Targeting cancer with proton beams: Developments at UCL Hospital

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Dept. of Radiotherapy Physics, UCLH

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Dept. of Medical Physics & Biomedical Engineering, UCL
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
Rationale for hadron beam radiotherapy
Brief history of Proton Beam Therapy

1946: Therapeutic use of proton beams first proposed by Robert Wilson


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):

<table>
<thead>
<tr>
<th>Facility</th>
<th>No.</th>
<th>Period</th>
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<tbody>
<tr>
<td>He</td>
<td>2054</td>
<td>1957-1992</td>
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<tr>
<td>Pions</td>
<td>1100</td>
<td>1974-1994</td>
</tr>
<tr>
<td>C-ions</td>
<td>15736</td>
<td>1994-present</td>
</tr>
<tr>
<td>Other ions</td>
<td>433</td>
<td>1975-1992</td>
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<tr>
<td>Protons</td>
<td>118195</td>
<td>1954-present</td>
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<tr>
<td>Grand Total</td>
<td>137179</td>
<td></td>
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Facilities in Clinical Operation and No. of Patients Treated (1955-2014)

Patients Treated with Protons and C-ions in North America, Asia, and Europe

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*

*Int J Particle Ther. 2015;2(1):50-54
• 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)
• 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)
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
<table>
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<tr>
<th>Paediatric</th>
<th>2009 Framework assumption</th>
<th>2012 Updated assumption</th>
<th>Adult</th>
<th>2009 Framework assumption</th>
<th>2012 Updated assumption</th>
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<td>Chordoma/Chondrosacoma</td>
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<td>15</td>
<td>Ocular/Orbital</td>
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<td>Rhabdomyosarcoma (Orbit)</td>
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<td>15</td>
<td>Chordoma</td>
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<td>15</td>
<td>15</td>
<td>Chondrosarcoma</td>
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<td>30</td>
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<tr>
<td>Rhabdomyosarcoma (Pelvis)</td>
<td>10</td>
<td>10</td>
<td>Para- Spinal / Spinal Sarcoma</td>
<td>180</td>
<td>180</td>
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<td>Osteosarcoma</td>
<td>3</td>
<td>3</td>
<td>Meningioma</td>
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<td>Ewings</td>
<td>9</td>
<td>9</td>
<td>Acoustic Neuroma</td>
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<td>5</td>
<td>Craniospinal NOS (Pineal)</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Ependymoma</td>
<td>25</td>
<td>25</td>
<td>Head &amp; Neck &amp; Paranasal Sinuses</td>
<td>300</td>
<td>300</td>
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<tr>
<td>Low Grade Glioma</td>
<td>5</td>
<td>5</td>
<td>PNET(medulloblastoma)</td>
<td>30</td>
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<td>Optic Pathway Glioma</td>
<td>12</td>
<td>12</td>
<td>Difficult cases</td>
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<tr>
<td>Craniopharyngioma</td>
<td>15</td>
<td>15</td>
<td>TYA</td>
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<tr>
<td>Medulloblastoma (PNET)</td>
<td>70</td>
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<tr>
<td>Hodgkins</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Retinoblastoma</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Meningioma</td>
<td>3</td>
<td>3</td>
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<td>Intracranial germinoma</td>
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<td>Nasopharynx (H&amp;N)</td>
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<td>15</td>
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<tr>
<td>Difficult Cases-Esthe/Neuro/Liver</td>
<td>5</td>
<td>5</td>
<td></td>
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<td>Very Young Age</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Total</td>
<td><strong>252</strong></td>
<td><strong>330</strong></td>
<td>Total</td>
<td><strong>1,110</strong></td>
<td><strong>1157</strong></td>
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</table>
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
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.

VARIAN MEDICAL SYSTEMS SELECTED TO EQUIP TWO NATIONAL PROTON THERAPY CENTERS IN ENGLAND

Mar 11, 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.
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:

- 24 Hour/day
- Clinical time:
  - 5 days per week
  - 14 Hours per day
- Quality Assurance Checks
- Maintenance Requirements
- Research
Beam delivery system: Passive scattering
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 \( \sigma \) (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.,* JACQUES 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

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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

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

Ming Yang1,2, X Ronald Zhu1,2, Peter C Park1,2, Uwe Titt1,2, Radhe Mohan1,2, Gary Virshup3, James E Clayton3 and Lei Dong1,2,4

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 Ginztion Technology Center, Varian Medical Systems, 3120 Hansen Way, Palo Alto, CA 94303, USA

Comparison of plans calc’d on normal and truncated CT datasets

2-3 mm diff in calculated range
Site-specific range uncertainties caused by dose calculation algorithms for proton therapy

J Schuemann, S Dowdell, C Grassberger, C H Min 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

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
Inelastic nuclear interaction

Positron-emitting isotope produced

Annihilation

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

$^{11}$C or $^{15}$O

Positron-emitting isotope produced

Annihilation

511 keV gammas

2 – 15 MeV gammas

(Existing imaging systems designed for gamma energies of a few hundred 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


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

<table>
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<tr>
<th>Category</th>
<th>FY’12 Annualized</th>
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<tr>
<td>PEDI/CNS</td>
<td>191</td>
</tr>
<tr>
<td>GU</td>
<td>311</td>
</tr>
<tr>
<td>THORACIC</td>
<td>261</td>
</tr>
<tr>
<td>HN</td>
<td>63</td>
</tr>
<tr>
<td>OTHER</td>
<td>32</td>
</tr>
<tr>
<td>TOTAL</td>
<td>857</td>
</tr>
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</table>
Prostate

Proton therapy

IMRT
Image-guidance

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

Protons are sensitive to changes in density along their path because of their physical characteristics of a finite range. Setup errors could lead to shifts in the Bragg peak, which could affect the dose delivered to target volume and adjacent structures of interest. Systematic rotational setup errors of \( \pm 5^\circ \) or horizontal couch shifts of \( 3^\circ \) rendered clinically insignificant dose changes to the target volume and critical structures. These findings suggest that field margins such as were used in the design of these plans are sufficient to ensure target coverage in the event of rotational setup errors of \( \pm 5^\circ \).
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.,* SEUNG TAEK 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

Standardized treatment planning methodology for passively scattered proton craniospinal irradiation

Annelise Giebeler, Wayne D Newhauser, Richard A Amos, Anita Mahajan, Kenneth Homann and Rebecca M Howell
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

- Simultaneous spot optimization
- Spot spacing = 1 cm
- Distal & prox. margins = 0 cm
- Lateral margin = 0.8 cm
Post-irradiation photography!
Cone-Beam Computed Tomography and Deformable Registration-Based “Dose of the Day” Calculations for Adaptive Proton Therapy

Catarina Veiga, MSc¹; Jailan Alshaikh, MSc¹,²; Richard Amos, MSc²; Ana Mónica Lourenço, MSc¹,³; 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 IMPT₃₈ plan, (C) the SFUD₃₈ plan, and (D) the IMPT₅₈ 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.
Thoracic

Obtain 4D-CT data

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

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

Summary

Intensity modulated proton therapy (IMPT) can offer improved dose conformity 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.

IMPT vs IMRT
MLD reduction: 4.4 Gy

IMPT vs PSPT
MLD reduction: 4.3 Gy
Esophagus V65: 3% vs 10%
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., Dorte 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.)
Predicted risk of cardiac effects with modern cardiac-sparing radiation therapy techniques
UCL Proton Therapy Research Group
5,000 mile commute!
Thank you!