An introduction to proton beam therapy

ABSTRACT

Radiotherapy is a highly effective anti-cancer treatment commonly used alongside systemic therapies and surgery to achieve long-term cancer-free survival. Conventional radiotherapy uses photon beams to deliver a high dose of radiation to the tumour volume to eradicate cancer cells. This has to be offset against the irradiation of surrounding normal tissues, as increasing this dose causes more treatment-related toxicity. In August 2018, the NHS's first high energy proton beam therapy centre opened at The Christie NHS Foundation Trust in Manchester. A second NHS centre is scheduled to open in 2020 at the University College London Hospitals NHS Trust. Proton beam therapy may offer dosimetric advantages compared to conventional radiotherapy as a result of its characteristic dose deposition – proton beams deliver a comparatively higher proportion of their dose to the target volume relative to normal tissues, without significant exit doses when compared to conventional photon therapy. Therefore proton beam therapy may be indicated for certain tumours situated next to critical organs or in the paediatric population where quality of life and the reduction of secondary effects from radiation are particularly significant. The indications for proton beam therapy and patient outcomes after treatment will be carefully monitored and evaluated in order to provide a robust evidence base for its use.

The potential application of ionizing radiation in medicine, using photons, was first demonstrated over 100 years ago (Roentgen, 1896). Since then a multitude of advances has ensured that radiation now plays a vital role in the management of cancer and it is used as a treatment modality, often in combination with surgery or chemotherapy, in 40% of patients cured of their disease (Tubiana, 1992). The main aim of radiotherapy is to deliver a high dose of radiation to the tumour volume to eradicate cancer cells. This must be offset against the irradiation of surrounding normal tissues, as increasing this dose causes more treatment-related toxicity. Currently the most widespread use of radiation therapy in the UK is delivered using high energy X-rays or photons delivered by linear accelerators. Increasingly the reduction in normal tissue doses is achieved in routine clinical practice using advanced radiotherapy techniques such as intensity-modulated radiotherapy and volumetric-modulated arc therapy.

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Proton beam therapy may offer further dosimetric advantages compared to conventional photon treatments. This is a result of the characteristic dose deposition properties of proton beams which deliver a comparatively higher proportion of their dose to the target volume relative to normal tissues, without significant exit doses when compared to conventional photon therapy. As such, proton beam therapy can help maintain or escalate the prescribed dose to the tumour volume, without exceeding acceptable doses to adjacent healthy structures, and can ultimately reduce the overall energy deposition in normal tissues. This has important consequences for tumours situated next to critical organs, or in the paediatric population where quality of life and the reduction of secondary effects from radiation are particularly significant.

Since 2008, as part of the NHS Proton Beam Overseas Programme, NHS England has been selecting clinically appropriate patients and sending them abroad for proton beam therapy treatment, usually to the USA. In general, these patients include adults with skull base and paraspinal tumours and the paediatric, teenage and young adult population diagnosed with particular cancers (Crellin, 2018). In August 2018, the NHS's first high energy proton beam therapy centre opened at The Christie NHS Foundation Trust in Manchester. A second NHS centre is scheduled to open in 2020 at the University College London Hospitals NHS Trust. These new centres mean that NHS patients will be able to receive proton beam therapy closer to home and will be increasing reviewed by physicians within general hospitals. There are also private centres that may offer proton beam therapy in the UK which are not commissioned by NHS England. As of the end of August 2019, 90 patients have started treatment at the NHS proton beam therapy centre at The Christie. This number of patients and the types of indications treated will continue to increase as further indications are commissioned by the NHS and with increased clinical trial activity evaluating proton beam therapy treatment.

The principles of radiotherapy

Radiotherapy in clinical practice uses ionizing radiation. When radiation passes through tissues it transfers energy by interactions with atoms and molecules along its path. This can produce ions (electrically charged particles) and secondary electrons within cells that can directly damage DNA by altering its chemical structure or, through subsequent cascading reactions, produce highly reactive free radicals that damage DNA. Ultimately the biological effect is cell death, either through an inability to repair the genetic damage, or through a loss of reproductive capacity.

The energy transferred and deposited in cellular tissues is quantified as the 'absorbed dose'. It is expressed in energy (J) absorbed per unit mass (kg) which uses the units of Gray (Gy). The prescribed dose is typically given over several weeks in multiple sessions (fractions), generally once a day from Monday to Friday. Fractionation spares normal tissues by allowing time for repair and repopulation of normal cells, thereby reducing side effects experienced by patients. It also increases the effects of radiotherapy on tumours through reoxygenation and reassortment of cancer cells into radiation-sensitive phases of the cell cycle.

The number of radiotherapy sessions required depends on the aim of therapy. For a palliative dose a single fraction may be sufficient to relieve symptoms and control disease for a period of time. In contrast when the aim is to eradicate a solid tumour, radiotherapy may take place over several weeks. Furthermore, radiation therapy can be used in combination multi-modality treatment strategies, e.g. with chemotherapy, surgery and immunotherapy.

Differences between conventional radiotherapy and proton beam therapy

Conventional external beam radiotherapy typically uses high-energy X-rays (photons) to deliver radiation to tumours. This is done using a linear accelerator (commonly referred to as a linac) which accelerates electrons that collide with a heavy metal target to produce high energy X-rays. They are then collimated to conform to the shape of the target volume. The photons produced are massless, uncharged quanta of energy. In contrast a proton is one of the building blocks of the atom and is a large positively charged particle. For proton beam therapy, proton beams are accelerated in a larger particle accelerator, called a cyclotron (although some centres use a synchrotron which performs a similar role in a slightly different way). In the cyclotron protons are accelerated to energies required for treatment before being steered down a beam line to the treatment room.

Figure 1 shows the layout of the proton therapy centre at The Christie showing the cyclotron, beamline and treatment rooms.

The most significant difference between the two radiotherapy techniques is related to the physical properties of the proton particle. Proton beams penetrate tissue to a limited depth, depositing most of their energy at the end of their path as their velocity decreases until they have given up all of their energy. This means their radiation dose builds up into a peak and then falls off sharply with no dose given after a finite range. In contrast, photons enter and pass though tissues depositing energy (and therefore radiation dose) as they travel, eventually exiting the body at the other side. To deliver a high dose of conformal radiation to the tumour volume, and to spare adjacent normal tissue structures, multiple photon beams of varying angles must be used, overlapping about the target volume.

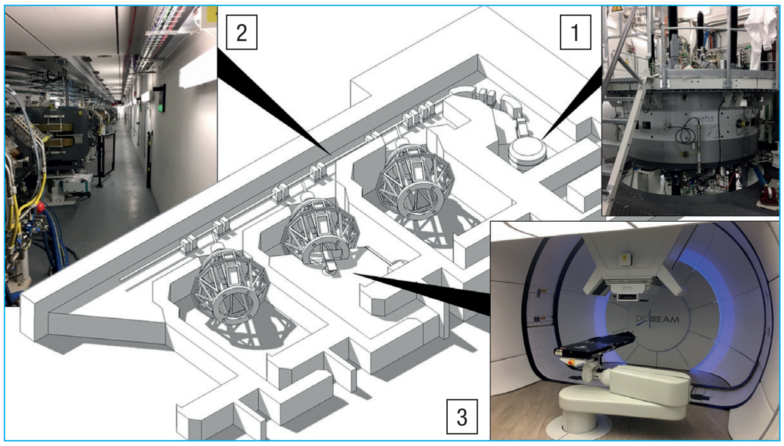

Figure 1. Layout of the proton therapy centre at The Christie. Protons are accelerated in the cyclotron (1) from which they are extracted and steered along a beamline (2) which directs the proton beam to each of the treatment rooms (3).

For protons the position of maximum dose deposition is called the Bragg peak. The depth and width of the Bragg peak is a function of beam energy and the composition of the tissues within the beam path. The Bragg peak can be small compared to the size of the volume that needs treating. To achieve coverage of the tumour volume in depth a 'spread out Bragg peak' may be created, using different proton energies. This is illustrated in *Figure 2* where a number of weighted Bragg peaks at different ranges are combined to provide a uniform dose over the area of interest along with a comparison against a photon depth dose curve.

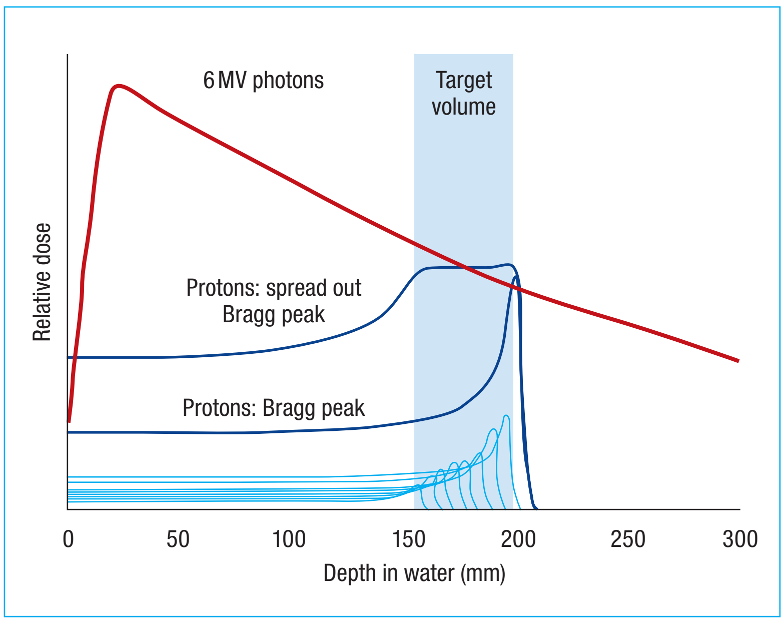

Figure 2. Comparison of proton and photon dose deposition in water. Multiple monoenergetic proton beams at different energies and with different intensities can be combined to cover a target volume with a uniform prescribed dose. The integral dose (the total amount of energy absorbed by the patient) required to deliver the prescribed dose to the target volume can be greatly reduced with protons. For the photon beam there is a short initial build-up of dose which does provide some skin sparing but this is not observed for proton beams.

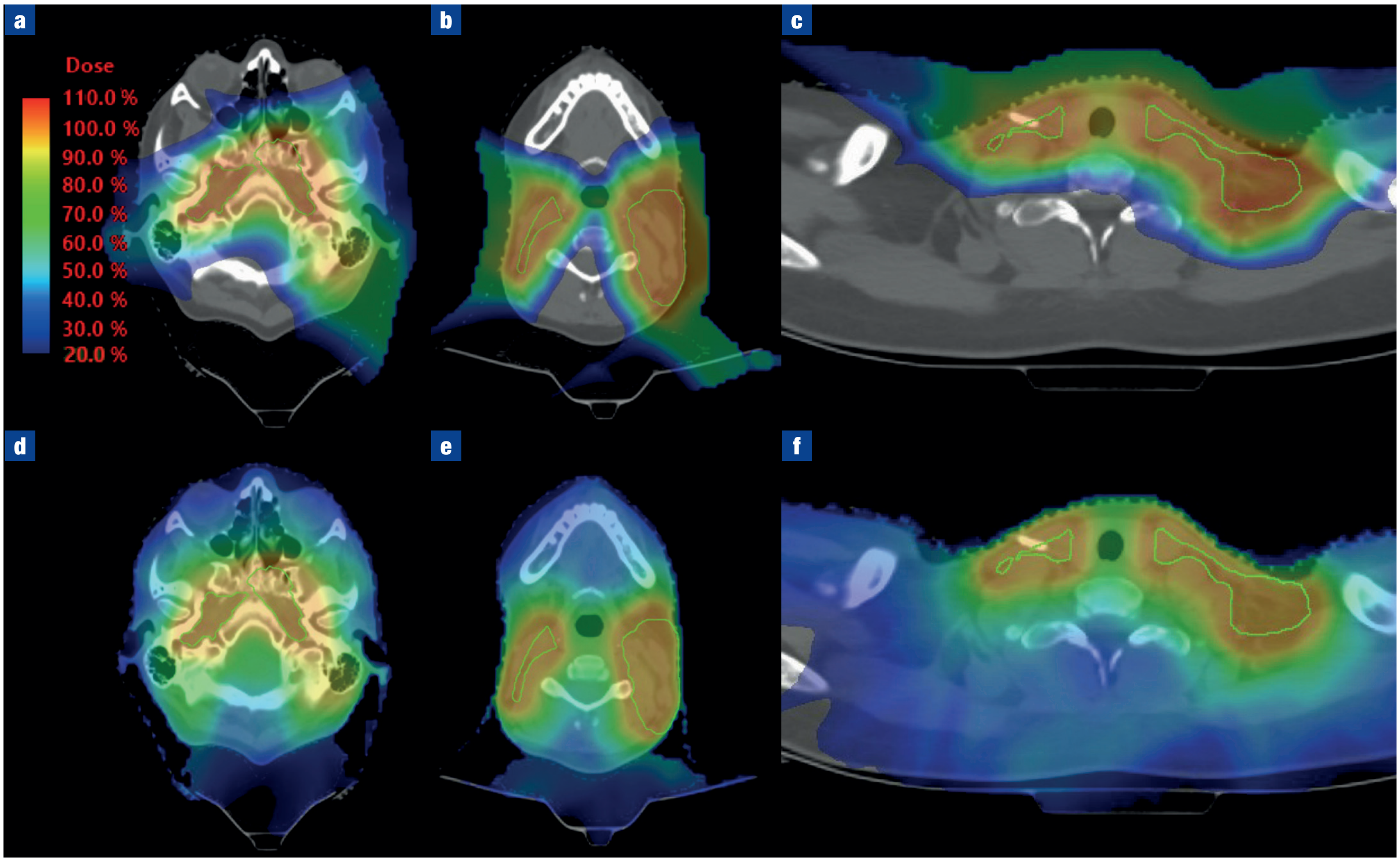

Figure 3. Cross-sectional slices at different locations of **(a-c)** proton and **(d–f)** photon plans for a patient with nasopharyngeal cancer. The dose is shown in a colourwash between 20% and 110% of the prescribed dose. The red/orange areas correspond to a higher radiation dose that will be delivered to the tumour volume, whereas the blue areas indicate low doses of radiation that will be delivered to the surrounding normal tissues. The smaller volume of normal tissues that will receive a low dose of radiation (blue areas) with a proton plan is apparent.

The most advanced and increasingly prominent way of delivering proton beam therapy is to use a narrow proton pencil beam which is scanned through the tumour volume. The tumour is therefore treated in layers; the whole target volume covered with a specific proton beam energy, before the next layer is scanned with a different beam energy until the delivered dose encompasses the longitudinal extent of the tumour. This is called 'pencil beam scanning' or 'spot scanning' proton therapy. Pencil beam scanning also allows optimization of where the dose will be deposited, named intensity-modulated proton therapy, which allows for improved conformality analogous to intensity-modulated radiotherapy for photon treatments. Although it may seem that a single proton beam can deliver a conformal dose in the target, multiple beams from different angles are often used to further optimize the dose distribution. *Figure 3* illustrates the difference between two radiotherapy plans for the same patient – a proton plan and a photon volumetric-modulated arc therapy plan for a patient with nasopharyngeal cancer.

Clinical challenges with proton beam therapy

There are a number of technical aspects that must be considered with the use of proton beam therapy and uncertainties in treatment planning. As a result of their finite range and sharp distal fall-off, proton beams are particularly sensitive to changes in position and tissue composition along the beam path. These can occur as a result of daily variation in patient set-up for treatment, as a result of organ motion with breathing, or with changes in patient anatomy such as weight loss during treatment. Small differences can shift the Bragg peak, at which most of the proton's energy is deposited, leading to a large dose discrepancy at this point. Furthermore, the range at which the proton beam terminates (the Bragg peak) is subject to some uncertainty. These uncertainties must be taken into account when planning treatment. While it may seem attractive to stop a proton beam directly in front of an organ at risk so that it receives little dose, this is avoided in practice as range uncertainties present a risk of delivering a high dose to this region.

There is therefore a need for high quality daily image verification, because of these range uncertainties with changes in tissue densities, for planning processes to account for potential uncertainties up front and a frequent need to adapt treatments to ensure proton beam therapy is delivered as intended. *Figure 4* highlights this shift in dose for a single beam in a plan as a result of anatomical changes. Where the beam passes through additional tissue that was not present at the planning scan the range of the proton beam is reduced resulting in potential under-coverage and a need for plan adaptation.

Furthermore, the biological effect of protons on tissues in comparison to conventional photon treatment is still not fully understood. Protons are considered to be slightly more effective than photons in their ability to cause DNA damage in tissues along their path. This relative biological effectiveness is generally treated to be a constant value throughout the patient. However, as the velocity of protons decreases at beam termination, the radiobiological effectiveness increases, which equates to more damage within cells in a given volume. This variation at the end of the proton beam range is not entirely understood or explicitly accounted for in treatment planning and also increases uncertainties about dose delivered to the target volume, although much consideration is put into the planning process to minimize its effect.

Current indications for use

Proton beam therapy is already a well-established treatment option for many tumour types and disease sites. Since the NHS's overseas programme opened in 2008 over 1100 patients have been approved for treatment (Crellin, 2018). Most of these patients have been treated in the USA, but some have travelled to Switzerland and Germany for proton beam therapy. Two-thirds of these are paediatric patients in whom decreasing the overall absorbed dose in normal tissues is especially important. In children, radiotherapy has a profound effect on normal tissues including bone, tissue, nerves and the developing brain. Furthermore, secondary malignancies are a major source of mortality and morbidity in paediatric cancer survivors. Data from these patients treated abroad with proton beam therapy show that clinical outcomes such as local control and overall survival are comparable to photon radiotherapy for paediatric CNS cancers, with an acceptable toxicity profile (Indelicato et al, 2017). An increase in long-term function is also anticipated as a result of the reduced overall radiation dose to the brain, but this can only be borne out with lifelong follow up.

Additionally, proton beam therapy has numerous theoretical advantages over photon radiotherapy for craniospinal tumours with its ability to deliver high dose radiation with steep dose gradients to reduce dose to adjacent critical structures. At The Christie, patients have been treated for a range of indications, including head and neck cancers, sarcomas and CNS cancers, over a range of age groups. Ongoing research aims to recognize the potential of proton beam therapy for additional clinical indications in a variety of other treatment sites.

Further considerations

There is a significant financial cost associated with proton beam therapy. The original business case approved to build the two UK proton beam therapy centres was £250 million (Crellin, 2018). Compared to existing practice, there may be additional costs with the training of radiotherapy staff and daily requirements with more frequent verification imaging and requirement for re-planning compared to photon radiotherapy. There will be an additional demand on surrounding hospital resources – as a large proportion of patients treated are paediatric, adolescent or young adult, specialist services are required for adequate support. However, as this technology develops the cost of proton treatment is expected to lessen over time.

KEY POINTS

- Proton beam therapy is now being routinely delivered on the NHS in the UK for selected tumour types.
- Proton beam therapy may offer dosimetric advantages over conventional radiotherapy as a result of its characteristic dose deposition – proton beams deliver a comparatively higher proportion of their dose to the target volume relative to normal tissues, without significant exit doses when compared to conventional photon therapy.
- Proton beam therapy therefore may have a therapeutic advantage in the treatment of tumours situated in close proximity to critical organs and/or in the paediatric population where quality of life and the reduction of secondary effects from radiation are particularly significant.
- The indications for proton beam therapy and patient outcomes after treatment will be systematically evaluated in order to provide a robust evidence base for its use.

Conclusions

Around 1500 patients will be funded annually within the NHS for treatment at The Christie Hospital, Manchester and University College London Hospital. Around 700 of these will be analysed and evaluated as part of clinical trials or commissioning processes (Hague et al, 2018). This will enable proton beam therapy to be delivered within a safe environment, alongside a robust clinical follow-up programme, ultimately aiming to produce reliable outcome

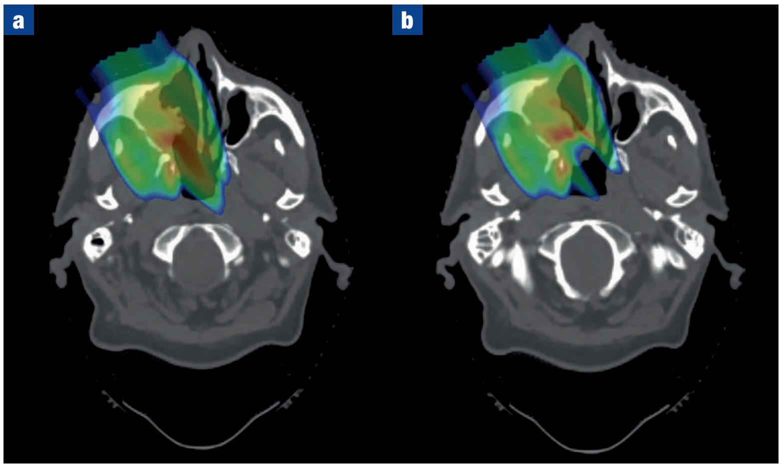

Figure 4. **a.** Planning computed tomography scan and **(b)** repeat computed tomography scan. The effect of anatomical changes on the planned dose distribution for a single beam in the nasal cavity. Where the beam passes through a higher density region than was present on the computed tomography scan the result is a distortion of the planned dose distribution which may necessitate plan adaptation.

data and establish an evidence base for the use of proton beam therapy in adults, alongside the known benefits in the paediatric population.

It is important to highlight to cancer patients that for the vast majority of cancers proton beam therapy has not been proved to be more clinically effective or to significantly reduce side effects from treatment. In many cases, conventional radiotherapy is still a very safe and effective treatment and the preferred treatment modality. Precision radiotherapy is undergoing a renaissance which is being driven by continuously evolving computing systems and newer technologies enabling advanced photon radiotherapy techniques to deliver high conformal doses of radiation to tumours, which may not necessarily be improved upon with proton beam therapy. It is likely that its unique dose advantage in dose escalation or reducing critical side effects will be realized within a small population of patients already treated with these photon techniques. Whatever the outcome, the NHS seeks to be at the forefront of this practice changing technology and research into proton beam therapy. **BJHM**

Conflict of interest: none.

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