Clinical Commissioning Policy Statement
Proton Beam Therapy for Oesophageal Cancer in Adults (1874)

Commissioning Position

Summary

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

Information about proton beam therapy in oesophageal cancer

The intervention

Proton Beam Therapy (PBT) provides radiation by delivering a beam of proton particles rather than X-Rays. 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.

Radiotherapy is routinely offered as a curative treatment for oesophageal cancer. However, this can result in significant side effects. PBT may have the potential to cause less damage to surrounding tissues, and therefore cause less acute and late radiotherapy side effects, while maintaining cure rates. However, the current evidence is insufficient to support the routine commissioning of PBT for oesophageal cancer.

Committee discussion

The condition

Oesophageal (gullet) cancer is the 13th most common cancer in the UK, with approximately 10,000 new diagnoses per year. The UK incidence of oesophageal cancer is the second highest in Europe for males, and highest for females. The disease is more common in men than women and is becomes more common with increasing age.

Oesophageal cancer is more common in people living in the most deprived areas. The risk of oesophageal cancer is increased by obesity, alcohol and smoking, as well as chronic acid reflux. The UK mortality rate is the highest in Europe. It is the 4th highest cause of cancer death in males and 7th highest cause of cancer death in females (CRUK, 2018). Survival decreases with increasing age.

Current treatments

Oesophageal cancer is a clinically challenging disease requiring a multidisciplinary approach, often requiring a combination of surgery, radiotherapy and chemotherapy to optimise the chance of cure. The treatment regime will be chosen for an individual patient, taking into account a number of factors, including patient fitness, extent of cancer spread, size of cancer and cancer cell type.

Currently, 19% of patients diagnosed with oesophageal cancer have surgery as their primary curative treatment option (Cancer Research UK, 2018). Chemotherapy and/or radiotherapy are often given to patients before and/or after surgery. The majority of new diagnoses have advanced disease and curative treatments cannot be attempted. For patients who are potentially curable, giving chemoradiation (chemotherapy and radiotherapy together) prior to surgery has been shown to substantially improve the chance of cure (van Hagen et al, 2012),

but is associated with considerable side effects and decline in quality of life (Jacobs et al, 2014). Clinical trials have confirmed that there is an increase in surgical complications, including heart problems and pneumonia following chemoradiation (Bosch et al, 2014; Yang et al, 2018), and an increased chance of death soon after surgery in those aged over 65 (Lester et al, 2017). For some patients, chemoradiation is given alone without surgery as a curative treatment option.

Comparators

Surgery is the primary treatment option for people with oesophageal cancer as it offers the best chance of cure. This may be given in combination with chemotherapy and/or radiotherapy either before or after surgery. Chemoradiation can be given without surgery if surgery is not possible due to medical reasons. It is important to note that only a small proportion of patients can undergo treatment with curative intent, as usually the disease is too advanced. Palliative (non-curative) treatment options include external beam radiotherapy (EBRT), brachytherapy, palliative chemotherapy, stenting and best supportive care.

Clinical trial evidence

There is no high level published clinical trial evidence investigating the superiority of proton beam therapy over current treatment modalities for effectiveness or reduced toxicity in oesophageal cancer.

Three papers were submitted to the Clinical Panel as part of the policy proposition. Two contained the findings from retrospective reviews of patients treated with PBT as well as other modalities of radiotherapy. The third was a meta-analysis which did not explicitly have PBT as a treatment modality and therefore does not add to the evidence on the clinical effectiveness of PBT in treating oesophageal cancer. However, it does add information about the magnitude of benefit of using chemoradiation prior to surgery and highlights the toxicity of the combined modality treatment.

The Panel found insufficient evidence to demonstrate the superiority of proton beam therapy over current standard treatment to justify routine commissioning for this indication.

Paper 1: Lin et al 2017 Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for oesophageal cancer

Retrospective treatment and outcome data from three academic US Institutions is reported for 580 patients who had oesophageal cancer and were treated with surgery and three different radiation modalities –protons, photons delivered by intensity modulated radiotherapy (IMRT) or photons delivered by conformal techniques (using computers to generate a 3D model of the tumour to target the tumour and spare normal tissue as much as possible). Contemporary data from 2007 to 2013 were reviewed. Outcomes of interest included pulmonary, gastrointestinal (GI), cardiac, wound healing complications, length of in-hospital stay and 90-day postoperative mortality.

The authors report that radiotherapy modality was statistically significantly associated with the incidence of pulmonary, cardiac and wound complications and length of stay, with improved outcomes seen in patients who received PBT. The 90-day postoperative mortality was approximatively 4% with photons and 0.9% with protons. Though collaboration across institutions is a strength in allowing the outcomes of a larger cohort of patients treated with various modalities in the same period to be reviewed, the retrospective nature of the analysis and the lack of matched controls potentially allowed the introduction of bias. Another significant source of bias in the study is the fact that the use of the different modalities was not evenly

distributed across all 3 institutions and so the findings could be a function of the institution of treatment and not necessarily the specific radiotherapy modality.

Paper 2: Fang et al, 2018 Lymphocyte-sparing effect of Proton Therapy in Patients with Oesophageal Cancer treated with Definitive Chemoradiation

This paper evaluates the treatment outcomes experienced by retrospectively pairing patients (200 pairs) matched by clinical and disease characteristics as well as two treatment modalities – IMRT or PBT and chemotherapy for oesophageal cancer. The patients were treated in a single institution between 2004 and 2016. The authors wanted to assess if the specific advantages of PBT over IMRT could also be lymphocyte-sparing, as sustained grade 4 lymphopaenia is reported to be prognostic for poorer overall survival and cancer specific outcomes for patients with oesophageal cancer.

The authors report that treatment with IMRT, increased age, and greater planning target volume were associated with increased risk of grade 4 lymphopaenia. They further assert that radiation modality was associated with lymphocyte reduction in patients with tumours in the lower oesophagus but not for those with tumours in the upper or middle oesophagus. They also found that cancer treatment outcomes appeared to be improved by the use of proton beam therapy. There were several study limitations. The study was a retrospective analysis meaning there could be confounding factors that could not be accounted for. A significant limitation is the fact the treatment modality was determined by insurance coverage of the patients meaning that those receiving PBT tended to be older. This could introduce significant bias into the study as older patients may for other reasons have a poorer prognosis and so lead to the blunting of any potential effect of PBT treatment.

Paper 3: Zhao et al (2018) Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or the gastroesophageal junction: a meta-analysis based on clinical trials
The paper presents the findings of a meta-analysis with a total of 866 patients. The two treatment modalities assessed were chemotherapy prior to surgery and chemotherapy and radiotherapy prior to surgery. The modality of radiotherapy given is not further explored, and PBT was not investigated as part of this study. The addition of radiotherapy was shown to improve survival compared to chemotherapy alone, but this was at the cost of significant side effects, hence the rationale for exploring alternative radiotherapy techniques (such as PBT) which may reduce morbidity.

The findings of this meta-analysis do not add to the development of an evidence base assessing the effectiveness or superiority of PBT over other modalities of radiotherapy in the treatment of oesophageal cancer.

Adverse events

The above literature shows that there are fewer adverse events reported with proton beam therapy, specifically a reduction haematological and cardiopulmonary adverse events, compared with photon radiotherapy.

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)

Documents that have informed this policy statement

Lin S.H., Merrell K.W., Shen J. et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for oesophageal cancer. Radiother Oncol 2017 Jun; 123(3):376-381

Fang P, Shirashi Y., Verma V. et al, Lymphocyte-sparing effect of Proton Therapy in Patients with Oesophageal Cancer treated with Definitive chemoradiation. International Journal of Particle Therapy, Winter 2018;4(3): 23-32

Zhao X., Ren Y., Hu Y. et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or the gastroesophageal junction: a meta-analysis based on clinical trials. PLOS 2018; https://doi.org/10.1371/journal.pone.0202185

Additional References

Bosch D.J., Muijs C.T., Mul V.E. et al. Impact on neoadjuvant chemoradiotherapy on postoperative course on curative-intent transthoracic esophagectomy in esophageal cancer patients. Ann Surg Oncol 2014 Feb;21(2):605-11

CRUK website, https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/causes-risks, accessed December 2018

Jacobs M., Macefield R.C., Elbers R.G. et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after oesophageal cancer surgery. Qual Life Res 2014; 23:1097-1115

Lester S.C., Lin S.H., Chuong M. et al. Mulit-institutional analysis of Trimodality Therapy for Esophageal Cancer in Elderly Patients. Int J Radiat Oncol Biol Phys 2017 Jul 15;98(4):820-828

Van Hagen P., Hulshof M.C.C.M., van Lanschot J.J.B. et al. Preoperative chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med 2012; 366: 2074-2084

Yang H., Liu H., Zhu C. et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol. 2018 Sep 20;36(27):2796-2803