Introduction to Proton Therapy

JAI Octoberfest, 3rd October 2014

Claire Timlin
Particle Therapy Cancer Research Institute, University of Oxford
Introduction to Radiotherapy and Proton Therapy
The Evolution of External Beam Radiation Therapy

1950's
The First Cobalt Therapy Unit and Clinac

1970's
Cerrobind Blocks Electron Therapy

1980's
Computerized 3D CT Treatment Planning

1990's
Dynamic MLC and IMRT
High resolution IGRT
Particle Therapy

2000's?
Functional Imaging

Standard Collimator
Multileaf Collimator

Slide courtesy of Prof. Gillies McKenna
Goal of RT

- **Maximise Tumour Dose**
- **Minimise Normal Tissue Dose**

**Radiation Induced Toxicity:**
- **Central Nervous System**: blindness, deafness, paralysis, confusion, dementia
- **Bowel**: colostomy, chronic bleeding.
- **Lung**: shortness of breath, pneumonias
- **Kidney**: renal failure and hypertension
- **Reproductive organs**: sterility
- **Everywhere**: severe scarring in medium to high dose regions, possible increase in induced cancers in low-medium dose regions
Photons/X-rays dose deposition

Depth-dose curve – single beam

- **“skin sparing”** (due to build-up of electronic equilibrium)
- Near-exponential fall-off (typical of uncorrelated catastrophic events)

Multiple Beams:
- Reduced dose to organs at risk
  - Fewer complications
- Increased tumour dose
  - Higher probability of tumour control
- However:
  - Large volumes of low-intermediate dose
• 1946: Therapy proposed - Robert R. Wilson, Harvard Physics

• 1955: 1st Proton Therapy - Lawrence Tobias University of California, Berkeley

• 1955-73: Single dose irradiation of benign CNS lesions - Uppsala, MGH, St Petersburg, Moscow
Components of the proton depth dose curve:

- Bethe-Bloch formula
  - Coulomb interactions with atomic electrons

- Scattering, energy spread and interactions with atomic nuclei

Illustrations from M. Goitein “Radiation Oncology: A Physicist’s-Eye View” © Springer, 2007
Proton dose deposition

Incident energy is modulated to form a proad dose and clear Bragg peak to cover the tumour.

The Daily Telegraph Australia
Medulloblastoma in a Child

With X-rays

With Protons

3/10/2014
Orbital Rhabdomyosarcoma

X-Rays

Protons/Ions

Courtesy T. Yock, N. Tarbell, J. Adams
Proton Therapy in Action

Anaplastic Ependymoma Brain Tumour

http://news.bbc.co.uk:80/1/hi/england/7784003.stm
http://news.bbc.co.uk/1/hi/england/7795909.stm
http://news.bbc.co.uk/1/hi/england/7906084.stm

Pre-treatment  During-treatment  Post-treatment

CPC, Friedmann, NEJM, 350:494, 2004

Slide courtesy of Prof. Gillies McKenna
Number of treatment centres worldwide

- Protons: 40 operational, ~40 in development
- Carbon: 8 operational, 4 in development

> 93,000 patients
> 10,000 patients
Proton Therapy Centre World Map
Protons - low energy
Protons – high energy
Carbons
Many more in the planning stages....

Planned Sites in US and China
• Clatterbridge
  – 1989: First hospital based proton therapy at Clatterbridge, near Liverpool
  – ~2500 patients with ocular melanoma; local control ~97%.
  – Targets the cancer
  – Avoids key parts of eye (optic nerve, macula, lens)

• Simon to talk about UCLH and Manchester....
Production and Delivery of Medical Proton Beams
Beam Production and Acceleration

- Ion source
  - Plasma accelerated in electric field

- Acceleration
  - Cyclotron
    - Fixed magnetic field
    - Fixed energy
    - Constant frequency
  - Synchrotron
    - Fixed radius
    - Variable magnetic field
    - Synchronous frequency

- Future accelerators that do the job better?
Beam Transport

- Gantries

- Fixed Beams

- Clinical Indications
  - Flexibility
  - Space
  - Cost
Beam Delivery - Scattering

Courtesy of T. Lomax, PSI, Switzerland.
Exploiting depth control

Exploiting charge
Some challenges in Proton Therapy

• Acceleration and Beam transport:
  – Faster spot scanning
  – More compact accelerators and gantries
  – Beam switching and splitting

• Uncertainty in planned vs. delivered dose:
  – Range uncertainties
  – Relative biological effectiveness

• Treatment delivery
  – Organ motion
  – Hypo-fractionation

• Which clinical indications?
  – Cost-effectiveness
  – Ethics

• Lack of data and models to predict late effects e.g. second cancers
Some possible solutions

- Accelerator development
- Radiobiological modelling and experiments
- Advanced treatment planning and delivery techniques
  - Novel, high resolution, minimally damaging imaging
  - Dose validation/online dosimetry
- Consistent data recording and data sharing
- Clinical studies with long-term follow-up
University of Oxford’s hope for Protons
Targeted cancer treatment pathway

Early Stage Cancer Patient

Population Health Science

Molecular Stratification

Big Data Institute

Target Discovery Institute

Structural Genomics Consortium

Experimental Cancer Medicine Centre

Precision Cancer Medicine Institute

Increased Cures

Courtesy of Gillies McKenna
 PHYSICALLY TARGETED

- Robotic Surgery
- Proton Therapy
- HIFU

PHysiologically Targeted

- Molecular Imaging

MOLECULARLY TARGETED

- Deep Genomic Sequencing
- Biomarker Driven
- Biologically targeted
Oxford Precision Medicine Institute

Genomics

Particle Therapy

Targeted Agents

Robotic Surgery

Courtesy of Gillies McKenna
The Evolution of Cancer Therapy

Increased Effectiveness, Reduced Toxicity

Molecular Imaging

Nanotechnology

Proton Therapy

CT, MRI, PET

(\text{CF}_3)_{180}

1980

1990

2000

2010

2020

Targeted Agents

HIFU

Robotics

Genomics

Courtesy of Gillies McKenna
• Thank you....

...........any questions?
Induction and cell kill

What is the form of the induction function? Linear, quadratic?

Form of cell killing function known with some certainty at clinical energies, the parameters are tissue dependent and can have large uncertainties.

Risk needs to be
- accurately modelled
- confirmed experimentally
- taken into account when deciding on the optimal treatment plan

\[ P_{tr} = P_I P_S \]

Probability of transforming a cell

Probability of the cell survives

Probability of inducing a potentially malignant mutation
Second cancer risk
Second cancer risk
Multiscale, voxelised TCP calculation for GBM

**Cell Level**
- Cellularity
- Cell automaton model
- Tumour microenvironment: \( P_0 \)

**Voxel Level**
- Dose matrix
- Treatment plan DICOM files
- Structure matrix
- Pre-treatment clonogenic cell density (CCD)
- Post treatment CCD

**Patient Level**
- Radiobiological parameters e.g. \( \alpha, \beta \)
- Clinical Data
- Tumour recurrence time
- Predicted TCP

**Additional Points**
- Genetic heterogeneity: Stem vs. non-stem
- Number of fractions
- Number of fractions
- Number of fractions
- Number of fractions
• Photons and protons (at clinical energies) have similar biological effects
  – Clinically a modifier (RBE) of 1.1 is applied to physical dose for protons

• For heavier ions (e.g. C) RBE has large uncertainties

• RBE needed* to calculate physical dose to administer to achieve prescribed biological dose

*maybe there is a better way?
New treatment regimes requiring new methods of optimisation?
Where does the 1.1 come from?