Background

Contrary to popular opinion, the concept of treating cancer using high energy beams of protons is not new. First conceived in 1946, following a period in which patients were treated only in laboratory facilities, the first hospital-based facility opened in 1990 at Loma Linda University Medical Center (United States). Currently there are 67 centres in operation, with a further 32 in the construction or planning stages. This rapid expansion has been driven by the potential clinical advantages of proton beam therapy (PBT) over conventional photon radiotherapy (RT) due to the interaction characteristics of protons.

Being positively charged particles with mass, protons lose energy as they traverse patient anatomy, slowing down and becoming more densely ionising as they approach their end-of-range, at which point they stop. This results in a distribution with a low entrance dose increasing to a maximum, the Bragg peak, beyond which no further dose is deposited. By comparison, photons continue depositing dose at depths beyond that of the target (figure 1). The depth of the Bragg peak is determined by the initial energy of the proton beam, which is selected to deposit the maximum dose at the position of the target. A therapeutic dose can be realised with reduced dose to surrounding healthy tissue compared to RT (figure 2) resulting in the potential for reduced acute and late toxicities, reduced secondary cancer risk and an improvement in patients’ quality of life.

Proton beam therapy in the UK

Paediatric patients are most likely to benefit from a reduction in secondary cancer risk. As such, since 2008 the UK Government has funded proton therapy for a limited set of paediatric patients at centres in the US and Europe. The growing clinical evidence of effectiveness, coupled with reduced construction costs, led to the funding of two NHS centres in the UK. Following a bidding process, the UK Government announced in 2012 that it would fund the provision of two proton centres, at University College London Hospitals (UCLH) NHS Foundation Trust in London and The Christie NHS Foundation Trust in Manchester. These two centres will operate as a single national service on two sites, capable of delivering high energy proton therapy beams that can treat tumours deep within the body.

Construction work at both centres began in the summer of 2015, with the first patients due to be treated in 2018 at The Christie and in 2019 at UCLH. Each facility will use the ProBeam proton therapy system, supplied by Varian Medical Systems (Palo Alto, CA), consisting of a 250MeV superconducting cyclotron serving three treatment rooms with fully 360° rotating gantries. At full capacity, the two centres will treat 1,500 patients a year, for a range of paediatric and complex adult indications.

Proton beam therapy physics

When in the treatment room, the equipment looks somewhat similar to a RT gantry. Patients are treated isocentrically on a carbon fibre couch and imaged using orthogonal x-ray imaging or cone beam CT. Patient immobilisation devices are broadly the same, but differences in proton and photon attenuation mean they may need to be redesigned or composed of different materials. However, behind the scenes there are big differences between PBT and RT equipment. Protons are accelerated to approximately half the speed of light by a separate single cyclotron or synchrotron and are then transported to the different treatment rooms using high strength magnets. The 70 tonne gantries, capable of rotating around a 1mm isocentre, are three storeys in height because the proton mass leads to a large radius of curvature. Another major difference, for multi-gantry centres, is the need to share the beam. The accelerator can only provide protons to one room at a time, so each treatment room has to queue for beam delivery. The control system allows this to be done with optimal efficiency, however, and the majority of the time a patient spends in a treatment room is taken up with image-guided alignment ahead of PBT irradiation.

There are two primary types of PBT delivery: passive scattering and pencil beam scanning. In passive scattering the proton pencil beam from the accelerator and beam transport system is scattered into a broad-beam within the delivery nozzle, and modulated along the beam axis with a range modulator to create a spread-out Bragg peak (SOBP). This broad-beam field is then shaped laterally using a brass aperture and distally using a range compensator. This results in a dose distribution that is conformal to the lateral and distal edges of the target, although due to the fixed SOBP width, not conformal to the proximal side of the tumour volume. Passive scattered beam delivery requires custom-made apertures and compensators for each field for every patient. Producing these devices is not only inefficient, but when protons scatter from them they produce neutrons that contribute to the patient dose in an uncontrolled manner.

As such, most new centres use pencil beam scanning delivery systems, in which the proton beam pencil shape is maintained and its position is deflected using scanning magnets. Dose is delivered to tumours on a layer-by-layer basis, with the proton beam effectively ‘painting’ the tumour cross section at a particular depth with dose. Different layers are irradiated by placing material degraders upstream at the point of beam extraction from a cyclotron, or by varying the beam energy before extraction from a synchrotron. There is therefore no need for the production and use of apertures or compensators, keeping production time and neutron dose to a minimum. As the pencil beam paints the tumour cross-section, the time it spends in each position can be controlled. This therefore allows for intensity-modulated proton therapy (IMPT) – analogous to intensity-modulated radiotherapy (IMRT) – in which the dose per field may be highly modulated, but the combined dose of all fields is usually uniform. This allows for highly complex and conformal dose distributions to be delivered. The IMPT planning process is similar to IMRT planning, requiring the use of an optimiser and objectives carefully chosen by the planner. Most current proton therapy centres have passive scattering delivery systems, but advances in technology mean that almost all new centres, including UCLH and The Christie, will be equipped with pencil beam scanning systems.

Accurate and effective PBT delivery requires precise knowledge of the proton Bragg peak position. However, the proton range is subject to a number of uncertainties. Sources of uncertainty include: The need to convert the x-ray CT image into a dataset relevant for PBT planning (ie a map of relative stopping powers, RSPs); uncertainties in the
ionisation energy of tissues, which determines how the protons lose energy in tissue; and uncertainties in the compensator design (only for passive scattering). In addition to these uncertainties, specific to PBT, are the same uncertainties from which RT suffers: CT imaging inaccuracies; CT grid size; dose calculation inaccuracies; and patient set up. This range uncertainty is accounted for by distal and proximal margins, typically equal to 3.5% of the range of the proton beam plus 1mm. Therefore, to treat a tumour with a distal edge 20cm deep in tissue, an 8mm distal margin needs to be added beyond the clinical target volume to account for the proton range uncertainty. PBT practitioners also need to be mindful of uncertainties in the relative biological effectiveness at the distal edge of the Bragg peak, giving rise to an uncertainty in the biological range of the proton beam. These physical and biological range uncertainties are considered when choosing beam angles, especially when organs-at-risk are in close proximity to the target.

Another source of proton range uncertainty is variable patient anatomy along the beam path. These variations are caused by respiratory motion; changes in bowel or bladder filling, for example; tumour shrinkage; and patient weight changes during treatment. Attempts to mitigate these effects include careful beam angle selection; 4DCT-based treatment planning; gated delivery; and adaptive re-planning based on repeat CT scanning during a course of treatment.

In order for PBT to maximise its effectiveness, it is of paramount importance that this range uncertainty is reduced. Much current PBT research is therefore focused on ways to better locate the position of the proton Bragg peak. One approach is to remove the uncertainty introduced when converting the x-ray CT image to proton RSPs, using a proton radiography calibration or by directly acquiring an RSP dataset using a dedicated proton CT system. Dual-energy CT scanning also offers the potential for more accurate characterisation of the patient tissues. Other approaches aim to measure the position of the Bragg peak in vivo, using a PET scan immediately after irradiation or through the detection of high-energy gamma rays emitted along the proton path (known as prompt gamma imaging). To date, none of these techniques are being used in routine clinical practice, although the first few results in patients are starting to be published.

In conclusion

PBT is a rapidly expanding, exciting, changing field. The development of the state-of-the-art NHS facilities will benefit appropriately indicated patients in the UK. The national and international commitment to research and development will continue to improve the accuracy of PBT delivery, and allow us to utilise the Bragg peak advantage to its greatest potential.

References

2. PT COG. Particle therapy facilities in operation, under construction and in the planning stage (as of May 2016). 2016.