European Journal of Cancer 62 (2016) 112–123

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Innovative radiotherapy of sarcoma: Proton beam radiation

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Received 16 November 2015; received in revised form 13 April 2016; accepted 14 April 2016

KEYWORDS
Proton beam radiation;
Sarcoma

Abstract This review on proton beam radiotherapy (PBT) focusses on an historical overview, cost-effectiveness, techniques, acute and late toxicities and clinical results of PBT for sarcoma patients. PBT has gained its place among the armamentarium of modern radiotherapy techniques. For selected patients, it can be cost-effective.

1. Introduction and overview

Protons are charged particles with mass that travel a fixed distance in tissue that is related to the accelerating energy. They have physical advantages over X-rays (i.e. photons) by depositing the bulk of their energy in a narrow range at the depth related to the accelerating energy. This nidus of energy deposition is referred to as the 'Bragg Peak', beyond which there is no energy delivered, hence avoiding any radiation (RT) dose to the normal tissues distal to the Bragg Peak (Fig. 1). Protons can deliver similar or higher RT doses to tumour targets with up to 50–60% less integral or 'total body' RT dose compared to the highest technology photon techniques like intensity-modulated RT (IMRT) [1]. The current generation of proton equipment can also perform intensity modulation, which is referred to intensity-modulated proton therapy (IMPT) which yields highly conformal RT doses around the tumour. Because of

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http://dx.doi.org/10.1016/j.ejca.2016.04.015
0959-8049/

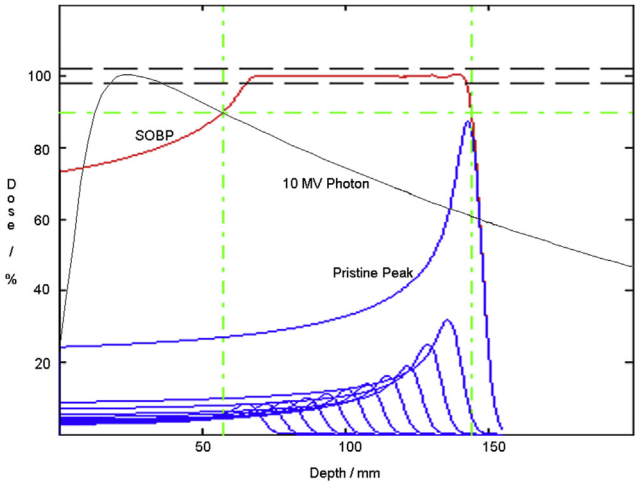

Fig. 1. Proton Bragg peaks of increasing energy and range (courtesy of Hanne Kooy, PhD, Massachusetts General Hospital, Boston, MA).

these properties, proton beam radiotherapy (PBT) is already felt to be optimal for treatment of children with solid tumours who require RT and is being actively studied for multiple tumour types in adults.

Protons are US Food and Drug Administration (FDA) approved for treatment of patients in the United States of America (USA). Medicare and commercial payers provide coverage for PBT for selected and evolving indications. Randomised phase II or III studies comparing IMRT versus PBT are currently in progress or planned for brain tumours and head and neck, non-small-cell lung, hepatocellular, prostate, and breast cancers. There are 14 operating proton centers in the USA and 21 in Europe with other facilities in various stages of construction and planning [2].

Proton facilities have traditionally entailed a particle accelerator (cyclotron or synchrotron) and magnetic beam line(s) to steer protons into three to five treatment rooms, using either fixed beams or (more expensive) rotational gantries. The cost of these facilities is generally in the range of €100–150 million depending on size and configuration of the facility. The cost for PBT has been estimated to be approximately 2.7–3.2 times more than IMRT, much of it related to the upfront capital expenditure and ongoing maintenance. PBT costs otherwise (physician consultation, computed tomographic simulation, treatment planning, and treatment delivery) are comparable [3,4]. Single room proton facilities have recently opened with lower cost, ~€27 million per gantry-based room. These facilities also allow a 'modular' concept, starting with one room, leaving space for additional rooms and beam lines to the accelerator at a later date [5]. Despite the higher initial capital cost, protons have been estimated to be cost-effective for some diseases/anatomic sites, primarily paediatric, because of the reduction in medical costs that would be associated with treatment of late effects related to the larger volumes of normal tissues radiated if treatment were given with photons [6–8].

From a radiobiological point of view, it can be stated that the density of energy deposition along their track in tissue increases as the mass of the charged particle increases. Therefore, the linear energy transfer (LET) for carbon ions is higher than the LET for protons. Clinical proton beams are considered to be of low LET with a comparable relative biological effectiveness (RBE) to photons, designated as 1.10 by the International Commission on Radiation Units and Measurement [9].

Carbon ions are also charged particles, with 12 times the mass of a proton. Physically, their greater mass and charge produce a denser track of ionisation and, biologically, more double-stranded DNA breaks. They have a higher RBE, estimated to be ~2.5 times greater than protons. The RBE, however, changes over the course of the carbon particle track and requires very sophisticated modelling for patient treatment [10]. Carbons do have a sharper lateral penumbra than protons, particularly at deeper ranges. However, they do produce spallation products distal to the Bragg peak, delivering unwanted dose distal to the target. Interesting data from Japan and Germany suggest encouraging results for sacral chordomas, pelvic recurrences of rectal cancer, peripheral non-small-cell lung cancer, and pancreatic cancer [10]. Because the RT schedules for carbon ions have tended to be hypofractionated and not strictly comparable to those generally used with protons, it is unclear in the absence of randomised comparative studies whether the clinical results to date represent a clinical advantage over protons, and, if so, is it related to simply higher dose, the alternative fractionation schedules tested, or reflective of the higher RBE for carbon ions. Higher RBE by itself is not an advantage, proven by the use of neutrons which had a higher RBE but poor physical dose distribution and resulted in much greater normal tissue side-effects than photons [11]. For the higher RBE to have a clinical advantage, the RBE needs to be higher in the tumour compared to the surrounding normal tissue and the normal tissue has to relatively spared from greater RT damage by the physical and/or biologic properties of the heavier charged particle. Randomised studies comparing carbon ions with protons are underway in Heidelberg, Germany looking at skull base chordomas and chondrosarcomas, sacral chordomas, and glioblastomas. Some facility designs allow delivery of both protons and carbon ions, but these are more costly than a proton facility. The cost of a combined carbon-proton facility was estimated in 2010 as €138 million compared to €94.9 million for a proton-only facility and €23.4 million for a photon-only facility [4]. Currently, carbon ion therapy is not FDA approved in the USA and therefore considered investigational.