

Clinical Commissioning Policy Statement Proton Beam Therapy for Craniospinal Irradiation in Adults (201003P) [URN:1841]

Commissioning position

Summary

Proton beam therapy (PBT) for craniospinal irradiation (CSI) in adults is recommended to be available as a treatment option through routine commissioning within the criteria set out in this document.

Information about proton beam therapy in adult craniospinal irradiation

The intervention

PBT provides radiation by delivering a beam of proton particles rather than X-Rays (photons). The physical properties of protons may result in a significantly reduced 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 can have some advantages over conventional radiotherapy in certain groups of patients, such as children, or where the cancer is close to a critical part of the body such as the spinal cord.

Craniospinal irradiation (CSI) is the term used to describe the delivery of radiation therapy to the whole brain and spinal cord and is used with curative intent in certain primary brain or spinal tumours. The tumour types are ones which predominate in the paediatric, teenage and young adult age ranges, and are very rare in older adults (aged >25 years). CSI is most often given in combination with chemotherapy and after surgery. The management pathway is complex and has time critical factors in order to maximise tumour control and cure rates. For types of cancer requiring CSI, there is supporting evidence of improved treatment outcomes, such as reduction in acute side effects including spinal deformities, infertility and cardiac toxicity, when PBT is utilised.

There are expected to be 15-25 adults in total per year in England who require CSI and who would fulfil the criteria for this policy, as discussed below. For the whole of the UK, the expected numbers are 18 – 30 patients per annum.

The referral process, as outlined in the Service Specification Proton Beam Therapy Service (All Ages) (NHS England Reference: 170071S), 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 to ensure continuity of care.

Committee discussion

The Clinical Panel considered the evidence presented and considered that the proton treatment may provide benefits for this indication.

See the committee papers ([link](#)) for full details of the evidence.

The condition

There are several diagnoses and clinical indications fulfilling the criteria for this policy. This is not a single population or diagnosis and involves selected subpopulations of patients. In general, the patient should have a clear indication for CSI defined as being curable (leading to normal or near-normal life expectancy); have a reasonable disease specific 5-year survival expectation; and have no comorbidities likely to limit life expectancy to less than 5 years.

1. Standard risk medulloblastoma. This is the most common indication for CSI, and most commonly occurs in children. There are approximately 12 patients over the age of 25 years diagnosed with medulloblastoma per year in England (Public Health England, 2017). Between 66% and 85% (Sengupta et al, 2017; Carrie et al, 1994) of these cases would be standard risk medulloblastoma, and so in summary approximately 8-10 patients per year would require CSI for standard risk medulloblastoma. The actual number suitable for PBT could be lower if some were unfit for travel within an appropriate timeframe.

Standard risk medulloblastoma is defined as:

- Histologically confirmed medulloblastoma,
- Non-metastatic (i.e. no metastases on MRI brain and spine and clear CSF),
- Post surgery residual disease of <1.5cm²,
- Histological subtypes: classical, desmoplastic, nodular (large cell, anaplastic are not included).

2. Intracranial germinomas. A germinoma is a type of germ cell tumours which are rare tumours which overall occur at a rate of around 1 per million per annum, equivalent to around 53 new cases per annum in England, of which only 15 patients per annum would be expected to be aged >25 years (WHO, 2016; CBTRUS Statistical Report, 2017). Around 40% - 67% of patients aged >25 years will have germinomas, implying 6 - 10 patients with intracranial germinomas per annum aged >25 years in England. Adults with both localised and metastatic intracranial germinomas are currently usually treated with CSI. Germinoma (localised and metastatic) is exquisitely radiosensitive, with excellent cure rates.

It is therefore expected that 6-10 adult patients per year in England may require CSI, and should receive PBT as long as the delay between referral and treatment does not lead to a risk of clinically significant adverse outcomes, especially for metastatic patients.

3. Very rare selected indications for CSI. There are some extremely rare presentations of other central nervous system tumours where CSI is indicated and meets the prognostic criteria as described above (the patient should have a clear indication for CSI which is defined as being curable (leading to normal or near-normal life expectancy); have a reasonable disease specific 5-year survival expectation; and have no comorbidities likely to limit life expectancy to less than 5 years).

Current treatments

Current standard treatment for medulloblastoma comprises maximal surgical resection of the primary tumour, followed by radiotherapy to the whole brain and craniospinal axis (craniospinal irradiation, CSI) with an additional dose ("boost") to the tumour bed, followed by chemotherapy. Cure rates for standard risk medulloblastoma are in the region of 85% but this is at the expense of significant toxicity.

Current standard care for adult intracranial germinomas in the UK is CSI with photon radiotherapy. The unwanted radiation dose which is delivered outside the desired area when treating with conventional photon radiotherapy, especially to the tissues in front of the whole length of the spinal canal, causes well documented long-term side effects. Late side effects of

CSI include early menopause or subfertility in females, a substantial risk of radiation induced second malignancies, as well as effects on cardiac, lung and thyroid function.

Comparators

CSI with photon radiotherapy.

CSI with photon radiotherapy results in cure rates for standard risk medulloblastoma in the region of 85% but this is at the expense of significant toxicity.

Late side effects of CSI with photons include early menopause or subfertility in females, a substantial risk of radiation induced second malignancies, as well as effects on cardiac, lung and thyroid function.

Clinical evidence

Three papers were submitted to the Clinical Panel for consideration as part of the policy. Two contain the findings from observational studies of 90 adult patients with various tumours requiring proton craniospinal irradiation (p-CSI), mainly medulloblastomas. A third paper reports the clinical outcomes after p-CSI in children with standard risk medulloblastoma. All three papers are reviewed.

Paper 1: Brown et al, 2013

Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma

Brown et al report their findings from a retrospective study of 40 adult patients with histologically-confirmed medulloblastoma, comparing the efficacy and acute toxicity of proton craniospinal irradiation with conventional photon CSI for adults with medulloblastoma. Patients' records were selected from the period 2003 to 2011 with proton beam irradiation becoming available in the institution from 2006. All the patients had had surgery prior to the radiation treatment but the timing of their chemotherapy regimen relative to radiation therapy varied as determined by treating physicians. Overall survival, progression free survival and the monitoring of acute toxicities were outcomes of interest.

The authors report no significant differences between the 2-year overall survival (94% for protons versus 90% for photons) and progression free survival (94% for protons versus 85% for photons) for the two groups. Regarding acute toxicities, the authors report that patients receiving proton radiation experienced statistically significant reductions in weight loss (mean 1.2% versus 5.8%), grade 2 or greater nausea and vomiting (26% versus 71%) and oesophagitis needing medical management (5% versus 57%). Proton patients also had smaller reduction in white blood cells, haemoglobin and platelets, each of which was statistically significant.

Paper 2: Barney et al, 2014

Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation

Barney et al reviewed the medical records of 50 patients aged 16 – 63 years treated consecutively with proton craniospinal irradiation. They had malignancies of varying histologies including medulloblastomas (38%), germ cell tumours (30%), and eight other tumour types. All patients underwent surgery and 80% received chemotherapy in addition to the proton irradiation. Overall survival, progression free survival and the monitoring of acute toxicities were outcomes of interest.

The authors report low rates of acute toxicities with no treatment interruptions. The median weight loss during p-CSI was 1.6% (range 10% weight loss to 14% weight gain). As regards nausea and vomiting, the majority of patients had either no nausea or vomiting (34%) or only mild symptoms (46%), and the worst toxicity was grade 2 in 20% of patients. Only 5 patients

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(10%) experienced grade ≥ 2 anorexia resulting in weight loss $>5\%$ of the baseline weight. Cytopenias, though noticeable, were of limited duration. The median percentages compared to baseline of white blood cells, haemoglobin and platelets at nadir during radiotherapy were 52% (range, 13% - 100%), 97% (65% -112%) and 61% (10% - 270%), respectively and increased after four weeks. The longest follow up was just under five years (59 months) with a median of 20 months. The overall survival and progression free survival at 2 years were 96% and 82% respectively, and at 5 years were 84% and 68% respectively. The authors conclude longer follow-up is needed to evaluate whether the reduction in toxicity translates into improvements in long-term treatment-related morbidity and overall disease outcomes.

The study limitations include those associated with retrospective studies – specifically selection bias. The heterogeneous nature of the patient group as well as the ongoing treatment received, and lack of comparator group, also provides challenges in evaluating the outcomes reported.

Paper 3 Eaton et al, 2016.

Clinical outcomes among children with standard-risk medulloblastoma treated with proton and photon radiation therapy: A comparison of disease control and overall survival.

Eaton et al report the findings from a multi-institution cohort of 88 children and young adults aged 3 – 21 years with standard risk medulloblastoma treated with chemotherapy and proton or photon CSI between 2000 and 2009. The patients treated with p-CSI were prospectively enrolled in a trial in one institution and they were matched to a historical cohort of patients treated with photons. All patients had surgery and chemotherapy. Outcomes of interest were overall survival (OS), recurrence-free survival (RFS) and patterns of failure.

The authors report no significant difference in the OS or RFS between the two cohorts. The 6-year OS rates were similar for protons (82.0%) and photons (87.6%). For RFS, the 6-year rate for p-CSI was estimated as 78.8% and for photons as 76.5%. Patterns of treatment failure were similar between the 2 cohorts. The authors conclude disease control with proton and photon radiation therapy appears equivalent for standard risk medulloblastoma.

Overall, the papers reviewed suggest that in these tumours, p-CSI is not inferior to photon CSI for medium term outcomes but results in lower rates of acute toxicity for patients.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting: england.CET@nhs.net.

Links to other policies

NHS England. 2018. Service Specification for Proton Beam Therapy Services. (NHS England Reference: 170071S)

NHS England. 2020. Clinical Commissioning Policy: Proton Beam Therapy for children, teenagers and young adults in the treatment of malignant and non-malignant tumours (NHS England Reference: 200808P)

References

- Aleman B.M., Moser E.C., Nuver J., Suter T.M., Maraldo M.V., Specht L. et al. Cardiovascular disease after cancer therapy. *EJC Suppl* 2014;12(1):18-28.
- Barney C.L., Brown A.P., Grosshans D.R., McAleer M.F., de Groot J.F., Puduvalli V. et al. Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation. *Neuro Oncol* 2014;16(2):303-9.
- Brown A.P., Barney C.L., Grosshans D.R., McAleer M.F., de Groot J.F., Puduvalli V.K. et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2013;86(2):277-84.
- CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro-Oncology* 2017;19 (Suppl 5): v1-v88.
- Carrie C., Lasset C., Alapetite C., Haie-Meder C., Hoffstetter S., Demaille M.C. et al. Multivariate analysis of prognostic factors in adult patients with medulloblastoma. Retrospective study of 156 patients. *Cancer* 1994;74(8):2352-60
- Eaton B.R., Esiashvili N., Kim S., Weyman E.A., Thornton L.T., Mazewski C. et al. Clinical Outcomes Among Children With Standard-Risk Medulloblastoma Treated With Proton and Photon Radiation Therapy: A Comparison of Disease Control and Overall Survival. *Int J Radiat Oncol Biol Phys* 2016;94(1):133-138.
- Giebel A., Newhauser W.D., Amos R.A., Mahajan A., Homann K., Howell R.M.. Standardized treatment planning methodology for passively scattered proton craniospinal irradiation. *Radiat Oncol*. 2013 Feb 3;8:32.
- Lester-Coll N.H., Morse C.B., Zhai H.A., Both S., Ginsberg J.P., Gracia C.R. et al. Preserving Fertility in Adolescent Girls and Young Women Requiring Craniospinal Irradiation: A Case Report and Discussion of Options to Be Considered Prior to Treatment. *J Adolesc Young Adult Oncol* 2014;3(2):96-99.
- Mulrooney D.A., Yeazel M.W., Kawashima T., Mertens A.C., Mitby P., Stovall M. et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ* 2009;339:b4606.
- Newhauser W.D., Fontenot J.D., Mahajan A., Kornguth D., Stovall M., Zheng Y. et al. The risk of developing a second cancer after receiving craniospinal proton irradiation. *Phys Med Biol* 2009;54(8):2277-91.
- Public Health England. Report of the Working Party for Higher Risk Breast Screening. First published February 2015. Accessible at <https://www.gov.uk/government/publications/breast-screening-working-party-report-on-higher-risk-women>
- Public Health England - Office for Data Release [accessed 2017]
- Sengupta S., Pomeranz Krummel D. & Pomeroy S. The evolution of medulloblastoma therapy to personalized medicine. *F1000Res* 2017;6:490.

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Louis D.N., Ohgaki H., Wiestler O.D. & Cavenee W.K. (eds). WHO classification of tumours of the central nervous system, revised 4th edition, 2016. International Agency for Research on Cancer (IARC), Lyon, France.

Yoon M., Shin D.H., Kim J., Kim J.W., Kim D.W., Park S.Y. et al. Craniospinal irradiation techniques: A dosimetric comparison of Proton Beams with Advanced and Standard Photon Radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;81(3):637-646.

Zhang R., Howell R.M., Homann K., Giebeler A., Taddei P.J., Mahajan A. et al. Predicted risks of radiogenic cardiac toxicity in two pediatric patients undergoing photon or proton radiotherapy. *Radiat Oncol* 2013;8(1):184.