

Targeting cancer with proton beams: Developments at UCL Hospital

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Significance of radiotherapy

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

- \Rightarrow 49% are cured by surgery
- ⇒ 40% are cured by radiotherapy
- ⇒ 11% are cured by chemotherapy









Rationale for hadron beam radiotherapy





Brief history of Proton Beam Therapy

- 1946: Therapeutic use of proton beams first proposed by Robert Wilson¹ ¹Wilson RR. Radiological use of fast protons. *Radiology.* 1946;47:487-491
- 1954: First patient treated at the UC Lawrence Berkeley Laboratory (LBL) – Treated the pituitary gland with beams passing entirely through the brain.



- 1957: Proton radiosurgical techniques for brain tumors developed at the Gustaf-Werner Institute, Uppsala, Sweden
 - First to use range modulation
- 1961: Radiosurgery of small intercranial targets at the Harvard Cyclotron Laboratory
- 70s 80s: Physics facilities worldwide notably, the Paul Scherrer Institute (PSI) in Switzerland
- 1989: The world's first hospital-based low-energy ocular proton beam therapy facility opened at Clatterbridge Cancer Centre, UK
- 1990: The world's first hospital-based high-energy proton beam therapy facility opened at Loma Linda University Medical Center, California
- 2000s : Rapid growth in number of proton facilities internationally



Particle Therapy Statistics in 2014

Martin Jermann, MSc

Secretary of the Particle Therapy Cooperative Group Paul Scherrer Institute, Villigen, Switzerland

Total of all facilities (in and out of operation):						
Не	2054	1957-1992				
Pions	1100	1974-1994				
C-ions	15736	1994-present				
Other ions	433	1975-1992				
Protons	118195	1954-present				
Grand Total	137179					

0

-2002

2006

2004

2008





2009 2010 2011

2012

Ref.: PTCOG, 2015

Personal experience in proton beam radiotherapy

2002 – 2005:



- •First hospital-based high-energy proton therapy facility in the world.
- •First patient treated in 1990
- •18,362 patients treated by end of 2014^*

2005 – 2013:





- •World-leading cancer treatment and research center.
- •Proton Therapy Center opened in 2006
- •First in the USA to treat with PBS in 2008
- •5,838 patients treated by end of 2014^{*}





- •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)



THE UNIVERSITY OF TEXAS

MDAnderson Cancer Center

Making Cancer History[®]

- •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)













THE UNIVERSITY OF TEXAS MDAnderson Cancer Center





Current Indications for NHS Patients Travelling Abroad for PBT



- Adult
- Base of Skull & Spinal Chordoma
- Base of Skull Chondrosarcoma
- Spinal & Paraspinal Bone and Soft Tissue Sarcomas (Non Ewing's)



Paediatric

- Base of Skull & Spinal Chordoma
- Base of Skull Chondrosarcoma
- Spinal & Paraspinal 'adult type' Bone and Soft Tissue Sarcomas
- Rhabdomyosarcoma
- Orbit
- Parameningeal & Head & Neck
- Pelvis
- Ependymoma
- Ewing's Sarcoma
- Retinoblastoma
- Pelvic Sarcoma
- Optic Pathway and other selected Low Grade Glioma
- Craniopharyngioma
- Pineal Parenchymal Tumours (not Pineoblastoma)
- Esthesioneuroblastoma



Paediatric			Adult		
Indication	2009 Framework assumption	2012 Updated assumption	Indication	2009 Framework assumption	2012 Updated assumption
Chordoma/ Chondrosacoma	15		Ocular/Orbital	2	25
Rhabdomyosarcoma (Orbit)	5		Chordoma	60	60
Rhabdomyosarcoma (Parameningeal and H&N)	15		Chondrosarcoma	30	30
Rhabdomyosarcoma(Pelvis)	10		Para- Spinal / Spinal Sarcoma	180	180
Osteosarcoma	3		Meningioma	100	100
Ewings	9		Acoustic Neuroma	100	100
PPNET	5		Craniospinal NOS (Pineal)	10	10
Ependymoma	25		Head & Neck & Paranasal Sinuses	300	300
Low Grade Glioma	5		PNET(medulloblastoma)	30	30
Optic Pathway Glioma	12		Difficult cases	300	123
Craniopharyngioma	15		ТҮА		200
Medulloblastoma (PNET)	70				
Hodgkins	5				
Retinoblastoma	5				
Meningioma	3				
Intracranial germinoma	10				
Nasopharynx (H&N)	15				
Difficult Cases-Esthe/Neuro/Liver	5				
Very Young Age	20				
Total	252	330	Total	1,110	1157

What will UK service look like?

- 2 sites selected
 - The Christie (Manchester)
 - UCLH (London)
- 2 Sites, 1 Service
 - Integrated clinically within the hospital setting
 - Integrated with existing conventional photon facilities
 - Collaboration across all areas
 - Referral
 - Protocol Development
 - Technology
 - Research
 - Due to open in 2018/2019



Why UCLH?



- Geographical access
- Viable centre size
- Integrated radiotherapy department
- High quality and recognised complex case mix
 - Largest paediatric practice in Europe

University College London Hospitals

Green light for proton beam therapy centre

11 Mar 2015

The Department of Health has announced the preferred contractors for the building and supply of equipment for the proton beam therapy (PBT) service which will treat hundreds of patients each year at University College Hospital from 2018.



Green light for proton beam therapy centre Press Release Posted 11 March 2015

The Department of Health has announced the preferred contractors for the building and supply of equipment for the proton beam therapy (PBT) service which will treat hundreds of patients each year at The Christie from 2018.



VARIAN MEDICAL SYSTEMS SELECTED TO EQUIP TWO NATIONAL PROTON THERAPY CENTERS IN ENGLAND Mar 11, 2015



University College London Hospitals NHS Foundation Trust

Zakrzewska P, Pitt M, **Amos RA**, D'Souza D & Ahmed T.

Application of building information modelling (BIM) in the design, construction, and operations management of a complex proton beam therapy facility in central London.

Proceedings of PTCOG 54. Int J Particle Ther. 2015;2(1):331-332















Operational Expectations

Facility opening times:

- 24Hour/day
- Clinical time:
 - 5 days per week
 - 14 Hours per day
- Quality Assurance Checks
- Maintenance Requirements
- Research



Beam delivery system: Passive scattering



Depth (mm)

Beam delivery system: Pencil beam scanning

- 94 Energies: 72.5 221.8 MeV
- Range: 4.0 30.6 cm
- Adjustability: 0.1 cm
- Max field size: 30x30 cm²
- Beam size: 5 14 mm σ (air)
- Energy absorber (*range shifter*)











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.

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.*

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

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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

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 Virshup³, James E Clayton³ and Lei Dong^{1,2,4}

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³ Ginzton Technology Center, Varian Medical Systems, 3120 Hansen Way, Palo Alto, CA 94303, USA Wu R, **Amos RA**, *et al.* Effect of CT truncation artifacts on proton dose calculation. (Abstract) *Med Phys* **35**, 2697 (2008)







Thoracic phantom scanned with tissue equiv. material truncated



Site-specific range uncertainties caused by dose calculation algorithms for proton therapy

J Schuemann, S Dowdell¹, C Grassberger, C H Min² and H Paganetti

Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA







LAD: Left Anterior Descending artery

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 deliverypCT only possible pre- or post-delivery

Prompt gamma

Prompt γ emission within nanosecondsOnly applicable for on-line range verification

PET

Possible on-line, or short time after irradiationBiological wash-out can be an issue

MRI

•Retrospective range verification as a function of tissue change.

Proton CT





511 keV gammas

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





Proton Beam Range Verification using Off-site PET by Imaging Novel Proton-Activated Markers

Jongmin Cho, Geoffrey Ibbott, Matthew Kerr, Richard Amos, and Osama Mawlawi

Proceedings: 2013 IEEE Nuclear Science Symposium & Medical Imaging Conference, Seoul, Korea.



Fig. 1. Proton nuclear interaction cross sections of ⁶³Cu and ⁶⁸Zn in comparison with tissue endogenous elements – ¹²C and ¹⁶O.

Proton Radiation Biology Considerations for Radiation Oncologists

Wendy A. Woodward, MD, PhD,* and Richard A. Amos, MSc, FIPEM^{†,‡}

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Biological effect: Biology based planning



What is the most important metric for proton planning?





Parallel plate ion-chamber



"Peakfinder" system



Multi-layer ion chamber (MLIC)



2D scintillation detector

Desirable:

 Fast and accurate 3D dosimetry for treatment plan verification and machine QA

Holy Grail:

- *In vivo* range verification and on-the-fly adaptive PBS delivery:
 - On-board image-guidance (*CBCT, MRI*);
 - Pre-treatment WEPL verification (*pCT, p-radiograph*);
 - Fast detection during treatment (prompt gamma);
 - Fast comparison with daily on-board imaging of anatomy;
 - Fast adjustment to spot delivery pattern;
 - Self-verification of pencil beam trajectories and energies;
 - Repeat *in vivo* verification.



PBT patient mix (2012)

Making Cancer History®



	FY'12 Annualized
PEDI/CNS	191
GU	311
THORACIC	261
HN	63
OTHER	32
TOTAL	857

Prostate



Proton therapy

IMRT

Image-guidance

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









AP x-ray image







Rt Lat DRR

Rt Lat x-ray image

to ensure target coverage in the event of rotational setup

errors of $\leq 5^{\circ}$.

DOSIMETRIC CHANGES RESULTING FROM PATIENT ROTATIONAL SETUP ERRORS IN PROTON THERAPY PROSTATE PLANS

SAMIR V. SEJPAL, M.D., M.P.H.,* RICHARD A. AMOS, M.S.,* JAQUES B. BLUETT, M.S.,* LAWRENCE B. LEVY, M.S.,* RAJAT J. KUDCHADKER, PH.D.,* JENNIFER JOHNSON, M.S.,* SEUNGTAEK CHOI, M.D.,* AND ANDREW K. LEE, M.D., M.P.H.*

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Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 1, pp. 40-48, 2009

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

Standardized treatment planning methodology for passively scattered proton craniospinal irradiation

Annelise Giebeler^{1,2,4}, Wayne D Newhauser^{1,2,5}, Richard A Amos^{1,2}, Anita Mahajan³, Kenneth Homann^{1,2} and Rebecca M Howell^{1,2*}









Giebeler et al. Radiation Oncology 2013, 8:32 http://www.ro-journal.com/content/8/1/32







Comparison of Discrete Spot Scanning and Passive Scattering Craniospinal Proton Irradiation

J Stoker*, R Amos, Y Li, W Liu, P Park, N Sahoo, X Zhang, X Zhu, M Gillin, MD Anderson Cancer Center, Houston, TX

Conclusion:

This work demonstrates the potential for improved robustness of proton craniospinal irradiations using a DSS delivery method, as well as significant decreases in clinic expenses. The use of apertures to define the sagittal plane field edge for DSS delivery improves the dose to target.



Head & Neck



Spot-scanning beam proton therapy *vs* intensity-modulated radiation therapy for ipsilateral head and neck malignancies: A treatment planning comparison

Shravan Kandula, M.D.,* Xiaorong Zhu, Ph.D.,[†] Adam S. Garden, M.D.,* Michael Gillin, Ph.D.,[†] David I. Rosenthal, M.D.,* Kie-Kian Ang, M.D., Ph.D.,* Radhe Mohan, Ph.D.,[†] Mayankkumar V. Amin, C.M.D.,* John A. Garcia, C.M.D.,* Richard Wu, Ph.D.,[†] Narayan Sahoo, Ph.D.,[†] and Steven J. Frank, M.D.*

*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; and [†]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX



Medical Dosimetry 38 (2013) 390-394

IMPT H&N - Example



Post-irradiation photography!





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

Catarina Veiga, MSc¹; Jailan Alshaikhi, MSc^{1,2}; Richard Amos, MSc²; Ana Mónica Lourenço, MSc^{1,3}; Marc Modat, PhD⁴; Sebastien Ourselin, PhD⁴; Gary Royle, PhD¹; Jamie R. McClelland, PhD⁴

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, intensitymodulated radiation therapy; IMRT, intensity-modulated radiation therapy; SFUD, single-field uniform dose.



Thoracic

Obtain 4D-CT data



Avg, MIP, and breathing phase data sets transferred to Eclipse TPS, and all registered to the Avg. CT.

MedTec: Knee-and-Feet Lok™

Dose calculated on Avg CT



Verification plans are calculated on at least T_0 and T_{50} , using original compensator and aperture designs, to evaluate coverage in extreme phases



T₀ (end inspiration phase)



T₅₀ (end expiration phase)











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

ARTICLE IN PRESS

International Journal of Radiation Oncology biology • physics

Summary

Intensity modulated proton therapy (IMPT) can offer improved dose conformality but also has increased uncertainties, particularly when used to treat moving targets. We report here our preliminary experience with the clinical implementation of IMPT for thoracic cancer and describe clinical indications, motion analysis and management, plan optimization and robustness analysis, and quality assurance. Our data indicate that IMPT treatment for thoracic cancer with tumor motion <5 mm is safe with use of the approach developed at our institution.

Clinical Implementation of Intensity Modulated Proton Therapy for Thoracic Malignancies

Joe Y. Chang, MD, PhD,* Heng Li, PhD,[†] X. Ronald Zhu, PhD,[†] Zhongxing Liao, MD,* Lina Zhao, MD,* Amy Liu, MS,[†] Yupeng Li, PhD,^{†,‡} Narayan Sahoo, PhD,[†] Falk Poenisch, PhD,[†] Daniel R. Gomez, MD,* Richard Wu, MS,[†] Michael Gillin, PhD,[†] and Xiaodong Zhang, PhD[†]

*Department of Radiation Oncology and [†]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas; and [‡]Applied Research, Varian Medical Systems, Palo Alto, California





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



NCRI National Cancer Research Institute	Cinical and Translational Radio Research Works	otherapy ng Group	CTRad Exe Ch Deput Workstrea Consumer re Ex-officio NCRI Se	cutive Group nair y Chair m co-chairs presentatives members cretariat	
	Workstream 1 Science base	Wor Phas	kstream 2 se l/II trials	Workstream 3 Phase III trials and methodology	Workstream 4 New technology, physics, quality assurance
	 Preclinical studies Radiation-drug interactions Radiobiology Biomarkers and imaging Physics and imaging 	 Phas Expe Cance Biom imag Syste thera radio 	e I/II studies rimental er Medicine narkers and ing emic pies and therapy	 Phase III trials Linking with NCRI clinical studies groups (CSGs) Trials methodology development for evaluating novel radiotherapy approaches 	 New technologies (e.g. proton therapy, stereotactic body radiotherapy, functional imaging) Quality assurance Radiotherapy physics Databases



Proton Physics Research & Implementation Group

http://www.pprig.co.uk/pprig/



ucl

National Physical Laboratory http://www.npl.co.uk

University College London Hospitals

http://www.uclh.nhs.uk

NHS Foundation Trust

The Christie NHS



The Clatterbridge Cancer Centre http://www.clatterbridgecc.org.uk/

University Hospital NHS Birmingham **NHS Foundation Trust**

University Hospitals Birmingham

http://www.uhb.nhs.uk/



The St James's Institute of Oncology

http://www.leedsth.nhs.uk/patients-and-visitors/ourhospitals/st-james-university-hospital



University College London http://www.ucl.ac.uk/

UNIVERSITY OF University of Surrey http://www.surrey.ac.uk/



The University of Manchester http://www.manchester.ac.uk/





The University of Manchester





UCL Proton Therapy Research Group



5,000 mile commute!









Thank you!

HARDER