Clinical Commissioning Policy Statement
Proton Beam Therapy for Adult Lymphoma (URN: 1852) [190702P]

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Commissioning Position

Summary

NHS England has reviewed the evidence to treat lymphoma with proton beam therapy in adults and have concluded that there is not enough evidence to make the treatment available through routine commissioning.

Information about Proton Beam Radiotherapy for Adult Lymphoma

The intervention

Proton Beam Therapy (PBT) provides radiation by delivering a beam of proton particles rather than X-Rays. The physical properties of protons results 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 has 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. However, for many groups of patients or types of cancer, including adults (>25 years old) with lymphoma, where lower treatment doses are required, there is as yet little evidence of improved treatment outcomes, such as better cancer control or reduced side-effects, when compared to conventional photon-based radiotherapy treatment.

Committee discussion

The condition

Lymphoma includes a range of conditions broadly divided into Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). It is a common cancer with more than 15,000 cases in the UK in 2015 (CRUK, 2018). More than 14,000 of these occur in people aged 25 years and over. Rates of HL in people aged >25 have increased by more than 60% over the last 20 years and rates of NHL have increased by more than 30% (CRUK, 2018). Overall survival rates from lymphoma are high with more than 80% of people with HL and more than 60% of people with NHL surviving their lymphoma for 10 years or more (CRUK, 2018). Approximately 20% of NHL patients and 30% of HL patients receive radiotherapy as part of their treatment (RTDS, 2018). This equates to more than 3000 people aged 25 years and over treated with radiotherapy for lymphoma in the UK each year.

Current treatments

Conventional photon-based radiotherapy is an effective treatment for lymphoma when used either alone or in combination with chemotherapy. Modern radiotherapy for lymphoma is usually delivered to the parts of the body originally affected by the disease ('involved-site radiotherapy').

The area of the body irradiated can therefore vary widely depending on the areas affected; e.g. neck, mediastinal or abdominal treatment, as well as other more rarely involved sites.

Conventional radiotherapy, delivered using simple 3D-conformal techniques, has proven to be effective for all of these sites with relatively low estimated risks of long-term side-effects in most adult patients (Witkowska et al, 2015). Given the excellent long-term survival in many types of lymphoma, there is long-established concern regarding possible late side effects of treatment, particularly radiotherapy, such as second cancers and cardiovascular disease. This is exemplified by Hodgkin lymphoma where, over the past few decades, the dose and extent of radiotherapy given in combination with chemotherapy has been systematically reduced as part of a series of randomised controlled trials (Canellos et al, 2010; Meyer et al, 2012; Raemaekers et al, 2014; Engert et al, 2012).

The most recent trials have attempted to omit radiotherapy entirely in patients who respond well to chemotherapy but, for example, in early-stage HL (Meyer et al, 2012; Raemaekers et al, 2014) and for bulky disease in diffuse large B-cell NHL (Zimmermann et al, 2016), the complete omission of radiotherapy has proven to result in poorer disease control.

In summary, the only reason not to use radiotherapy for many lymphoma indications is concern over late side effects rather than it not being an effective treatment. Attention has therefore switched to the development of more advanced radiotherapy techniques that can deliver the same effective treatment whilst minimising the dose to normal tissues, thus reducing the estimated risk of late side effects.

Comparators

1) Intensity-modulated radiotherapy (via fixed fields or as arc therapy). This is conventional photon radiotherapy delivered using more sophisticated techniques to allow a more conformal dose distribution and a lower risk of acute and long-term side-effects in some circumstances. The treatment is still delivered to the same dose and in the same number of fractions as simple 3D-conformal techniques.

2) Deep-inspiration breath-hold radiotherapy. Patients with mediastinal lymphoma may be treated with a breath-hold technique in combination with conventional photon-based radiotherapy. This can reduce the incidental radiation dose to the heart and lungs leading to lower estimated risks of long-term side effects.

Clinical trial evidence

Summary of evidence

Three papers were submitted to the Clinical Panel as part of the policy proposition. One contained the findings from an observational trial, another reported long terms risks based on theoretical modelling of the outcome of different treatment scenarios and a third was a non-systematic review of the use of proton therapy in lymphoma. Therefore, we were only able to consider findings from the observational trial in informing the policy decision.

The Panel found no convincing evidence that demonstrated superiority of proton beam therapy over current standard treatment.

Paper 1. Hoppe et al 2017. Consolidative proton therapy after chemotherapy for patients with Hodgkin Lymphoma

The early outcomes among 138 patients are reported using registry data from three US Institutional disease registries. Patients were recruited prospectively to be followed up if they

were diagnosed with HL and treated with chemotherapy followed by consolidative PBT over a seven-year period from 2008 to 2015. PBT was delivered using involved site radiation therapy (ISRT). Reporting protocols across the institutions were not standard. The patients ranged in age from 6 to 57 years (median 20 years) and were followed up over a range of 5 to 92 months with a median follow-up of 32 months. Outcomes of interest were 3-year relapse-free survival rates, the number of recurrences and reported toxicities.

The 3-year relapse-free survival rate was 92% for all patients. Patients who experienced a partial response to chemotherapy had a significantly higher risk of relapse compared with the patients who experienced a complete or unknown response to chemotherapy. In the study period, 10 recurrences occurred with seven in the radiation field. No grade 3 radiation-related toxicities were observed during the follow up period.

Though collaboration across institutions is a strength, the study is subject to the weakness of an observational study and has no comparators. Treatment of HL is generally highly effective, and patients generally have a long-life expectancy after treatment. The risk of late effects after radiotherapy is therefore particularly important. The findings after three years of follow-up are therefore insufficient to draw conclusive results on the superiority of proton beam as a treatment plan and continued follow-up is important to assess the late effects.

Paper 2: Rechner et al, 2017. Life years lost attributable to late effects after radiotherapy for early stage Hodgkin's lymphoma: The impact of proton therapy and/or deep inspiration breath hold

Deep inspiration breath-hold and PBT are both known to reduce the dose of radiation therapy (RT) to normal tissues. The paper uses risk models to assess the risk of late effects of radiotherapy for (HL with mediastinal involvement. The life years lost (LYL) is calculated for 22 theoretical patients with mediastinal HL given RT delivered in four scenarios - Intensity modulated radiation therapy (IMRT) in free breathing and in deep inspiration breath hold and proton therapy in free breathing and in deep inspiration breath hold.

The authors found the lowest LYL was for proton therapy in deep inspiration breath hold. They also reported that deep inspiration breath hold, PBT and the combination of deep inspiration breath hold and PBT significantly reduced the LYL compared to IMRT in free breathing.

This paper does not contribute to the evidence base of clinical effectiveness from empirical studies but is useful in informing the choice of treatment techniques where a variety of treatment modalities are available.

Paper 3: Tseng et al 2017. Evidence-based review on the use of Proton Therapy in Lymphoma from the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee.

The authors aim to draw attention to the potential for the use of proton therapy in the treatment of lymphoma by highlighting from published literature, the potential of PBT in reducing the late morbidity associated with radiation dose, comparing proton therapy with photon irradiation and highlighting outcomes reported in studies in which proton therapy has been used.

The paper does not have any original trial or modelled data and is not further reviewed.

There have been several publications reporting the possible dosimetric benefits of delivering radiotherapy for lymphoma using PBT. However, in adult patients (aged >25 years) the proven lower relative risk of late toxicities from radiotherapy treatment (per unit dose), combined with

theoretical uncertainties over the delivery of PBT for thoracic tumours and the advances in conventional photon-based radiotherapy (as outlined above), mean that the evidence for using PBT routinely for the treatment of lymphoma in adults in limited. The intended policy of 'Not Routinely Commissioned' will support this commissioning position for NHS England.

Adverse events

Adverse events were not demonstrated in the literature provided.

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 Provisional Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links to other Policies

Radiotherapy Service Specification (https://www.england.nhs.uk/wp-content/uploads/2013/06/b01-radiotherapy.pdf)

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.

Documents that have Informed this Policy Statement

Hoppe B.S., Hill-Kayser C.E., Tseng Y.D.,Flampouri S.,Elmongy H.M., Cahlon O. et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin Lymphoma. *Annals of Oncology* 2017: 28(9)2179-2184.

Rechner L.A., Maraldo M.V., Vogelius I.R., Zhu X.R., Dabaja B.S., Brodin N.P. et al. Life years lost attributable to late effects after radiotherapy for early stage Hodgkin's lymphoma: The impact of proton therapy and/or deep inspiration breath hold. *Radiother Oncol* 2017 Oct; 125(1): 41-47.

Tseng Y.D., Cutter D.J., Plastaras J.P., Parikh R.R., Cahlon O., Chuong M.D. et al. Evidence-based review on the use of Proton Therapy in Lymphoma from the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. *Int J Radiat Oncol Biol Phys* 2017 Nov 15; 99(4):825-842

Additional references

Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/hodgkin-lymphoma#heading-Zero. Accessed November 2018.

Canellos G. P., Abramson J. S., Fisher D. C., LaCasce A. S. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *Journal of Clinical Oncology*. 2010;28(9):1611–1615.

Engert A., Haverkamp H., Kobe C., et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *The Lancet*. 2012;379(9828):1791–1799.

Meyer R. M., Gospodarowicz M. K., Connors J. M., et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *New England Journal of Medicine*. 2012;366(5):399–408.

Raemaekers J. M. M., André M. P. E., Federico M., et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin's lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *Journal of Clinical Oncology*. 2014;32(12):1188–1194.

Radiotherapy Dataset (RTDS) 2018.

Witkowska M., Majchrzak A & Smolewski P. The Role of Radiotherapy in Hodgkin's Lymphoma: What has been achieved during the last 50 years? *Biomed Res Int.* 2015: 485071.

Zimmermann M., Oehler C., Mey U., Ghadjar P. & Zwahlen D.R. Radiotherapy for Non-Hodgkin's lymphoma: Still standard practice and not an outdated treatment option. *Radiation Oncology.* 2016: 11(110).