

Clinical Commissioning Policy: Proton Beam Therapy for Children, Teenagers and Young Adults in the treatment of malignant and non- malignant tumours

NHS England Reference: 1783



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First published: 28/09/2020

Publishing Approval Reference: 000826

**Prepared by NHS England Specialised Services Clinical Reference Group for
Radiotherapy**

Published by NHS England, in electronic format only.

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Policy Statement

NHS England will commission proton beam therapy for the treatment of children, teenagers and young adults with malignant and non-malignant tumours in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About tumours in children, teenagers and young adults

While cancer in childhood and early adult life are not common, they are still one of the leading causes of death in those age-groups. Childhood cancer accounts for 1% of all cancers, occurring in children ages 0 (from birth) to up to the 16th birthday. Most of

the cancers affecting children differ from those affecting adults. They occur in different parts of the body, appear differently under the microscope and respond differently to treatment.

Cancers in teenagers and young adults (TYA) (aged from 16 years to around 25 years of age) account for less than 1% of all cancers. The spectrum of cancer types in this age group is also distinct from those seen in both children and adults. However, tumour types more commonly seen in young children (referred to as 'paediatric-type' tumours) may occasionally also be seen in the TYA population and in older patients.

Cancer in children, teenagers and young adults encompasses a wide range of individual diagnoses, each of which is treated according to specific clinical protocols and treatments according to stage (extent of spread) and body site.

In children, around 40% are leukaemias and lymphomas (forms of blood cancer), 25% are brain tumours, with the remainder comprising a wide range of other tumours (Children's Cancer and Leukaemia Group [CCLG]). In the teenage and young adult population, although lymphomas and leukaemias are common, the spectrum of disease is wider and includes germ cell tumours (cancers of the ovaries or testes), brain tumours, melanomas (a type of skin cancer), and sarcomas (Teenagers and Young Adults with Cancer [TYAC]).

Treatment is frequently complex and intensive but cure rates among children are much higher than for most adult cancers. About 80% of childhood cancer is cured. Rarely, non-malignant conditions, for example desmoid fibromatosis, may also require radiotherapy as part of their treatment regimens.

About current treatments

Standard pathways of care vary depending on the type of cancer and may include chemotherapy, surgery and/or radiotherapy.

One third of survivors of childhood cancer report severe or life-threatening complications up to 30 years after the diagnosis of cancer. This can be due to side effects of cancer treatment, and radiotherapy is a significant contributing factor.

Late effects of radiotherapy are related to a number of factors, including the age of the child, the total dose of radiation, the volume of tissue treated and the critical structures within the radiation field. Late effects of radiotherapy can include effects on IQ, learning and memory, pituitary dysfunction requiring life-long hormone replacement, risk of vascular sequelae such as stroke, infertility, premature menopause, risk of cardiac, renal and lung toxicity and the risk of secondary radiation induced malignancy. These risks are particularly high in this age range due to the vulnerability of growing tissues compared to mature adults.

About the new treatment

Proton beam therapy (PBT) is a potential alternative to conventional radiotherapy. Proton beam therapy provides radiation by delivering a beam of proton particles rather than X-rays. The physical properties of protons result in a significantly reduced radiation dose being deposited in the normal tissue beyond the tumour. This is in contrast to X-rays where there is dose extension beyond the tumour.

This leads to two main advantages. Firstly, the reduction in the volume of normal tissue irradiated when treating tumours in children, teenagers and young adults is expected to lead to an improvement in the quality of survival by reducing the long-term side effects of treatment. Secondly, proton beam therapy may have the ability to treat tumours which are adjacent to normal tissue where the normal tissue tolerance would prevent X-ray radiotherapy from delivering an effective dose. In this case proton beam therapy would be able to deliver an effective dose of radiation to the tumour and avoid irradiating the surrounding normal tissue beyond its tolerance thereby leading to increased cure rates. This is particularly advantageous for radioresistant tumours where higher doses are required to optimise chance of cure.

What we have decided

NHS England has carefully reviewed the evidence to treat children, teenagers and young adults with proton beam therapy for malignant and non-malignant tumours. We have concluded that there is enough evidence to consider making the treatment available.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission proton beam therapy for the treatment of malignant and non-malignant tumours in children, teenagers and young adults.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

2. Definitions

Childhood cancer (also known as paediatric cancer): refers to cancer (1% of all cancers) occurring in children ages 0 (from birth) to 16 (up to 16th birthday). It encompasses a wide range of cancers, each of which is treated according to specific clinical protocols and treatments according to stage (extent of spread) and body site.

Intensity modulated radiotherapy (IMRT): IMRT is an advanced form of conventional radiotherapy using many fields, or rotational fields (e.g. VMAT, RapidArc, Tomotherapy), to shape the dose of radiation to match the tumour and is very precise. By doing this it reduces the high/intermediate dose to surrounding normal tissues in relation to 3-Dimensional conformal radiotherapy but increases the low dose bath to more normal tissue, so may cause an increase in some late side effects e.g. second malignancy, vascular sequelae.

Multidisciplinary team (MDT): a group of health care workers who are members of different disciplines (may include surgeons, radiologists, histopathologists, paediatric oncologists, clinical oncologists, specialist nurses, physiotherapists, occupational therapists, play specialists, paediatric radiographers, anaesthetists, physicists, dosimetrists etc.), each providing specific services to the patient. The activities of the team are brought together using a care plan.

Proton beam therapy (PBT): provides radiation by delivering a beam of proton particles rather than X-rays. The physical properties of protons result in a

significantly reduced radiation dose being deposited in the normal tissue beyond the tumour. This is in contrast to X-rays where there is dose extension beyond the tumour.

Photon radiotherapy (PRT): also known as conventional radiotherapy, provides radiation by delivering a beam of photons (X-rays). The vast majority of radiotherapy is delivered via this method.

Teenagers and young adults (TYA): refers to patients aged 16 to around 25 years old. 'Paediatric type' tumours are more common in this age-group than the older adult population.

Total body irradiation (TBI): radiotherapy to the whole body, a treatment option for some patients with haematological disorders prior to stem cell transplantation.

3. Aims and Objectives

This policy document considered: Proton beam therapy for children, teenagers and young adults with the paediatric spectrum of tumour types.

The objectives were to: establish, via an evidence review, the safety and efficiency of treatment with proton beam therapy compared to photon radiotherapy.

4. Epidemiology and Needs Assessment

Most of the cancers affecting children, teenagers and young adults differ from those affecting adults. They occur in different parts of the body, appear differently under the microscope and respond differently to treatment.

Children are diagnosed with a wide range of cancers in the UK. Around 40% are leukaemias and lymphomas, 25% are brain tumours, with the remaining conditions comprising a wide range of solid tumours (CCLG). Treatment is frequently complex and intensive but cure rates among children are much higher than for most adult cancers, and overall more than 80% of children are completely cured (Gan & Spoudeas, 2014).

The spectrum of cancer types in teenagers and young adults is distinct from those seen in both children and adults. However, tumour types more commonly seen in young children or older adults may occasionally also be seen in the TYA population. The most common tumour types in TYA patients include: (i) lymphomas; (ii) germ cell tumours; (iii) central nervous system tumours; (iv) malignant melanomas; (v) acute leukaemias; and (vi) sarcomas. More than 80% of teenagers and young adults survive their cancer for five years or more, however, survival is significantly lower in teenagers and young adults than in children for several types of cancers, including sarcomas, lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). Factors relating to diagnosis, different treatment protocols and low levels of participation in clinical trials are thought to explain some of the differences (TYAC, 2016).

One third of survivors of childhood cancer report severe or life-threatening complications up to 30 years after the diagnosis of cancer (Oeffinger et al, 2006; Mertens et al, 2008). Causes are multifactorial but radiotherapy is a significant contributing factor. PBT has dosimetric advantages to conventional radiotherapy, meaning that in many cases, less normal tissue is irradiated. The NHS has been sending selected patients abroad for PBT since 2008. Most of these patients have undergone cancer treatment, but rarely, non-malignant conditions, for example desmoid fibromatosis, require radiotherapy and have been included in the proton overseas programme.

Table 1 below (data from RTDS) shows the number of children, teenagers and young adults who have received conventional radiotherapy and have been accepted for PBT overseas over the last 3 years in (or referred from) England. It is estimated that of the total referrals accepted for PBT overseas, approximately 90% of children, teenagers and young adults will have gone abroad for their treatment.

Table 1: Children and young people, by age, receiving conventional radiotherapy and accepted for treatment abroad with PBT, 2014-16

Year	Proton Beam Therapy			Photon Radiotherapy		
Age (years)	0-15	16-24	Total	0-15	16-24	Total
2014	102	17	119	494	595	1089
2015	136	37	173	490	628	1118
2016	129	42	171	479	675	1154

Source: Radiotherapy Dataset (RTDS); PBT Referral Activity

It is anticipated that a large proportion of children, teenagers and young adults who currently undergo PRT will undergo PBT instead. Those who have no added benefit from PBT (for example, total body irradiation, whole brain radiotherapy, extremity sarcoma, palliative radiotherapy) will continue to be treated with conventional radiotherapy. At full capacity, which is estimated to be in 2022, the NHS PBT service will be able to treat 330 paediatric patients and 220 teenage and young adult patients annually. Although patients have been referred overseas for PBT treatment since 2008, this represents a substantial increase on current levels. It is estimated that only 300 paediatric patients per year will require conventional radiotherapy.

5. Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

The following review was commissioned by NHS England to analyse the published evidence base for safety and clinical outcomes for the use of PBT in children, teenagers and young adults. It does not include dosimetric studies or international consensus guidelines. Eleven papers were included in this review.

Medulloblastoma

- Paulino et al 2018 reported results in 84 children with medulloblastoma. They reported rates of hearing loss of grade 3 or 4 on the SIOP Boston scale¹; after PBT, these were 15/75 (20%), and after photon radiotherapy (PRT) 21/91 (23%), $p=0.63$. The authors report three other measures of hearing loss, but

¹ A hearing loss scale: grade 0 = ≤ 20 dB loss at all frequencies, grade 1 = > 20 dB sensorineural hearing loss (SNHL) above 4 kHz, Grade 2 = > 20 dB SNHL at 4 kHz, Grade 3 = > 20 dB SNHL at or above 2 kHz, Grade 4 = Grade 2 = > 40 dB SNHL at or above 2 kHz.

none showed a significant difference in its incidence between the participants treated with PBT and PRT.

- Eaton et al 2016 reported 77 children with medulloblastoma treated with craniospinal radiation. Adjusted odds ratios were 0.13 for hypothyroidism (95% confidence interval (CI) 0.04 to 0.41, $p < 0.001$), 0.06 for sex hormone deficiency (95% CI 0.01 to 0.55, $p = 0.013$) and 0.30 for endocrine replacement therapy (95% CI 0.09 to 0.99, $p = 0.047$). For participants' height, the standard deviation score parameter estimate was 0.89 (indicating greater height with PBT, 95% CI 0.24 to 1.54, $p = 0.008$).
- Eaton et al 2016's results are not reliable, because of biases in age, diagnostic testing and acceptance of treatment between the two groups. Differences in the timing and purpose of data collection may also have introduced bias.
- Hirano et al 2014 published a health economic model of PBT versus PRT for medulloblastoma, considering only the risk of hearing loss and its impact on quality of life. Three different measures of quality of life were used: EQ-5D²: (£16,100/quality-adjusted life-year (QALY)), HUI3³ (£8710/QALY) and SF-6D⁴ (£14,900/QALY).
- These costs per QALY are well below the threshold of acceptable value of money for the NHS, suggesting that the extra costs of PBT are justified. However, hearing loss rates supported by modern evidence lie outside the sensitivity ranges used by Hirano et al 2014, casting doubt on the reliability of their conclusions.

Ependymoma

- Sato et al 2017 reported a study involving 79 children with intracranial ependymoma. Toxicity rates (for example, vasculopathy, cranial nerve palsies, radiation necrosis and posterior fossa syndrome) after PBT were 3/41 (7.3%); after PRT they were 5/38 (13.2%), ($\chi^2 = 0.237$, $p = 0.626$).
- Gunther et al 2015 reported MRI abnormalities with associated symptoms in 72 children with ependymoma. In those receiving PBT, 4/37 (11%) had

² A standardised instrument for measuring health status

³ The Health Utilities Index 3, a rating scale used to measure general health status and health-related quality of life

⁴ Short form 6 dimension is a measure of health utility

abnormalities with symptoms (for example, seizures, cranial nerve palsies, posterior fossa syndrome), compared with 3/35 (8.6%) after PRT ($\chi^2 = 0.006$, $p=0.938$).

Craniopharyngioma

- Bishop et al 2014's study included 52 children with craniopharyngioma. The authors reported several adverse effects of treatment, though none showed a significant difference in rates between participants receiving the two treatments:
 - Vascular morbidity, including Moyamoya, stroke, and vessel malformations: PBT 2/21 (10%), PRT 3/31 (10%), $p=1.0$
 - Visual morbidity: PBT 1/21 (5%), PRT 4/31 (13%), $p=0.637$
 - Hypothalamic obesity: PBT 4/21 (19%), PRT 9/31 (29%), $p=0.523$
 - Endocrinopathy; PBT 16/21 (76%), PRT 24/31 (77%), $p=1.0$.

Salivary gland tumours

- Grant et al 2015 published a small study of 24 children with malignant salivary gland tumours. They report rates of several local adverse effects:
 - Dermatitis: PBT 7/13 (54%), PRT 6/11 (55%), $p=1.0$.
 - Dysphagia: PBT 0/13 (0%), PRT 3/11 (27%), $p=0.08$
 - Otitis externa: PBT 1/13 (8%), PRT 2/11 (18%), $p=0.58$
 - Mucositis: PBT 6/13 (46%), PRT 10/11 (91%), $p<0.05$.
- The reporting of adverse effects was a simple count, not an annual rate, and the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group. Also, correction for multiple testing meant that none of the reported differences is statistically significant.

Retinoblastoma

- Sethi et al 2014 reported results in 86 children with retinoblastoma. The rate of second malignancies in the field irradiated by PBT were 0/55 (0%), 95% confidence interval (CI) not reported; after PRT the rate was 4/31 (14%), 95% CI 3% to 31% ($p=0.015$). Corresponding rates for second malignancies

anywhere were [figure not reported]/55 (5%), 95% CI 0% to 21%, and 4/31 (13%), 95% CI 3% to 31% respectively (p=0.120).

- The median length of follow-up for participants treated with PRT was nearly twice that in those who received PBT, but the authors made no adjustment for duration of follow-up. The annual rate of adverse events may have been significantly higher among the PBT group.
- However, in this paper, the proton group included both patients who had had protons only AND those who had mixed plans (i.e. protons and photons) and so their conclusion regarding the benefit of PBT may be an underestimate.

Tumours at several sites

- Kahalley et al 2017 reported a study of 123 children with brain tumours. Those who received PBT had no statistically significant decline in intelligence quotient (IQ) (p= 0.130). The children who received PRT has a loss of 1.1 IQ points per year (p= 0.004). However, a comparison of the change in IQ over time between the two groups revealed no significant difference in rates of decline (p= 0.509).
- The authors conclude that “this study does not provide clear evidence that [PBT] results in clinically meaningful sparing of global IQ significantly exceeding that of modern [PRT] protocols”.
- Yock et al 2014 analysed the health-related QoL in 120 children with brain tumours. Using the PedsQL⁵ Core Module, they reported:
 - mean PedsQL total core score: PBT 75.9, PRT 65.4, unadjusted p=0.002
 - physical summary score PBT 78.4, PRT 68.1, unadjusted p=0.015
 - psychosocial summary score: PBT 74.5, PRT 64.0, unadjusted p=0.001.
- This study is affected by biases from family income, socio-economic status, ethnicity and changes in treatment techniques. It is also incorrectly analysed.
- Song et al 2014 reported a study of 43 children with malignancies at various sites, with measures of rates of these adverse effects:

⁵ The PedsQL is a validated assessment of health-related QoL for children with or without chronic health conditions. Scores are from 0 to 100, with 100 representing the best quality of life. PedsQL total scores are in two major sub-domains, physical and psychosocial.

- Leukopaenia: grade 3⁶: PBT 14/30 (57%), PRT 6/13 (46%); grade 4⁷: PBT 2/30 (7%), PRT 4/13 (31%); p=0.069
 - Anaemia: grade 3⁸: PBT 0/30 (0%), PRT 2/13 (15%), p=0.493
 - Thrombocytopenia: grade 3⁹: PBT 6/30 (20%), PRT 4/13 (31%); grade 4¹⁰: PBT 1/30 (3%), PRT 3/13 (23%); p=0.012
 - Platelet transfusion: PBT 5/30 (17%), PRT 6/13 (46%), p=0.042
 - Dysphagia: PBT 14/30 (47%), PRT 2/13 (15%), p=0.086
 - Diarrhoea: PBT 0/30 (0%), PRT 3/13 (23%), p=0.023.
- Correction for multiple testing of the authors' significance threshold renders all the reported differences non-significant.
 - There is a substantial amount of evidence comparing adverse results of PBT and PRT. However, the studies that we found were inconclusive, biased and/or incorrectly analysed. None provided reason to believe that PBT is associated with a lower risk of adverse treatment effects than PRT.
 - Ideally, randomised trials are needed with appropriate analysis to resolve the uncertainties still present despite the studies included in this review. However, recruitment into such trials would be very difficult, which puts the feasibility of such an approach into question.

There is a lack of evidence which precludes conclusions about the relative safety of PBT and conventional radiotherapy, about the quantification of safety advantages, about effects on second malignancies or about cost implications of different treatments.

Although there is a lack of level 3 comparative evidence of outcomes following protons versus photons for malignancies in children, teenagers and young adults, this does not take into account modelled dose distributions, which are a vital and ubiquitously utilised tool for predicting radiotherapy outcomes for both conventional radiotherapy and PBT.

⁶ Grade 3: <2000 – 1000/mm³ (<2.0 – 1.0 x 10⁹ /L)

⁷ Grade 4: <1000/mm³ (<1.0 x 10⁹ /L)

⁸ Hb 6.5 to 8 g/dl.

⁹ <1.0 – 0.5 x 10⁹ /L

¹⁰ < 0.5 x 10⁹/L (< 500/mm³)

Late effects of radiotherapy are common and may manifest months to years after therapy, affecting the long-term quality of life of survivors and are generally irreversible. PBT dose distributions give similar doses to the target volume but the volume of normal tissue exposed to low doses may be reduced compared with advanced photon based techniques (Fogliata et al, 2009; Merchant et al, 2008; Lin et al, 2000), thus also reducing the risk of associated side effects to that tissue (Moeller et al, 2011; Hug et al; 2002).

PBT is, in most cases, offering an equivalent chance of cure to conventional radiotherapy, but also a theoretical reduction in long term side effects (Moeller et al, 2011; Fogliata et al, 2009; Merchant et al, 2008; Lin et al, 2000). That being said, there are expected to be some cases (for example, skull base and spinal tumours) where the dosimetric advantages of protons give the opportunity for dose escalation and a potential improvement in cure rate, particularly for radioresistant tumours (Hug et al, 2002).

In many circumstances it is possible to link particular doses of radiotherapy to a precise evolution of the risk and functional impact of side effects with time (Merchant et al, 2008). This data is sufficiently secure that it is possible to use dose planning studies to model with great accuracy the impact of reducing the dose on patient outcomes using protons. The dose difference is clear and degree of benefit expected to be so large that in such cases PBT has now been internationally adopted as treatment of choice for some groups of patients. A good example is in childhood brain tumours, where precise maps of the impact of radiotherapy dose with brain micro-anatomy, age and volume to normal tissues is known. Whilst the emphasis in PBT is on late toxicity, acute effects should not be forgotten. In some cases, these are very significant, for example, craniospinal radiotherapy for childhood medulloblastoma, where the whole body exit dose of conventional radiotherapy makes children very unwell. CSRT with PBT can reduce the whole body exit dose potentially enabling treatment to be better tolerated (Yuh et al, 2004).

Both PBT and conventional radiotherapy, and advancements in these techniques, rely on modelled dose distributions, which allow prediction of both effects on the tumour and effects on normal tissues. Where dose comparison studies suggest

benefit in outcomes, a so called 'model-based approach' is suggested and is the basis of the Proton Programmes in Holland and Denmark (Langendijk et al, 2013; Grau, 2013). In some cases, the evidence is so strong that randomised trials would not be ethically possible and so cohort studies will be performed and comparisons with conventional radiotherapy historic control series used to validate the model approach. Where randomised trials are possible they should be performed but this will become increasingly rare.

In summary, there is extensive literature describing the dosimetric advantages of PBT compared to conventional radiotherapy, which leads to less irradiation of normal surrounding tissue. Particularly in young patients, who have many years in which to accumulate and live with late radiotherapy toxicities, this offers a great theoretical advantage. Due to this, PBT for young people is internationally considered to be the treatment of choice. PBT has been used for many years across the world safely, including within services commissioned by the NHS England via the overseas programme. The NHS will continue to offer PBT as an option for children, teenagers and young adults undergoing curative intent radiotherapy, where PBT offers an advantage regarding volume of normal tissue irradiated, and therefore a theoretical reduction in long term side effects. Given the uncertainties regarding definite long term clinical gain (due to lack of long term follow up data from randomised controlled trials in this group of patients), clinicians and patients/guardians will discuss the pros and cons of PBT versus PRT using a decision-making aid, which will offer a structured format for discussion.

6. Criteria for Commissioning

PBT treatment will be routinely commissioned for patients meeting the following criteria:

- A clear indication for radiotherapy and defined as curable (leading if cured to normal or near-normal life expectancy) and with a reasonable disease specific 5 year survival expectation and no comorbidities likely to limit life expectancy to less than 5 years.

- A Children's Principal Treatment Centre (PTC) or Teenagers and Young Adult's PTC multi-disciplinary team (MDT) confirms that treatment with PBT is an option.
- Age from birth up to about 25 years of age.
- There should be NO evidence of distant metastases, with the exception of certain tumours which remain curable when metastatic, for example, metastatic intracranial germinoma, rhabdomyosarcoma and Ewing's Tumours with limited volume lung metastases that have demonstrated a good partial response on radiological reassessment after chemotherapy.
- Adequate performance status and medically sufficiently stable to undergo PBT without a delay which may lead to increased risk of recurrence or a compromise to cure rate and combined treatment pathways.
- Patients requiring radiotherapy for indications where there is no dosimetric advantage for protons over photons will be excluded (for example, TBI, whole brain radiotherapy, extremity sarcomas (see Appendix 2 for further details, although this list is not exhaustive. Some referrals will need to be discussed with the PBT teams on a case-by-case basis).
- Shared Decision-Making Tool: this will be utilised by clinicians as a framework for discussing radiotherapy with patients and their guardians, including the knowns and unknowns regarding benefits and risks for PRT versus PBT. This will comprise a question and answer grid, containing the top most frequent questions from patients with answers (accommodating lowest quartile health literacy). Training will be provided for paediatric clinical oncologists who will use the tool (face to face training and an e-learning tool).

If an adult over the age of 25 years is diagnosed with a typical paediatric diagnosis requiring radiotherapy and meeting all other (non age-specific) criteria as above, they may be referred for PBT and individual cases will be considered by the panel.

7. Patient Pathway

Children, teenagers or young adults with cancer (or benign tumours requiring radiotherapy) will all be cared for by a specialist MDT. Treatment may consist of a

variable combination of surgery, chemotherapy and radiotherapy in complex pathways, and in many cases within the context of clinical studies or trials.

It is essential that any surgery should be carried out within designated specialised units to ensure adequate imaging, MDT care and quality of resection to allow best outcomes of combined modality care required for many of these tumours.

When radiotherapy is considered and patients are eligible according to these criteria, consideration should be made by the MDT for referral for PBT. When available and applicable, the opinion of national advisory groups or national MDT's should be sought. This is offered to patients and their parents and carers using the framework provided by the shared decision-making tool. There may be complex and good medical or social reasons why PBT is not considered to be possible or the best treatment for individual patients. Reasons for the patient not being referred should be documented in the medical notes.

An appropriate clinical oncologist will have a direct consultation with patients (and parents and carers) about the aims and objectives of treatment using the shared decision-making tool. A formal clinician (clinical oncologist) to clinician (radiation or clinical oncologist in the proton centre) referral is then made via the PBT referral portal, following direct consultation with patients and parents and carers about the aims and objectives of treatment using the shared decision-making tool. Imaging will be sent to the proton centre via the secure image exchange portal.

On completion of treatment follow-up will be undertaken by the both the referring PTC (in line with local Network guidelines) and the PBT centre. All patients receiving PBT will be receive annual follow-ups at the PBT centre for the first five years post treatment, after which the follow-up interval will be increased to every five years, for up to 20 years post treatment. The PBT centre will collect clinical outcome data on all patients and referring clinicians and teams are expected to provide relevant clinical information. The specific collection of acute and late PBT side effects and outcomes will be undertaken by the proton treatment centre.

8. Governance Arrangements

Decisions for whether referral is made will be made jointly between the paediatric clinical oncologist and patient (or their representative e.g. parent) using the decision-making tool. This will give a framework for discussing theoretical pros and cons of proton treatment, as well as the limitations currently present regarding evidence base for different indications.

The referral process specifies detailed information required from referring clinicians and teams to allow clinical decision on treatment.

Full treatment details and summaries will be communicated directly to the referring clinical teams.

9. Mechanism for Funding

PBT is funded through NHS England Specialised Services directly.

10. Audit Requirements

The Proton Administrative team will keep data on activity and treatment and high-level outcomes. NHS England have mandated that follow-up information will be returned from referring centres. A more detailed outcomes programme has been developed and funded, which involves the collection of extensive details regarding acute and late side effects as well as patient outcomes.

11. Documents which have informed this Policy

This document updates and replaces - Clinical Commissioning Policy: Proton Beam Radiotherapy (High Energy) for Paediatric Cancer Treatment (2013)

https://www.engage.england.nhs.uk/consultation/specialised-services-consultation/user_uploads/pbt-paediatric-policy.pdf

This policy should be read in conjunction with, and aligns to, the NHS Proton Service Specification and Standard Operating Procedure:

<https://www.england.nhs.uk/wp-content/uploads/2018/07/proton-beam-therapy-service-all-ages.pdf>

12. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for routine commissioning.

13. References

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Appendices

Appendix 1: Decision-Making Tool

Decision aid – proton beam therapy for childhood cancer

Information to help parents and carers of children with cancer, those close to them, and their healthcare professionals discuss the options

1. What are the options?

Radiotherapy is an established, successful treatment for childhood cancer. Most patients receive radiotherapy alongside other treatments such as chemotherapy and surgery. Over the years, research has helped doctors understand which combination of treatments is best for each tumour type. Specialist radiotherapy doctors called 'clinical oncologists' work with the whole oncology team to agree and coordinate the most effective radiotherapy treatment plan for each patient.

The majority of radiotherapy for childhood cancer is delivered by external beam radiotherapy in an outpatient setting. The radiation is beamed at the tumour from outside of the body. Each treatment lasts a few minutes and treatment is given daily (five days per week) over a period of 3 to 7 weeks (depending on the dose being delivered which, in turn depends on the tumour type being treated). Chemotherapy can be given alongside radiotherapy for particular tumours.

Conventional radiotherapy (sometimes called photon radiotherapy) uses X-rays and has been used to treat children for many years now. As more and more children survive cancer, there is now growing evidence that certain types of cancer treatment can affect a patient's health later in life. Doctors are now focusing on how to make treatments kinder and safer to avoid or reduce side effects that may happen years after treatment has finished.

Proton beam therapy is a specialised type of radiotherapy using a radiation beam made up of high-energy protons instead of photons (or x-rays) as used in standard radiotherapy. The difference between the two is that when the proton beam hits the tumour cells, it stays within the tumour and doesn't carry on travelling through the

body. Therefore, the amount of normal tissue affected by the radiation is reduced and this in turn is thought to reduce some of the long term side effects.

The cure rate for both proton therapy and standard radiotherapy is the same for the vast majority of patients but there are some advantages of proton therapy specifically for children.

2. What does the NHS recommend?

After carefully looking at the evidence, the NHS has been recommending the use of proton beam therapy for the treatment of some childhood cancers for several years now. Proton beam therapy is not the best treatment for every child with cancer so, this is considered initially by the local expert paediatric oncology team and, if proton therapy is considered suitable, a referral is made to a panel of specialist paediatric radiotherapy experts who consider each child's case on its individual merits.

It is important that proton beam therapy should be given in a well-equipped unit by an experienced and fully-trained team. It is more complicated and time-consuming to deliver than standard radiotherapy and has to be carefully integrated with other treatments to get the best results. For some tumour treatment protocols, chemotherapy is given alongside radiotherapy and so it is imperative that the proton centre has close links with a hospital that is experienced in administering chemotherapy and managing the side effects in children and young adults. There also has to be appropriate specialist support for families in terms of full integration with other specialist children's services.

In December 2018, high energy proton beam therapy became available for NHS patients at the Christie Hospital in Manchester. The second NHS high energy proton facility is planned to open at University College Hospital, London in 2020. An increasing number of NHS patients will be treated in the NHS PBT service, however until the NHS PBT service reaches full capacity, the NHS will continue to fund treatment for some patients abroad at either the University of Florida Proton Therapy Centre, Jacksonville in the USA or the West German Proton Therapy Centre in Essen, Germany.

3. The choice for you

For the vast majority of patients needing treatment with radiotherapy the cure rate with conventional radiotherapy is exactly the same as that with proton beam therapy. The advantages of proton beam therapy are that it can potentially reduce some long term side effects from treatment; however, proton beam therapy does not always offer any advantage over standard radiotherapy. This depends on the location and/or type of tumour being treated. Proton beam therapy has to be delivered in highly-specialised treatment units and this can mean being away from home for 6-8 weeks which can be a challenge for some families. Sometimes either the cancer itself, the treatment, or other medical problems can make travelling away from their local healthcare system very difficult. Once radiotherapy is complete, your child will be followed up by their local team who will liaise closely with the proton centre.

4. How do the benefits and drawbacks of conventional radiotherapy and proton beam therapy compare?

There is very little evidence directly comparing the treatment outcomes of conventional radiotherapy and proton beam therapy for childhood cancer. This is because paediatric tumours are uncommon, and that the main clinical differences are in long-term side effects which may arise many years after treatment is complete. There is however some evidence of equivalent cure rates comparing both types of radiotherapy and radiotherapy doctors anticipate that the special properties of the proton beam will reduce the intensity of long term side effects to some extent. The following table provides some information, based on expert guidance, which clinicians use to help decide whether proton therapy is the right treatment for an individual child.

	Conventional X-ray Radiotherapy	Proton Beam Therapy
How effective is the treatment at curing my child's tumour?	The cure rate for conventional radiotherapy is the same as that for proton beam therapy for the majority of paediatric cancers	The cure rate for proton beam therapy is the same as that for conventional radiotherapy for the majority of paediatric cancers
How long is the radiotherapy treatment?	The total dose and number of treatments is the same for both conventional and proton radiotherapy. However,	The total dose and number of treatments is the same for both conventional and proton radiotherapy. However, the treatment

	<p>the treatment time (per day) with conventional radiotherapy is usually shorter. Appointments for treatment are usually approximately 20 minutes.</p>	<p>time (per day) with proton beam therapy is usually longer as the treatment takes longer to deliver. Appointments for treatment are usually approximately 40 minutes.</p>
<p>Will my child require a general anaesthetic for treatment?</p>	<p>Children need to be able to lie very still during treatment to ensure accuracy. The need for a general anaesthetic is considered on an individual basis but in general children receiving conventional radiotherapy are less likely to need an anaesthetic because the treatment time is shorter.</p>	<p>Children need to be able to lie very still during treatment to ensure accuracy. The need for a general anaesthetic is considered on an individual basis but in general young children receiving proton beam therapy are more likely to need an anaesthetic because the treatment time is longer.</p>
<p>How likely is the radiotherapy to cause side effects in other parts of my child's body?</p>	<p>All treatment for cancer will have some potential short and long term side effects. Modern radiotherapy, delivered by an experienced team, is safe and effective. There can be some side effects with conventional radiotherapy related to the radiotherapy beam passing through or near to important structures near the tumour being treated.</p>	<p>All treatment for cancer will have some potential short and long term side effects. Modern radiotherapy, delivered by an experienced team, is safe and effective. Proton beam therapy can reduce the chance of some side effects happening. Proton therapy is therefore a good choice for children whose bodies are still growing and maturing, and for patients whose tumours are close to vital organs. The impact of less radiation exposure helps reduce the risk of long-term side effects occurring in the patient making it a safer treatment option for some children. There may be minor potential differences on the impact on some normal tissues to protons (called relative biological effectiveness or RBE). This can even slightly increase the risks of treatment, so this will be born in mind</p>

		when advising if protons are suitable.
Can this treatment be given in my nearest radiotherapy centre?	Radiotherapy for children with cancer needs to be given by a specialist team in order to achieve the best possible outcome for your child. This means that you may have to travel away from home for your child to receive their radiotherapy. Your local paediatric oncology team will be able to explain this to you in more detail and introduce you to their specialist paediatric radiotherapy colleagues.	<p>It is important that proton beam therapy is given in a well-equipped unit by an experienced and fully-trained team. It is more complicated and time-consuming to deliver than standard radiotherapy and has to be carefully integrated with other treatments to get the best results. There also has to be appropriate specialist support for families.</p> <p>Since 2008, patients in the UK have been sent overseas for treatment via the NHS Proton Therapy Overseas Programme to two centres in the US and one in Germany. These centres have been carefully selected for their experience, infrastructure and support for children undergoing complex cancer treatment. They are regularly inspected by NHS England and work in partnership with children's cancer specialists in the UK.</p> <p>The first NHS UK proton beam facility opened at the end of 2018 at the Christie Hospital in Manchester. A second one is being built at University College London Hospital due to open in 2020. These centres have been carefully designed to deliver world-class radiotherapy specifically for children, with the appropriate support of specialist paediatric cancer doctors and nurses, on</p>

		<p>recognised established patient care pathways. The two NHS centres will need to build up towards full capacity after they have opened so there will still be a need to send some children and their families abroad for treatment in the short term. The ultimate aim is that all children eligible for proton therapy will be treated at one of the two NHS centres in the UK. Proton therapy in the UK, however, will still mean being away from home for 6-8 weeks which may be a challenge for some families.</p>
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Appendix 2: Paediatric Indications suitable for conventional radiotherapy (photons or electrons)

Indications where patients' life expectancy unlikely to yield a significant clinical benefit with PBT	
Patients with biologically aggressive diseases with poor prognoses	<p>Diffuse Midline Glioma (Including Diffuse Intrinsic Pontine Glioma - DIPG)</p> <p>High Grade Glioma</p> <p>CNS Atypical Teratoid Rhabdoid Tumour (ATRT) (incompletely resected, recurrent, poor performance status or unstable on chemotherapy)</p>
Patients with extensive metastatic disease treated with purely palliative intent (i.e. for symptom control only) with limited life expectancy.	<p>Any anatomical site</p> <p>Variable number of fractionation regimes</p>
Radical, Adjuvant and Palliative Indications where the anatomical site location and/or an extensive Radiotherapy Target volume renders PBT unlikely to yield a clinical benefit (no significant Organs at Risk sparing and/or integral dose benefit)	
Distal limb primary sites (without pelvic or thoracic extension)	<p>E.g. Ewings/Rhabdomyosarcoma/Osteosarcoma Adult-type sarcomas Fibromatosis</p>
Extensively wide RT Target volume	<p>Total Body Irradiation (pre BMT conditioning- all disease indications)</p> <p>Total Nodal Irradiation</p> <p>Whole Brain RT E.g. Cranial Boost with TBI –CML/ALL BMT Primary Cerebral Lymphoma Palliative WBRT</p> <p>Whole Lung Irradiation (in absence of additional focal boost to e.g. chest wall/mediastinum/spine etc.) E.g. Ewing's sarcoma RMS</p>

	<p>Wilms tumour Hodgkin's lymphoma</p> <p>Whole abdominal/Pelvic Irradiation E.g. Ruptured Wilms tumour Desmoplastic small round blue cell tumour</p>
<p>Superficial RT volume (preferentially treatable with Electrons or Orthovoltage radiation modalities)</p>	<p>E.g. Cutaneous/scalp lesions (includes benign (e.g. keloid) and malignant conditions)</p>

Appendix 3: Low grade gliomas and glioneuronal tumours

Selected Low Grade Gliomas are included, namely those with a more circumscribed growth pattern (Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma), as well as paediatric type Diffuse Astrocytomas and Oligodendrogliomas (which do not have IDH mutations or 1p19q codeletion but have a range of other changes e.g. BRAF V600 or KRAS mutations, alterations in MYB or FGFR1), and adult type Oligodendroglioma which is IDH-mutant and 1p19q co-deleted. Low grade Glioneuronal tumours e.g. Ganglioglioma are also included. Adult type Diffuse Astrocytoma, WHO grade II, IDH mutant and 1p19q non co-deleted is excluded. Typically this will show ATRX loss and TP53 mutation, but these changes are not present in all cases.