Clinical Commissioning Policy Statement
Proton Beam Therapy for Hepatocellular Carcinoma (1842) [190701P]

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Commissioning position

Summary

NHS England has reviewed the evidence to treat hepatocellular carcinoma (HCC) with proton beam therapy (PBT) and have concluded that there is not enough evidence to make the treatment available through routine commissioning.

Information about proton beam therapy in liver tumours

The intervention

Radiotherapy is a highly effective treatment for many cancers. PBT is an alternative to conventional radiotherapy, which provides radiation by delivering a beam of proton particles rather than photon (X-ray) radiotherapy. 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. For some types of cancer, including primary liver cancers, there is supporting evidence of improved treatment outcomes, such as better cancer control when effective radiotherapy doses are delivered. However, it is not always possible to deliver these high doses of radiation utilising conventional photon therapy because the surrounding liver (parenchyma) is sensitive to radiation and often has a background of scarring that has predisposed development of the cancer; or the tumour is often situated to a critical organ (e.g. stomach or duodenum) that is more sensitive to critical irreversible damage at doses of radiation lower than that required to control the cancer.

Committee discussion

The condition

Hepatocellular carcinoma (HCC) (primary liver cancer) is the second most common cause of cancer deaths in males worldwide. In the UK, primary liver cancer is relatively uncommon accounting for 2% of all new cancer cases, and is more common in men than women (Jemal et al, 2011). HCC usually develops in the context of liver cirrhosis (scarring of the liver) and the most common aetiological (causal) factors are hepatitis B (HBV) and C (HCV) viral infections, alcohol misuse, and diabetes/metabolic syndrome. Liver cancer incidence rates and mortality rates are expected to rise in the UK in the next 20 years (Cancer Research UK, 2018).

Current treatments

Currently the best option for patients to achieve long term survival remains surgery (resection or liver transplantation). However, only 20% of patients diagnosed in England will have surgery to remove the tumour as part of their primary treatment. This is because surgery would not be clinically appropriate due to the locally advanced nature of the disease or reduced hepatobiliary function and comorbidities such as concomitant infections and alcohol misuse.

For patients who have local disease inoperable by performance status, comorbidity or tumour location and are not eligible for transplant, the NHS palliative treatment options are sorafenib, trans-arterial chemo-embolisation (TACE), photon radiotherapy and radiofrequency ablation. All of these treatments are given with palliative intent, and life expectancy for such patients is generally less than a year.

Precision radiotherapy for HCC allowing a more effective dose of radiotherapy is only a recent option made possible with technological advances enabling the delivery of high-precision radiotherapy (Kalogeridi et al, 2015; Yu & Feng, 2018) such as SABR. Yoon et al in 2018 demonstrated an improved progression free survival and overall survival with the addition of radiotherapy for hepatocellular carcinoma. Radiotherapy may be indicated in any stage of HCC management as a palliative intervention.

Comparators

Photon (X-ray) radiotherapy (NHS funded), radiofrequency ablation (NHS funded), SABR, selective internal radiotherapy (SIRT), high intensity focussed ultrasound (HIFU). SABR is not currently routinely commissioned by NHS England and is subject to an ongoing Commissioning through Evaluation project. SIRT is not currently routinely commissioned for HCC.

Clinical trial evidence

The body of evidence regarding the effectiveness and safety of PBT in the treatment of HCC remains small. Two clinical papers were submitted to the Clinical Panel as part of the policy proposition; both were systematic reviews and not original research. A third paper submitted was a cost utility modelling, based on assumptions about effectiveness that were derived from phase II studies. Therefore, this did not add to the evidence on clinical effectiveness.

The two systematic reviews demonstrated a low level of evidence of benefit of proton beam therapy. One paper concluded that there was a low level of evidence, suggesting a strong rationale to enrol patients into prospective studies. The other more recent paper found no randomised controlled trials or controlled studies that compared charged particle therapy with photon therapy directly.

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

Paper 1. Dionisi F et al. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review. Radiotherapy and Oncology. 2014 111: 1–10

This paper aimed to review the literature concerning the use of proton therapy systematically in the treatment of hepatocellular carcinoma, focusing on clinical results and technical issues. The literature search was conducted according to a specific protocol in the Medline and Scopus databases by two independent researchers covering the period of 1990–2012. Both clinical and technical studies referring to a population of patients actually treated with protons were included. The PRISMA guidelines for reporting systematic reviews were followed. A final set of 16 studies from seven proton therapy institutions world-wide were selected from an initial dataset of 324 reports. Seven clinical studies, five reports on technical issues, three studies on treatment related toxicity and one paper reporting both clinical results and toxicity analysis were retrieved. Four studies were not published as full papers. Passive scattering was the most adopted delivery technique. More than 900 patients with heterogeneous stages of disease were treated with various fractionation schedules. Only one prospective full paper was found. Local control was approximately 80% at 3–5 years; average overall survival at 5 years was 32%, with data comparable to surgery in the most favourable groups. Toxicity was low (mainly gastrointestinal). Normal liver V0Gy < 30%volume and V30Gy < 18–25%volume were suggested as cut-off values for hepatic toxicity. The good clinical results of the selected papers are counterbalanced by a low level of evidence. However, the rationale to enrol patients in prospective studies appears to be strong.

Paper 2. Qi W et al. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis. Radiotherapy and Oncology 2015. 114;289-295

A systematic review and meta-analysis to compare the clinical outcomes and toxicity of HCC patients treated with charged particle therapy (CPT) with those of individuals receiving photon therapy. Relevant clinical studies were identified through searching databases. Primary outcomes of interest were overall survival (OS) at 1, 3, 5 years, progression-free survival (PFS), and locoregional control (LC) at longest follow-up. 73 cohorts from 70 non-comparative observational studies were included. Pooled OS was significantly higher at 1, 3, 5 years for CPT than for conventional radiotherapy (CRT). PFS and LC at longest follow-up was also significantly higher for CPT than for CRT while comparable efficacy was found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up. Additionally, high-grade acute and late toxicity associated with CPT was lower than that of CRT and SBRT.

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 the specialised commissioning Clinical Effectiveness Team email.

Links to other policies

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

Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma (https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/07/16022_FINAL.pdf)

Clinical Commissioning Policy Statement: Selective Internal Radiation Therapy (SIRT) for the treatment of unresectable primary and secondary liver cancer. (https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/07/b01-psa-sirt.pdf)

Documents that have informed this policy statement

Dionisi F., Widesott L., Lorentini S. & Amichetti M. Is there a role for proton therapy in the treatment of hepatocellular carcinoma? A systematic review. *Radiotherapy and Oncology.* 2014 111: 1–10

Qi W., Fu S., Zhang Q. & Guo X.M. Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis. *Radiotherapy and Oncology* 2015; 114;289-295

Leung H.W.C. & Chan A.L.F. Cost-utility of stereotactic radiation therapy versus proton beam therapy for inoperable advanced hepatocellular carcinoma. *Oncotarget* 2017; 8(43):75568-75576

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Yoon S.M., Ryoo B.-Y., Lee S.J., Kim J.H., Shin J.H., An J.H. et al. Efficacy and Safety of Transarterial Chemoemolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinpoma with Macroscopic Vascular Invasion. *JAMA Oncol* 2018; 4(5):661-669

Yu Y. & Feng M. Radiotherapy for Hepatocellular Carcinoma. *Semin Radiat Oncol* 2018 Oct;28(4):277-287