Ion Beam Therapy – should we prioritise research on helium beams?

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Follow-up from the EUCARD2 workshop, ION Beam Therapy: Clinical, Scientific and Technical Challenges (Birmingham, Jan 2016)
Overview

• Radiotherapy – where are we now?
• Background on protons and ions
  – Dose distribution comparisons
  – Lateral penumbra
  – RBE, OER and potential of heavier ions
• What’s so interesting about Helium?
• Research topics for this network
  – biological / immunological
  – medical physics
  – physics
Introduction

• This network provides a wonderful opportunity for the STFC and clinical communities
• It may be a once in a lifetime opportunity

• We should keep away from incremental developments and aim for big steps… but find a niche that is really ready for exploration
• Could He beam radiotherapy be that niche?
Radiotherapy: Current status

- Intensity Modulated Radiation Therapy is now widespread and (should be) driving down treatment related toxicities
- 4D CT for planning is quite routine for moving targets
- X-ray cone beam CT is now widely available for image guidance
- These improvements have enabled Stereotactic ABlative Radiotherapy (SABR) to become widespread for selected indications (for smaller early stage lung cancers can double survival for patients compared to previous extended fractionation radiotherapy approaches)
- In UK, SABR is being tested in an extended set of sites under a national evaluation project
- MRI for planning is still not as widespread as it should be but many centres are turning attention to this
- Products for MRI guidance are coming and could change the way radiotherapy is delivered / prescribed
A note on x-ray SABR

- Stereotactic Ablative Radiotherapy (SABR) delivered with x-rays is now becoming widespread
- It features very high doses per fraction and treatments delivered in a few fractions (typically 3, 5 or 8 fractions)
- Doses per fraction can be as high as 20 Gy (compared with traditional 2 Gy fractions)
- The SABR community is actively exploring the potential of these dosing scheme to provide an enhanced immune stimulus
- It is likely that many trials of SABR doses with drugs that stimulate immune activity will follow…
Potential reasons why higher doses of low-LET may be ineffective in advanced cancers

- Advanced tumors including lung, esophageal, and malignant brain tumors (GBMs) have shown no further increase in local & regional control with dose escalation
- Potential reasons (pointing to the use of ions) could be
  - Increased toxicity in normal tissues surrounding the tumor (e.g., central location of lung tumors)
  - Circulating tumor cells (CTCs) attack and overwhelm the immune system – cancer initiated immune suppression (all tumors shedding CTCs)
  - We may not know the true target harboring the most aggressive part of the tumors (GBMs)

Reinhard Shulte, EUCARD2 meeting, Birmingham, January 2015
## Properties of particles used for therapy

<table>
<thead>
<tr>
<th>Particle</th>
<th>Charge</th>
<th>Mass</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>photon</td>
<td>-</td>
<td>$h\nu$</td>
<td>-</td>
</tr>
<tr>
<td>e</td>
<td>-1</td>
<td>$1\ m_o$</td>
<td>stable</td>
</tr>
<tr>
<td>p</td>
<td>-1</td>
<td>$276\ m_o$</td>
<td>$2 \times 10^{-8}$ s</td>
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<tr>
<td>n</td>
<td>0</td>
<td>$1835\ m_o$</td>
<td>12 min</td>
</tr>
<tr>
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<td>+1</td>
<td>$1832\ m_o$</td>
<td>stable</td>
</tr>
<tr>
<td>a</td>
<td>+2</td>
<td>4 amu</td>
<td>stable</td>
</tr>
<tr>
<td>C</td>
<td>+6</td>
<td>12 amu</td>
<td>stable</td>
</tr>
<tr>
<td>Ne</td>
<td>+10</td>
<td>20 amu</td>
<td>stable</td>
</tr>
<tr>
<td>Ar</td>
<td>+18</td>
<td>40 amu</td>
<td>stable</td>
</tr>
</tbody>
</table>

where $m_o$ is the electron rest mass, and 1 amu is approximately $1835\ m_o$

From “Nuclear Particles in Cancer Treatment”, JF Fowler
Approaches to cancer treatment

ANTIPROTONS

C-Lateral

He-Lateral

IMRT
Ion beam facilities

- **Japan**
  - NIRS (since 1994)
  - Gunma
  - Hyogo,

- **China**
  - Shanghai
  - Lanzhou

- **Europe**
  - Heidelberg (now including Marburg also)
  - CNAO, Pavia
  - MedAustron (commissioning)

- **United States**
  - UT Southwestern and UCSF design studies are ongoing
  - MD Anderson, moving towards ions from 2018

8 treating centres
1 Commissioning
2/3 major initiatives

Costs of these facilities are likely to be around 3x the cost of similar capacity proton facilities
Kidney Cancer: Stage I, T1a N0 M0
National Institute of Radiological Sciences, Chiba, Japan carbon ions, 80GyE / 16fr. /4wks

Can radical surgery be avoided?

Better cancer screening might create extra need to use physics solutions

Slide Courtesy of Prof Bleddyn Jones
Very brief summary of clinical ion beam data

- **Japan** (from Reinhard Schulte, EUCARD2 meeting, Birmingham Jan 2016)
  - Sacral chordomas – good results in terms of control and low morbidity compared with surgery
  - Prostate – good results in terms of control and low morbidity compared to IMRT (would need trial data to confirm – maybe against SBRT?)
  - Lung – Ok but very similar to x-ray SABR
  - Pancreas – approaching 50% survival at 3 years – extraordinary results – suggestive of immunological response

- **Germany** (from Alex Jensen, EUCARD2 meeting, Birmingham Jan 2016)
  - Adenoid cystic – good results, ongoing trial (ACCEPT) combining IMRT, C-ion boost and cetuximab
  - H&N SCC – good preliminary indications from study of induction chemo, then combining IMRT, C-ion boost and cetuximab
Key Question

Where results of ion beam treatments are very good is this primarily a result of
  – Dose distribution ? Or
  – Biological characteristics of the dose ? Or
  – Both
Dose Reporting in Ion Beam Therapy

Proceedings of a meeting organized jointly by the International Atomic Energy Agency and the International Commission on Radiation Units and Measurements, Inc. and held in Ohio, United States of America, 18–20 March 2006

UPPER: Range straggling
LOWER: Lateral deflection
Lateral penumbra: Comparison of protons and electrons

(Koehler and Preston 1971)
Summarising dose distribution issues...

Collimation improves lateral penumbra of scanned protons to more closely match ions.

Ions always better than protons, and C, O better than He.

Proton CT reduces uncertainty in proton and ion beam range.
Bethe formula: dependence on charge of ion

- For ions other than protons, the energy loss includes a term in $z^2$ (where $e_z$ is the charge on the incident ion).

<table>
<thead>
<tr>
<th>particle</th>
<th>charge</th>
<th>$z^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>proton</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Alpha</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>carbon</td>
<td>6</td>
<td>36</td>
</tr>
</tbody>
</table>

Assumes ion is “fully stripped”
Radiobiological complexity of ions SOBP

Figure 8.9. The relationship between the linear energy transfer of radiation (LET) and (a) its relative biological effectiveness (RBE); (b) the oxygen enhancement ratio (OER).
RADIOBIOLOGY: heavy ions

There are several radiobiological factors of concern. For instance:

RBE

*RBE enhances the dose in and around the tumor volume – although for heavy ions it is very different from 1.0 which makes it tricky to adjust for (and, see Wilkens and Oelfke, IJROBP 70:262 2008)*

possibly an advantage for heavy–ions

Oxygen enhancement ratio (OER)

*the OER of heavy ions is lower than that of X-rays (but C-ions are only halfway there) – so may overcome radio-protective property of tumor hypoxia*

probably an advantage for heavy–ions

Repair of radiation damage

*heavy ions exhibit lack of repair of radiation damage to both tumor and normal tissue*

probably a disadvantage for heavy–ions

Cell-cycle dependency

*with X-rays there is a strong dependence of damage on position in the cell cycle (for some systems) with heavy ions, this is lost*

probably a disadvantage for heavy–ions
Ion therapy: A new radiobiology?

- The traditional line of investigating the benefits of ion beam therapy has been to treat radio-resistant cancers with ions.
- New research should focus on interaction of high LET and hypofractionation with the immune system and targeting innate immunosuppressive mechanisms.
- For 2016, we (ie UCSF) are planning to launch a collaborative research program addressing the compelling question whether high LET ions have an advantage in this respect.

Reinhard Shulte, EUCARD2 meeting, Birmingham, January 2015

In his presentation at the same meeting, Radhe Mohan also identified pre-clinical experiments on immune response stimulation as critical on their roadmap towards ions.
What’s so interesting about Helium?

• Dose distribution is good, and at depth could be better than protons even with collimation for protons.
• At SABR-type doses per fraction, these small dosimetric advantages might be important?
• Concomitant dose due to ion break-up and neutrons will be higher than protons but should be much less than ions.
• Radiobiology is much less complex than heavier ions and there are open questions to be addressed
  – For tumours where hypoxia is important in the role of heavier ions – He is not likely to offer much advantage
  – To what extent do He beams trigger an immunological response?
• Accelerators and gantry systems could be much more compact (and therefore cheaper) than for carbon ions.
Implementation of spot scanning dose optimization and dose calculation for helium ions in Hyperion

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Conclusion – the advantage of $^4$He seems to lie in the reduction of dose to surrounding tissue and to OARs.

**Fig. 3.** Dose volume histograms of a prostate (a), base-of-skull (b), pediatric neuroblastoma (c), and a head-and-neck tumor patient (d), planned using Hyperion employing the newly implemented algorithm for proton and $^4$He using physical dose contributions only.

**Fuchs et al.:** Dose optimization and dose calculation for helium ions

*Medical Physics, Vol. 42, No. 9, September 2015*
Questions about ions

• Should we be focussed on differences / changes / improvements in dose distributions?
  – Easier to simulate so useful work can be done
  – In comparison with protons, these are likely to be small and reducing with improved proton delivery technology

• Should we be focussed on differences in biology?
  – Needs facility access - harder
  – Only substantial differences here are likely to make ions clinically advantageous
Research topics for this network

• Biological / immunological
  – Contribute to understanding of the difference in immune stimulus that high dose per fraction, ions, protons and x-rays provide
    • Sensing technologies to rapidly monitor indicators of immune activity?
  – If there is a more powerful immune stimulus with ions, is this still triggered with He?
  – Can anything useful be done in cells?
  – Could a collaboration be formed with a treating centre overseas?
  – Developing advanced models of ion beam therapy action
  – Cocktails of ions – developing a biological rationale (and feeding accelerator design studies)
  – Modelling for second cancers / cancer induction.
Research topics for this network

• Medical Physics
  – Treatment planning studies – valuable but need to be very well done to really move things on (high degree of planner expertise and the best available systems – cost?)
  – Dosimetry / imaging – demonstrate proton CT technologies for ions – including He (depending on beam pulse characteristics)
  – MRI guidance?
  – Work to understand QA needs for ions and explore technologies
  – Whole body dose simulations (vital if He is to be considered for paediatrics).
  – Tissue equivalent materials appropriate to ions (ongoing work in UK for protons)
Research topics for this network

• Physics
  – Accelerator design studies / facility concept work. It does not seem obvious which accelerator design is optimum for a He beam facility. Cyclotrons, synchrotrons, NSFFAGs and linacs are all interesting
  – Gantry design studies – how small is possible for a He beam with (say) 30-35cm range?
  – For a “compact” He gantry, what carbon energy could be handled ? (feed this into treatment planning studies to see if such energies would still be useful)
  – Systems for rapid change of ion species, and change of current between imaging and treatment mode…
  – Detectors that handle the particular pulse characteristics of likely ion beam systems (sandpit?)
  – Collaborations with manufacturers
Final thought….  

Don’t forget the Cyclotron Trust / RCR programme of funded visits to centres overseas which for the future is oriented towards ion beam centres and prefers visits which involve a clinician and a scientist travelling together

https://www.rcr.ac.uk/posts/applications-open-201516-cyclotron-visiting-fellowships