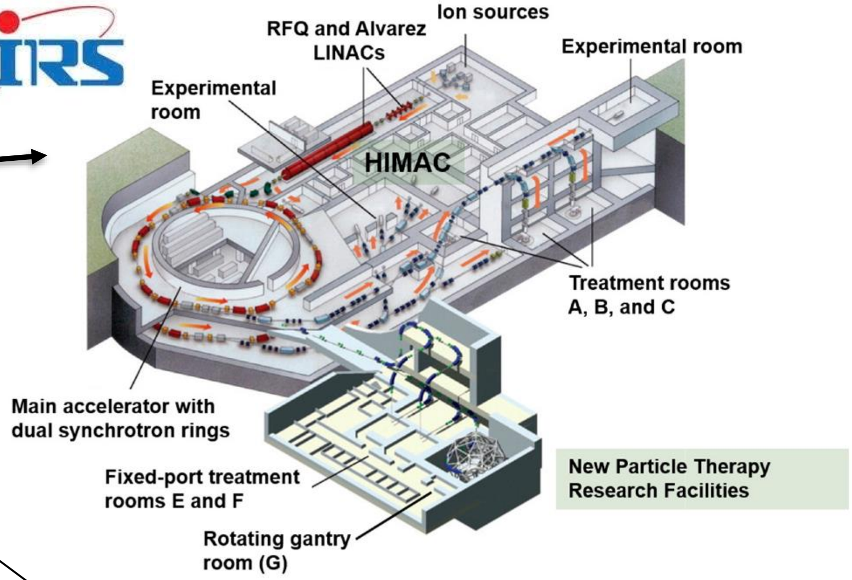
Prezado Y. *et al. Int J Radiat Oncol Biol Phys* 2019 Jun 1;104(2):266-271

Heavier-ion therapy



Heavy-ion facilities

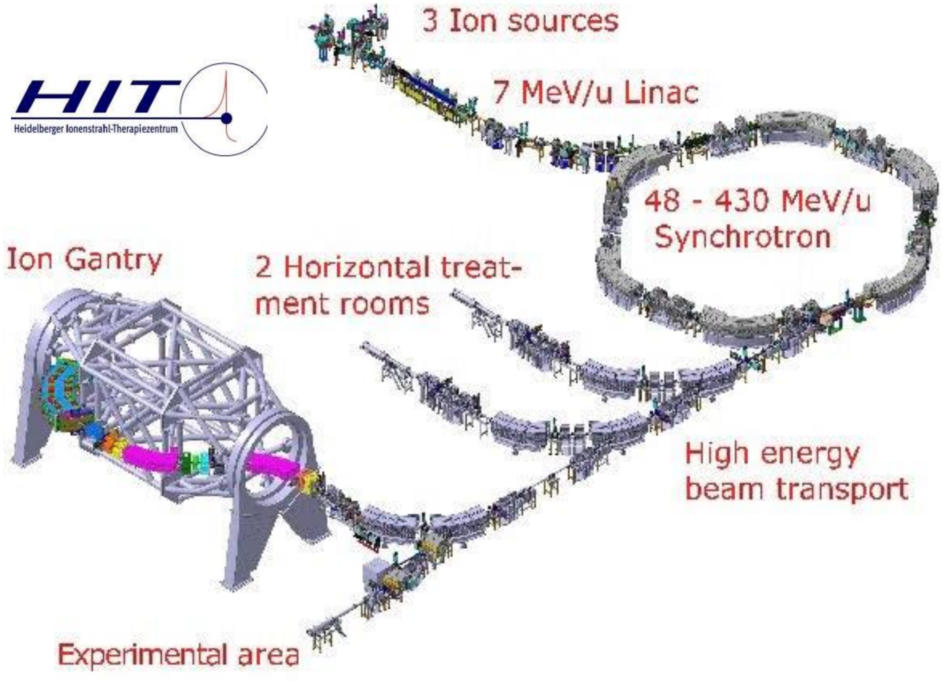
HIMAC at NIRS in Japan first to treat with C-ions in 1996

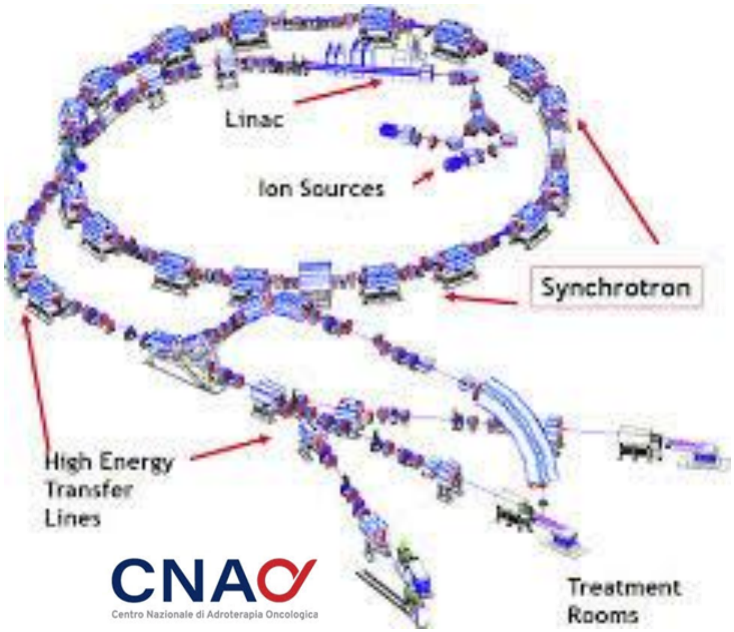


GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

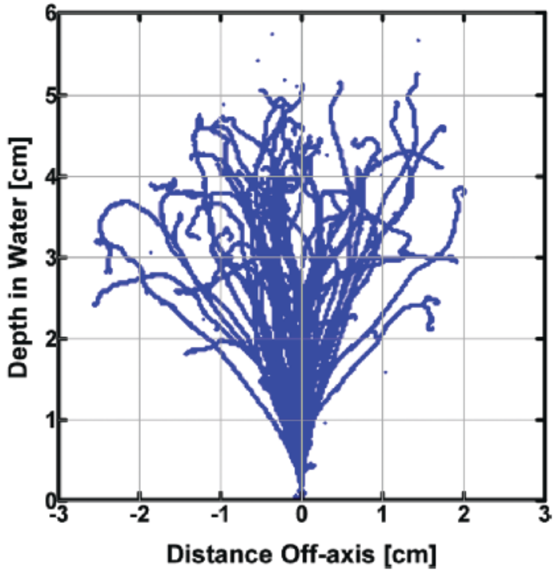
Heidelberger Ionenstrahl-Therapiezentrum

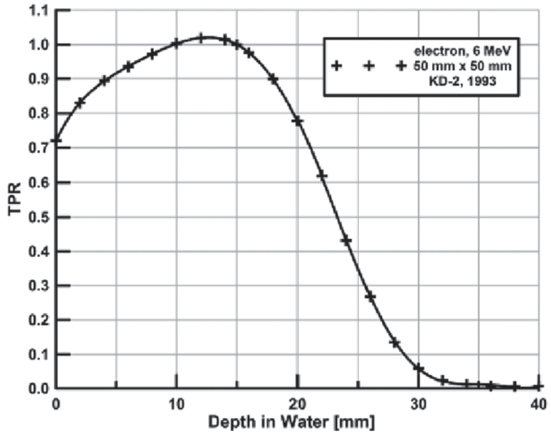




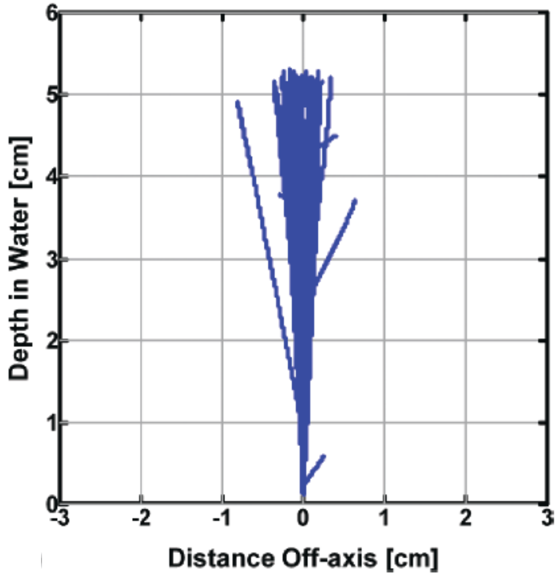
Centro Nazionale di Adroterapia Oncologica

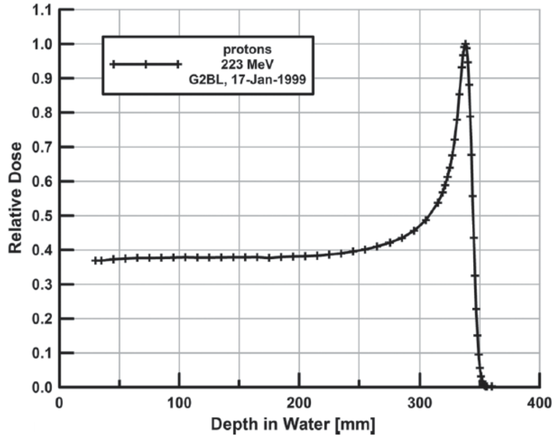
Electrons



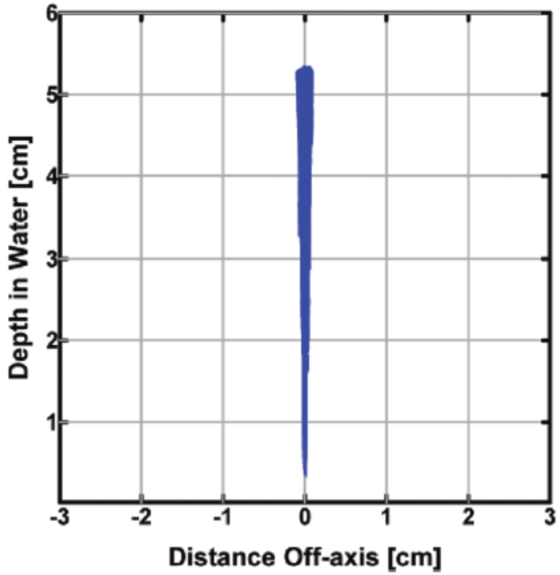


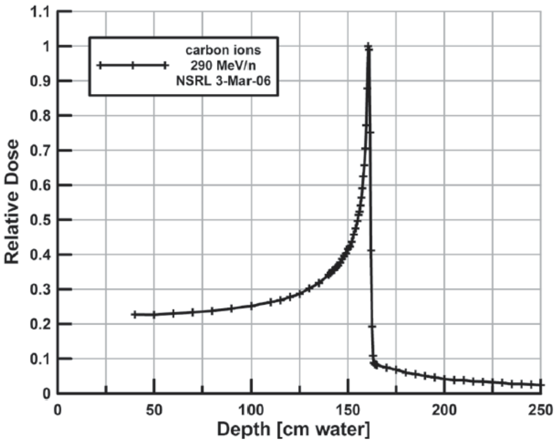
Protons

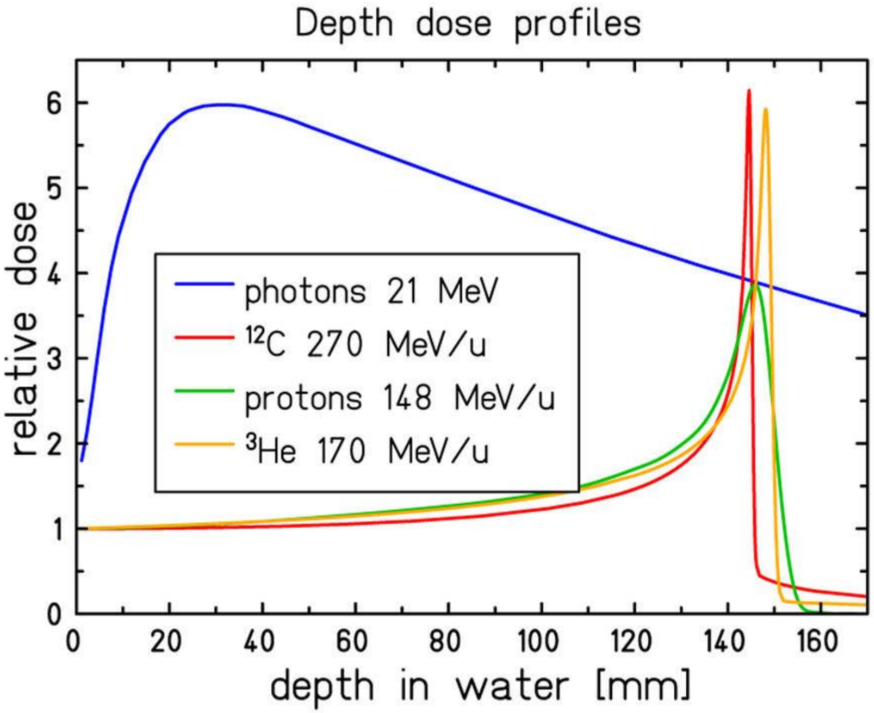




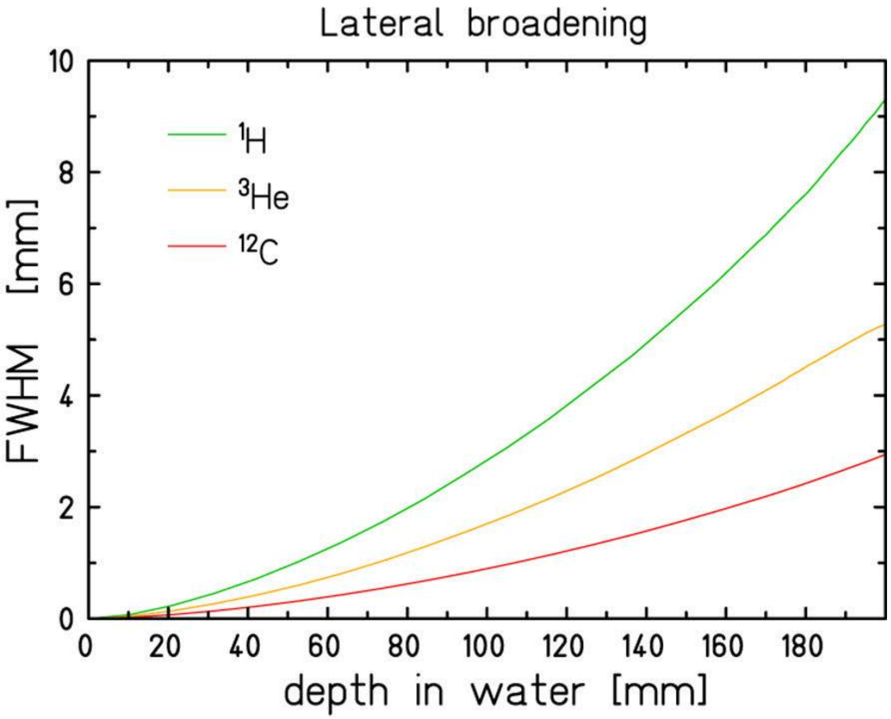
Carbon ions






Depth dose profiles
relative dose
depth in water [mm]
0
1
2
3
4
5
6
0
20
40
60
80
100
120
140
160
photons 21 MeV
^{12}C 270 MeV/u
protons 148 MeV/u
^{3}He 170 MeV/u

(a)

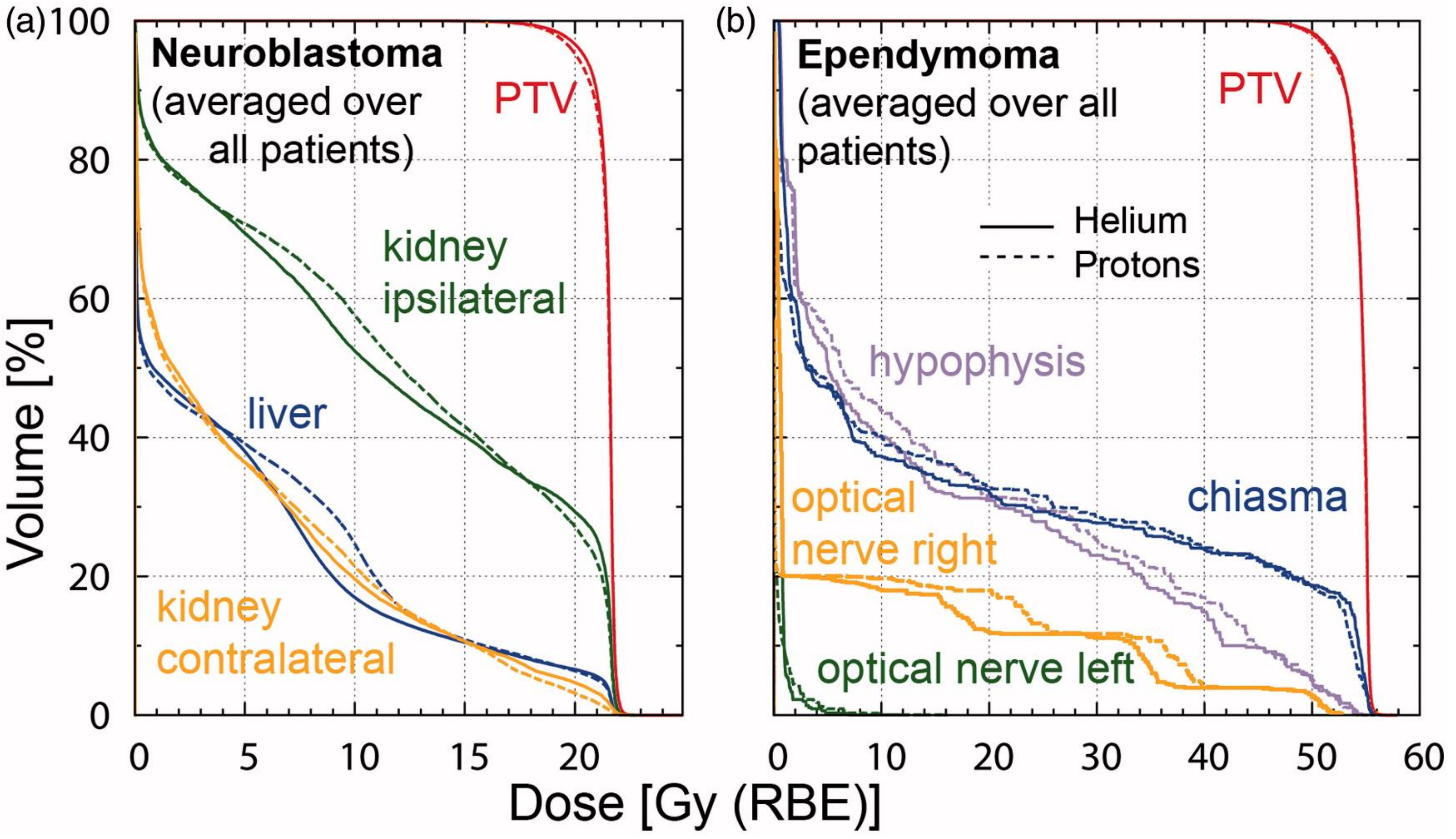

Lateral broadening
FWHM [mm]
depth in water [mm]
0
2
4
6
8
10
0
20
40
60
80
100
120
140
160
180
^{1}H
^{3}He
^{12}C

(b)

Can particle beam therapy be improved using helium ions? – a planning study focusing on pediatric patients

Barbara Knäusl[a,b], Hermann Fuchs[a,b], Karin Dieckmann[a,b] and Dietmar Georg[a,b]

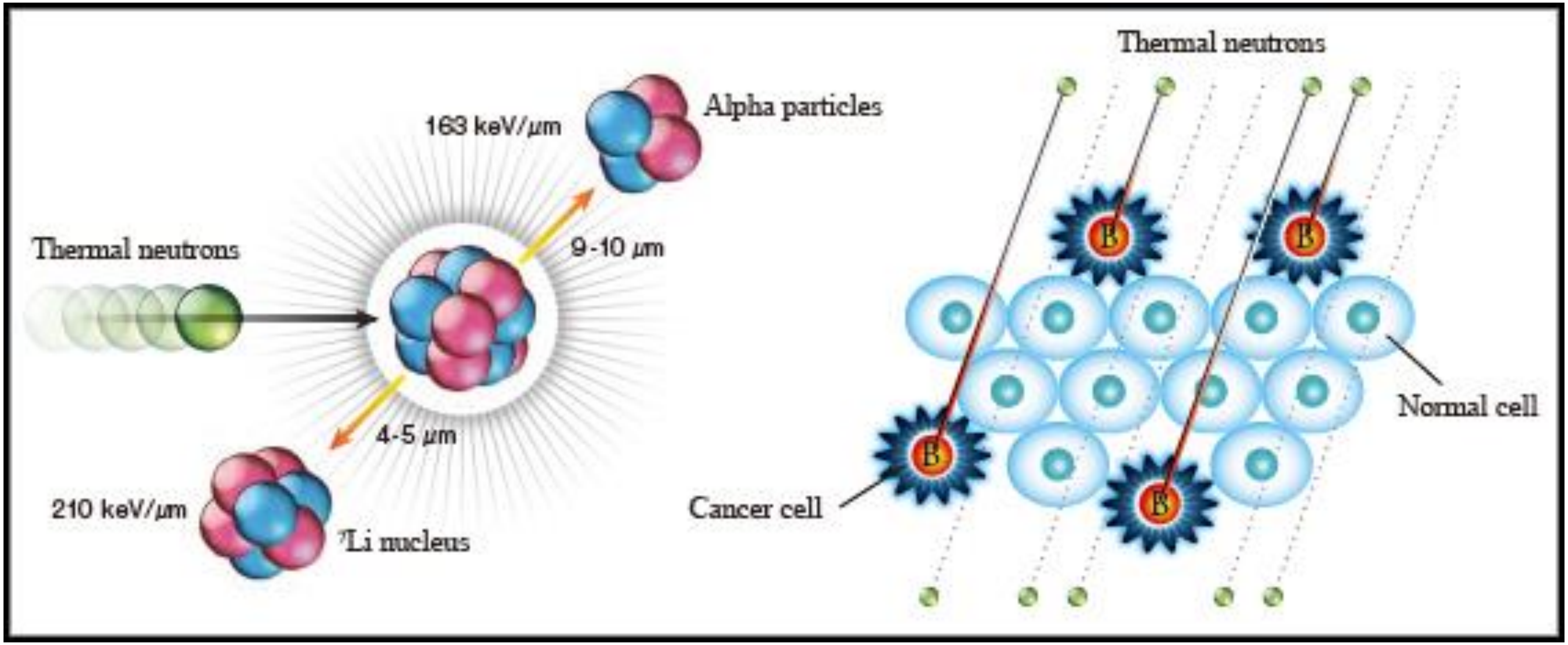
[a]Department of Radiation Oncology, Comprehensive Cancer Center, Austria, Medical University of Vienna/AKH Vienna; [b]Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria



ACTA ONCOLOGICA, 2016
VOL. 55, NO. 6, 751–759

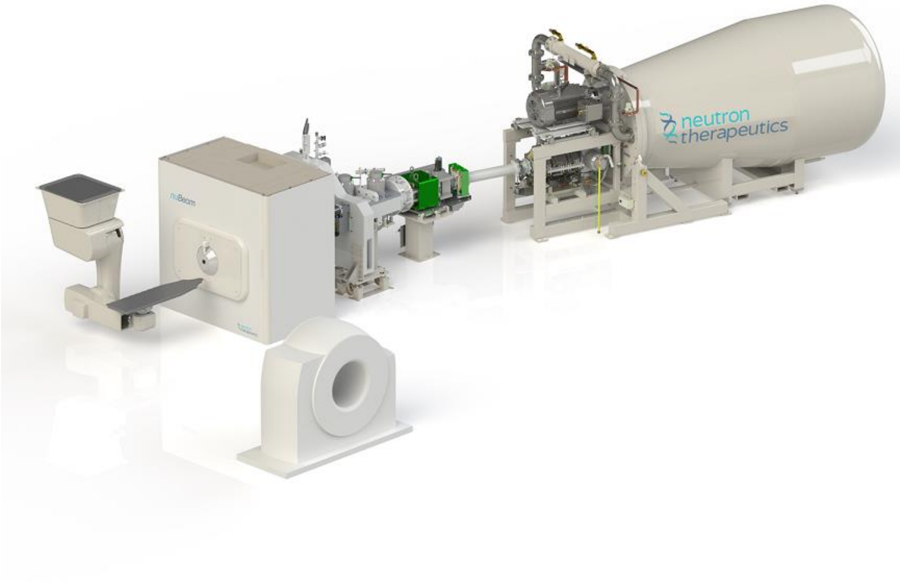
Boron Neutron Capture Therapy (BNCT)

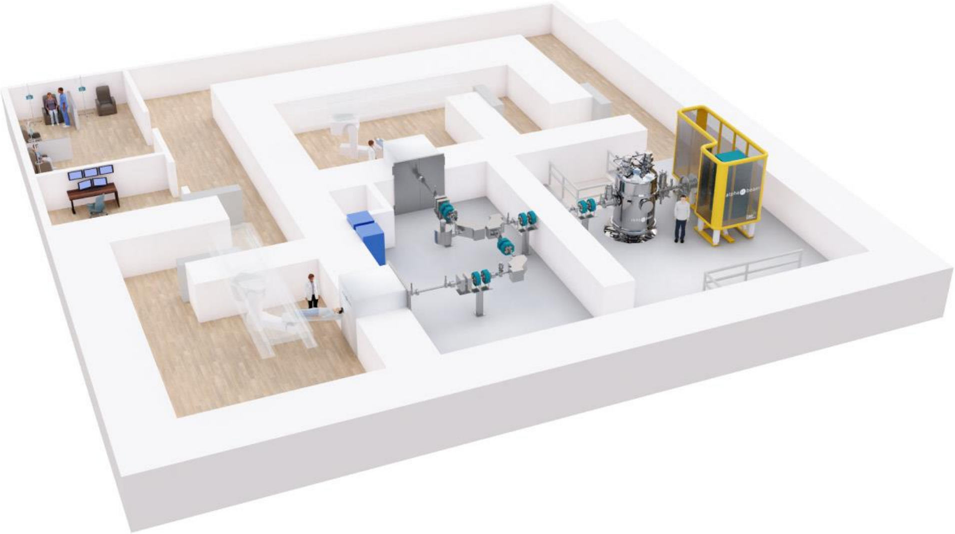
- First proposed by Gordon Locher in 1936.
- Patient infused with a non-toxic ^{10}B targeting drug which selectively accumulates in tumor cells.
  - *Drug traditionally used is boronphenylalanine (BPA) – others now being developed*
- Tumor irradiated with low energy (< 0.1eV) neutrons.
- Nuclear reaction emits ^{7}Li-ions and α-particles.
- These high-LET ions deliver therapeutic dose to ^{10}B-loaded cancer cells whilst limiting damage to surrounding normal cells without ^{10}B.



Accelerator-based BNCT clinical systems

- Early BNCT systems relied on reactor-based neutron sources – not suitable for hospital-based clinical facilities.
- Novel accelerator-based neutron sources enabling a renaissance in BNCT to occur.
- Clinical systems based on low-energy (approx. 2.5 MeV) proton accelerators.
- Research:
  - Dose verification;
  - Image-guided targeting;
  - ……





Questions?

r.amos@ucl.ac.uk

CALL FOR PAPERS

<u>Special Collection</u>:

Advances in Particle Therapy for Cancers

Guest Editor: ***Richard A. Amos***

Submission deadline: ***June 30th, 2023***

https://journals.sagepub.com/page/tct/collections/call-for-papers/advances-in-particle-therapy-for-cancers