BJR

https://doi.org/10.1259/bjr.20200247

Received: 13 March 2020 | Revised: 26 August 2020 | Accepted: 02 September 2020

Cite this article as:
Kirkby KJ, Kirkby NF, Burnet NG, Owen H, Mackay RI, Crellin A, et al. Heavy charged particle beam therapy and related new radiotherapy technologies: The clinical potential, physics and technical developments required to deliver benefit for patients with cancer. *Br J Radiol* 2020; **93**: 20200247.

GUIDELINES & RECOMMENDATIONS

Heavy charged particle beam therapy and related new radiotherapy technologies: The clinical potential, physics and technical developments required to deliver benefit for patients with cancer

[1,2,3]KAREN JOY KIRKBY, PhD, [1,2]NORMAN FRANCIS KIRKBY, [1,2]NEIL GUNN BURNET, [3]HYWEL OWEN, [1,2,4]RANALD IAIN MACKAY, [5,6]ADRIAN CRELLIN and [7]STUART GREEN

[1]Division of Cancer Sciences, University of Manchester, Manchester Cancer Research Centre, Manchester Academic Health Science Centre, Manchester, United Kingdom
[2]The Christie NHS Foundation Trust, University of Manchester, Manchester, UK
[3]University of Manchester/Cockcroft Institute, Manchester, United Kingdom
[4]Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK
[5]NHS England National Clinical Lead Proton Beam Therapy, Leeds Cancer Centre, Leeds Teaching Hospitals Trust, Leeds, UK
[6]St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[7]Department of Medical Physics, University Hospital Birmingham, Birmingham, Edgbaston, UK

Address correspondence to: Karen Joy Kirkby
E-mail: *karen.kirkby@manchester.ac.uk*

ABSTRACT

In the UK, one in two people will develop cancer during their lifetimes and radiotherapy (RT) plays a key role in effective treatment. High energy proton beam therapy commenced in the UK National Health Service in 2018. Heavier charged particles have potential advantages over protons by delivering more dose in the Bragg peak, with a sharper penumbra, lower oxygen dependence and increased biological effectiveness. However, they also require more costly equipment including larger gantries to deliver the treatment. There are significant uncertainties in the modelling of relative biological effectiveness and the effects of the fragmentation tail which can deliver dose beyond the Bragg peak. These effects need to be carefully considered especially in relation to long-term outcomes.

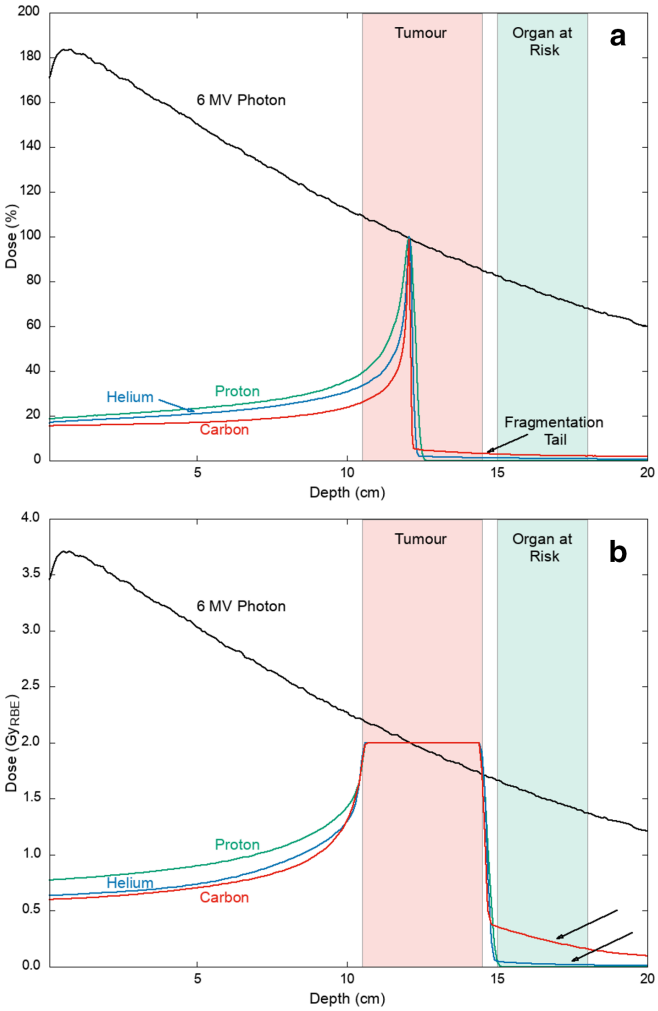
In 2019, a group of clinicians, clinical scientists, engineers, physical and life scientists from academia and industry, together with funding agency stakeholders, met to consider how the UK should address new technologies for RT, especially the use of heavier charged particles such as helium and carbon and new modes of delivery such as FLASH and spatially fractionated radiotherapy (SFRT).

There was unanimous agreement that the UK should develop a facility for heavier charged particle therapy, perhaps constituting a new National Ion Research Centre to enable research using protons and heavier charged particles. Discussion followed on the scale and features, including which ions should be included, from protons through helium, boron, and lithium to carbon, and even oxygen. The consensus view was that any facility intended to treat patients must be located in a hospital setting while providing dedicated research space for physics, preclinical biology and clinical research with beam lines designed for both *in vitro* and *in vivo* research. The facility should to be able to investigate and deliver both ultra-high dose rate FLASH RT and SFRT (GRID, minibeams etc.). Discussion included a number of accelerator design options and whether gantries were required. Other potential collaborations might be exploited, including with space agencies, electronics and global communications industries and the nuclear industry.

In preparation for clinical delivery, there may be opportunities to send patients overseas (for ^{12}C or ^{4}He ion therapy) using the model of the National Health Service (NHS) Proton Overseas Programme and to look at potential national clinical trials which include heavier ions, FLASH or SFRT. This could be accomplished under the auspices of NCRI CTRad (National Cancer Research Institute, Clinical and Translational Radiotherapy Research Working Group).

The initiative should be a community approach, involving all interested parties with a vision that combines discovery science, a translational research capability and a clinical treatment facility. Barriers to the project and ways to overcome them were discussed. Finally, a set of different scenarios of features with different costs and timelines was constructed, with consideration given to the funding environment (prer-Covid-19) and need for cross-funder collaboration.

Figure 1. (A) Depth–dose curves for photons (6 MV), protons (^{1}H), helium (^{4}He) and carbon (^{12}C) ions. For ^{1}H, ^{4}He and ^{12}C ions pristine Bragg peaks (single energy) are shown in Figure 1Aa (normalised to the same physical dose to the same depth within the in tumour). (B) shows biologically weighted (using LEM IV) SOBP for ^{1}H, ^{4}He and ^{12}C (again normalised to the same depth within the tumour) SOBP, (spread out Bragg peaks).



INTRODUCTION

Background

In April 2019, a group of clinicians, clinical scientists, engineers, physical and life scientists from academia, industry and the clinic met with stakeholders from the funding agencies for a 2-day workshop to examine the potential of new technologies for UK radiotherapy (RT). This paper documents their discussions and provides a starting point for future work. During the meeting, those involved were asked a series of questions, first discussed in multidisciplinary groups and then in subject-specific groups to combine a broad overview with in-depth detailed discussion and understanding. This paper summarises the deliberations and discussions that took place during this meeting.

It should be noted that the UK is not alone in having these discussions and brainstorming sessions. Most notably the debate on bringing charged particle therapy (using ions heavier than protons) back to the USA has resulted in two NIH exploratory programmes: North American Particle Therapy Alliance (NAPTA) led by the University of California San Francisco and a programme led by University of Texas Southwestern for a National Particle Therapy Research Centre (NPTRC). More recently in November 2019, the Mayo clinic announced that it would partner with Hitachi to build a carbon ion centre.

Charged particle therapy for treating cancer

Introduction:

In the UK, one in two people are diagnosed with cancer during their lifetimeand of those who survive 40% can attribute their cure to a treatment including radiotherapy (RT).[1,2] After surgery, radiotherapy is the most effective cure for cancer in the UK[2], but accounts for less than 10% of the UK cancer budget, making it an extremely cost-effective form of treatment. However, all current cancer treatments give rise to side-effects, and as more patients are living with and beyond cancer, reducing both acute and long-term side-effects is paramount. Avoidance of side-effects will also allow some improvement in tumour control through dose escalation to the tumour.

Charged particle therapy

One of the newer types of RT treatment uses protons or heavier ions. Unlike X-rays, protons (and heavier charged particles) deliver most of their dose in a well-defined Bragg peak (Figure 1A). This allows more dose to be delivered to the tumour whilst sparing the healthy tissues, surrounding it. In particular, for protons, there is no exit dose beyond the target. For heavier charged particles, a fragmentation tail is observed and this is part of the reason why proton beam therapy (PBT) is considered preferable for treating childhood cancers, through reduced effects on growth, organ function and second malignancy risk later in life. Charged particle beams also offer the potential for treating tumours which lie close to critical organs, such as the brain or spinal cord. Heavier ions, such as carbon, have a substantially smaller (sharper) penumbra, potentially providing a significant advantage in this setting.

Figure 1A shows the Bragg peaks for protons, helium and carbon ions, at a single energy. It can be seen that as the ion mass increases, the Bragg peak becomes sharper. By modulating the energy and position of the Bragg peak, the dose can be distributed over the entire tumour volume in a spread out Bragg peak (SOBP) (Figure 1B). In Figure 1A and B, the dose has been normalised but when compared to photons it can be seen that the relative damage in the tumour with respect to normal tissues increases for charged particle beams. In many countries, PBT has been the preferred option for particle therapy, for several reasons. Firstly, both the equipment and the build costs are cheaper and there are off-the-shelf, turn-key solutions for both the equipment and treatment planning software from a number of suppliers. Secondly, PBT equipment has a much smaller footprint than equivalent heavy charged particle facilities. Thirdly, the currently accepted view is that the most advanced treatments are more effectively delivered with gantries that can ideally rotate through 360° and which, when combined with robotic couches,

Figure 2. The HIT centre under construction in 2005. Note that this photograph was taken 15 years ago, and shows the construction of a full-scale clinical plus research facility including both proton and carbon ion delivery; helium delivery is currently under development. HIT, Heidelberg Ion Therapy.

are able to treat the patient from almost every angle. For heavier charged particles such as carbon larger heavier gantries need to be used because much larger magnets are needed in the gantry to deliver the beam to the treatment nozzle. For example, the gantry in the Heidelberg Ion-Beam Therapy Centre (HIT) weighs 640 tonnes Figure 2; although the new superconducting carbon ion gantry at the National Institute of Radiological Sciences (NIRS) in Japan weighs 300 tonnes, this is still larger and heavier than the "*state-of-the-art*" Varian gantry at The Christie Proton Beam Centre, which weighs 180 tonnes. Although there are commercial suppliers of systems that can deliver carbon and lighter charged particle beams such as helium (He), the systems are bigger, more expensive and 'less turn-key' than the equivalent PBT systems. Despite this, Japan has invested in carbon ion therapy with six centres and while these centres are also able to provide PBT (as they use synchrotron rather than cyclotron systems), the main treatment modality offered is ^{12}C. Similarly, Germany, Italy and Austria have made significant investment in ^{12}C ion centres at the Heidelberg Ion-beam Therapy Centre (HIT) (shown under construction in Figure 2) and the Marburg Ion-beam Therapy Centre (MIT) in Germany, CNAO in Italy and MedAustron in Austria. As mentioned previously, three ^{12}C ion centres are planned in the USA, but it is unclear at the moment whether they will have gantries.

More recently, interest has turned to helium ions, which may represent the optimum compromise solution for charged particle therapy, with greater tumour control than PBT, a smaller fragmentation tail, smaller gantries and less cost than carbon with an intermediate penumbra. However, at present, there is no commercial supplier of equipment for solely delivering helium ion therapy (although it is available with a range of other ions using synchrotrons) nor are there any clinical trials to support the hypothesis that He provides an optimum solution, although HIT is starting to undertake clinical trials with He.

Linear energy transfer (LET) and relative biological effectiveness (RBE):

The linear energy transfer (LET) for mono-energetic beams of charged particles increases with depth (as the energy of the particle decreases). The complexity and lethality of the DNA damage produced increases with LET.[3] In the entrance/plateau (lower LET) region, before the Bragg peak, single strand DNA breaks predominate (SSB, similar to X-ray damage), whilst complex, clustered DNA double strand breaks (DSB) are the predominant lesions in the high-LET region of the Bragg peak[4,5] and immediately distal to it. The biological effect, quantified as the relative biological effectiveness (RBE),* increases with depth and LET.

For PBT, most clinical treatments (worldwide) are given assuming that the same dose of protons delivers 1.1 times the biological effect of X-rays irrespective of depth, tissue type and oxygenation. RBE has become a "hot topic" in PBT with proponents arguing the need for a variable value[6] and pointing out that many of the experiments on which an RBE of 1.1 is based were carried out on rodents (or cells derived from them) whilst opponents have cautioned that successful clinical experience is based on this value and that there are dangers of overdosing normal tissue and under dosing the tumour if the value of 1.1 is changed.[7,8] Careful *in-vitro* and *in-vivo*s tudies[9–11] have indicated a rise in the RBE at the distal end of the Bragg peak and this is confirmed by mechanistic mathematical modelling.[12–14] Some authors have questioned if this rise in RBE may be the cause of brain necrosis observed in a minority of patients.[8] Some recent retrospective studies[15] appear to have confirmed this link, although similar correlations are not seen in all PBT centre.[16] Retrospective studies[17] on 430 patients found that in over 96.7%, there was less brain necrosis with PBT than with comparative X-ray RT. In 3.3% of patients an effect was observed; in all cases, this occurred when the distal end of the Bragg peak overlaps the periventricular region of the brain.

For carbon ions, a variable RBE is normally included in the clinical treatment plan. In Europe, this is largely based on the local effect model (LEM).[18] In Japan, the mixed beam model[19] was used until 2011 when it was replaced by the microdosimetric kinetic model (MKM).[20] The way in which RBE is reported, and thus the way in which dose is prescribed,differs significantly between most centres in Europe and Japan, making comparison of outcomes and data from trials difficult. Although significant steps are being taken, *e.g.* collaboration between CNAO in Italy and NIRS in Japan, there is an urgent need for further international collaboration and agreement on the physical parameters that are reported and the format in which this should be done.[21] The uncertainty in RBE and how it relates to long-term outcomes still needs to be addressed. Some commercial providers of treatment planning systems (RaySearch) now include treatment planning for carbon as well as protons and photons in their treatment planning software.

* RBE is defined as the ratio of the doses of a test and a reference radiation that have equal biological effect. This is a 'horizontal' comparator of effect, on a dose-response graph. Traditionally, the comparator was 250 keVp X-rays, although modern treatments are referenced to ^{60}Co MeV gamma rays.

Particle therapy in the UK

In the UK, low-energy PBT (up to 62 MeV) has been available at the National Health Service (NHS) centre in Clatterbridge near Liverpool for over 20 years. It has been used for the treatment of superficial tumours, particularly those of the eye and has been outstandingly successful.[22] In 2018, the NHS (in England) started treating patients with *state-of-the-art,* active spot scanning, high-energy (at energies up to 250 MeV) PBT at The Christie NHS Foundation Trust in Manchester. This centre uses a Varian superconducting (2.4 Tesla) cyclotron to supply three clinical treatment rooms, each equipped with a 360° gantry. There is also a purpose-built research room, which occupies the fourth gantry space, funded by the Christie Charity.[23] This room is designed to enable the translation of discovery science into the clinic and thereby keep the NHS treatment of patients at the forefront of technology. A second, high-energy NHS PBT centre will open in 2021 in London at University College London Hospitals NHS Foundation Trust (UCLH). At UCLH, three gantries will be used to treat NHS patients. The fourth gantry space is funded by a private provider and will also have some capacity for research. A number of private PBT centres also exist in the UK (the majority operated by Proton Partners International) and others are at the planning stage. These are single-room IBA solutions with partial gantries. An entirely different design concept using a linac-based technology with a fixed beam line is also being developed by AVO and is intended to operate at maximum energies between 200 and 250 MeV. A test site for this equipment is being developed at the Science and Technologies Facilities Council (STFC) laboratory in Daresbury in the north west of England.

UK overseas referral programme and PBT clinical trials

Since 2008, the NHS has been referring patients overseas for high energy PBT under the auspices of the Proton Overseas Programme[22,23] .The number of patients now treated abroad on this programme has dropped dramatically since The Christie started treating in 2018, but until UCLH opened and was fully ramped up it was planned that this programme would remain open. Covid-19 changed all of this and most UK PBT patients are now being treated at the Christie. Referral for PBT is via a national panel (originally for the overseas programme and now also addressing referrals for treatment at The Christie) which, to date, has referred over 1400 patients[22] . These patients were referred to PBT centres in Switzerland (Paul Scherrer Institute), USA (especially Jacksonville in Florida, with some treated in Oklahoma) and Germany (Essen). The NHS uses a prescribed list of indications, in combination with pragmatic national Multidisciplinary Team meetings, to select those patients who are most likely to benefit most from PBT treatment. In the clinical research arena, the National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Working Group (CTRad) has been organising national meetings to develop national PBT clinical trials. The first of these – TORPEDO,[24] a Phase III randomised trial comparing protons and X-rays for patients with oropharynx cancer is funded by CRUK and the Taylor Family Foundation and opened during 2020. Three other Phase III randomised trials on breast (PARABLE), good prognosis glioma (APPROACH) and oesophagus (PROTEUS) have recently been submitted for funding. A number of other smaller trials will also be undertaken through evaluative commissioning, *e.g.* the oropharynx trial NIPRO, or through links with the pharmaceutical industry, *e.g.* an immunotherapy radiotherapy trial which includes PBT. Through the CTRad initiative, a number of other trials ideas are in development, including a sinonasal Phase III trial, a re-irradiation study and large-scale trials on lung, liver, skull base meningioma and pancreas.

FLASH and spatially fractionated radiotherapy (SFRT)

Another area of worldwide interest that has the potential to transform radiotherapy is FLASH RT. FLASH is delivered at ultra-high dose rates (normally >40 Gy/s mean dose rate *vs* conventional RT dose rates ~0.16 Gy/s) and in large doses per fraction (so would require fewer fractions). The transformative potential of FLASH RT stems from experimental results obtained across different species (mouse, pig, cat, zebrafish) and various organs (lung, brain, skin, gut) that appear to show that FLASH RT significantly reduces damage to the healthy normal tissues surrounding the tumour.[25–38] Although there is also growing evidence that FLASH RT delays tumour growth, more evidence (over longer time periods) is needed to support claims of equivalent or increased tumour control.[26–29]

If validated preclinically and clinically and after very careful clinical evaluation, FLASH RT could mean a faster recovery and improved quality of life for patients. FLASH RT also has the potential to revolutionise the way in which we deliver RT to patients (larger and fewer fractions) and thus shorter treatment course - for patients and lower costs for the NHS. The FLASH RT effect appears to be dependent on a number of parameters which broadly fit into three categories.[30] These are:

- beam delivery: dose, dose rate, time of exposure, volume exposed etc;
- biology: *the impact on tumour/normal tissue environment*: effective oxygen diffusivity, cellular/metabolic oxygen consumption, reaction rates etc;
- radiolytic: radiation-induced oxygen depletion, reactive oxygen species etc. all of which still need to be fully characterised.

Several studies report that FLASH is agnostic of radiation quality (electrons, protons, X-rays) although most studies to date[25,31,32] have been undertaken with low-energy electrons (LEE). The mechanism(s) behind FLASH are still the subject of debate, the reduction of reactive oxygen species (ROS) after FLASH-RT has been measured[33] and tends to support the hypothesis, dating from the 1970s, that local oxygen depletion may be responsible for normal tissue sparing during FLASH RT.[34,35] The biological effect of FLASH RT in normal tissue has been the subject of significant worldwide interest[36,37] including in early clinical trials[36,37] . The efficient anti-tumour response described for FLASH RT remains to be investigated, as does lasting tumour control as opposed to simple tumour growth delay.

Similarly, SFRT[38,39] is an area of significant worldwide interest. The oldest form of SFRT is GRID therapy in which high doses (15–20 Gy) are delivered in one fraction with beams of around

1 cm^2, approximately spaced by 1 cm.[39] In SFRT, some areas of tumour and normal tissue receive low doses while others receive very high doses indeed. The observation of a highly non-linear inverse relationship between normal tissue radiosensitivity and tissue volumes[40] started to be exploited in the 1990s thanks to third-generation synchrotron sources providing kilovoltage X-ray beams with negligible beam divergence and high brilliance. This was the origin of the most extreme form of SFRT, the so called microbeam radiation therapy (MRT).[41] MRT uses 25–100 μm-wide beams spaced by 200–400 μm.

In such situations, physiologically induced tissue motions (such as blood pulsing) can easily be larger than the beam dimensions, necessitating ultra-high dose rate delivery to effectively "freeze" this motion. This domain therefore has clear cross-overs with FLASH delivery. At larger beam dimensions (in the mm range of so-called mini-beams), experimental data are also available in situations where target/tumour tissues receive approximately a "standard" dose but the mini-beam structure allows intervening target volumes to receive a greatly boosted dose. Studies with X-rays, electrons and protons are producing very exciting results, sparing normal tissue whilst still maintaining tumour control, even when parts of the tumour receive low doses. Some of these studies have been performed at conventional radiotherapy dose-rates, allowing a separation of this delivery mode from research into FLASH RT.

These are important topics for consideration in the context of a future charged particle facility since:

- technologically, it is currently possible to deliver FLASH PBT beams using the clinical cyclotron technology available in the PBT centres across the UK. Synchrotron centres such as GSI are also able to deliver experimental FLASH beams of heavier charged particles. It would be expected that any UK clinical or research facility would have a FLASH capability. For photon and electron FLASH, commercial clinical solutions are still in the development phase.
- the reduced lateral scattering of heavier charged particles compared with protons (and electrons) can in principle deliver a much sharper beam penumbra and so may be more amenable for mini-beam applications[42] than electrons or protons.

Questions considered

The meeting agreed that for the UK to continue to offer the very latest RT and the widest range of treatment options, there was a need to investigate the potential of heavy charged particle treatment, in combination with FLASH and SFRT, alongside PBT and X-ray RT.

It was agreed that any future clinical facility needs to be based within or adjacent to a hospital, mirroring the NHS provision of PBT. It was also agreed that this facility should be developed in partnership with a multidisciplinary research community, as there are still a large number of questions to be answered to define which treatment modalities would offer the greatest benefits for patients in the UK. This would need to include the ability to conduct preclinical research. Research would be needed to understand:

- the best ions to use for which treatment, including whether different ions might be better for different types of tumour. It should also include the effects of mixed charged particle treatment and where it could be best be utilised clinically. This is already being considered at HIT and NIRS;
- what type of accelerators should be used;
- whether gantries are needed and what other hardware and software options are available;
- what *in vitro* and *in vivo* pre-clinical research is required;
- the impact of FLASH RT and what research is needed to take it towards the clinic;
- the impact of SFRT and what research is needed to take it towards the clinic;
- and support the development of instrumentation and software platforms to meet the challenges of these new treatment methodologies;
- the need for a flexible approach to future-proof such a development.

It was agreed that different funding scenarios and timescales should be investigated. The group also agreed that competition about where any facility should be sited was not going to be helpful at this stage, following the lead of the previous UK PBT initiative. Instead, the group needs to work together to build a national case and only when the key requirements for such a facility have been identified would it be appropriate for different groups to bid to host it.

METHODS

To generate discussion and formulate, the recommendations summarised in this paper, individuals with a background in particle therapy research were invited to attend a 2-day meeting in March 2019 in Birmingham led by Prof Karen Kirkby and Prof Stuart Green. Representatives from all of the disciplines involved in heavy charged particle therapy, PBT, SFRT and FLASH in RT were invited. This included specialists in accelerator and particle physics and representation from CERN. It also included academic engineers, life and physical scientists, clinical scientists, clinicians, industrial representatives and representatives from funding bodies (STFC-UKRI, EPSRC, CRUK) and policy makers. The group included representatives from the NHS and private providers. It is appreciated that this group (41 people) only represents a snapshot of interested parties and it is envisaged that further meetings will be held to widen and deepen the discussions contained here.

The meeting consisted of presentations from experts in the field and discussions around predetermined questions, as shown in Table 1 . Trained facilitators were in attendance for the duration of the meeting to ensure the discussions involved everyone and stayed on topic. To generate a range of answers and in-depth discussions, attendees were first divided into multidisciplinary groups and posed a question.They were then split into profession-specific groups where they answered the same question, but now in depth. For the next question, the multidisciplinary groups were mixed so that no question was answered by the same

Table 1. Key questions presented to the meeting participants.

Is there a need for the UK to have a clinical facility for Heavier Ions?
If so, why?
Which would be the optimum ion?
Might different ions be better for different types of tumour?
What type of accelerators should be used?
What typeof delivery equipment (*e.g.*, gantry or not)?
How large should a facility be, and what should be its key features?
What is the potential timeline?
How can a facility be future-proofed?
How do we make this facility happen?
What are the potential barriers?
How can the barriers be overcome?
What are the research opportunities?
What facilities would be needed to undertake this research?
What is the potential impact of FLASH RT and what research is needed to take it towards the clinic?
What is the potential impact of SFRT and what research is needed to take it towards the clinic?
Define additional key questions based on scientific talks.

RT, radiotherapy; SFRT, spatially fractionated radiotherapy.

multidisciplinary group but the profession-specific groups obviously remained the same. The outcome of these discussions is covered in the body of this paper. To ensure that everyone was heard, facilitated brainstorming sessions were used with each participant invited to add one point in each go-around. During the brainstorming sessions, interruptions were not allowed and the brainstorming "go-arounds" continued to allow everyone to make their points and to be listened to. After this, those in each group were allowed to discuss the points made.

RESULTS AND DISCUSSION

Options and timeline

The group reached a general consensus about the need for a charged particle facility within the UK that also had the ability to deliver FLASH and SFRT. This was discussed principally for ^{4}He and ^{12}C ions, although ions as heavy as ^{16}O and lighter ions such as ^{11}B and ^{6}Li were also considered. The group also concluded that a flexible approach was needed which could adapt to potential future funding calls and which could also generate an evidence base. Although the options and timeline came out at the end of the discussions, these are shown below as they impact on the following sections. The options, detailed in Table 2, are:

- a clinical and research facility, incorporating new accelerator and gantry design, offering a full range of ions, full gantry-based clinical capability and a research room equipped with both pre-clinical and *in vitro* beam lines;
- a clinical and research facility, using existing technology, with a small range of ions (H, He, C), with a clinical capability including a carbon gantry and the ability to test alternative patient positioning technologies; this option also includes a research room (as Option 1 above);
- a clinical and research facility similar to two above, using existing technology, He and H ions only, including a gantry and a research capability;
- a preclinical research facility (50–60 MeV/u*) that incorporates new aspects of accelerator and gantry design (or alternatives) for a range of ions (H, He, Li, B, C, O) with both an *in vitro* and *in vivo* capability;
- as Option 4 above but operating at a lower energy (20 MeV/u*) using existing technology such that heavy ions such as ^{12}C can only be used preclinically *in vivo* for superficial tumours. Also has an *in-vitro* capability.

*Energies are given in MeV/u (MeV per atomic mass unit) to aid comparison with protons.

The timeline is obviously faster for the solutions which use existing technology and, *e.g.* if funding was available now, Option 5 could probably be available in 2–3 years, and Options 2 and 3 in 5 years. For Options 1 and 4, many of the designs for new accelerators already exist and in some cases partial testing has taken place. For Option 1, it may be better to start by developing Option 4 as a proof of principle as this could probably be realised on a timescale of 5 years. The full development of Option 1, depending on the technology used, could be in 10–15 years.

As a reference, to develop the NHS-England PBT centres, the period of awareness-building was begun by key figures in the clinical community in 2003/4, and this gathered pace and

Table 2. Different options for a UK heavy ion facility, considering capabilities, flexibility and cost, in descending order

Option	Characteristics	Ions	Estimated cost	Timeline[¶]
1.	Clinical and research facility incorporating *new* accelerator and gantry design. Beams capable of penetrating 30 cm in water, so up to 425 MeV/u for Carbon ions. Two or more clinical treatment rooms and one research room containing both pre-clinical and *in vitro* beam lines where clinical beam delivery can be emulated.	H, He, Li, B, C, O	£400M	10 years
2.	Clinical and research facility using *existing* accelerator technology. Beams capable of penetrating 30 cm in water. One or more clinical treatment rooms with one or more gantries to deliver C ions. Capability to test alternative technologies for patient treatment (*e.g.* chairs) Possible smaller gantry for H or He treatment. Research room containing both pre-clinical and *in vitro* beam lines where clinical beam delivery can be emulated (as one above).	H, He, C	£200M	5 years
3.	Clinical and research facility similar to two above, using *existing* technology, but only delivers H and He ions; with gantry for both H and He ions. Beams capable of penetrating 30 cm in water. Capability to test alternative technologies for patient treatment (*e.g.* chairs) Research room containing both pre-clinical and *in vitro* beam lines where clinical beam delivery can be emulated (as 1 and 2 above).	H, He	£150M	5 years
4.	Pre-clinical research facility (50–60 MeV/u), *new* accelerator and gantry design (or alternatives). Capability for *in vitro* research. Not suitable for clinical treatment.	H, He, Li, B, C, O	£100M	5 years
5.	Preclinical research facility, lower energy (20 MeV/u), existing technology (similar to Option 4). Heavy ions, such as C, only preclinical for superficial tumours. Not for clinical treatment.	H, He, Li, B, C, O	£50M	2–3 years

SFRT, spatially fractionated radiotherapy.

Timeline does not include time to identify asuitable site and obtain planning permission.

Although the consensus focussed on protons and ^{12}C ions, B and Li ions (intermediate in mass) and heavier O ions, were also discussed. A facility should also have capability for FLASH and SFRTdelivery.

influence over the subsequent 5–6 years. NHS-England made the first formal announcement of an intention to commission facilities in England in 2010 and the decision to proceed with two centres in Manchester and London was announced towards the end of 2011. The first NHS patients began treatment in Manchester in 2018 and London is due to start treating in 2021.

Is there a need for the UK to have a clinical facility for heavier charged particles and if so on what scale?

General considerations

The answer from all groups to this question was an emphatic YES. The groups then went on to outline the sort of research that should be undertaken and the sort of facility that was needed to undertake it. The UK has a strong heritage of research in this field and there is a huge opportunity to build a world-leading national facility, which draws in strengths from across the academic, industrial and clinical sectors.

The discussions highlighted the need to have a flexible response to potential funding and to draw up timelines to achieve this (see above and Table 2). It is important to consider the possible accelerators that could be used for such a facility. At the moment, cyclotrons are the de-facto technology choice for PBT, while for heavier charged particles all existing clinical centres utilise synchrotrons. IBA does have a design for a carbon cyclotron which is being developed by a consortium in Caen in France (ARCADE). These, and the emerging technologies (discussed below), have advantages and disadvantages, and part of the research that will need to be undertaken for such a facility would be analysing which accelerator and gantry technology to use. The difference for heavier charged particles with respect to protons is the increased beam rigidity (which determines the strength of magnet required to bend the beam), which for 425 MeV/u carbon ions (30 cm range) is nearly three times that of equivalent-depth protons; thus more rigid ions require larger magnetic fields for an accelerator (or gantry) of the same size. Technologically, helium ions offer the advantage of lower rigidity and smaller, more compact accelerators (225 MeV/u helium gives 30 cm range). He, C and O ions can be readily obtained from conventional ion sources, which use gaseous species. Elements such as Li and B require more specialised source construction and operation.

The funders and policy makers also agreed that – yes – there is a need for the UK to have a heavier charged particle facility. There is a unique opportunity to understand biology, including DNA damage, which would provide a major opportunity for research. The facility would have to have a flexible research focus; *e.g.* it should have the option for using multiple charged particle species.

Clinical

There is a need for high-quality clinical data. At present, there is comparatively little high-quality data available for protons and even less for heavier charged species (He & C). X-ray RT is also continuing to improve, especially with increasing use of image-guided IMRT (intensity modulated radiotherapy), and MR (magnetic resonance) image guidance. This means that determining the clinical advantage of any new and emerging technology becomes harder and requires more sophisticated data collection and analysis. Thus, it is important to carefully define which cohorts of patients would be most likely to benefit from each form of treatment. This can start with PBT, as a first step, using initiatives such as the workshops on national PBT clinical trials being organised by CTRad. These could be extended to the use of heavier ions and new technologies such as FLASH and SFRT. Clinical "benefit" includes improving local control and reducing both acute and late toxicities. It also involves understanding the mechanisms which operate during FLASH and SFRT, and how all of these technologies can be combined with immunotherapy and chemotherapy.

A heavy charged particle facility for He might be more pragmatic, realistic and achievable. It would be smaller in physical size than a full-blown ^{12}C facility. However, is helium sufficiently different from protons? Is helium just protons but with a sharper penumbra? If so, is the likely clinical advantage large enough for the investment required? Should we be considering ^{12}C from the outset? Again, this relates back to funding and what is available within a relevant timescale (Section 3.1). Helium has a definite advantage in some particularly difficult anatomy, *e.g.* in meningioma where He might be used to reduce dose to optic nerve and pituitary because it has: a) lower LET than carbon which may spare normal tissue such as the pituitary; (b) the penumbra for He is sharper than for protons and therefore achieves better dose coverage of tumour adjacent to critical normal structures, as demonstrated in planning studies undertaken at HIT.[43] If the UK decided that it needed to include the ability to deliver ^{12}C ions, then there would probably need to be three gantries to allow for demand, based on the Heidelberg HIT experience. However, a mixed helium and carbon facility could be smaller and potentially cheaper, if one of the gantries was designed just for helium (see Option 2 in Table 2). A consideration of physics and commercialisation opportunities would be important. A "mixed" helium and carbon facility might have additional novelty, which might enhance the funding possibilities. Such a facility might be designed to compare gantry technology although a facility with two entirely different gantry technologies could also be deemed to be inefficient. Similarly, it could also incorporate a fixed beam, to allow comparisons between gantries and fixed beam. At least one gantry would be needed to investigate rotational charged particle therapy, including provision for research in arc-therapy treatment. Improvements in software and patient couch movements may enable novel adaptive technology to be incorporated into the design. A clinical facility would also need access to 3D imaging in the treatment position.

The clinical group were unanimous in their view that such a facility must be located in a hospital setting and provide dedicated research space for a range of research activities. Some consideration was given to commercial opportunities especially for translating technology solutions in to the clinic. Such a facility, concentrating on R&D, would expect to treat relatively small numbers of patients and would provide the research environment for developing an innovation pipeline from discovery research to the clinic. It would also provide the evidence base for the development of clinical trials. Such an R&D environment would be'high risk and high reward' (though entirely safe for patients). This means that not all research avenues will succeed and there needs to be robust management in place, with the courage to turn off unproductive avenues of research. This is analogous to the approach adopted by the big pharmaceutical companies who do not expect all compounds to succeed. Without this breadth, we may not be investigating enough science or exploiting the resource put in to it.

Clinical medical physics

There is a need for a UK initiative to develop a compact facility containing at least a single gantry room and quality assurance (QA) room that is capable of using protons and He (or heavier ion) SFRT and FLASH. This is broadly in agreement with the conclusion of the clinical group described above although it does add in a FLASH and SFRT capability together with QA. This group again highlighted the need for excellent imaging capabilities, both online and pretreatment and for adaptive planning. Patient pathways should be considered to ensure streamlined high throughput with adaptive functionality.

With regard to treatment planning, it would not be appropriate to develop our own planning system, as there are already commercial solutions in this field. It is essential to build biologically augmented planning into these planning systems. The latest generation of mechanistic models[12–14] allows a much better linkage to the tumour and normal issue microenvironment and real biological end points. Carefully designed studies will allow these be to validated clinically. There may be opportunities to send patients overseas (for ^{12}C or ^{4}He ion therapy) using a similar model to that used for protons in the Proton Overseas Programme. This would generate a clinical evidence base which could be used to make the case for such a facility. As discussed above, there may also be an opportunity, via CTRad, to develop clinical trials (with clinical partners in Europe) where an arm of the trial uses C or He ions.

Acceleratorand enabling technologies

In the discussion of future infrastructure, it is useful to mention that the UK already has access to a number of low-energy beam lines, which are capable of delivering a range of ions for research purposes. These are either university-based cyclotrons (*e.g.* Birmingham, protons and He up to 40 MeV), or systems based around ion implantation or tandem accelerators for ion beam

analysis or nuclear research. These include University of Surrey (2keV–2MeV, singly charged), Dalton Cumbria Facility (up to 5MeV singly charged). Higher-energy clinical proton beams are available from cyclotrons at Clatterbridge (62 MeV), and The Christie (250 MeV). Through Varian's FLASHForward™† consortium, FLASH proton beams have been demonstrated from the Varian clinical equipment and Varian and IBA are developing the dosimetry for FLASH beams as part of the EU project INSPIRE.‡ Within INSPIRE, The Paul Scherrer Institute in Switzerland is developing transmission FLASH treatment planning,[44] while University of Manchester and The Christie have been developing an understanding of the parameter space for PBT FLASH[30], and Varian are developing new dosimetry systems to accurately measure the doses being delivered during PBT FLASH.

The UK has significant accelerator development capabilities focused around the national laboratories at Rutherford Appleton Laboratory (RAL) and Daresbury Laboratory (both part of UKRI STFC). Significant programmes in accelerator research have already been funded, including: the EMMA programme that experimentally demonstrated the feasibility of novel FFAG (fixed-field alternating gradient) electron accelerators for the first time, leading to a comprehensive design study for rapid treatment with protons and carbon ions (PAMELA), a high-energy proton-only design study (NORMA), and a helium-specific FFAG design (HEATHER); significant development of plasma-based acceleration of protons and ions (which are also capable of delivering FLASH and SFRT) includes the so-far world's highest-energy plasma acceleration of protons up to ~100 MeV; development of the world's highest-gradient (53 MV/m) proton linac for particle therapy (PROBE). STFC retains significant expertise in constructing and operating proton accelerator systems, in particular the ISIS 800 MeV proton synchrotron.

Other considerations include: whether radioactive ion species such as ^{11}C might provide an additional adjunct to the research (*e.g.* for simultaneous range verification during treatment); whether carbon ion treatment might be supported by higher-energy proton irradiation for imaging purposes (proton CT) (as has been suggested at MedAustron[45] ; how imaging methods such as MRI might be incorporated in to such a facility; and whether gantries are required for all treatments or for just a subset. It will be important to be able to incrementally develop both research and clinical infrastructures, and a balance must be struck between shorter-term developments of established technology and longer-term investment in methods that may offer game-changing advantages either for UK facilities or for emerging markets in the future.

The present status of PBT has demonstrated the urgent need for new instrumentation to plan and monitor treatments (*e.g.* proton CT) and the adoption of existing imaging modalities (*e.g.* MRI) in the pursuit of personalised, optimised and adaptive treatments. Different radiation types and high near-instantaneous doses of FLASH will set new demands. Rapid developments in machine learning (*e.g.* Deep Learning) will affect the capabilities to plan and to actively monitor and adapt treatments.

Accordingly, our recommendations are that:

- innovative technology should continue to be developed in the UK;
- the development should span government, academia, the clinic and industry;
- further studies should be conducted to identify the preferred accelerator technology of choice for development;
- such development should incorporate necessary parallel developments in imaging, feedback and control, machine learning and artificial intelligence and treatment planning for the optimal use of heavier charged particle therapy.
- the research and clinical objectives must be determined, and this should be clinically driven, based on the achievements of the global charged particle therapy community, but with modelling of where the unmet need is and which applications (including paediatric) may be the most attractive in providing a competitive edge to the UK development.

Physics

The physics group proposed the establishment of a National Ion Research Centre (NIRC) to enable research using protons and heavier charged particle research adjacent to a clinical facility and located in a hospital. They recommended strong industrial involvement building on UK academic, clinical and commercial expertise. Alongside, clinical and biological research which includes new modalities such as SFRT and FLASH, such a facility should also be able to conduct research in to:

- space radiation physics and biology;
- emulation of space weather and impact on global power and communication;
- semiconductor research, soft upsets etc;
- accelerator, beam delivery, gantry design and patient positioning (hardware and software);
- heavy ion radiobiology including drug and immune radiation combinations;
- high radiation environment technology, nuclear energy, decommissioning;
- fundamental studies, including new types of beams and beam delivery.

What is required is a flexible solution that can accelerate and deliver a number of different charged particles that might be used in ion therapy in the future.

Biology

There is a need for the UK to have a multi-ion facility that is capable of undertaking experiments *in vitro* (2D and 3D) and *in vivo*. This would allow the UK to explore new radiobiology, immune activation, drug-radiation combinations and new technologies such as SFRT and FLASH. It would also allow exploration of normal tissue toxicities and the effects of hypoxia on radiosensitisation of tumour and normal tissue. Having such a

† FLASHForward™ https://www.varian.com/en-gb/about-varian/research/flashforward-consortium accessed 17th Feb 2020
‡ INSPIRE https://protonsinspire.eu/ accessed 17th Feb 2020

facility would aid research and produce answers / evidence for a wide range of research questions. An animal facility is essential as not all research can be done *in vitro*.

Key features of this facility are that it should:

- be based in or adjacent to a hospital with a clinical research facility, not at an STFC site;
- have access to latest technology, microscopy, high throughput sequencing;
- have an animal facility close by with safe and efficient arrangements for transfer to and from the charged particle therapy facility;
- have access to the necessary quality assurance techniques in the room.

An alternative, cheaper option would be for the UK to focus efforts on developing a helium facility or a low energy facility (He, C) for preclinical work. Some delegates suggested that such a facility could also be used as an animal hospital, although there was not a consensus here. *In-vivo* radiobiology does not require the very high energy beams required for humans. However, we are currently lacking the evidence base to prove helium would be useful clinically and the funding will determine the scale of such a facility.

How do we make such a facility happen, potential barriers and how do we overcome?

General considerations

After the initial discussion, the groups came together to discuss how to make such a facility happen and to identify the potential barriers. There was a consensus that a **community approach** was needed that involved all interested parties with a vision that combined discovery science with a translational research capability leading to a clinical treatment facility. Cost would be the major determinant as to whether the route to a clinical facility would be staged, with a lower energy facility for *in-vitro* and preclinical research coming first to provide an evidence base for a clinical facility, or building the clinical facility from the outset and using the research capability to inform and develop the clinical treatments. Similarly, cost would be a determinant of whether such a facility should develop new accelerator and patient positioning technology (gantries, chairs) or whether an existing product from a manufacturer should be considered. It was agreed that it was important to have a number of solutions to fit with the available budget and scope of any funding call.

Build a multidisciplinary community

It was agreed that there was a need for a coordinated plan that involved the entire community and this needed to be extended to patients. Any bid would need to make a clinical case for this type of treatment. Here, clinical oncologists are key to developing a consensus view on which patients might benefit most from He or C treatment. There may be an option for a pilot overseas programme (along the lines of the Proton Overseas Programme). Developing an understanding of the percentage of patients who might benefit from such a facility would help to scope the size and capabilities required. Involving the wider community could be initially facilitated by CTRad and UKRI-funded Networks[§] including UKRI, CRUK and other funders. There will be a need to develop a research plan that is truly multidisciplinary – no one research council or funding body is likely to pay the full amount but there is an opportunity to make this a flagship for multidisciplinary research. The proposal needs active involvement from the NHS to ensure that any facility is clinically relevant and has the potential to transition and translate into patient treatment and benefit.

Potential barrier: what sort of facility? Solutions

A flexible approach is needed so that there is an opportunity to react to different funding calls when they arise. The highest cost and longest timescale option is a clinical facility, which offers a range of different ions, delivered through gantries, with the potential of other delivery techniques and incorporates a research capability. This facility would also provide the opportunity to incorporate new accelerator technology either at the outset or as part of its development (see Table 2). The lowest cost facility offers the opportunity for *in-vivo*- and *in-vitro* research and is a precursor to a clinical facility. This option could be expanded to act as a test-bed for new accelerator technology. The solutions also include using existing accelerator technology. This would shorten the timescale and reduce the costs but also reduces the adventure (for the accelerator community) and reduces potential innovation and commercialisation opportunities.

Potential barrier: do we need a gantry? Solution

Gantries that are capable of rotating through 360° around the patient combined with robotic patient treatment couches are currently recognised as offering the best treatment option for PBT. However, as the ion mass (and beam rigidity) increases so does the size, mass and cost of the gantry. This presents an opportunity to test the latest generation of patient chairs, which their manufacturers believe offer comparable treatment efficacy and comfort to gantries. It is also an opportunity for the accelerator community to develop a new generation of compact gantries.

Potential barrier: is there a clinical need? Solution

The centres in Japan and Germany argue that their results indicate the efficacy of ^{12}C ion treatment. The Japanese centres have demonstrated spectacular results for pancreatic cancer[46] and this led to interest in the USA in trials in this field.[47] There was agreement at the meeting that the UK community needs to forge links with the heavier ion community internationally as regular access to heavier charged particle facilities for research would help to develop and build the evidence base. Similarly, there is an opportunity to develop an overseas programme similar to that for PBT. There may also be opportunities via CTRad to develop clinical trials involving heavier ions actively working with colleagues in Austria and Germany. The clinical question at the heart of these trials would be key to getting them funded but having a national approach with the whole community working together would help in formulating the right questions. In this way, we could

§ STFC Advanced Radiotherapy Network; EPSRC Grand Challenge Network+ in Proton Therapy **EP/N027167/1**

start to build the evidence base that would be required to build a clinical facility.

Potential barrier: finance/funding for such a facility? Solution

Normally, Government will only fund such large amounts when there is a strong partnership with industry, and thus there is a real need to ensure that the community that is being developed has strong links to industry and the clinic and involves government, NHS and patient stakeholders. It is also important that all partners are involved from the outset and the patient view is central. The cost of such a facility is a barrier, but a flexible and stepwise approach may substantially mitigate this barrier. Sustainability needs to be built into the development of the facility with a cost model that ensures its future viability. Obviously, this depends on the type of facility being developed but it is important to ensure that it is fully utilised and that other avenues of potential research collaboration are exploited. For example, apart from clinical research, high energy heavy ions can be used to emulate the solar wind and space weather, so such a facility has potential users from the military, electronics and global communications industries. Likewise, there are energy and security applications as well as applications in the nuclear industry for emulating reactor walls and ageing of natural containment facilities.

CONCLUSIONS

After an intense 2 days of discussions, the gathered community had shared and grown their enthusiasm to engage in developments to understand and clinically evaluate charged particle beam radiotherapy, which also included a capability for FLASH and spatially fractionated RT. There was a consensus that the UK needs to look at options for building a National Ion Research Centre (NIRC) for developing charged particle beam therapy. It was important that ideas for an NIRC were based of clinical and scientific merit and its location should be determined at a later date (this follows the successful approach adopted for PBT). It was also important that a truly multidisciplinary approach was adopted that brings together academic scientists (life and physical sciences) and engineers, with those who work in the clinical environment (clinicians, physicists and radiographers) and with those from industry, policy makers, funders and patients.

Key unanswered questions include whether the nature and pattern of DNA damage generated by charged particle beams, after mediation and filtering by the tumour/tissue microenvironment, are able to generate triggers for immune activation which are different and greater than photon/proton/electron beams. Critically for the design of research/clinical facilities, there needs to be a better understanding of whether the mode of delivery of those ion beams, whether conventional, FLASH or SFRT, changes the paradigm in significant and useful ways which give further advantage over photon / proton / electron beams.

The group proposed a number of potential scenarios for an NIRC which would largely depend on the type and amount of funding available, but agreed the need for an agile and flexible response. They also looked at potential barriers and how to overcome them. It was agreed that an NIRC would need to engage across the funding spectrum and also engage with NHS-E and patient groups. The consensus was that an NIRC needed to be based within a hospital and should be capable of delivering a range of ions that should include ^{4}He and ^{12}C. It was generally agreed that the ideal solution would be capable of treating patients with a gantry, but a solution which developed such a facility via a preclinical, lower energy facility should also be considered if funding was not available for the full clinical facility. Having a research capability was seen as essential, but ensuring that this was multidisciplinary and brought in a wide range of expertise was also key to the development of such a centre. Solutions that used existing accelerator technology were probably the fastest to achieve and were also probably less costly.

NCRI CTRad was seen as vital to the development of such a centre, as it already had many of the key people within its membership, it also has the mechanisms for developing clinical trials ideas for both charged particle therapy FLASH and SFRT. Similarly, there may be opportunities for developing charged particle therapy and FLASH trials by engaging with the NHS-E overseas programme in the post-Covid-19 environment. Our vision for the future is one which harnesses a national multidisciplinary approach to develop a world leading clinical and research capability in charged particle therapy.

ACKNOWLEDGEMENTS

We are indebted to Dr Nicholas Henthorn for providing the diagrams used in Figure 1 and to Lauren Hewitt for help in preparing the manuscript and for facilitating the meeting, to Helena Kondryn and Zoe Lingard for alsofacilitating the meeting. KJK,NFK, NGB, and RIMare supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre. This work was supported by Cancer Research UK via funding to the Cancer Research Manchester Centre [C147/A25254] and UK RadNet Manchester [C1994/A28701].
We are also grateful to the Engineering and Physical Sciences Research Council (EP/R023220/1) Grand Challenge Network+ in Advanced Proton Therapy, the Science and Technology Facilities Council (ST/N002423/1) Global Challenge Network+ in Advanced Radiotherapy, the European Union's Horizon 2020 research and innovation programme (730983) INSPIRE project for support.

CONTRIBUTORS

Allinson N, Angal-Kalinin D, Ashenden M, Burrows P, Chadwick AL, , Debus J, Dosanjh M, Durante M, Edgecock R, Farr J, Geddes N, Giaccia A, Hammond E, Hollinshead K, Henthorn N, Hewitt L, Kondryn H, Lazarus I, Long K, McKenna G, Merchant MJ, Noro M, Nisbet A, Oelfke U, Owen H, Poynter A, Prezado Y, Ratoff P, Robertson K, Schettino G, Seddon B, Taylor MJ, Thomas R, Towe S, Vojnovic B, Watts S

REFERENCES

1. Ahmad AS, Ormiston-Smith N, Sasieni PD. Trends in the lifetime risk of developing cancer in Great Britain: comparison of risk for those born from 1930 to 1960. *Br J Cancer* 2015; **112**: 943–7bjc.2014. doi: https://doi.org/10.1038/bjc.2014.606
2. Achieving a World Class Radiotherapy Service across the UK, CRUK..
3. Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. variations as a function of biological endpoint, dose, and linear energy transfer. *Phys Med Biol* 2014; **59**: R419–72. doi: https://doi.org/10.1088/0031-9155/59/22/R419
4. Tommasino F, Durante M. Proton radiobiology. *Cancers* 2015; **7**: 353–81. doi: https://doi.org/10.3390/cancers7010353
5. Casiraghi M, Schulte RW. Nanodosimetry-Based plan optimization for particle therapy. *Comput Math Methods Med* 2015; **2015**: 1–13. doi: https://doi.org/10.1155/2015/908971
6. Jones B. Why RBE must be a variable and not a constant in proton therapy. *Br J Radiol* 2016; **89**: 20160116. doi: https://doi.org/10.1259/bjr.20160116
7. Underwood T, Paganetti H. Variable proton relative biological effectiveness: how do we move forward? *Int J Radiat Oncol Biol Phys* 2016; **95**): : 56–8p.. doi: https://doi.org/10.1016/j.ijrobp.2015.10.006
8. Indelicato DJ, Flampouri S, Rotondo RL, Bradley JA, Morris CG, Aldana PR, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol* 2014; **53**): : 1298–304p.. doi: https://doi.org/10.3109/0284186X.2014.957414
9. Saager M, Peschke P, Brons S, Scholz M, Huber PE, Debus J, Karger CP, et al. OC-0517: investigation of the RBE variation of protons in the rat spinal cord within a spread-out Bragg peak. *Radiotherapy and Oncology* 2017; **123**: S273–410. doi: https://doi.org/10.1016/S0167-8140(17)30957-X
10. Chaudhary P, Marshall TI, Perozziello FM, Manti L, Currell FJ, Hanton F, et al. Relative biological effectiveness variation along monoenergetic and modulated Bragg peaks of a 62-MeV therapeutic proton beam: a preclinical assessment. *Int J Radiat Oncol Biol Phys* 2014; **90**: 27–35. Epub 2014 Jun 28. doi: https://doi.org/10.1016/j.ijrobp.2014.05.010
11. Marshall TI, Chaudhary P, Michaelidesová A, Vachelová J, Davídková M, Vondráček V, et al. Investigating the implications of a variable RBE on proton dose fractionation across a clinical pencil beam Scanned Spread-Out Bragg peak. *Int J Radiat Oncol Biol Phys* 2016; **95**: 70–7. Epub 2016 Feb 13. doi: https://doi.org/10.1016/j.ijrobp.2016.02.029
12. Ingram S, Warmenhoven J, Henthorn N, Smith E, Burnet N, Mackay R, et al. 'Mechanistic modelling supports entwined rather than exclusively competitive DNA double-strand break repair pathway', *Scientific Reports*. *Vol* 2019;. , : 6359pp. 63599, no. 1.
13. Henthorn N, Warmenhoven J, Sotiropoulos M, Aitkenhead A, Smith E, Ingram S, et al. Clinically relevant nanodosimetricsimulation of DNA damage complexity from photons and protons', *RSC Advances*. 2019;.
14. Smith E, Henthorn N, Warmenhoven J, Ingram S, Aitkenhead A, Richardson J, et al. In Silico Models of DNA Damage and Repair in Proton Treatment Planning: A Proof of Concept', *Scientific Reports*. 2019;. doi: https://doi.org/10.1038/s41598-019-56258-5
15. Eulitz J, Lutz B, Wohlfahrt P, Dutz A, Enghardt W, Krause M, et al. Assessment of clinical RBE variability in proton therapy.. 2019;PTCOG58, June 15th.
16. Schuemann JP, Giantsoudi D, Niemierko A, Maquilan G Jr, Shih HA, et al.Paganetti Brain Necrosis in Adult Proton Therapy Patients Do necrotic regions have elevated linear energy transfer? *Int J RadiatOncolBiol Phys* 2019; **105**(Issue 1) VolumeSupplement, Page S230 DOI.
17. Harrabi S, Gudden C, Adeberg S, Bougatf N, Haberer T, Rieken S, et al. OC-0514: radiation necrosis after proton beam therapy - when and where does it happen? *Radiotherapy and Oncology* 2017; **123**: S271**123**(S): p. S271. doi: https://doi.org/10.1016/S0167-8140(17)30954-4
18. Grün R, Friedrich T, Elsässer T, Krämer M, Zink K, Karger C, et al. Scholz. *M Impact of enhancements in the local effect model (LEM) on the predicted RBE-weighted target dose distribution in carbon ion therapy Physics in medicine and biology* 2012; **57**: 7261–74.
19. Kanai T, Furusawa Y, Fukutsu K, Itsukaichi H, Eguchi-Kasai K, Ohara H. Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. Radiat Res. 1997;147:78–85. 38; Kanai T, Endo M, Minohara S, et al. *Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int J RadiatOncolBiol Phys* 1999; **44**: 201–10.
20. Inaniwa T, Furukawa T, Kase Y, Matsufuji N, Toshito T, Matsumoto Y, et al. Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model. *Phys Med Biol* 2010; **55**: 6721–37. doi: https://doi.org/10.1088/0031-9155/55/22/008
21. Fossati P, Matsufuji N, Kamada T, Karger CP. Radiobiological issues in prospective carbon ion therapy trials. *Med Phys* 2018; **45**: 1096–110. doi: https://doi.org/10.1002/mp.12506
22. Matthew limb how NHS investment in proton beam therapy is coming to fruition BMJ. **2019**l313 : (Published 11 February 2019.
23. Burnet NG, Mackay RI, Smith E, Chadwick AL, Whitfield GA, Thomson DJ, et al. Proton beam therapy: perspectives on the National health service England clinical service and research programme. *Br J Radiol* 2020; **93**: 20190873. doi: https://doi.org/10.1259/bjr.20190873
24. Price J, Hall E, West C, Thomson D. TORPEdO - A Phase III Trial of Intensity-modulated Proton Beam Therapy Versus Intensity-modulated Radiotherapy for Multi-toxicity Reduction in Oropharyngeal Cancer. *Clin Oncol* 2020; **32**: 84–8. Epub 2019 Oct 8. doi: https://doi.org/10.1016/j.clon.2019.09.052
25. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, et al. Ultrahigh dose-rate flash irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med* 2014; **6**: 245ra93245. doi: https://doi.org/10.1126/scitranslmed.3008973
26. Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond J-F, Petit B, et al. Irradiation in a flash: unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s. *Radiother Oncol* 2017; **124**: 365–9. doi: https://doi.org/10.1016/j.radonc.2017.05.003
27. Montay-Gruel P, Acharya MM, Petersson K, Alikhani L, Yakkala C, Allen BD, et al. Long-Term neurocognitive benefits of flash radiotherapy driven by reduced reactive oxygen species. *Proc Natl Acad Sci U S A* 2019; **116**: 10943–51. doi: https://doi.org/10.1073/pnas.1901777116
28. Schüler E, Trovati S, King G, Lartey F, Rafat M, Villegas M, et al. Experimental platform for ultra-high dose rate flash irradiation of small animals using a clinical linear accelerator. *Int J Radiat Oncol Biol Phys* 2017; **97**: 195–20310.1016/j.ijrobp.2016.09.018. doi: https://doi.org/10.1016/j.ijrobp.2016.09.018
29. Durante M, Bräuer-Krisch E, Hill M. Faster and safer? *FLASH ultra-high dose rate in radiotherapy British J Radiology* 2018; **91**): : 20170628p..

30. Rothwell B, Kirkby NF, Chadwick AL, Merchant MJ, Kirkby KJ. Flash radiation: modelling oxygen depletion kinetics as a mechanism for induced radio-resistance submitted. *International Journal of Radiation Oncology, Biology, Physics* 2020;.
31. Montay-Gruel P, Bouchet A, Jaccard M, Patin D, Serduc R, Aim W, et al. X-Rays can trigger the flash effect: ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice. *Radiother Oncol* 2018; **129**: 582–8. doi: https://doi.org/10.1016/j.radonc.2018.08.016
32. Vozenin M-C, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond J-F, et al. The advantage of flash radiotherapy confirmed in mini-pig and Cat-cancer patients. *Clin Cancer Res* 2019; **25**: 35–42. Epub 2018 Jun 6. doi: https://doi.org/10.1158/1078-0432.CCR-17-3375
33. Montay-Gruel P, Acharya MM, Petersson K, Alikhani L, Yakkala C, Allen BD, et al. Long-Term neurocognitive benefits of flash radiotherapy driven by reduced reactive oxygen species. *Proc Natl Acad Sci U S A* 2019; **116**: 10943–51. Epub 2019 May 16. doi: https://doi.org/10.1073/pnas.1901777116
34. Hendry JH. Quantitation of the radiotherapeutic importance of naturally-hypoxic normal tissues from collated experiments with rodents using single doses. *Int J Radiat Oncol Biol Phys* 1979; **5**): : 971–6p.. doi: https://doi.org/10.1016/0360-3016(79)90602-3
35. Hendry JH, Moore JV, Hodgson BW, Keene JP. The constant low oxygen concentration in all the target cells for mouse tail radionecrosis. *Radiat Res* 1982; **92**: , (No. 1): 172–81. doi: https://doi.org/10.2307/3575852
36. Bourhis J, Montay-Gruel P, Gonçalves Jorge P, Bailat C, Petit B, Ollivier J. Jeanneret-Sozzi W[5], Ozsahin M, Bochud F, Moeckli R, Germond JF, Vozenin MC. *Clinical translation of FLASH radiotherapy: Why and how? RadiotherOncol* 2019; **139**: 11–17.
37. Vozenin M-C, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond J-F, et al. The advantage of flash radiotherapy confirmed in mini-pig and Cat-cancer patients. *Clin Cancer Res* 2019; **25**: 35–42. doi: https://doi.org/10.1158/1078-0432.CCR-17-3375
38. Billena C. Khan A J A Current Review of Spatial Fractionation: Back to the Future?International Journal of Radiation Oncology*Biology*Physics. **104**(Issue 1): 177, --87Volume1 May 2019, Pages.
39. Prezado Y, Dos Santos M, Gonzalez W, Jouvion G, Guardiola C, Heinrich S, et al. Transfer of Minibeam radiation therapy into a cost-effective equipment for radiobiological studies: a proof of concept. *Sci Rep* 2017; **7**: 17295. doi: https://doi.org/10.1038/s41598-017-17543-3
40. Zeman W, Curtis HJ, Gebhard EL, Haymaker W. Tolerance of mouse-brain tissue to high-energy deuterons. *Science* 1959; **130**: 1760–1. doi: https://doi.org/10.1126/science.130.3391.1760-a
41. Slatkin DN, Spanne P, Dilmanian FA, Sandborg M. Microbeam radiation therapy. *Med Phys* 1992; **19**(no. 6): 1395–400. doi: https://doi.org/10.1118/1.596771
42. Brualla-González L, Vázquez-Luque A, Zapata M, González-Castaño DM, Luna-Vega V, Guiu-Souto J, et al. Development and clinical characterization of a novel 2041 liquid-filled ionization chambers array for high-resolution verification of radiotherapy treatments. *Med Phys* 2018; **45**: 1771–81. doi: https://doi.org/10.1002/mp.12816
43. Tessonnier T, Mairani A, Chen W, Sala P, Cerutti F, Ferrari A, et al. Proton and helium ion radiotherapy for meningioma tumors: a Monte Carlo-based treatment planning comparison. *Radiat Oncol* 2018; **13**: 2(1):2. Published. doi: https://doi.org/10.1186/s13014-017-0944-3
44. van de Water S, Safai S, Schippers JM, Weber DC, Lomax AJ. Towards flash proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates. *Acta Oncol* 2019; **58**: 1463–9. doi: https://doi.org/10.1080/0284186X.2019.1627416
45. Ulrich-Pur F. Imaging with ion beams at MedAustron', presentation at 2nd Ion Imaging Workshop, 11th. June 2019Manchester, UK. Available from: www.ionimaging.org.
46. Kawashiro S, Yamada S, Okamoto M, Ohno T, Nakano T, Shinoto M, et al. Multi-Institutional study of Carbon-ion radiotherapy for locally advanced pancreatic cancer: Japan Carbon-ion radiation oncology Study Group (J-CROS) study 1403 pancreas. *Int J Radiat Oncol Biol Phys* 2018; **101**(Issue 5), : 1212, --21VolumePages1. doi: https://doi.org/10.1016/j.ijrobp.2018.04.057
47. Trial of carbon ion versus photon radiotherapy for locally advanced, unresectable pancreatic cancer (CIPHER..