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Review paper

History of hadron therapy accelerators

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ABSTRACT

In the last 60 years, hadron therapy has made great advances passing from a stage of pure research to a well-established treatment modality for solid tumours. In this paper the history of hadron therapy accelerators is reviewed, starting from the first cyclotrons used in the thirties for neutron therapy and passing to more modern and flexible machines used nowadays. The technical developments have been accompanied by clinical studies that allowed the selection of the tumours which are more sensitive to this type of radiotherapy. This paper aims at giving a review of the origin and the present status of hadron therapy accelerators, describing the technological basis and the continuous development of this application to medicine of instruments developed for fundamental science. At the end the present challenges are reviewed.

Introduction

Hadron therapy (often written as “hadron therapy” and also known as “particle therapy” or “ion beam therapy”) is a specific type of oncological radiotherapy, which makes use of fast hadrons (non-elementary particles made of quarks and antiquarks) to obtain better dose depositions when compared with the ones of X-rays used in conventional radiotherapy.

Today only two types of hadrons are used to treat solid tumours – protons and fully stripped carbon ions – but other hadrons, such as neutrons, charged pions, antiprotons, helium ions (i.e. alpha particles) and other light ions nuclei (like lithium, oxygen, up to silicon ions) have been either used or planned to be used for the treatment of tumour patients. Protons are nowadays an important tool in clinical practice due to the about fifty hospital-based centres in operation and to the continuously increasing number of facilities proposed worldwide. Very promising results have been obtained with carbon ion beams, especially in the treatment of specific radioresistant tumours, but clinical trials are still needed to define the tumours types to be treated and to optimize the protocols.

Hadron therapy is a multi-disciplinary field in which physics, biology, medicine and engineering meet. The continuous technological improvements of medical particle accelerators are the result of the development of research accelerators used in nuclear and high-energy physics. Moreover rotating gantries, which deliver the clinical beam to the patient from different angles, have been developed for both protons and carbon ions.

In this paper a review of the origin and present status of hadron therapy accelerators is presented by describing the technological basis and the continuous improvements in an historical perspective. In this context it's important to underline that a modern hadron therapy facility is not only made of its accelerator. Indeed, the cost of the accelerator can be estimated to be 20–30% of the overall cost of the high-technology part of a multi-room centre, the rest being the cost of the building, of the beam lines and of the equipment of 3–4 treatment rooms, of the diagnostic tools and of the control and treatment planning systems.

Even if these subjects are not addressed in this paper, it is worth mentioning that the history of hadron therapy accelerators has moved on together with the development of precise and highly selective imaging technique such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). Furthermore, the improvement of the computational tools has allowed the development of more robust and flexible treatment planning systems.

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X-rays developments and first treatments with hadron beams

Robert “Bob” Wilson is the father of hadron therapy for his 1946 seminal paper [1] in which, after realizing that depth-dose profiles of protons in matter have significant increase at the end of their range – the so-called “Bragg peak” – he proposed to make use of this property for treating deep seated tumours. Nevertheless, this important observation would not have developed into a very effective and not invasive way of treating some type of solid tumours if three important discoveries and inventions had not been made in the fifty years preceding Wilson's work.

The first one was the discovery of the X-rays by Wilhelm Conrad Roentgen, who, at the end of 1895, detected for the first time the effect of a new type of radiation on a fluorescent sheet while he was doing a series of experiments on electrons, accelerated in a glass tube by a potential difference of about 20 kV. His discovery was published at the end of December 1895 [2]. On 13th January 1896, Röntgen demonstrated the properties of X-rays (as he called this new kind of rays, “*for the sake of brevity*”) to Kaiser Wilhelm II.

With the discovery of X-rays, Röntgen originated a series of extraordinary developments not only in fundamental physics, but also in medical diagnosis and cancer treatment. Only three weeks later, in Liverpool, the physicians Robert Jones and the physicist Oliver Lodge used an X-ray radiograph to image a bullet embedded in a boy's hand [3]. In parallel to diagnostic applications, X-rays were also used in tumour therapy. At the end of January 1896 in Chicago, Emil Grubbe irradiated (without success) the breast of a woman [4]. The irradiation of a patient with a stomach cancer by Victor Despeignes in Lyon is documented in an article of July 1896 [5]. One year later the Viennese doctor Leopold Freund used X-rays to successfully cure a skin tumour in a five-year-old girl [6].

By the beginning of the twentieth century all laboratories and many hospitals had electron tubes similar to Röntgen's one (Fig. 1). They were the precursors of accelerators for radiotherapy and X-ray imaging.

The second fundamental contribution to tumour cure with radiations was the invention of the electron linac, which arose from the association of three friends: the American physicist William Webster Hansen and the two brothers of Irish origin, Russell and Sigurd Varian. In 1937 the three of them – working in a basement in the Stanford physics department, with $100 funding from the university – succeeded in constructing their first working “klystron”, a device that can produce megawatt microwave impulses. After the war Bill Hansen built an electron linear accelerator to bombard nuclei and study them. Hansen chose a frequency of 3 GHz and produced microwaves both with a klystron and with a generator known as “magnetron” in which, applying the same principle of the klystron but adding a strong magnetic field, the electron beam followed a circular orbit. His first linac was 90 cm long and in 1947 accelerated electrons to 1.7 MeV. In 1948 the three friends founded Varian Associates, a company to manufacture klystrons and linear accelerators.

Today Varian Medical Systems is still the leading company producing radiotherapy equipment and, in particular, therapeutic electron linacs. In 2012 Varian had a 50% share of the total market distributing more than 1000 linacs. Overall there are more than 20,000 electron linacs at present that, in the advanced world, irradiate (with the X-rays produced by 4–10 MeV electrons hitting high density and high Z materials) about 2000 patients every 1 million inhabitants.

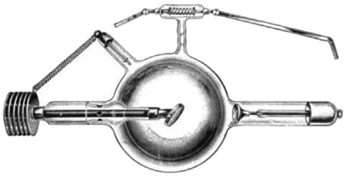

Figure 1. At the beginning of the twentieth century Crookes' tubes like this one were the standard sources of X-rays (taken from Ref. [7]).

The third event, that opened the way to hadron therapy, was in 1929 the invention of the cyclotron by Ernest Orlando Lawrence. On April the 1st 1929 in Berkeley, Lawrence had the idea of adding a magnetic field to the linear accelerator recently proposed by Wideröe [8]. The first cyclotron had a diameter of 4 inches (about 10 cm), and was able to accelerate protons up to 80 keV. In few years many cyclotrons were built at Berkley and in 1932 Lawrence and collaborators were able to produce a 4.8 MeV proton beam with their 27-inch cyclotron (Fig. 2) [9].

The invention of the cyclotron was a milestone not only in the development of nuclear physics but also for its use in medicine. In 1935 Lawrence asked his brother John, who was a medical doctor, to join him in Berkeley and use the new 27-inch cyclotron accelerator for medical purposes. Although the principal activity of the laboratory was nuclear research, Lawrence was indeed very interested in medical applications and several cyclotron-produced radionuclides were soon used in studies of physiology, both in animals and humans. The foundations of the three important applications of radioisotopes still relevant today – radiotracing in biology, diagnosis in medicine, and brachytherapy – were laid down at that time.

The first hadrons used in radiotherapy, soon after the construction of the first cyclotron by Lawrence and Livingstone, were fast neutrons. In 1936 the first experimental studies were published by the Lawrence brothers [10] and, at the end of September 1938, the first patients were treated with neutrons, produced with the more powerful 37-inch cyclotron which accelerated deuterons up to 8 MeV.

The fast neutrons, used for therapy, were produced by bombarding a beryllium target. In the traversed tissues the neutrons transfer their energy mainly to highly ionizing protons, which have a value of the “Linear Energy Transfer” (LET) that is much larger than the one of the electrons put in motion by MeV photons produced by linacs. This is a favourable feature when treating “radioresistant” tumours, i.e. tumours tissues that are less sensitive to X-rays than the surrounding normal tissues. However neutron beams have an unfavourable depth-dose distribution and are difficult to collimate; these are the reasons for which they are no longer used

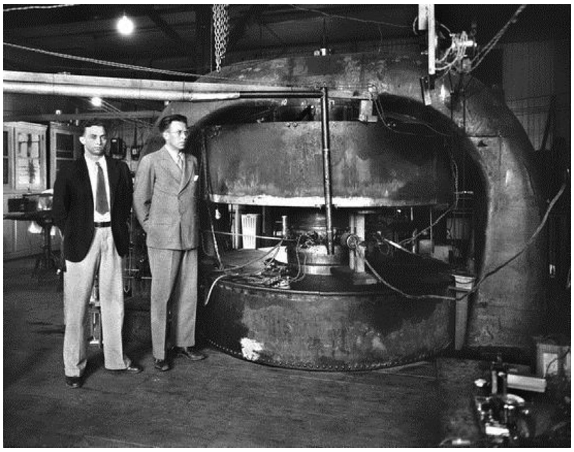

Figure 2. E. O. Lawrence (right) and M.S. Livingston (left) standing beside the 27-inch cyclotron (Berkeley Lab).