Particles for patients,
Radiotherapy with protons
(and other ions):
potential, problems and $$$s

...some UK and Australian hadron therapy initiatives...

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Context – there is no hadron therapy in Oz

- UK work towards national proton treatment facility, remaining links to research program/s there...
- Existing and developing Sydney research work....
  - Modelling: radiobiology, dosimetry, optimisation of radiotherapy applications
  - Dosimetry: developments for 3D and for dynamic treatment delivery
  - links to nano- developments and molecular imaging work
- + Uni Wollongong
  - Detectors, dosimetry, planning, etc
- National discussion of an Australian hadron therapy research and clinical facility, H, He, C... ions;
- National steering committee for hadron therapy centre..., ANSTO...
  - Medical Physics involvement
- Possible national bid/discussion....
Conventional (photon) radiotherapy

- Ionising radiation $\rightarrow$ direct or indirect cell damage ... $\rightarrow$ kill/control ...  
- **The Fundamental Problem**: damage too to normal tissues, particularly close to target/tumour volume...
- $\rightarrow$ limit to radiation dose deliverable
- $\rightarrow$ treatment methods/techniques...
- eg multi-beam
- $+\,$ accuracy/precision demands...
- $\leq 1\%$, 1mm...
- $\rightarrow$ continual driver for developments...
Current s-of-t-a (photon) radiotherapy

- Intensity modulation (IMRT)
- integrated 2-D and 3D imaging.....  → IGRT

Current developments:
- adaptive RT for changes /motion
- Other motion management,
- 4-D approaches to planning and delivery, incl. robotics...
- dose distributions, shaped well re TV and OaR..., rest of vol/dose?
Proton beam radiotherapy overview

• Why protons - physics and dose distribution
  – delivery systems
  – energy/range modulation
  – scattered beams and scanning beams
  – treatment planning and dosimetry
  - technology and developments...
  - some current direct research

• → clinical advantages...

• Problems and costs
Proton beam radiotherapy - advantages

- dose up- and down- stream from target
- sharp edges to beam....
- sharp fall-off at end of range
- sparing of nearby tissues
- number of beams/directions...

Energy/range modulation

15 MeV photons
protons
SOBP
(Spread out Bragg peak)

250 MeV
Or normalising at max dose point...
Protons vs Photon SCRT

Simple geometries:
Protons show no clear advantage.

(Baumert et al 2001)
Protons vs Photon SCRT

Irregular tumours with concavities: protons show advantages

What about IMRT?

(Baumert et al 2001)
Treatment plan example; nasopharynx

- Fewer beams required
- Much more sparing of critical normal tissues
- Ideal distributions for brain, eyes, base of skull....
- Paediatric RT, growth, secondary cancer, etc...
- Other sites...

Courtesy Tony Lomax, PSI....

X-rays: IMRT
protons: IMPT
Paediatric RT

- sizes
- radiosensitivity
- growth, expression of problems
- late side effects
  - Endocrine
  - Bone growth
  - Functional impairment
  - 2nd cancer

Courtesy, Tony Lomax, PSI
Design and Technology
Costs and space: much greater

- up to 250 (350) MeV particle accelerators
- (cyclotron/synchrotron) and delivery systems
Proton therapy unit: schematic

University of Florida: typical, 250 MeV

cyclotron/synchrotron

Gantry: 3-storey, 100 tons

Fast switching magnets - patient/room workflows
Current Proton therapy in the UK

- 62 MEV proton facility at Clatterbridge Centre for Oncology
- Protons have 30mm penetration in tissue (approx.)
- over 20 years experience in treatment of ocular melanoma
Proton therapy of the eye

Small Fixed Beam Treatment

Treatment facility at TRIUMF, Vancouver, Canada.
Worldwide proton beam use

- ~ 30 proton centres worldwide, in 14 countries; rapid recent increase...US, Europe, Japan,...; >85k patients
- + a few (Japan, Germany, Italy) using C ions (radiobiology + physics advantages; few patients, research only...) > 9k patients

- UK, currently one centre: 60MeV, 3 cm, eye treatments;
- UK Dept of Health: approved one national centre on 2 (or 3?) sites for 250 MeV, 25 cm....; being built...
- In academic public RT centres; strong research/ clinical trial remit...

www.ptcog.org...
UK referral recommendations

Limited evidence-based criteria ...

ie tight referral criteria

- Paediatrics: range of **childhood** tumours...
- Base of skull
- Brain, head and neck...
- Spinal/paraspinal tumours
- Ocular tumours
- Difficult anatomy sites/previous treatment
- 1-2% of patients

- No prostate???
UK referral recommendations

Limited evidence-based criteria ...

- Total: 1500 UK patients per year (+++?)...
- At 2 geographical sites,
- ...of 4-6 treatment rooms each

- Some modelling (Sweden) suggests to 20% of patients benefit if part of their treatment, eg boost, is with p (eg UK, 30k/yr??)

- Australia: scaling UK by population (and see Barton Australian modelling: 500-650 patients per year, 1 x 3 or 4 treatment room centre (if Swedish modelling accepted, up to 10k patients per year???)

Courtesy, Tony Lomax, PSI
UK

• tight referral criteria.......; current up to 400 abroad, via SLAs....
• Referral panel, 70% or so approved

• 2 centres approved to be built, UCLH, London, and Christie Manchester; timescale....2016/17? → 1500 or so per year

• (3rd centre later?)
• Trial assessment and evaluation, still tight referral criteria
• ? Widen access later still?
1500 per year?

- Modelling of conservative/restricted evidence-based referral
- → 1-2% of patients
- (some modelling, eg Swedish, indicate the up to 20% of patients could benefit from part of their RT from protons...)
- → for UK population, 250 paediatric patients; and 1250 adults
Potential Clinical Advantages of Protons

- Spares normal critical organs
- Lower integral dose
- Reduction in Late Effects

Superior dose distribution leads to:
- Allows dose escalation
- Enhanced tumour kill
- Optimise Clinical Outcome
Some problems and potential solutions
Problems → research opportunities

- Radiobiology: variable along range, distal effects...
- Microstructure of tissues..., incl. cavities (eg air)
- Range uncertainty, range straggling...
- Daily variability of patient...
- Changes in anatomy and tumour...
- Overly conformal dose distributions may result in marginal misses; ‘robust’ modelling/treatment planning....
- Inter-play effects of moving beam and moving target/OaR...

- Requires novel approaches to dosimetry...
- Modelling/planning/delivery....
- and dosimetric and geometric verification, pCT...
- eg 3D/4D real-time dosimeters, position sensitive detectors/imagers, direct energy deposition verification (self-induced PET and/or prompt gamma imaging, etc)
Passive scattering

Historically most common
Cumbersome – mounting/storage, individual manufacture
Treatment planning… distributions…
NEUTRONS!

Just beginning to move to spot scanning methods….. (PSI pioneered; now some commercial systems …)
Range modulation

Physical (Perspex) modulators that rotate in the proton beam, designed per depth variation required.
Making protons useful 1. Passive scattering in practice

Single passively scattered field

Three passively scattered fields

Fixed extent SOBP leads to poor sparing of normal tissue proximal to target

Conformation of dose can be improved through the use of multiple fields

Tony Lomax, AAPM Summer School, Colorado Springs, June 2003
Treatment planning?

- Single field?
- → multiple field, field patching
- where are critical structures? W.r.t range uncertainty
Active scanning

NO additional hardware
Less Neutron dose
IMPT – TPS
Inhomogeneities, movement
3D Spot scanning techniques
Tony Lomax, PSI, Switzerland; note, Leeds/Sydney link/collaboration on robust proton treatment planning

Dynamic treatment, requires 3D (and 4D) dosimetry

- pencil beam spread, spot size
- beam control
- fast energy switching and beam control
- position-sensitive verification
- motion interplay (fast re-scanning)


TRIUMF, Vancouver, Canada.
Spot Scanning

Optimisation/modelling/dose calculation

Plan optimisation

Selected spots

Spot weight optimisation

Courtesy of Tony Lomax

PSI…
Orbital rhabdomyosarcoma...
Radiobiology and dosimetry?

• Protons are low LET radiation

• » Adopted Proton RBE value is 1.1

• » Dose Specification (current convention) Cobalt Gray Equivalent Dose CGE = 1.1 x (Proton Physical Dose)

• » Dose Specification (ICRU Report 78 )
  – RBE-weighted proton absorbed dose DRBE(Gy) = 1.1 x D(Gy), D is proton absorbed dose
• Proton LET is depth dependent, maximum near Bragg Peak

• RBE is depth dependent, Maximum near the Bragg Peak

• Higher effective dose near the distal edge
• An issue for distal organ sparing
Effect of macro-inhomogeneity cf micro-structure; physics
Clinical effects of variations?

Fig. 15. Fatty replacement of the bone marrow as a consequence of irradiation can be visualized through T1-weighted MR imaging. a MRI scan taken before the treatment. b The planned dose distribution, and c an MRI scan taken after treatment [20].

Krejcarek et al  IJROBP 2007, 68, 646
Clinical effects of variations?

Mori, NIRS, 2011)
Treatment planning and modelling for ‘robust’ optimisation ...

- Model worst case error analysis for set up errors, changes and range errors
  - Simulate/model and optimise with robustness criteria included
  - Calculate max dose – min dose
  - Compare relative robustness of different treatment options
  - Choose optimum solutions for each patient
- Fast multi-solution 3D and 4D modelling, and multi-criteria optimisation;
  - Ideally real-time or semi-real-time for adaptive...???

Ruth Harding et al, Leeds + Sydney + PSI, 2012/13
Treatment planning and modelling for ‘robust’ optimisation (‘one bite’...)

- Model worst case error analysis for set up errors and range errors
  - Simulate/model and optimise with robustness criteria included
  - Calculate max dose – min dose
  - Compare relative robustness of different treatment options
  - Head-and-neck tumour cases; IMPT; consider doses to spinal canal and brainstem
  - Selecting initially 4 patients where (conventional photon) treatment changes meant they had been re-scanned and hence had two datasets of scans
  - Remodel original distributions onto new image dataset and evaluate dose changes

Ruth Harding et al, Leeds 2012
Beam arrangements; 3 and 5 beam
Results

- 2/4 four patients → doses to brainstem and spinal canal above tolerance, if uncorrected
- 3-beam IMPT plans less robust than 5-beam
- eg patient 4

<table>
<thead>
<tr>
<th>max spinal canal dose (Gy)</th>
<th>Original plan</th>
<th>Recalculated on rescan</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 beam IMPT</td>
<td>40.1</td>
<td>73.4</td>
</tr>
<tr>
<td>5 beam IMPT</td>
<td>41.4</td>
<td>62.2</td>
</tr>
<tr>
<td>5 beam IMRT</td>
<td>47.2</td>
<td>63.3</td>
</tr>
</tbody>
</table>
‘dose error histogram’ evaluation

Worst case set up error in Gy if treated in single fraction

- brainstem
- ctv70
- ctv56
- ptv 70
- ptv56
- spinal canal

Relative Volume

0 5 10 15 20 25 30 35

0 0.2 0.4 0.6 0.8 1 1.2
Costs and technologies
cf complex photon RT
cf equipment costs, 5-10 x per tr,

University of Florida: typical, 250 MeV

cyclotron/synchrotron

Gantry: 3-storey, 100 tons

Fast switching magnets
Some numbers  (using UK bid figures)

• Cost of a 3 or 4 room centre: $100-200M
  – Depends on what is in it, what proton technology, how linked to RT centre
• Annual cost: $20-30 M
• - depends on caseload, case split, etc
• Cost per patient around $40k

• Sending abroad could be n x this.....!
Developments in technology

• Smaller systems? Developing:
  – Smaller conventional designs...: now...
  – Gantry mounted supercon synchrocyclotron, 180 deg gantry rotation + robotic couch: now...
  – Clinical DWA (dielectric wall accelerator)
  – FFAG – fixed field alternating gradient accelerator
  – Laser generated/plasma acceleration...
  – All these, ??? 5-10 years???
Developments in technology

• Smaller systems? Developing:
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Developments in technology

• Smaller systems? Developing:
  – Gantry mounted supercon synchrocyclotron, 180 deg gantry rotation + robotic couch: now...
  +
  – Clinical DWA (dielectric wall accelerator)
Developments in technology

• Smaller systems? Developing:
  – Laser generated/plasma acceleration...
Titanium foil with proton-rich dot

Laser incidence

吹-off plasma

Accelerated protons

Hot electron cloud

Target-normal, quasi-static electric field

Australian plans

• Current working group of ANSTO, radiation oncologists, medical physicists, Dept of Innovation, etc. incl. UoS SoP IMP
• Clinical, scientific, economic case for national research and clinical H,He,C ion facility
• Synchrotron-based…. CERN design...
• With research lines and research time.....
• Where???
• Opportunities....
• Other possibilities???
Some UK thinking re proton centres
Referral: Adult annual caseload Protons

- Choroidal melanoma 100
- Ocular/orbital 25
- Chordoma BoS 60
- Chondrosarcoma 30
- Paraspinal/Spinal sarcoma 180
  - Inc chordoma
- Meningioma 100
- Acoustic Neuroma 100
- CSRT-pineal 10
- H&N, Paranasal sinuses 300
- PNET (intracranial) 30
- Difficult cases 300
- Total 1235

• + paediatrics...
Paediatric services

- High cure rates
- Developing normal tissues
  - Vulnerable
- Late side effects
  - Endocrine
  - Bone growth
  - Functional impairment
  - Second malignancy
- Cost Effectiveness

- Dose distributions
- Dose
- Target volumes
- Morbidity & Normal tissue effects
- Timing
- Access at younger age
- Fragmentation of care episodes
Service Specification

- NHS Clinical Service
- High Quality Protons
- Minimum 230MeV
- Passive scattering and Spot scanning
- Gantry
- Efficient
- Radiotherapy support services on site
- Clinical trials

- Integrated with conventional radiotherapy
  - Duplication planning resources CT/MRI/PET
  - Staffing
  - Photon mix

- Paediatric Experience
- Paediatric Oncology
- Neurosurgery
- Paediatric Anaesthesia
- Accommodation
Paediatric services - How can it work?

- Complex
- Multimodality
  - surgery
  - chemotherapy
- Multi-professional
- Family considerations
- Preserve local MDT / professional roles
- Need significant work on pathways

- 1 or 2 centres
- 250 children per annum
- 30% anaesthesia
  - Younger age
- Networks and pathways
- In-reach to treatment centres
- Integration
One problem (clinical)

• Danger of Fragmentation care

• Geographical Access

• Viable Centre size
  = Throughput
  = Working hours

• Highest quality and most difficult case mix
• networks
Main Criteria; for competitive bids

1. Clinical quality
2. Benefits to patients, including travel, access, etc
3. Deliverability
4. Technology considered and mature, but flexible for development
5. Flexibility, research and innovation; future development...
6. Commitment to R&D and clinical links to existing RadOnc and other related specialist services including neurosurgery
7. How they will link to other specialist and support services
8. Patient pathways by disease site
9. Capacity in their supporting services to deliver services for an increased volume of patients (future planning...)
10. Clinical governance processes for PBT and intention to have all cases in trials, etc and to audit all cases
11. Commitment to the development by the local SHA and cancer networks.