Chapter

History and Overview of Proton Therapy

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Abstract

The use of proton therapy in oncology is not a new idea. The unique physical properties of protons and potential advantages in radiation therapy were initially recognized in the 1940s. Since the first patients were treated in the 1950s, technology and clinical applications have evolved as evidenced by the increasing number of proton therapy centers and patients being treated throughout the world. This chapter will review the history of proton therapy providing a detailed overview of the cyclotron and synchrotron techniques used and how they have advanced with time.

Keywords: proton therapy, charged particle, history, oncology

1. Introduction

Radiation therapy is a standard local treatment in oncology with nearly 50% of cancer patients receiving radiation at some point in their disease course [1, 2]. This is most often used in combination with surgery, chemotherapy and, more recently, immunotherapy [3, 4]. The underlying principle of using ionizing radiation in oncology is based on its transfer of energy to tissues resulting in DNA damage, the acquisition of mutations that disrupt cell physiology and cell death [5, 6]. Determining the optimal radiation delivery modality, dose, treatment strategy and combination of other therapies have been an active area of investigation for decades [7, 8]. Advances in physics, radiology and radiobiology have allowed the field of radiation oncology to evolve resulting in more favorable clinical responses while minimizing toxicity to normal structures [9].

Several discoveries near the end of the 19th century gave birth to the discipline of radiation sciences. At Würzberg University in Germany, Wilhelm Conrad Roentgen's experiments using a cathode-ray tube led to the discovery of x-rays. His seminal findings that a "ray" can pass through most solid objects, but not bone or metal is, of course, still a central tenet in radiology practice today. The discovery of radioactivity by Henri Becquerel and identification of polonium and radium by Marie Curie soon followed that resulted in scientific advances that would lead to a new era bridging the gap between modern technology and medical sciences [10].

The discoveries made by Roentgen, Becquerel and Curie laid the groundwork for industries in healthcare to begin the production of devices to generate high-energy beams for diagnostic and therapeutic purposes throughout the early to mid-20th century. The roots of proton therapy can be traced to these initial technological undertakings [11]. In more recent years, radiation oncology entered a new era with the advent of three-dimensional (3D) treatment planning systems. This allowed physicians, physicists and dosimetrists to computationally derive solutions to prior limitations in external beam radiation therapy planning. Intensity modulated radiation therapy is one such fundamental advance that optimizes conformal radiation delivery to a 3D target volume [12]. This widespread use of conformal radiation therapy with a focus on increasing tumor cell effect has revamped interest in the applications of proton therapy in oncology [13].

For this reason, this chapter will review the history and evolution of proton therapy to provide a framework for the later discussion of treatment planning, efficacy and future directions.

2. Proton discovery

Atoms are comprised of subatomic particles with a unit positive charge (protons), negative charge (electrons) and neutral charge (neutrons). Ernest Rutherford's initial studies on subatomic particles found that α and β rays derived from uranium and helium atoms consist of nuclei of α rays. These findings were substantial because they led to studies that revealed that when nitrogen gas is irradiated by an α particle it produces oxygen atoms and the nuclei of hydrogen atoms, which have a net positive charge. This unit with a net positive charge was termed the proton. Rutherford concluded that a nitrogen atom is composed of positively charged protons and negatively charged electrons, and that a nitrogen atom can be converted to oxygen and a proton (hydrogen atom nucleus) [14, 15]. Following the discovery of the proton, James Chadwick at Lawrence Berkeley Laboratory discovered the neutron and studies subsequently began assessing potential applications of fast neutron radiation therapy [16–18].

3. Protons vs. photons

Photons are high-energy x-rays and are the traditional modality used in external beam radiation therapy. Photon therapy typically relies on several beam directions to achieve a uniform dose distribution to a target volume in order to treat disease and minimize toxicity to structures at risk. This is because, within tissues, photons exhibit a decreasing energy deposition with higher depth. Proton therapy, a form of charged-particle therapy, differs from photon therapy regarding energy transfer within tissues as proton velocity is inversely proportional to the energy transferred within tissues [19]. Therefore, by reducing their velocity based on electromagnetic interactions with atoms in tissue, the higher energy they can transfer to a pre-determined depth.

This concept of a "peak" was initially discovered by William Bragg in the early 1900's and is known as the "Bragg peak." The Bragg peak, or energy deposition as a function of tissue depth, has potential to deliver higher doses to a target volume while maintaining dose-constraints of nearby critical structures [20]. The potential for increased tumor cell effect while reducing dose to structures at risk is one of the underlying factors in the medical interest of proton therapy.

4. Early stages of proton therapy in medicine

In 1946, Robert Wilson was the first to recognize the potential medical applications of proton therapy [21]. By utilizing the concept of the Bragg peak and knowledge that protons exhibit decreasing velocity as they travel through tissue, Wilson postulated that these physical properties could be advantageous for targeting disease deep within healthy tissue. Needless to say, his idea was well ahead of the time. Wilson stated,

> *"These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well-defined small volumes within the body will soon be feasible" [21].*

Of course, Wilson highlighted concepts that are still fundamental in the modern practice of radiation oncology.

In 1954, the first patients were treated at Lawrence Berkeley Laboratory with proton therapy using a cross-firing technique with a 340 MeV proton beam [22]. The target was the pituitary gland for hormone suppression in patients with metastatic breast cancer. In these patients, the Bragg peak was not used due to difficulties in approximating the range. This technique was able to concentrate the dose to the pituitary with a single-fraction. In 1958, a three-fraction schedule was utilized for pituitary radiation [23].

The Gustav Werner Institute in Uppsala, Sweden was the first to incorporate the Bragg peak and concepts proposed by Robert Wilson into proton therapy studies. A 185 MeV cyclotron was used to treat the initial set of patients in the late 1950s to early 1960s, which included work by stereotactic radiosurgery pioneer Lars Leksell [24–27]. Interestingly, high doses per fraction were used due to time constraints at the cyclotron. The spread-out Bragg peak with a rotating technique was used in order to produce range-modulated beams [28, 29]. Together, the use of protons as a "neurosurgical tool" for "cerebral surgery" was used to treat dozens of patients during this time [30]. The applications of delivering larger doses of intracranial radiation to precisely defined targets are still prominent today. The innovation of Larsson, Leksell and others is best demonstrated by quoting their 1958 Nature article that says,

> *"with high-energy protons a sharply delimited lesion can be made at any desired site in the central nervous system" [30].*

In collaboration with Massachusetts General Hospital, the Harvard Cyclotron Laboratory launched their program in the 1960s using a 160 MeV cyclotron also incorporating the Bragg peak proposed by Wilson [31]. Again, neurological targets were identified for radiosurgery, with a focus on pituitary irradiation [32]. Patients with conditions such as acromegaly and Cushing's disease had their skull placed in a head frame in order to target the "beam spot" within the sella turica [32]. The authors reported satisfactory results, which included the reduction of complications with added experience. Their success gained recognition and received funding by agencies such as the National Cancer Institute.

In the early 1970s, the Department of Radiation Oncology at Massachusetts General Hospital expanded proton therapy to patients with sarcoma, head and neck cancer and melanoma [33–35]. In 1979, another oncologic advance developed by this department was the idea of the use of proton therapy for men with prostate cancer [36]. Seventeen men with localized prostate cancer were treated with boost proton therapy. During the 12 to 27-month follow-up, 16 of these patients were locally controlled. In general, side-effects were mild, which included urethral stricture in two patients. Minimal rectal toxicity was reported in follow-up.

Throughout the 1970s, Russia initiated several proton therapy programs. These occurred at several institutions including the Joint Center for Nuclear Research, the Institute of Theoretical and Experimental Physics and a collaboration between the Petersburg Nuclear Physics Institute and the Central Research Institute of Roentgenology and Radiology. The Institute of Theoretical and Experimental Physics was the largest of these programs [37], which used a 7.2 GeV proton synchrotron. Using the Bragg peak, pituitary irradiation of breast and prostate cancer patients was performed. By 1981, nearly 600 patients with breast and prostate cancer as well as others with bone metastases, lymph node malignancies, osteosarcoma, melanoma, cervical cancer and eye tumors were treated [37, 38]. This expanded the applications of proton therapy not only for pituitary irradiation, but for several extracranial conditions.

Although Japan is a large user of proton therapy today [39], they had only treated 11 patients with proton therapy alone and 18 patients with a proton boost into the early 1980s [40]. Their efforts took place at the National Institute of Radiological Sciences in Chiba and subsequently at the Particle Radiation Medical Science Center in Tsukuba. Since that time, proton therapy has greatly expanded in Japan with more than 10 centers available for treating patients [39].

5. Expansion of proton therapy

Throughout the 1980s, proton therapy was primarily used for intracranial stereotactic radiosurgery [41]. However, clear advantages of proton therapy were demonstrated in treating patients with conditions with otherwise limited therapeutic options such as chondroma and choroidal melanoma [42–44]. While proton therapy centers had provided benefit to many patients throughout the world, in the 1970s and 1980s, a severe limitation was that they were located at research institutions. This limited the number of patients being treated since these centers had several ongoing research projects that required beam time. Moreover, it inconvenienced both the medical team and patients due to the requirement to travel to the research centers for treatment.

In 1990, the first proton therapy center based out of a hospital was built at the Loma Linda University Medical Center [45]. This was an undertaking that required Fermilab to develop the synchrotron and the Harvard Cyclotron Laboratory to design the gantries. Soon after its implementation, Loma Linda University Medical Center established itself as a leader in proton therapy. The large number of patients treated during the 1990s at Loma Linda provided evidence that proton therapy had the potential to be an important modality in radiation oncology. Since its operation began, Loma Linda University Medical Center has remained a prominent proton therapy institute and research center [46].

Following the initial success of Loma Linda University Medical Center, the proton therapy center at the Harvard Cyclotron Laboratory was transferred to the Massachusetts General Hospital for clinical use in 2001. Around this time, Indiana University also implemented a hospital-based proton therapy center. This increase in hospital-based proton therapy centers and technological advances allowed radiation oncology departments to recognize the possibility of widespread use that could lead to continued advances in clinical settings. This is evidenced by a drastic increase over time in the number of proton therapy facilities worldwide [47].

6. Evolution of proton therapy technology

As detailed above, initial proton therapy centers utilized a cyclotron, which circulates particles using an electromagnetic field and accelerates them based on an energy selection system [48]. This process continually produces a single batch of protons. The major advance of synchrotron systems was the ability to accelerate particles of different energy levels, which produces pulses of protons and results in a more energy efficient process [48].

Initially, cyclotron and synchrotron systems produced beams the width of a "pencil", which made treating larger targets difficult. Thus, scattering foils were used to broaden beam width. However, use of a single scattering foil was insufficient due to limitations in achieving reproducible beam flatness. In the late 1970s, the double scattering system was incorporated at the Harvard Cyclotron Laboratory, which could accurately reproduce beam flatness to homogenously cover larger treatment volumes [49]. This required materials with specific physical properties to ensure a beam of desired width [50].

At the Gustav Werner Institute in Uppsala, Sweden, Larsson introduced the concept of magnetic beam scanning to replace the previously used scattering techniques [25]. Many types of magnetic beam scanning techniques have been proposed. Initially, spot scanning was developed, but 3D continuous scanning soon became widely used. Technological advances in 3D beam scanning techniques were later developed that produced more conformal beams that were highly effective at reducing the dose to structures at risk [51]. As the advent of intensity modulated radiation therapy changed the modern practice of radiation oncology, intensity modulated proton therapy has become increasingly used at proton centers. The physical properties of protons and ability to modulate dose along the beam axis has highlighted the advantages of intensity modulated proton therapy and its ability to improve tumor cell effect while sparing structures at risk when compared to photon therapy [52].

7. Conclusion

The advantages of proton therapy were recognized early in its history by Wilson as well as the early treatment centers at Lawrence Berkeley Laboratory, the Gustav Werner Institute and the Harvard Cyclotron Laboratory. Since proton therapy is particularly attractive for cases where there is a risk of important structures being irradiated, intracranial targets, such as the pituitary gland, were the first to be treated [22, 23]. This evolved from single fraction to multiple fraction treatments [23]. The benefits of sparing nearby, sensitive structures were later highlighted by treating chondroma and choroidal melanomas [35, 42–44]. In fact, these became some of the most commonly treating conditions at the Harvard Cyclotron Laboratory.

Proton therapy has demonstrated more favorable dose distributions when compared to photon therapy in several tumor types [53–55]. However, it is unclear if these superior dose distributions will translate to better outcomes and, if so, the patients who would receive the most benefit will need to be identified. Moreover, hospital facilities will need to weigh these potential benefits with the financial and space requirements of a proton beam. Although there is strong evidence for advantages in pediatric patients [56], there continues to be debate in other diseases such as prostate cancer [57]. Clinical trials are ongoing to identify the optimal radiation modality in various clinical scenarios [58].

Conflict of interest

The Authors declare no conflict of interest.

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References

[1] Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. Lancet Oncology. 2006;7(7):584-595. DOI:10.1016/S1470-2045(06)70759-8.

[2] Barton MB, Jacob S, Shafiq J, Wong K, Thompson SR, Hanna TP, Delaney GP. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiotherapy and Oncology. 2014;112(1):140-144. DOI:10.1016/j.radonc.2014.03.024.

[3] Lichter AS, Lawrence TS. Recent advances in radiation oncology. New England Journal of Medicine. 1995;332(6):371-379. DOI:10.1056/NEJM199502093320607.

[4] Tang C, Wang X, Soh H, Seyedin S, Cortez MA, Krishnan S, Massarelli E, Hong D, Naing A, Diab A, Gomez D, Ye H, Heymach J, Komaki R, Allison JP, Sharma P, Welsh JW. Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunology Research. 2014;2(9):831-838. DOI:10.1158/2326-6066.CIR-14-0069.

[5] Roos WP, Kaina B. DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis. Cancer Letters. 2013;332(2):237-248. DOI:10.1016/j.canlet.2012.01.007.

[6] Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461(7267):1071-1078. DOI:10.1038/nature08467.

[7] Ellis F. Dose, time and fractionation: a clinical hypothesis. Clinical Radiology. 1969;20(1):1-7. DOI:10.1016/s0009-9260(69)80043-7.

[8] Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nature Reviews: Cancer. 2011;11(4):239-253. DOI:10.1038/nrc3007.

[9] Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. Nation Reviews: Cancer. 2004;4(9):737-747. DOI:10.1038/nrc1451.

[10] Reed AB. The history of radiation use in medicine. Journal of Vascular Surgery. 2011;53(1 Suppl):3S–5S. DOI:10.1016/j.jvs.2010.07.024.

[11] Tian X, Liu K, Hou Y, Cheng J, Zhang J. The evolution of proton beam therapy: Current and future status. Molecular and Clinical Oncology. 2018;8(1):15-21. DOI:10.3892/mco.2017.1499.

[12] Bortfeld T. IMRT: a review and preview. Physics in Medicine and Biology. 2006;51(13):R363–R379. DOI:10.1088/0031-9155/51/13/R21.

[13] Yuan TZ, Zhan ZJ, Qian CN. New frontiers in proton therapy: applications in cancers. Cancer Communications (London, England). 2019;39(1):61. DOI:10.1186/s40880-019-0407-3.

[14] Cohen M. Rutherford's curriculum vitae, 1894-1907. Medical Physics. 1995;22(6):841-859. DOI:10.1118/1.597487.

[15] Todd N. A brief history of Lord Rutherford's radium. Notes and Records of the Royal Society of London. 2014;68(3):279-300. DOI:10.1098/rsnr.2013.0070.

[16] Catterall M, Rogers C, Thomlinson RH, Field SB. An investigation into the clinical effects of fast neutrons. Methods and early observations. British Journal of Radiology. 1971;44(524):603-611. DOI:10.1259/0007-1285-44-524-603.

[17] Chadwick MB. Neutron, proton, and photonuclear cross-sections for radiation therapy and radiation protection. Radiation and Environmental Biophysics. 1998;37(4):235-242. DOI:10.1007/s004110050124.

[18] Chadwick MB, Barschall HH, Caswell RS, DeLuca PM, Hale GM, Jones DT, MacFarlane RE, Meulders JP, Schuhmacher H, Schrewe UJ, Wambersie A, Young PG. A consistent set of neutron kerma coefficients from thermal to 150 MeV for biologically important materials. Medical Physics. 1999;26(6):974-991. DOI:10.1118/1.598601.

[19] Newhauser WD, Zhang R. The physics of proton therapy. Physics in Medicine and Biology. 2015;60(8):R155–R209. DOI:10.1088/0031-9155/60/8/R155.

[20] Brown A, Suit H. The centenary of the discovery of the Bragg peak. Radiotherapy and Oncology. 2004;73(3):265-268. DOI:10.1016/j.radonc.2004.09.008.

[21] Wilson RR. Radiological use of fast protons. Radiology. 1946;47(5):487-491. DOI:10.1148/47.5.487.

[22] Lawrence JH. Proton irradiation of the pituitary. Cancer. 1957;10(4):795-788. DOI:10.1002/1097-0142(195707/08)10:4<795::aid-cncr2820100426>3.0.co;2-b.

[23] Lawrence JH, Tobias CA, Born JL, Mc CR, Roberts JE, Anger HO, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. Cancer Research. 1958;18(2):121-134.

[24] Larsson B. Blood vessel changes following local irradiation of the brain with high-energy protons. Acta Societatis Medicorum Upsaliensis. 1960;65:51-71.

[25] Larsson B. Pre-therapeutic physical experiments with high energy protons. British Journal of Radiology. 1961;34:143-151. DOI:10.1259/0007-1285-34-399-143.

[26] Leksell L, Larsson B, Andersson B, Rexed B, Sourander P, Mair W. Lesions in the depth of the brain produced by a beam of high energy protons. Acta Radiologica. 1960;54:251-264. DOI:10.3109/00016926009172547.

[27] Leksell L, Larsson B, Andersson B, Rexed B, Sourander P, Mair W. Research on "localized radio-lesions". VI. Restricted radio-lesions in the depth of the brain produced by a beam of high energy protons. AFOSR TN United States Air Force Office of Scientific Research. 1960;60-1406:1-13.

[28] Falkmer S, Fors B, Larsson B, Lindell A, Naeslund J, Stenson S. Pilot study on proton irradiation of human carcinoma. Acta Radiologica. 1962;58:33-51. DOI:10.3109/00016926209169546.

[29] Fors B, Larsson B, Lindell A, Naeslund J, Stenson S. Effect of high energy protons on human genital carcinoma. Acta Radiologica: Therapy, Physics, Biology. 1964;2:384-398. DOI:10.3109/02841866409134071.

[30] Larsson B, Leksell L, Rexed B, Sourander P, Mair W, Andersson B. The high-energyprotonbeamasaneurosurgical tool. Nature. 1958;182(4644):1222-1223. DOI:10.1038/1821222a0.

[31] Kjellberg RN, Sweet WH, Preston WM, Koehler AM. The Bragg peak of a proton beam in intracranial therapy of tumors. Transactions of the American Neurological Association. 1962;87:216-218.

[32] Kjellberg RN, Kliman B. Bragg peak proton treatment for pituitary-related conditions. Proceedings of the Royal Society of Medicine. 1974;67(1):32-33.

[33] Robertson JB, Williams JR, Schmidt RA, Little JB, Flynn DF, Suit HD. Radiobiological studies of a high-energy modulated proton beam utilizing cultured mammalian cells. Cancer. 1975;35(6):1664-1677. DOI:10.1002/1097-0142(197506)35:6<1664::aid-cncr2820350628>3.0.co;2-#.

[34] Suit HD, Goitein M, Tepper J, Koehler AM, Schmidt RA, Schneider R. Explorotory study of proton radiation therapy using large field techniques and fractionated dose schedules. Cancer. 1975;35(6):1646-1657. DOI:10.1002/1097-0142(197506)35:6<1646::aid-cncr2820350626>3.0.co;2-1.

[35] Gragoudas ES, Goitein M, Koehler AM, Verhey L, Tepper J, Suit HD, et al. Proton irradiation of small choroidal malignant melanomas. American Journal of Ophthalmology. 1977;83(5):665-673. DOI:10.1016/0002-9394(77)90133-7.

[36] Shipley WU, Tepper JE, Prout GR, Jr., Verhey LJ, Mendiondo OA, Goitein M, Koehler AM, Suit HD. Proton radiation as boost therapy for localized prostatic carcinoma. Journal of the American Medical Association. 1979;241(18):1912-1915.

[37] Chuvilo IV, Goldin LL, Khoroshkov VS, Blokhin SE, Breyev VM, Vorontsov IA, Ermolayev VV, Kleinbock YL, Lomakin MI, Lomanov MF, et al. ITEP synchrotron proton beam in radiotherapy. International Journal of Radiation Oncology • Biology • Physics. 1984;10(2):185-195. DOI:10.1016/0360-3016(84)90003-8.

[38] Savinskaia AP, Minakova EI. Proton hypophysectomy and the induction of mammary cancer. Meditsinskaia Radiologiia (Mosk). 1979;24(2):53-57.

[39] Sakurai H, Ishikawa H, Okumura T. Proton beam therapy in Japan: current and future status. Japenese Journal of Clinical Oncology. 2016;46(10):885-892. DOI:10.1093/jjco/hyw102.

[40] Kanai T, Kawachi K, Kumamoto Y, Ogawa H, Yamada T, Matsuzawa H, Inada T. Spot scanning system for proton radiotherapy. Med Phys. 1980;7(4):365-369. DOI:10.1118/1.594693.

[41] Suit H, Goitein M, Munzenrider J, Verhey L, Blitzer P, Gragoudas E, Koehler AM, Urie M, Gentry R, Shipley W, Urano M, Duttenhaver J, Wagner M. Evaluation of the clinical applicability of proton beams in definitive fractionated radiation therapy. International Journal of Radiation Oncology • Biology • Physics. 1982;8(12):2199-2205. DOI:10.1016/0360-3016(82)90570-3.

[42] Gragoudas ES, Goitein M, Verhey L, Munzenreider J, Urie M, Suit H, Koehler A. Proton beam irradiation of uveal melanomas. Results of 5 1/2-year study. Archives of Ophthalmology. 1982;100(6):928-934. DOI: 10.1001/archopht.1982.01030030936007.

[43] Austin-Seymour M, Munzenrider JE, Goitein M, Gentry R, Gragoudas E, Koehler AM, McNulty P, Osborne E, Ryugo DK, Seddon J, et al. Progress in low-LET heavy particle therapy: intracranial and paracranial tumors and uveal melanomas. Radiation Research Supplement. 1985;8:S219-S226.

[44] Gragoudas ES, Seddon J, Goitein M, Verhey L, Munzenrider J, Urie M, Suit HD, Blitzer P, Koehler A. Current results of proton beam irradiation of uveal melanomas. Ophthalmology. 1985;92(2):284-291. DOI:10.1016/s0161-6420(85)34058-7.

[45] Slater JM, Archambeau JO, Miller DW, Notarus MI, Preston W, Slater JD. The proton treatment center at Loma Linda University Medical Center: rationale for and description

of its development. International Journal of Radiation Oncology • Biology • Physics. 1992;22(2):383-389. DOI:10.1016/0360-3016(92)90058-p.

[46] Slater JD. Development and operation of the Loma Linda University Medical Center proton facility. Technology in Cancer Research & Treatment. 2007;6(4 Suppl):67-72. DOI: 10.1177/15330346070060S411.

[47] Hu M, Jiang L, Cui X, Zhang J, Yu J. Proton beam therapy for cancer in the era of precision medicine. Journal of Hematology & Oncology. 2018;11(1):136. DOI:10.1186/s13045-018-0683-4.

[48] Mohan R, Grosshans D. Proton therapy - Present and future. Advanced Drug Delivery Reviews. 2017;109:26-44. DOI: 10.1016/j.addr.2016.11.006.

[49] Koehler AM, Schneider RJ, Sisterson JM. Flattening of proton dose distributions for large-field radiotherapy. Medical Physics. 1977;4(4):297-301. DOI:10.1118/1.594317.

[50] Gottschalk B. On the scattering power of radiotherapy protons. Medical Physics. 2010;37(1):352-367. DOI:10.1118/1.3264177.

[51] Kawachi K, Kanai T, Matsuzawa H, Inada T. Three dimensional spot beam scanning method for proton conformation radiation therapy. Acta Radiologica Supplementum. 1983;364:81-88.

[52] Kooy HM, Grassberger C. Intensity modulated proton therapy. British Journal of Radiology. 2015;88(1051):20150195. DOI:10.1259/bjr.20150195.

[53] Fuss M, Poljanc K, Miller DW, Archambeau JO, Slater JM, Slater JD, Hug EB. Normal tissue complication probability (NTCP) calculations as a means to compare proton and photon plans and evaluation of clinical appropriateness of calculated values. International Journal of Cancer. 2000;90(6):351-358. DOI:10.1002/1097-0215(20001220)90:6<351::aid-ijc7>3.0.co;2-j.

[54] St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, Loeffler JS, Tarbell NJ. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. International Journal of Radiation Oncology • Biology • Physics. 2004;58(3):727-734. DOI:10.1016/S0360-3016(03)01574-8.

[55] Isacsson U, Hagberg H, Johansson KA, Montelius A, Jung B, Glimelius B. Potential advantages of protons over conventional radiation beams for paraspinal tumours. Radiotherapy and Oncology. 1997;45(1):63-70. DOI:10.1016/s0167-8140(97)00097-2.

[56] Jagsi R, DeLaney TF, Donelan K, Tarbell NJ. Real-time rationing of scarce resources: the Northeast Proton Therapy Center experience. Journal of Clinical Oncology. 2004;22(11):2246-2250. DOI:10.1200/JCO.2004.10.083.

[57] Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? Journal of Clinical Oncology. 2007;25(24):3603-3608. DOI:10.1200/JCO.2006.09.0811.

[58] Suit H, Kooy H, Trofimov A, Farr J, Munzenrider J, DeLaney T, Loeffler J, Clasie B, Safai S, Paganetti H. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. Radiotherapy and Oncology. 2008;86(2):148-153. DOI:10.1016/j.radonc.2007.12.024.