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Overview

Proton Beam Therapy – the Challenges of Delivering High-quality Evidence of Clinical Benefit

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Abstract

The use of proton beam therapy (PBT) offers the opportunity to improve greater conformality of radiotherapy treatment delivery in some patients. However, it is associated with a high capital cost and the need to build new dedicated facilities. We discuss how the global radiotherapy community can respond to the challenge of producing high-quality evidence of clinical benefit from PBT in adult patients. In the UK, the National Cancer Research Institute-funded Clinical and Radiotherapy Translational group has established the PBT Clinical Trial Strategy Group. An eight-point framework is described that can assist the development and delivery of high-quality clinical trials.

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Key words: Proton beam therapy; external beam radiotherapy; clinical trials

Introduction

Proton beam therapy (PBT) is an important treatment modality in the modern radiotherapy armamentarium. The high capital costs, the need to build new dedicated facilities and the limited high-level evidence of clinical benefit in adult malignancy create a major challenge for the global radiotherapy community. This article will discuss the different approaches that can be used to generate the necessary evidence base.

Background

Despite the continuing rise in gross domestic product spent on healthcare in developed countries, this is failing to keep up with the rapid pace of new treatments in clinical medicine [1]. There is a well-defined pathway for the evaluation of new systemic cancer treatments and in some countries mechanisms are in place to assess their cost-effectiveness and availability. There is typically a

substantial investment in the evaluation of such treatments from the pharmaceutical industry.

By contrast, as new technological developments are introduced, evaluation is initially focused on safety rather than efficacy. Its development and subsequent adoption is commonly based on theoretical or perceived benefit and other incentives, including potential financial benefit, in some healthcare systems. High-quality evidence for clinical benefit is less common and frequently based on observational studies. The generation of high-quality evidence generally requires significant academic funding. In radiotherapy, it is not uncommon for the clinical trials to be carried out after significant adoption of the new treatment approaches.

In the surgical domain, the introduction of robotic surgery centres was achieved by major financial investment relying heavily on charitable and philanthropic sources. However, high-quality randomised clinical trials against the standard of care for this new approach are uncommon. A recent Cochrane review [2] did not find evidence of significant benefit for the use of robotic-assisted prostate cancer surgery. Aggarwal *et al.* [3] recently reported changing patterns of radical

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prostatectomy centres. The increased use of robotic surgery has played a significant role, as well as minimum patient volume requirements, in contributing to the closure of some cancer surgery units. In rectal cancer, Jayne *et al.* [4] reported no evidence of clinical benefit for robotic compared with laparoscopic surgery in an international phase III trial of patients with rectal cancer. The new expensive technology does not always lead to better patient outcomes.

Evaluating Proton Beam Therapy

How can the radiotherapy community respond to the challenge of delivering the high-quality evidence that shows the clinical benefit of PBT? We have a significant track record of generating high-level evidence through practice-changing clinical trials using photons. Many were carried out as two-arm phase III trials. Examples of the breadth and depth of these achievements in the last two decades are summarised in a recent review of five tumour sites (breast, prostate, head and neck, bladder and anorectal) [5]. However, some of these trials required up to a decade to achieve their large sample size to assess long-term outcomes including locoregional control and survival.

Most of the trials in the review evaluated the delivery of three-dimensional conformal external beam photon radiotherapy. However, the widespread introduction of external beam photon-based stereotactic ablative radiotherapy and intensity-modulated radiotherapy (IMRT) has taken place without randomised clinical trials. Retrospective single-centre cohort series lack the rigour of prospective trials, including quality assurance of contouring, planning and treatment delivery. However, for example, the UK carried out two randomised trials of three-dimensional conformal versus IMRT in breast and head and neck cancer, showing reduced toxicity with IMRT [6,7]. Interestingly, the head and neck trial reported an increase in fatigue in the IMRT arm. A possible mechanism for this finding was an increased radiotherapy dose to the cerebellum and brainstem with the use of IMRT [8]. This unexpected but important clinically relevant finding was only identified through standardised prospective toxicity collection and the randomised comparison of IMRT with three-dimensional conformal radiotherapy.

Generating High-quality Evidence

Anthony Zietman has described, in this special issue, the precarious path of PBT development in the USA leading to demands from healthcare providers for high-quality clinical evidence to justify the increased costs [9]. In the case of PBT, the significant capital cost investment and the relatively small number of facilities are key factors driving the demand for high-quality evidence to support its use. Although there is consensus regarding the indications for PBT in paediatric and skull base indications, there remains a significant lack of high-quality clinical evidence for most adult patients and including randomised clinical trials. This article will focus on this adult patient population.

There is no international consensus on the best approach to generate the highest-level evidence for PBT. A model-based approach has been proposed for the selection of patients for PBT [10]. This will be used in the Netherlands to select patients who would probably benefit from PBT, those who should be treated with conventional photons and a minority of patients where there is uncertainty and where (randomised) clinical trials could be used to compare the two treatment modalities.

The emphasis with this approach is to generate high-quality prospective multicentre data for most patients treated with PBT. Some of the challenges associated with this approach include the need for high-quality contemporary normal tissue complication probability models for optimised IMRT. Further variables include the dynamic delivery and motion effects, range uncertainties along with variable linear energy transfer and related variable radiobiological effectiveness with protons.

Other countries are conducting or planning clinical trials. In the USA, there is increasing support from insurers to fund PBT treatment in clinical trials, although the full cost of PBT may not be met. As well as the UK, the Netherlands and Denmark are due to open their first PBT centres in 2018. In the UK, centres will open in Manchester in autumn 2018 and in University College London Hospitals in 2020. As the international critical mass of PBT centres increases, how should we design and deliver high-quality clinical trials? In this issue, Zietman [9] comments that the UK is very well placed to design and deliver the trials that other countries find difficult to perform.

So how can the UK respond to this challenge? In the UK, radiotherapy clinical trials and radiotherapy research is coordinated by the National Cancer Research Institute (NCRI)-funded Clinical and Radiotherapy Translational group (CTRad) [11]. Our aim is to maximise quantity and quality of life for patients receiving radiotherapy by optimising tumour control and minimising toxicity [12]. CTRad has a broad multidisciplinary membership with four workstreams covering the breadth of radiotherapy research from basic science, all phases of clinical trials to new technology and radiotherapy quality assurance. It brings together research active National Health Service professionals, university academics and patients. We hold clinical trial proposals meetings twice yearly to evaluate new concepts and assist in their development before and after funding. However, PBT trial development is more complex and requires special attention [13]. The CTRad PBT clinical trial strategy group was therefore first convened in August 2017 to specifically address proton beam clinical trials development. Collectively, we have identified an eight-point framework to address the challenge (Figure 1):

- (i) Identifying the important scientific question: Across the adult tumour sites there is a need to decide whether clinical trials will focus on the reduction of long-term treatment-related toxicity and/or the improvement of cancer-specific end points including locoregional control or survival. Efficacy trials may consist of dose escalation and/or new agent

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