CANCER RESEARCH UK POLICY BRIEFING: THE FUTURE OF PROTON BEAM THERAPY IN THE UK

MAY 2019

For many patients, radiotherapy is an important part of treatment, playing a key role in both palliative and curative treatment. Around 40% of patients should receive radiotherapy as part of their cancer treatment [1].

There are various types of radiotherapy. Conventional radiotherapy uses an external beam of x-rays and is the most common form, but there are others – including internal radiotherapy, and proton beam therapy (PBT). PBT is a highly specialised type of radiotherapy that uses a beam of protons. It promises greater precision, reducing side-effects and allowing a higher dose of radiation to be given to the tumour. In the UK, PBT plays an established role in treating some cancers in children and adults, mostly those close to critical structures such as the brain stem or spinal cord. However, there is still a lack of long-term evidence proving its superiority over conventional RT in most cancer types. It is also a highly complex, technical treatment and significantly more expensive than conventional RT.

The NHS has been commissioning high-energy proton beam therapy in specific indications for over ten years, as part of an overseas programme [2]. There has also been NHS provision of low-energy proton beam therapy to treat eye cancer since 1989. However, NHS patients will now be able to access high-energy proton beam therapy within the UK, in two NHS centres, with The Christie Hospital in Manchester now open and UCLH in London opening in 2020. Several private centres are also opening across the UK. This is an exciting time, meaning some patients are now able to access treatment closer to home. A significant proportion of these centres’ activity will be clinical trials, making a vital contribution to the global evidence base for proton beam therapy and answering the outstanding questions about the long-term efficacy of this innovative treatment.

This briefing sets out Cancer Research UK’s viewpoint on the future of PBT in the UK, in terms of both service delivery and research. While developing this briefing we sought insight from clinical and research experts, as well as those involved in commissioning and delivering PBT services.

KEY POINTS:

- The promise of PBT is increased precision, which is very important in specific indications. However, PBT is a relatively new treatment and much less is known about its planning and delivery compared to conventional, x-ray-based RT.
- Proton beam therapy plays an established role in treating many childhood cancers and some rare cancers in adults which are close to vital organs. However, in most indications there is not a strong evidence base. The UK should seek to build the evidence base gradually through robust clinical trials and evaluative commissioning approaches.
- Given the high cost involved, and the impressive technological advances developing, in parallel, in conventional x-ray-based RT, it is important that any additional use of PBT can be justified by good evidence that it will give patients a better outcome than the best quality, cutting-edge, conventional RT.
- CRUK is strongly supportive of the NHS’s gradual approach to building the evidence base and capacity for PBT, which is a pragmatic route for this highly complex treatment.
- All NHS PBT delivery must be monitored in-depth and there should be detailed, long-term follow-up of all patient outcomes – not just in clinical trials. We support the approach being taken by NHS England and would like to see this same framework applied across the UK. UK health services must be aware of and engaged with the clinical trial landscape, so that they are ready to implement new PBT indications that will benefit patients. Early engagement between commissioners and researchers will help ensure smooth and rapid adoption of new PBT indications as the evidence builds.

**INTRODUCTION TO PROTON BEAM THERAPY**

All radiotherapy works by aiming high doses of radiotherapy at cancer, damaging the cells’ DNA and causing them to die. Unlike conventional radiotherapy, which uses X-rays (high-energy waves made of photons) to kill the cells, PBT uses a beam of heavy particles called protons. Protons behave differently while travelling through the body, with the radiation stopping abruptly after it reaches its target, unlike x-rays, which give radiation along the length of the beam.

Conventional radiotherapy is a long-established and proven treatment, with many decades of experience and research, as well as advanced techniques to make it more precise and model the dose. This is not yet the case for proton beam therapy, which is much newer, however this treatment does have some unique benefits.

The promise of PBT is that a lower dose of radiation is given to normal surrounding tissue, reducing the toxicity of the treatment. This is particularly important for tumours that are next to critical organs, for example the brain stem or spinal cord, or for children whose brains are still developing.

In these cases, the most critical factor is avoiding radiation dose to healthy tissue. However, in other cases it can be beneficial to give a low dose of radiation to surrounding healthy tissue, in case there are also cancer cells there. Conversely, low doses of radiation to healthy tissues can increase the risk of secondary malignancies, and so this is a complex balance of risk.

Furthermore, PBT is much less well-understood than conventional RT. While the principle of treating cancer with radiation is the same, the two treatments are very different and there are still uncertainties about how to plan effective PBT. This is in contrast to conventional radiotherapy, where dosage can be modelled much more accurately and where there are many ways to ensure it is targeted to the tumour, minimising the dose given to healthy tissues – as well as techniques such as hypofractionation. PBT also requires specialist equipment, which needs highly specialist staff to operate.

For this reason, it is crucial that new uses of PBT are based on strong clinical evidence aligned with a deeper biological understanding, to confirm that it is superior to conventional radiotherapy – something that is, for the most part, lacking except for in the specific scenarios mentioned above.

This is also important given the significant cost involved in PBT. For the NHS to build a new PBT treatment chamber it can cost £42 million compared to £1.8 million for a standard linear accelerator. A course of PBT treatment is also more expensive than conventional RT.
THE EVIDENCE BASE FOR PROTON BEAM THERAPY

PBT can be beneficial because it gives a lower dose of radiation to the normal tissue surrounding a tumour, and the radiation dose falls off sharply at the edge of the beam. This precision means that accuracy of the beam is even more important for avoiding adverse effects. This is particularly beneficial for certain situations, including:

- Childhood cancers: PBT plays an established role in treating some childhood cancers. This is because less radiation is given to surrounding healthy tissue, so PBT can limit the damage given to developing organs (especially the brain). Modelling suggests a reduction in the risk of developing secondary malignancies, however there is a limited amount of data showing the long-term outcomes for children and young adults who have had PBT.
- Tumours next to sensitive tissue, such as the brain or spinal tissue. This is because radiation reaching those healthy tissues would be more damaging. However, this is not the case for all brain tumours; PBT is most effective when a tumour has defined edges [7].

In most adult indications, there is a lack of high-quality clinical evidence for PBT [8][12]. Despite significant global interest in PBT, this evidence base has not grown significantly, and in some cases has weakened [9]. Some European studies in the early 2000s predicted PBT accounting for 10-15% of radical radiotherapy treatment in future, however in our view the current evidence base does not support this. The NHS is currently planning capacity for 1-1.5% of all radical radiotherapy and will review this as the evidence base develops [5].

As NHS UK PBT services will seek to build this evidence base through clinical trials and evaluative commissioning programmes, this evidence base will grow. It is likely that PBT could benefit niche subgroups of patient populations who would usually have conventional RT, where PBT would result in a higher dose to the tumour than conventional RT or would lead to a much-reduced risk of severe toxicity [5].

The first UK trial launched was in throat cancer, where conventional RT can cause severe side-effects through damage to healthy tissue. Other research projects are being developed, including for lung cancer, pelvic tumours, gynaecological tumours and lymphoma [5].

The reality contrasts with the perception of PBT as a superior, uniquely life-saving treatment that has been presented in the media and by some private providers. In particular, despite a lack of evidence, there has been significant international activity in using PBT to treat prostate cancer. This has largely been commercially-driven [9]. PBT for prostate cancer has since been described as the ultimate practice of ‘no value’ medicine, with no proven additional benefit to justify its high cost compared to the plethora of alternative treatments available [10] – including advanced treatments such as stereotactic radiotherapy and robotic-assisted surgery, and vastly improved conventional radiotherapy with image guidance and pre-rectal spacers [11].

Several important research questions remain about the role of proton beam therapy, and where it has value over conventional radiotherapy. For example, direct comparisons studying PBT's role in increasing efficacy of treatment or decreasing toxicity for equivalent efficacy.

There is also more to be learned about the possibility of combining PBT with chemotherapy, and resistance mechanisms for PBT, among many other questions. Underlying all of this, there must be an assessment of the cost-effectiveness of PBT compared to conventional RT.
PROTON BEAM THERAPY FACILITIES IN THE UK

The NHS has been treating patients with low-energy proton beam therapy since 1989, at the Clatterbridge Cancer Centre in Liverpool. This service is specifically for people with a rare type of eye cancer.

Since 2008, the NHS has been running an overseas programme for PBT, to allow people with specific types of cancer – mostly children – to access PBT. So far, more than 1,400 patients have received PBT as part of this programme [5].

In 2011 the UK Government announced a £250 million National NHS Proton Beam Therapy Service, so that up to 1,500 patients a year could have their treatment closer to home [5]. The centre at the Christie in Manchester has now opened; a further centre will open at UCLH in London, both with strong links to leading academic research centres and specialist hospitals. Although based in England, these facilities will treat patients from across the UK, both routinely and through clinical trials, with the exception of non-complex cases from South Wales. A UK-wide panel hosted by NHS England assesses each individual case to determine whether that particular person would benefit from PBT, taking each decision in line with the evidence-based NHS England commissioning policies.

Over time, these centres will replace the overseas programme, with the full transition expected to conclude by 2022, with capacity for up to 1,500 patients a year [5]. The NHS estimates the cost for each patient’s treatment will be between £41,000–£43,000. A substantial portion of their activity will also be in the context of clinical trials, in both paediatric and adult indications, to build the evidence base. A similar phased capacity approach is developing in Denmark and Holland [12].

There is also a private PBT facility in Newport, South Wales and one in Northumberland, with several other private facilities due to open shortly. The Newport facility has been commissioned for a small number of patients from South Wales [13]. It is not yet clear what role these centres will play in the UK landscape in the future, in either clinical practice or research.

Conversely, the US has seen a rapid expansion of PBT, mainly for prostate treatment, and some centres are now becoming financially unsustainable as it has become clear that this indication lacks a strong evidence-base; some health insurers are also refusing to pay for the treatment [19].

CRUK is therefore strongly supportive of the NHS’s approach to building the evidence base for PBT, which is a pragmatic route for this highly complex treatment. Given the high cost involved, and the impressive technological advances developing, in parallel, in conventional x-ray-based RT, it is important that any additional use of PBT can be justified by good evidence that it will give patients a better outcome than the best quality, cutting-edge, conventional RT.

UK COMMISSIONING OF PROTON BEAM THERAPY

In July 2018, NHS England published a service specification for proton beam therapy facilities [14]. CRUK fully supports this service specification and believe it strikes the right balance between ensuring appropriate access to PBT while ensuring patient safety is maintained. We support this approach for the following reasons:
- There is a clear emphasis on the integration of research and routine care. This is very important given the relative uncertainty in the evidence base, and means expertise will grow within the centre, benefiting patients.
- There is a single national referral mechanism, NHS Clinical Commissioning Policies and clinical review panels, to ensure equity in access across the UK. There will be close monitoring to ensure there is equitable access.
- It specifies careful follow-up, including a detailed clinical outcomes framework to support both clinical trials and routine care. This level of detail is welcome and is important in ensuring there is consistent high-quality care, given the complexity of PBT.
- The specification emphasises close integration with a wide range of specialist services, and an expert team based within the service. This is particularly important for children: the NHS overseas programme has found that emergencies are not uncommon in paediatric and TYA patients, and so close integration is crucial.[3]

Until recently, the only provision for NHS patients across the UK was through the overseas programme[2]. NHS-England are now leading a gradual ramp-up of activity at The Christie, with UCLH following on from 2020 with the national clinical panel overseeing access.

Wales have taken a separate approach; there is a separate service specification specific to Wales[15]. The Rutherford Cancer Centre in Newport has since been commissioned as a referral option for a very small number of “non-complex” adults in South Wales. “Complex” adults and children having PBT will continue to be treated through either the overseas programme or NHS PBT facilities.

The “non-complex” adults having PBT in Newport will remain under the care of their referring hospital but will have their PBT treatment at the Rutherford Centre. The Welsh Government expect fewer than five patients per year to be eligible for referral to the Centre[15]. It is not clear how “complex” and “non-complex” patients are differentiated. In the interests of patient safety and quality, NHS England has agreed that all referrals from South Wales will be reviewed by the panel who will also advise on patient complexity.

Given the very small numbers of patients involved, and the complexity of PBT, it is even more important that the quality of care is monitored and compared with other PBT facilities commissioned by the NHS. Every patient receiving PBT should be monitored for a long time after their treatment, in detail. The clinical outcomes framework outlined in NHS England’s service specification is a promising step towards this and will require support from Public Health England to ensure there is reliable and meaningful long-term follow-up data, both on the effectiveness of the treatment itself and side-effects. We would like to see every patient having PBT in the UK to follow this same standard.

**PBT RESEARCH**

The UK approach to building the evidence base for PBT has so far been coordinated by the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group.[8] This is welcome and important, as the UK has a strong history of leadership in practice-changing radiotherapy trials.[16] There are many research questions to be answered regarding PBT, ranging from basic research to randomised control trials that will define the role it will play in future patients’ treatment.

There are several enabling factors needed to ensure the success of these trials:
- In research into rare cancers, the number of patients in the UK can be too small to conduct a clinical trial. In those cases, international collaboration is essential. It is therefore important that the UK can participate in multinational trials.

- Engagement with patients, families, the public and health professionals will be important. This is important both in terms of managing expectations of this new treatment, and the uncertainty about the value of PBT over conventional RT in some indications.

Health services must be aware of and engaged with the clinical trial landscape, so that they are ready to implement new PBT indications that will benefit patients. This is true for all treatments but is especially so for PBT given the complexity of treatment delivery. Health services should especially consider the commissioning implications of ongoing trials, to ensure services can match any increasing demand, and should engage with researchers so that trials are designed in a way that will enable changes in practice and commissioning to be made quickly if they give positive results.

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References


