

Proton Beam Therapy (PBT) Small Cohort Cases Clinical Guidance

Purpose

This guidance provides a structured framework to support equitable access to PBT for small cohorts of patients where PBT may provide clinically meaningful benefit over optimised photon radiotherapy in a group where patient numbers are insufficient for a formal clinical trial. Clinically meaningful benefit refers to an expected improvement in tumour control, reduction in major toxicity, preservation of organ function, or avoidance of otherwise unacceptable compromise in treatment delivery when compared with optimised photon radiotherapy.

The guidance is based on clinical consensus and evidence-informed practice, developed by site specialists from the NHS England-commissioned PBT centres and reformats previous indication specific NHS Programme guidance; it outlines situations where eligibility for PBT can be adequately defined, ensuring tight selection criteria and equity of access for eligible patients.

Definition

Small cohort cases in PBT includes rare or atypical cases, or individual clinical scenarios where standard routine commissioning pathways, clinical trials, and evaluative commissioning studies (ECIPs) are not suitable and evidence is limited. Small cohort cases are characterised by biological, anatomical, or dosimetric factors where other forms of radiation therapy may compromise target coverage, exceed organ at risk tolerance, or result in clinically significant morbidity or reduction in quality of life.

Inclusion Criteria for Small Cohort Case Consideration

Cases considered eligible under current routine commissioning policies ([here](#)), PBT clinical trials ([here](#)), or formal evaluative commissioning (ECIP) studies ([here](#)), are not covered by this guidance, and supersede the guidance given in this document. For cases outside the above, individual patients may be eligible for PBT under any of the following small cohort guidance appendices:

- [Appendix 0](#): General Inclusion Criteria for Small Cohort Cases
- [Appendix 1](#): Extended CNS Indications
- [Appendix 2](#): Malignancy and Pregnancy
- [Appendix 3](#): Oesophago-Gastric Indications
- [Appendix 4](#): Previous Irradiation Compromising Safe Delivery of Curative Treatment to Metachronous Primary Cancers
- [Appendix 5](#): Solid Organ Transplantation Associated Indications for PBT
- [Appendix 6](#): Germline Mutations and Increased Risk of Radiation Induced Malignancy (RIM)

*Appendices 3-6 provide specific examples of the general inclusion criteria set out in Appendix 0.

For cases to be fully reviewed, referrers should document in their referral that the criteria set out in the relevant small cohort case appendix have been actively considered/addressed and all relevant information supporting the referral be articulated. This will likely include objective information such as test or investigation results and/or photon plans based on available imaging; include all available information that supports the case for PBT. **Failure to do so will result in the referral being returned to the referrer for further information. Once sufficient information is received a decision can then be made on suitability for PBT.**

Governance and Decision Making

All cases should be referred through the NHS Proton Referral Portal (<https://protons.protontherapyreferrals.nhs.uk/login>) for consideration by a National PBT Panel who assess cases against the small cohort criteria. For those fulfilling the criteria for small cohort cases, they will then be allocated to an individual PBT Provider. The PBT Provider specialist MDT will evaluate whether there is significant clinical benefit in using PBT over other forms of optimised and optimal radiation therapy, they will also consider other technical and disease specific factors that may impact on the effectiveness of PBT. In the event of a particularly difficult case or a need for formal second opinion review, the second PBT Centre MDT may be asked to assess the case to ensure there is consensus.

The PBT Joint Services Committee (JSC) is responsible for reviewing the criteria regularly and sanctioning development of further indication specific small cohort clinical guidance (such as those in the Appendix). The JSC is also responsible for monitoring referral and acceptance rates to ensure equity of access and consistency of approach to acceptance respectively.

Outcomes will be collected through the PBT Clinical Outcomes collection systems of PBT Provider Trusts and the NHS Proton Registry. Patients should be counselled that treatment under this guidance forms part of an evaluative programme and that access to PBT is conditional on consent to outcome data collection. Small cohort cases will subsequently transition to an Evaluative Commissioning in Protons (ECIP) programme for formal evaluation by a designated Study Management Group (SMG), which will advise the JSC on the clinical effectiveness and benefit of PBT in these indications. This guidance is intended as an interim measure until those studies are established.

Appendix 0: General Inclusion Criteria for small cohort cases

Routine commissioning policies, PBT clinical trials, ECIPs, and other small cohort appendices take precedence.

Patient Criteria (all must be satisfied)

1. The case/clinical scenario is considered rare or atypical
2. There needs to be a clear indication for radiation therapy
3. Good performance status 0-1
4. No co-morbidities likely to limit life expectancy to <5 years
5. Treatment intent is curative and 5-year survival expectation >40%
 - a. In highly selected cases, meaningful extension of local control and very low metastatic potential may allow PBT to be used for disease control
 - b. PBT would enable delivery of radical radiotherapy that cannot be safely achieved using optimised photon radiotherapy. Referrers need to demonstrate both the following:
 - i. Respecting organ at risk (OAR) tolerance) would significantly compromise CTV coverage and would lead to significant reduction in local control
 - ii. Exceeding OAR tolerance would lead to life limiting or significant life changing toxicity
6. No evidence of distant metastasis
 - a. In highly selected cases, where the presence of metastasis is likely not to be life limiting, such cases may be considered eligible
7. Reirradiation of recurrent cancer is not an approved indication

Appendices 3-6 provide specific examples of the general inclusion criteria set out in this appendix. Indications/clinical scenarios that fall outside those appendices should be considered under the criteria in this appendix.

Appendix 1: Extended CNS Indications

Routine commissioning policies remain unchanged:

- Patients 30yo and under are routinely commissioned (see [here](#) for eligibility).
- Adult Craniospinal Irradiation patients are routinely commissioned (see [here](#) for eligibility)

This guidance applies to adult CNS tumours where PBT may enable delivery of a radical treatment with improved organ at risk sparing compared to photon radiotherapy.

Patient Criteria

- Selected indications in young adults 31-40yo (exceptionally >40yo):
 - Primary malignant intracranial germ cell tumours
 - Craniopharyngioma
 - Cranial ependymoma (as for Paediatric and TYA policy), should be gross totally resected, and adjuvant radiotherapy should be indicated
 - Paediatric type low grade gliomas e.g. pilocytic astrocytoma
 - Spinal CNS tumours (e.g. ependymoma, meningioma, schwannoma) with good prognosis, specifically where proton therapy would avoid irradiating the heart or possible ovarian irradiation.
 - Vestibular schwannoma and other cranial nerve schwannomas unsuitable for surgery or stereotactic radiosurgery. Compared to fractionated photon therapy, proton therapy reduces integral dose. Hearing preservation appears inferior with proton therapy and cranial nerve toxicity is comparable or possibly worse; where best hearing preservation is important, fractionated stereotactic photon therapy may be preferable to proton therapy.

Appendix 2: Malignancy and Pregnancy

This guidance applies to patients requiring radiotherapy during pregnancy where treatment delay is not clinically appropriate and fetal radiation exposure must be minimised.

Patient Criteria

In all cases, radiotherapy must be with potentially curative intent and should offer significant potential benefit, in terms of foetal dose reduction, over photon therapy. Cases will be individually assessed by PBT site specialist MDTs. Decision making should include multidisciplinary discussion involving obstetrics, foetal medicine and medical physics where appropriate.

References

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3. Blommaert J, De Saint-Hubert M, Depuydt T, Oldehinkel E, Poortmans P, Amant F, Lambrecht M. Challenges and opportunities for during pregnancy. *Acta Obstet Gynecol Scand*. 2024 Apr;103(4):767-774. doi: 10.1111/aogs.14645. Epub 2023 Jul 25. PMID: 37491770; PMCID: PMC10993337.

Appendix 3: Oesophago-Gastric Indications

Routine commissioning policies remain unchanged.

This guidance applies to a small subset of adult patients with oesophageal or gastro-oesophageal junction malignancies where conventional treatment approaches are not feasible due to comorbidity or prior treatment.

Patient Criteria

Selected indications to be approved in adults with confirmed histology and tumour location in the upper gastro-intestinal tract (oesophageal, gastroesophageal junction) where conventional chemotherapy - surgery and chemo-radiotherapy have been deemed unacceptable by site specialist MDT assessment.

- **Restrictive lung disease:** Any patient where background chronic Lung conditions which preclude the delivery of photon therapy e.g. COPD with FEV1 < 1.5 and / or TLCO < 40%, Interstitial lung disease including pulmonary fibrosis of any aetiology, Idiopathic Lung Fibrosis with [GAP stage 1](#), iatrogenic pneumonitis (e.g. previous systemic therapy induced pneumonitis which has recovered i.e. not in acute phase)
- **Cardio-pulmonary co-morbidity:** Any patient with a cardiomyopathy that would be at higher risk of decompensation e.g. HOCM, ARVD, Takotsubo cardiomyopathy

In all cases, radiotherapy must be with radical intent and offer significant potential clinical benefit over photon therapy. The ‘General Inclusion Criteria for small cohort cases’ outlined in [Appendix 0](#) apply.

References

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Appendix 4: Previous Irradiation Compromising Safe Delivery of Curative Treatment to Metachronous Primary Cancers

Routine commissioning policies remain unchanged.

This guidance applies to patients with metachronous primary cancers requiring radiotherapy, where previous radiation therapy **limits delivery of further radiotherapy**.

Background

Conventional radiotherapy is a commonly used part of modern curative cancer care and many treatment pathways. An 'in-field' new tumour, de-novo or a radiation induced malignancy (RIM), may arise in a patient who has previously received radiotherapy. In this scenario PBT can be considered to deliver a radical treatment dose whilst respecting normal dose constraints which might otherwise limit the delivery of radical radiotherapy. Normal tissues and organs have established safe doses above which significant toxicity is recognised. In some cases, an alternative strategy using surgery or other forms of radiotherapy such as SABR may be acceptable options.

Patient Criteria

1. Where there is an indication for potentially curative radiotherapy and a metachronous cancer, and a history of radiotherapy to some of the normal tissues at risk in a past radiotherapy treatment course.
2. It would not be possible to deliver radical radiation therapy to the metachronous primary without exceeding organ at risk (OAR) tolerance with optimal (and optimised) photon radiotherapy. Previous irradiation alone is insufficient justification for PBT.
3. This is not re-irradiation for a recurrent tumour which remains a non-commissioned indication and subject for clinical research.
4. PBT MDT assessment and treatment planning may determine the past radiotherapy doses to organs at risk, overlap with new treatment beam delivery and assessment of clinical benefit.
5. A discussion with the patient of risks, benefits, and alternatives is essential.
6. The patient should always be considered for surgery or radiosurgery in preference to PBT where possible and the referral should explicitly state the reasons why these are not suitable options.

In all cases, radiotherapy must be with radical intent and offer significant potential clinical benefit over photon therapy. The 'General Inclusion Criteria for small cohort cases' outlined in [Appendix 0](#) apply.

Appendix 5: Solid Organ Transplantation Associated Indications for Proton Beam Therapy (PBT)

Routine commissioning policies remain unchanged.

This guidance applies to patients with malignancy following solid organ transplantation where conventional treatment options pose unacceptable risk.

Background

Solid organ transplants are associated with higher rates of certain malignancies due to the associated immunosuppressive drug regimens and therapeutic options may be limited.

Examples:

- Surgery for an oesophageal cancer in a past heart or lung transplant patient would be a high mortality procedure and considered unacceptable. Similarly, standard options of conventional IMRT and chemotherapy may deliver unacceptably high doses to surrounding organs including the heart and lung. The use of PBT enables delivery of a lower dose to these organs and may allow a potentially curative option.
- Conventional IMRT and chemotherapy in the treatment of squamous cancers of the anus and vulva in a patient with a pelvic transplanted kidney would risk unacceptable doses to the transplanted kidney, resulting in renal failure and potentially returning to dialysis.

Patient Criteria

- Patient with a histologically confirmed malignancy and tumour location where potentially curative radiotherapy treatment is indicated, but past solid organ transplant makes conventional radiotherapy options, or surgery alone offers an unacceptable option.

In all cases, radiotherapy must be with radical intent and offer significant potential clinical benefit over photon therapy. The ‘General Inclusion Criteria for small cohort cases’ outlined in [Appendix 0](#) apply.

Appendix 6: Germline Mutations and Increased Risk of Radiation Induced Malignancy (RIM)

Routine commissioning policies remain unchanged.

This guidance applies to patients with confirmed germline mutations that increase the risk of radiation induced malignancy.

Background

In patients with germline cancer predisposition syndromes associated with an increased risk of radiation-induced malignancy, PBT may offer a particular therapeutic advantage by reducing unnecessary irradiation of normal tissues. While the target dose must remain sufficient to achieve tumour control, the physical properties of protons allow substantial reductions in exit dose and integral dose compared with conventional photon radiotherapy. This may be especially relevant in patients with inherited abnormalities in tumour suppressor genes or DNA damage response pathways that confer an increased lifetime risk of subsequent malignancy following radiation exposure. Proton therapy therefore provides a means of maintaining the therapeutic benefits of radiotherapy while minimising avoidable radiation exposure to surrounding healthy tissues. Although direct clinical evidence demonstrating a reduction in radiation-induced malignancies in these patient groups remains limited, there is a strong dosimetric rationale for this approach, particularly in younger patients and those with a long life expectancy.

Patient Criteria

- Patients with germline mutations where radiotherapy may significantly increase the risk of inducing further tumours, especially Neurofibromatosis type II, Gorlin syndrome, Li-Fraumeni syndrome, hereditary retinoblastoma. [1-7]
- The patient should always be considered for surgery or radiosurgery in preference to PBT where possible and the referral should explicitly state the reasons why these are not suitable options.

In all cases, radiotherapy must be with radical intent and offer significant potential clinical benefit over photon therapy. The ‘General Inclusion Criteria for small cohort cases’ outlined in [Appendix 0](#) apply.

References

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