Treating Childhood and Adolescent Tumors with Proton Beam Therapy

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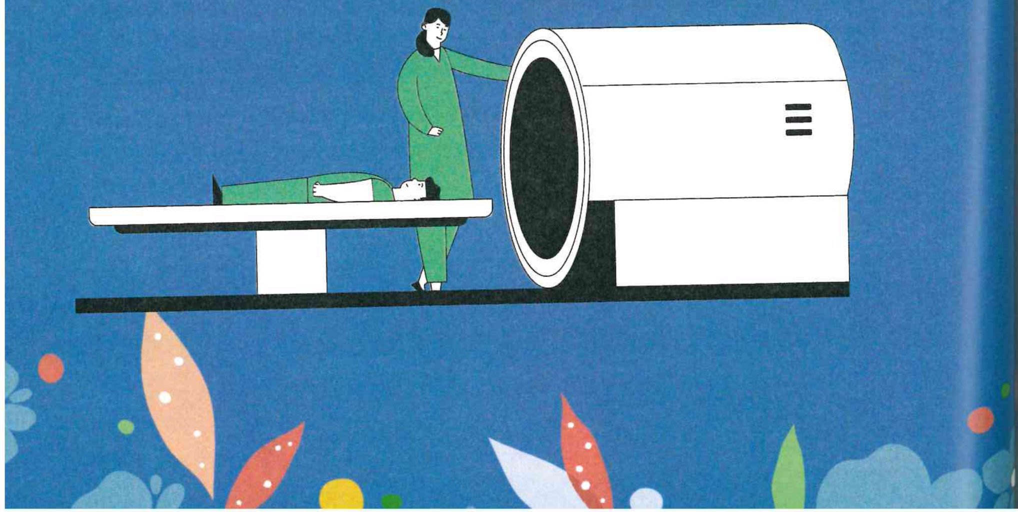
1 Background



Radiotherapy and proton beam therapy

Radiotherapy is highly effective and proficient at killing cancer cells. However, radiotherapy simultaneously kills non-cancerous(normal) cells, and can damage normal tissues which are included in the radiotherapy field.

Therefore, to fully exploit radiotherapy it is essential to safeguard normal tissues and minimize side effects. The development of radiotherapy has a history of continuing efforts to perfect a method that can selectively treat cancer cells while protecting normal tissues, and proton beam therapy (PBT) is the fruit of such attempts. The pivotal advantage of PBT is that it allows the radiation dose for cancer cells to be increased and the dose for normal tissues to be reduced. Such a feat is achievable because protons have distinct physical characteristics from conventional radiation(hereinafter referred to as X-rays). Specifically, protons do not penetrate further into the tissue after reaching a certain depth, unlike X-rays that pass through tissue.

Although scientists initially thought of using protons to treat cancer in 1946, it was only in the early 1990s that proton facilities were constructed in hospitals in the United States, and were used for the first time to treat cancer.

Japan, Germany, Belgium, and the US manufacture PBT devices, and currently, seven manufacturers in these countries supply PBT devices to at least 76 institutions worldwide[1]. The number of operational PBT facilities available for cancer treatment is expected to increase to 110 by 2025[2]. By the end of 2018, 18,000 patients received PBT worldwide, suggesting that PBT had been successfully in delivered to cancer and patients recognized as safe treatment[3].

However, the installation cost of a PBT facility inside a hospital is at least 3-4 times higher than that of an X-ray treatment facility and the maintenance cost of a PBT facility is also considerably high[4]. Therefore, the cost of PBT is inevitably high, and substantial medical evidence, as well as clinical benefits over X-ray-based therapy, is needed to warrant PBT. Covering for the cost of PBT at a national level would also lead to a significant socio-economic burden. Therefore, we need to deliberate whether PBT, considering its high cost, is suitable for all types of cancer within a limited health budget; the answer to this question would vary greatly depending on the medical and economic welfare of each country. This topic will be addressed later on in more detail in the "Cost-effectiveness and social implications of proton beam therapy" section. Fortunately, PBT is already covered by the National Health Insurance of Korea(Ministry of Health and Welfare notice 2015-145, September 1, 2015), and thus the economic burden on patients receiving PBT in Korea is not high. However, PBT is an expensive treatment, requiring huge investments for its implementation and operation; it may majorly contribute to the increment in the healthcare expenses borne by the government. Therefore, it is necessary to realize in which cases PBT has true benefits compared to other methods of radiotherapy.

In Korea, choosing a treatment modality is relatively unrestricted in comparison to countries such as the United Kingdom, Canada, and Australia where medical care is covered mostly by national taxes. In light of this, medical institutions and experts, as well as patients, must clearly understand both the indications and drawbacks of PBT to make appropriate decisions for optimal treatment.

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1) Penfold S. A positive move: Proton therapy in Australia. Australasian Physical & Engineering Sciences in Medicine 2018;41:1-2.
2) https://www.ptcog.ch/index.php/facilities-in-operation
3) https://www.ptcog.ch/index.php/patient-statistics
4) Peeters A, Grutters JP, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother Oncol. 2010;95(1):45-53.

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2 Introduction

Physical properties of proton beam

PBT can minimize the side effects that may occur during radiotherapy by reducing the amount of radiation to the normal tissues surrounding the tumor. Unlike ordinary radiation, which is absorbed in the highest amount near the skin and dwindles as it travels in the body, the proton beam shows a phenomenon called “Bragg Peak.” “Bragg Peak” is a characteristic sharp increase in dose near the end of the proton beam range. The proton beam shows a constant low dose distribution on the way to the tumor, creates a Bragg Peak over the tumor, and then immediately disappears after delivering a high dose of energy to the tumor. The Bragg Peak can be adjusted according to the size of the tumor being treated, a phenomenon known as “Spread-out Bragg Peak (SOBP)”(Figure 1). As a result, the protons deliver only a small amount of energy at the site of penetration and deliver the greatest amount

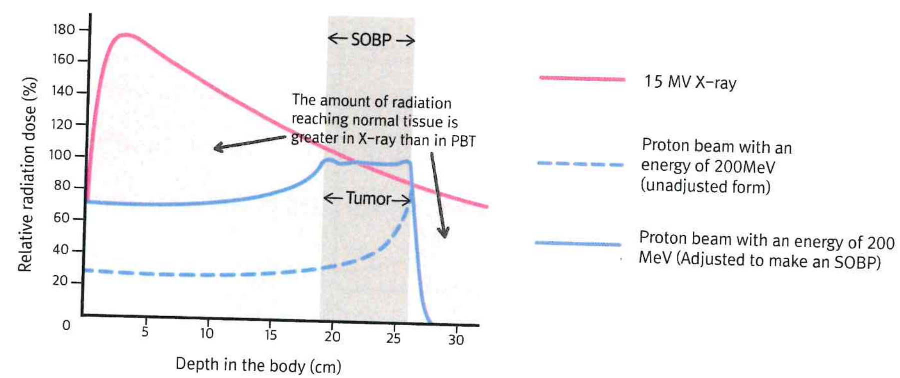

Figure 1 Comparison of radiation dose distribution between X-ray and proton beam

of energy at the tumor site. Beyond the Bragg Peak, there is a sharp fall in the radiation dose. Therefore, PBT can better focus the amount of radiation distributed to the normal tissues surrounding the tumor compared to X-ray-based therapy, thus resulting in fewer complications in the normal tissues.

Comparison between proton beam therapy and carbon ion therapy

In PBT, SOBP shows a clearer drop at the border between normal and tumor tissues than carbon ion therapy, which is another type of particle therapy. In the graph, the green line that indicates carbon particle therapy shows a characteristic dose tail caused by nuclear fragmentation at the

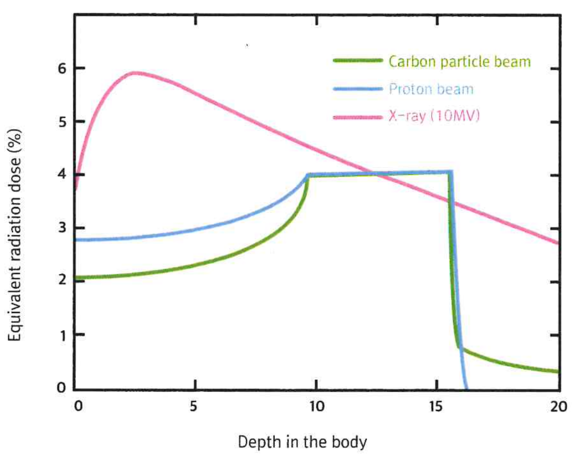

Figure 2 Comparison of radiation dose distribution between proton and carbon particle beams in the body[5)]

distal end of SOBP(Figure 2). Moreover, PBT has similar biologic effect to conventional X-ray, whereas carbon particle beam has a biological intensity three times greater than that of conventional X-ray.

Thus, PBT and carbon particle therapy can be used selectively on distinct occasions depending on the type of tumor and the purpose of treatment. For example, the chief use of PBT is to treat childhood and adolescent cancers where it is relatively more important to protect the normal tissue than provide radiation with a high biological intensity. In contrast, carbon particle therapy has more potent killing effects than PBT and is used when the tumor is large and cancer cells are resistant to conventional radiotherapy.

Methods to generate medical proton beams

Scattering and scanning modes are the two different methods of generating particle beam used in proton or carbon particle beam therapy. The scattering method involves a pencil lead-like thin beam and uses a scattering tool to evenly distribute the proton across the area of treatment. In order to distribute the proton beam in the shape of the tumor, the irradiation area is first shaped using a shielding material made

5) Modified from Figure 23.2 SOBP of Proton, Carbon, and X-ray: Perez & Brady's Principle and Practice of Radiation Oncology, 7th Edition, Chapter 23 Carbon Ions. ISBN 9781496386793, 2013. © 2019 Wolters Kluwer of brass. The depth at which proton penetrates is controlled by an acrylic compensator.

Conversely, the scanning mode involves using a magnetic device to control the direction and location of the beam, producing a dose distribution in a way similar to painting a canvas with various colors and shapes. Those particular features of the scanning mode do not require shielding material or a compensator. As a result, the number of neutrons generated from the proton beams that collide with the shielding material is reduced, and fewer microscopic neutrons reach the patients' body.

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Cost-effectiveness and social implications of proton beam therapy