e cancer medicalscience

Review Is there any benefit to particles over photon radiotherapy?

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Abstract

Particle, essentially, proton radiotherapy (RT) could provide some benefits over photon RT, especially in reducing the side effects of RT. We performed a systematic review to identify the performed randomised clinical trials (RCTs) and ongoing RCTs comparing particle RT with photon therapy. So far, there are no results available from phase 3 RCTs comparing particle RT with photon therapy. Furthermore, the results on side effects comparing proton and carbon ion beam RT with photon RT do vary. The introduction of new techniques in photon RT, such as image-guided RT (IGRT), intensity-modulated RT (IMRT), volumetric arc therapy (VMAT) and stereotactic body RT (SBRT) was already effective in reducing side effects. At present, the lack of evidence limits the indications for proton and carbon ion beam RTs and makes the particle RT still experimental.

Keywords: hadron, particles radiotherapy, proton, carbon ion beam, cancer

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Published: 09/12/2019

Received: 29/09/2019

Publication costs for this article were supported by e cancer (UK Charity number 1176307).

Introduction

Radiotherapy (RT) after surgery is the second main treatment in solid tumours and far in front of systemic treatment [1]. The use of modern RT with image-guided RT (IGRT), intensity-modulated RT (IMRT), volumetric arc therapy (VMAT) and stereotactic body RT (SBRT) drastically decreased the side effects [2, 3]. In the continuous process for improvement, it was suggested that proton therapy, due to its Bragg peak, and carbon ions, due to the Bragg peak and to a higher radiobiologic effect (RBE), could have a promising future and become the best

practice in radiotherapy. Randomised clinical trials (RCTs) are the gold standard to compare the effectiveness of one therapy over another [4]. Observational studies can only provide some indications about possible advantages from one therapy compared to another. The recent health technological assessment (HTA) report in Belgium [5] could not show any advantage for proton therapy over photon therapy. The Ludwig Boltzmann Institute published a recent systematic review for carbon ion beam RT [6]. They concluded that 'carbon ion beam RT (CIRT) can be described as a potentially less invasive cancer treatment due to its physical properties. Due to the lack of controlled trials, no conclusions may be drawn on the comparative effectiveness of CIRT when compared to conventional photon therapy. As of today, CIRT must be considered as experimental treatment' [6]. We reviewed the literature to identify the results from more recent RCTs on particle RT or ongoing trials.

Method

Because of the high quality and the extensiveness of both the Belgian HTA report [5] and the systematic review of the Ludwig Boltzmann Institute [6], we chose to update these two reports. The Belgian HTA report closed its search in July 2018, the review on CIRT was closed in August 2017. Therefore, we reviewed the literature for systematic reviews and primary studies comparing particle RT with photon therapy in the databases Medline, EMBASE and Cochrane Library since the closing search dates. Single-arm studies are not included in this study. For CIRT, we searched between September 2017 and February 2019; for proton therapy, we searched between August 2018 and February 2019.

Results

We could identify some new observational studies comparing a photon with particle therapy (Figure 1). The overall survival (OS) in breast cancer patients was assessed using the US National Cancer Database between 2004 and 2014. The OS of patients that received proton therapy was not statistically significantly longer than those that received photon therapy [Hazard ratio (HR) 0.85 (95% Confidence interval (CI) 0.68–1.07)] [7].

The preliminary results of a study in non-small cell lung cancer with underlying idiopathic pulmonary fibrosis showed a tendency of non-statistically significant better survival compared to X-ray (p = 0.08) for patients treated with proton therapy, especially in subgroups of GAP stages II and III at Samsung Medical Center in Korea [8]. In unresectable hepatocellular carcinoma, proton RT was associated with improved survival, which may be driven by decreased incidence of post-treatment liver decompensation [Adjusted hazard ratio (AHR) = 0.47 (95%CI 0.27–0.82)] [9].

Proton therapy in patients with chordomas and chondrosarcomas was associated with improved OS at 5 years, respectively, 100% versus 34.1% (p = 0.03) and 75.0% versus 19.1% (p = 0.05) using the US National Cancer Database for the years 2003–2014 [10]. A meta-analysis showed that particle therapy was more effective following surgery for chordoma than conventional RT with higher percentages of survival after 10 years for proton therapy [60% (95% CI, 43%–77%)] and CIRT [45% (95% CI, 36%–55%)] [11].

Proton therapy is associated with improved OS [HR 0.47 (95%CI 0.38–0.58)] compared to photon RT for patients with primary gliomas in the US National Cancer Database [12].

Consecutive patients with oesophageal cancer of the University of Texas MD Anderson Cancer Center receiving proton beam therapy (PBT) were compared with patients receiving intensity-modulated radiation therapy (IMRT). IMRT compared to proton therapy was associated with significantly worse OS [HR 1.45 (95%CI 1.09–1.94)] and worse progression-free survival [HR 1.56 (95%CI 1.19–2.05)] [13]. Shiraishi et al [14] performed a propensity matched-based study on key clinical variables in the same institution and found that PBT is associated with significant risk reduction in grade 4 lymphopenia during neoadjuvant chemoradiation therapy in oesophageal cancer.

A recent systematic review for intracranial benign tumours considers proton therapy as safe [15].

The overview of recently published included non-randomised comparative studies is presented in Table 1.

There are still no results available from RCTs. A review of clinicaltrial.gov in 2018 did not show any phase 3 RCT for carbon ion radiation therapy [16]. On the other side, there are several initiatives at a European level promoting research on particle therapy. The European particle therapy network (EPTN) creates a firm basis for evidence-based particle therapy at the European level. To achieve this, a work package will set up a worldwide unique prospective data registration programme for nine different tumour sites. Such a programme will provide more insights into the current practice across all European particle therapy centres and into the results of particle therapy with regard to radiation-induced toxicity and efficacy in terms of local control and survival [17, 18]. The European network for light ion hadron therapy (ENLIGHT) is another initiative related to hadron therapy (HT), and focuses on patient selection, clinical trials, technology, radiobiology, imaging and health economics [19]. Another European project summarises the data on carbon ion therapy [20]. Different evidence-based clinical trial strategies can be applied to investigate whether the use of protons over photons is justified: the choice of trial design depends on several factors, such as the primary study objective (efficacy versus prevention), the availability of high quality multivariable normal tissue complication probability (NTCP)-models, financial resources and national reimbursement policies [