REVIEW ARTICLE

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Proton Therapy: Technique of the Future to Treat Cancer Patients

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ABSTRACT

In recent years, there has been an increasing interest in using proton beam therapy to treat certain types of cancer in many countries around the world. However, some countries never used proton beam therapy and do not have any center for it. One of these countries is Iraq. Although the advantages of proton beam therapy over photon beam therapy to treat several types of cancer, it remains unused in Iraq and several countries. This may be due to the high cost of building a proton beam therapy center, a lack of information about this advanced modality that can save many lives, or the absence of a trained staff of oncologists, medical physicists, and technicians who know how to work with the proton beam therapy center. Here in this review, light will be shed on proton beam therapy and its advantages and disadvantages, and the specific types of cancers should be treated by this modality rather than photon beam therapy.

Keywords: Radiotherapy; Proton therapy; Cancer patients.

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INTRODUCTION

In the beginning, the idea of using a proton beam for therapy due to its characteristics over the photon beam was outlined by Wilson in 1946 [1]. He described in his article how accelerated proton can travel through the body in a nearly straight path, causing ionization of the tissue that passes through by losing a very small part of proton energy for each interaction that leads to a slowdown of the proton, and then the proton stops after finite range after giving almost all of its energy to the tissue at the end of its path, forming a peak, which is called a Bragg peak [1]. After Wilson presented his idea about proton therapy, scientists and researchers from all over the world performed many studies and experiments over the years to develop a technique that can be used to treat cancer patients with proton beam [2]. Developments were continued until the proton therapy modality became as we can see it these days.

Proton beam therapy may have clinical advantages compared with photon or electron radiation therapy for certain types of cancers, such as medulloblastoma and other cancers in pediatric patients, prostate cancer, central nervous system cancer, and breast cancer [3, 4]. Due to a more conformal distribution of the radiation dose, the risk of damaging normal tissues is diminished, which may allow dose escalation and a higher chance of recovery. If the only consideration was the radiation therapy's impact on cancer patients, proton therapy is more effective than traditional photon therapy [3, 5].

In recent years, several countries around the world have adopted proton beam therapy as an alternative modality to treat particular types of cancer. However, many other countries still do not yet have any center for proton therapy [6, 7], despite its features in comparison with the photon beam [8]. Several reasons prevent these countries from having their proton therapy centers; the first and most important one is the high cost of this modality [8, 9]. All healthcare systems face financial challenges, and new technologies-particularly those as complicated as proton therapy-must be able to pay for their higher operating costs as well as the investment required to bring them into clinical practice [10]. Other reasons may be a lack of information about this advanced modality that can save many lives or the absence of a trained staff of oncologists, medical physicists, and technicians who know how to work with proton beam therapy centers, especially in developing and poor countries.

In the current study, the physical properties of protons that

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make them superior to treating certain types of cancer that are surrounded by organs at risk, types of cancer that are better to treat with proton beam therapy rather than conventional radiation therapy, the cost for the building, and how to prepare a qualified trained team to manage the center with high efficiency will be discussed.

PHYSICAL PROPERTIES OF PROTONS

The proton is the hydrogen atom's nucleus. It has a mass of 1.6×10^{-27} kg and a single positive charge of 1.6×10^{-19} C (its mass is approximately 1840 times the electron's mass). The proton is composed of two up and one down quarks, which are kept together by gluons. The proton, which splits into a positron, neutron, and neutrino, is the most stable particle [11].

Protons interact with the atomic nuclei and electrons of the medium as they pass through it. Several types of interactions may occur. Columbic interaction with atomic electrons is one of the various types of interactions that can happen, in which protons collide with atomic electrons and transfer a portion of their kinetic energy to these electrons, leading to the excitation and ionization of atoms, thus resulting in absorbed dosage; After this collision, the majority of protons continue to move in a fairly linear trajectory due to their rest mass being 1832 times greater than that of an electron. The second type is Columbic interaction with the atomic nucleus which occurs when a proton approaches the atomic nucleus, resulting in a repulsive elastic force, and due to the substantial mass of the nucleus, it alters the proton's initial linear path with dissipating some of its energy. Also, there is a rare type of interaction which is called nuclear reaction, it occurs when a projectile proton enters the nucleus causing excitation to the nucleus which then releases one or more neutrons, proton, deuteron, tritons, or heavier ion to reach a more stable state. The last type of interaction is proton Bremsstrahlung, although theoretically possible, proton Bremsstrahlung has little effect at therapeutic proton beam intensities [9, 11].

These interactions result in an energy loss directly proportional to the square of the charge and inversely proportional to the square of the velocity [9, 11]. "As the proton loses energy, it slows down, and the rate of energy loss per unit path length increases. The rate of energy loss peaks as the proton velocity gets closer to zero toward the end of its range. The dose of a monoenergetic proton beam increases gradually with depth at first, then sharply toward the end of the range. The Bragg peak is the name given to this abrupt rise or peak in dose deposition at the end of the particle range. Figure 1 shows the dose distribution for one proton beam and its Bragg peak. A monoenergetic proton beam's Bragg peak is too small to encompass the majority of target volumes. By superposing multiple beams of varying energy, the Bragg peak can be dispersed to provide more depth coverage. These beams are referred to as spread-out Bragg peak (SOBP) beams. The SOBP beams are produced by covering the proximal part of the target volume with beams of diminishing energy and intensity and covering the distal end with a monoenergetic beam of high enough energy and range [11]. Figure 2 shows the distribution of SOBP depth dose.

It can be seen in both previous Figures 1 and 2 that immediately following the Bragg peak or SOBP, the depth-dose curve abruptly falls off to almost zero. This property makes the proton beam superior compared to the photon beam for treating cancers when normal organ preservation is a priority as the beam can be localized within the tumor area [12]. According to several studies, proton radiotherapy can reduce by approximately 50% of the irradiation dose to adjacent normal tissue compared with photon beams [13].

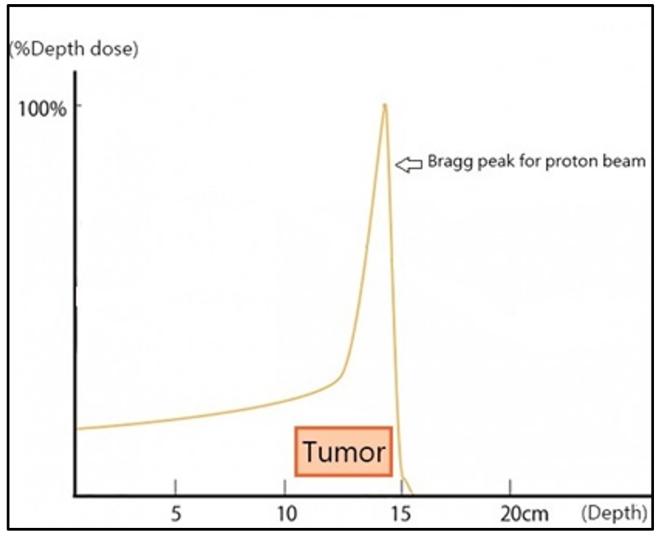

Figure 1. Dose distribution for one proton beam and its Bragg peak.

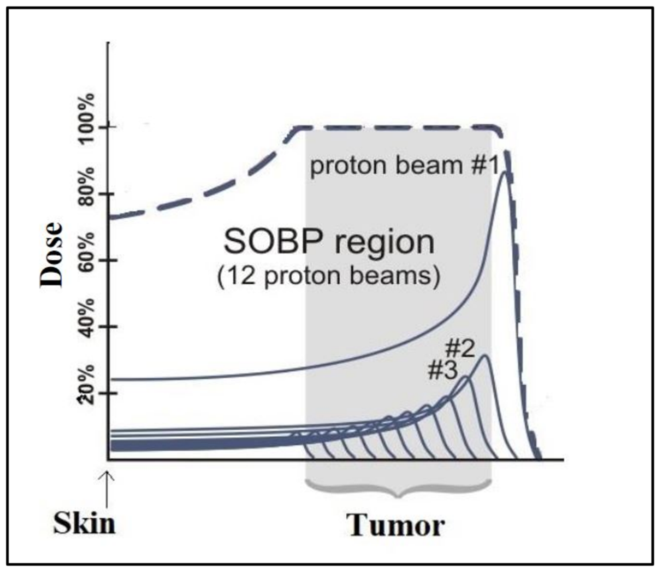

Figure 2. The distribution of Spread-out Bragg peak (SOBP) depth dose for 12 proton beams.

RADIOBIOLOGY OF PROTON THERAPY

Any ionizing radiation induces biological effects by producing free radicals called reactive oxygen species (ROS), and the production of ROS increases when ionization densities increase [14]. Protons show biological effectiveness in cell killing because the linear energy transfer (LET) has the highest value when a proton reaches the Bragg peak compared to X-rays. Elevated values of LET are linked to a localized energy deposition that causes more severe, irreversible biological harm [15].

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LET is an important factor that affects relative biological effectiveness (RBE). RBE is a concept that is used to evaluate a radiation type's biological efficacy to that of photons, which is the reference radiation type. The ratio of photon dose to proton dose required to inflict the same level of biological harm is thus known as the RBE of the proton. Clinical settings employ a general constant RBE of 1.1 when planning proton therapy. RBE is affected by physical parameters such as the proton beam energy, radiation dose, dose rate, fractionation strategy, the irradiation site, and the Bragg peak profile. Additionally, biological characteristics including the kind of tissue, oxygen saturation level, and stage of the cell cycle have an impact on it [16, 17].

The physical properties and radiobiology behavior of protons make the proton beam the best choice to treat many cancer types in comparison with photon beam.

TYPES OF CANCERS TREATED WITH PROTON THERAPY

Proton therapy could be better than photon therapy in treating non-metastatic cancers and cancers that are close to critical organs such as the heart, brain, and lungs. The types of cancers best treated with proton therapy have increased recently to include breast, cervical, gastrointestinal, lung, kidney, prostate, brain, spinal, throat, and pediatric cancers. Also, lymphoma, mesothelioma, and sarcomas can be treated with proton therapy [4, 18]. Below are some types of cancers that can be treated by protons better than photons.

BRAIN CANCER AND SPINAL TUMORS

Tumors of the brain are either benign or malignant [19]. Benign tumors don't spread to other organs and grow slowly. They often can be removed surgically. However, malignant tumors grow very fast and invade surrounding tissues. Tumors of the brain and spinal cord grow inside the brain or spinal cord which comprise the central nervous system [20].

Proton radiation therapy is considered an ideal choice to treat brain cancer and spinal tumors. This modality delivers the exact radiation dose to the tumor without reaching critical tissues that surround the tumor such as the rest of the brain, eyes, and spinal tissue [21]. When compared to photons, protons' effective properties allow physicians to provide a greater dose to the tumor while also providing superior normal tissue sparing. However, treatment with photons at the same level of dose results in unacceptable toxicity [22].

PEDIATRIC CANCERS

Children are more susceptible than adults to developing cancers like brain, leukemia, breast, skin, and thyroid cancer after being exposed to ionizing radiation because their organs and tissues are still developing. Additionally, because children live longer after radiation exposure due to primary treatment, there is an increased chance that they will develop other malignancies caused by radiation over their lifetime [23, 24]. Children who receive radiation for their treatment of cancer are at higher risk of developing second primary malignancies during their lifetime [25]. However, radiation therapy for pediatric cancer is a life-saving procedure [26].

Several photon radiation modalities include traditional modality, image-guided radiation therapy, three-dimensional conformal radiation therapy (3D-CRT), and intensity-modulated radiation therapy (IMRT). Indeed, the last modality is more precise than the others in delivering the radiation dose to the tumor. However, all of them still deliver unwanted doses to normal tissue on the radiation way to the tumor [26].

Recently, proton treatment has been determined by many researchers to be the most effective radiation therapy for pediatric malignancies because protons deliver precisely most of the radiation dose to the tumor area with limited exposure to the surrounding healthy tissue. Additionally, some tumors can resist low LET photons but are susceptible to high LET protons [27–29]. Due to its properties, proton therapy increases the quality of life for pediatric cancer patients by decreasing the probability of occurrence of second malignancies.

LUNG CANCER

Lung cancer comes in two varieties: Small-cell lung cancer and non-small-cell lung cancer [30], the most prevalent is the first one [31]. Nowadays, several treatment modalities are present to treat lung cancer such as surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these treatments [32]. The type of lung cancer and its spread determine the treatment method.

Some patients are treated with radiotherapy [33]. Radiotherapy includes either a photon beam or proton beam. Several photon beam modalities such as external beam, intensity modulated radiation therapy, brachytherapy, stereotactic body radiation therapy [34], all of these modalities deliver undesired radiation doses to critical organs and normal tissues surrounding the tumor in the lung [35].

Recently, oncologists have started to use proton therapy to treat non-small cell lung cancer patients instead of photon radiotherapy and lobectomy. Several studies have shown the dosimetric benefit of proton therapy for non-small cell lung cancer compared to conventional photon therapy, in proton therapy, a precise radiation dose is delivered to the tumor while no or minimal radiation dose is received by the lung parenchyma, heart, esophagus, and other surrounding normal organs at risk. Consequently, PBT preserves the patient's quality of life after the completion of therapy [36].

PROSTATE CANCER

Several modalities are used to treat localized prostate cancer, a radiotherapeutic approach is one of these modalities. Photon therapy can reach the tumor and kill it but may also harm the normal tissues and organs surrounding the tumor, while proton therapy can precisely kill the tumor sparing normal tissues and organs [37]. Many research studies and clinical trials showed that proton therapy is safer than photon therapy in the treatment of prostate cancer because proton treatment offers better dose profiles and better physical characteristics when compared to X-ray radiotherapy as mentioned previously. It's worth noting, that proton therapy does not affect testosterone levels, and the probability of a second cancer is very low, therefore, proton therapy is much better than photon therapy to treat prostate cancer [37–39].

CERVICAL CANCER

Cervical cancer is the primary cause of mortality for women worldwide [40]. Several techniques of photon therapy are used to treat cervical cancer. However, all these techniques deliver

Table 1. The success rate and complications of proton beam therapy in treating certain cancers in comparison with other modalities.

Cancer type	Proton therapy success rate (%)	Conventional radiation success rate (%)	Proton therapy complication rate (%)	Conventional radiation complication rate (%)
Prostate cancer	90	85	10	15
Pediatric brain tumors	95	88	5	12
Head and neck cancers	85	80	12	18
Lung cancer	80	75	20	25

unwanted radiation doses to normal tissues and organs surrounding the cervix. In contrast, protons have limited organ at-risk toxicity and unique advantages because of their limited range [41]. Several studies demonstrated that proton therapy could target the tumor without causing any harm to the normal organs surrounding the cervix. Given that it provides optimal rectum and bowel sparing, it may significantly lower acute and late toxicity [41, 42].

Several studies compared the efficacy and complications of proton therapy with those of other photon modalities in treating certain cancer types. These studies found that proton therapy has a higher success rate than conventional radiation therapy for all cancer types that have been included in these studies. Additionally, compared to conventional radiation therapy, the rate of complications from proton therapy was reduced [43, 44], as shown in Table 1.

ADVANTAGES AND DISADVANTAGES OF PROTON THERAPY

The dose distribution of proton therapy is highly conformal in comparison with photons, allowing the sparing of normal tissues and escalation of tumor doses, which leads to improving quality of life and reducing toxicity, for this reason, proton therapy is widely recommended for childhood cancers [45, 46]. The second and most important advantage of proton therapy is the sparing of the immune system, due to the short dose distribution of the proton beam resulting in minimized exposure of immune organs at risk and the circulating lymphocytes to radiation. There is a proof that the sparing of the immune system can improve end results [45, 47]. Also, proton therapy is effective for treating complex and deep-seated tumors [18].

The limitations or disadvantages of proton therapy are: Firstly, the proton therapy machine is more complex and sensitive in comparison with photon therapy, therefore, very well-trained staff is required [48], secondly, the proton therapy facility is more expensive compared to photon therapy facilities, and thus the cost of treatment is high [18, 45, 49]. Thirdly, proton therapy requires a longer treatment time compared to conventional radiation therapy [18, 49]. The other advantages and disadvantages of proton beam therapy are presented in Table 2.

Table 2. Summarizes the advantages and disadvantages of proton beam therapy [18, 45, 49].

Advantages
1. High-precision tumor targeting.
2. Minimal harm to the healthy tissues around.
3. Reduced possibility of adverse effects.
4. Effective for treating deep-seated and complex tumors.
5. Potential for higher cure rates.
6. Reduced short-term and long-term side effects.
Disadvantages
1. High cost.
2. Limited availability.
3. Requires specialized equipment and facilities.
4. Longer treatment times compared to conventional radiation.
5. Not suitable for all types of cancer.
6. Lack of comparative studies.

PROTON THERAPY FACILITY

At present, only 94 proton centers are operating worldwide, including those in scientific research institutes.The majority of these centers operate in Japan and the United States (www.ptcog.site), and their numbers are growing. Iraq has yet to acquire a proton center (https://proton-therapy.org/) [50].

Large and equipped with sophisticated machinery, the proton facility produces proton beams of energy that are enough to treat tumors at any depth using cyclotrons or synchrotrons, which are utilized in radiotherapy [11].

The main obstacle to the wider adoption of proton therapy is its cost, which is still three times higher than that of advanced photon radiation therapy. The major factors determining the cost discrepancy are the expenses associated with equipment, buildings, and operation, which require intensive procedures of quality assurance to ensure precise proton dose delivery to the patient [51]. The technology of the proton therapy facility is much more complex than the photon therapy facility. Therefore, highly trained and qualified staff are needed to operate the facility. The staff includes oncologists, medical physicists, health physicists, nurses, technicians, and engineers who repair the unit whenever any defect happens [52].

From what is mentioned above, the developing and poor countries cannot have their own proton therapy units and keep them working properly at this time. The question arises of how these countries, including Iraq, can have their own proton facility. Let us talk about Iraq: how can own a proton facility to treat patients? Firstly, the Ministry of Health should be persuaded that proton therapy is the best choice and much better than photon therapy to treat some types of cancer, such as pediatric cancers, prostate cancer, lung cancer, and all cancers located deep and surrounded by normal organs. Secondly, qualified medical staff should be prepared to work efficiently in a proton therapy facility. Also, qualified engineers and technicians should be prepared to be ready

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to repair any dysfunction or error that happens in the machine. All these people should be sent abroad to countries that have proton therapy facilities such as the USA and Japan, to take courses and attend workshops in order to learn efficiently about this technique. Thirdly, the Ministry of Health should allocate a sufficient and suitable area of land to build the facility building and the amount of money needed to purchase the proton therapy unit. Lastly, the cost of the treatment should be paid by the health insurance. Therefore, all patients who are referred by oncologists would have access to the apprperiate treatment. Even though the facility is costly, its benefits are worthwhile, especially for children who have cancer, as it improves the quality of their lives.

CONCLUSION

The main reasons for prefering proton therapy over photon therapy are its ability to spare the normal tissues and organs surrounding the tumor and to escalate the dose to the target. Proton therapy is considered the best choice for treating specific types of cancer, such as pediatric cancers and tumors located in anatomically difficult areas. Despite the physical and radiobiological characteristics of proton beams, many countries still do not have proton therapy facilities for several reasons, including the high cost of the facility, the cost of treatment, a lack of information about the importance of this modality over photon therapy, and the absence of well-trained staff. All countries should have proton therapy facilities due to the importance of proton therapy to improve the quality of life, especially for children, even if the facility has significant requirements as previously mentioned. It is possible that the current and future technological improvements in proton therapy will help gradually reduce the cost, and this may happen in the near future.

ETHICAL DECLARATIONS

Acknowledgment

None.

Ethics Approval and Consent to Participate

Not required.

Consent for Publication

Not required.

Availability of Data and Material

Not required.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

Al-Yasiri AY designed the study. Al-Yasiri AY and White N wrote the manuscript. Al-Yasiri AY formatted the reference with Endnote software. The authors read and approved the final version of the manuscript.

REFERENCES

[1] R. R. Wilson. Radiological Use of Fast Protons. *Radiology*, 47(5):487–491, 1946.

[2] Harald Paganetti. Proton Therapy: History and Rationale. In *Proton therapy physics*, chapter 1. Taylor & Francis Group, LLC, 2012.

[3] J. Lundkvist *et al.* Proton therapy of cancer:Potential clinical advantages and cost-effectiveness. *Acta Oncologica*, 44(8):850–861, 2005. doi: 10.1080/02841860500341157.

[4] S. Yajnik. *Proton Beam Therapy: How Protons are Revolutionizing Cancer Treatment.* Springer, 2013. doi: 10.1007/978-1-4614-5298-0.

[5] H. Suit *et al.* Proton Beams to Replace Photon Beams in Radical Dose Treatments. *Acta Oncologica*, 42(8):800–808, 2003. doi: 10.1080/02841860310017676.

[6] E. Rosenblatt, A. Meghzifene, O. Belyakov, and M. Abdel-Wahab. Relevance of Particle Therapy to Developing Countries. *Int. J. Radiat. Oncol.*, 95(1):25–29, 2016. doi: 10.1016/J.IJROBP.2015.12.370.

[7] N. A. S. Al Alwan. Cancer Control and Oncology Care in Iraq. *J. Contemp. Med. Sci.*, 8(1):82–85, 2022. doi: 10.22317/jcms.v8i1.1154.

[8] M. Goitein and M. Jermann. The relative costs of proton and X-ray radiation therapy. *Clinical Oncology*, 15(1), 2003. doi: 10.1053/clon.2002.0174.

[9] W. D. Newhauser and R. Zhang. The physics of proton therapy. *Physics in Medicine & Biology*, 60, 2015. doi: 10.1088/0031-9155/60/8/R155.

[10] M. Brada and T. Bortfeld. Proton Therapy: The Present and the Future. *Semin. Radiat. Oncol.*, 23(2):75–76, 2013. doi: 10.1016/j.semradonc.2012.11.001.

[11] J. P. Gibbons. Proton Beam Therapy. In *Khan's The Physics of Radiation Therapy- Sixth Edition.* LWW, 2020.

[12] H. Liu and J. Y. Chang. Proton therapy in clinical practice. *Chin. J. Cancer*, 30(5):315–326, 2011. doi: 10.5732/cjc.010.10529.

[13] H. Annison. Book review: Book review. *Criminology & Criminal Justice*, 11(3):277–278, 2011. doi: 10.1177/1748895811401979.

[14] F. Tommasino and M. Durante. Proton radiobiology. *Cancers*, 7(1):353–381, 2015. doi: 10.3390/cancers7010353.

[15] D. T. Goodhead. Energy deposition stochastics and track structure: What about the target? *Radiation Protection Dosimetry*, 122(1–4):3–15, 2006. doi: 10.1093/rpd/ncl498.

[16] L. Vanderwaeren, R. Dok, K. Verstrepen, and S. Nuyts. Clinical progress in proton radiotherapy: Biological unknowns. *Cancers*, 13(4):1–16, 2021. doi: 10.3390/cancers13040604.

[17] B. Jones. Proton radiobiology and its clinical implications. *Ecancermedicalscience*, 11:1–11, 2017. doi: 10.3332/ecancer.2017.777.

[18] Z. Chen, M. M. Dominello, M. C. Joiner, and J. W. Burmeister. Proton versus photon radiation therapy: A

clinical review. *Frontiers in Oncology*, 13(March):1–28, 2023. doi: 10.3389/fonc.2023.1133909.

[19] P. M. Black. Brain tumors. *N. Engl. J. Med.*, 324(22):1555–1564, 1991.

[20] M. A. W. M. Abdul-Aziz, A. E. E. D. M. Rashad, and H. A. Saleh. Malignant Recurrence of Benign Odontogenic Tumors (A Single Center Cross-Sectional Study). *Head and Neck Pathology*, 18(1):1–8, 2024. doi: 10.1007/s12105-024-01676-9.

[21] C. M. Freria *et al.* Serial systemic injections of endotoxin (LPS) elicit neuroprotective spinal cord microglia through IL-1dependent cross talk with endothelial cells. *Journal of Neuroscience*, 40(47):9103–9120, 2020. doi: 10.1523/JNEUROSCI.0131-20.2020.

[22] D. S. Gridley, R. S. Grover, L. N. Loredo, A. J. Wroe, and J. D Slater. Proton-beam therapy for tumors of the CNS. *Expert Review of Neurotherapeutics*, 10(2):319–330, 2010. doi: 10.1586/ern.09.150.

[23] P. Karlsson, E. Holmberg, M. Lundell, A. Mattsson, L. E. Holm, and A. Wallgren. Intracranial tumors after exposure to ionizing radiation during infancy: A pooled analysis of two swedish cohorts of 28,008 infants with skin hemangioma. *Radiation Research*, 150(3):357–364, 1998. doi: 10.2307/3579984.

[24] P.-L. Khong *et al.* ICRP Publication 121: Radiological Protection in Paediatric Diagnostic and Interventional Radiology. *Annals of the ICRP*, 42(2):1–63, 2013. doi: 10.1016/j.icrp.2012.10.001.

[25] A.T. Meadows *et al.* Second neoplasms in survivors of childhood cancer: Findings from the Childhood Cancer Survivor Study cohort. *Journal of Clinical Oncology*, 27(14):2356–2362, 2009. doi: 10.1200/JCO.2008.21.1920.

[26] K. R. Kutanzi, A. Lumen, I. Koturbash, and I. R. Miousse. Pediatric Exposures to Ionizing Radiation: Carcinogenic Considerations. *International journal of environmental research and public health*, 13(11), 2016. doi: 10.3390/ijerph13111057.

[27] R. Leroy, N. Benahmed, F. Hulstaert, N. Van Damme, and D. De Ruysscher. Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers. *International Journal of Radiation Oncology Biology Physics*, 95(1):267–278, 2016. doi: 10.1016/j.ijrobp.2015.10.025.

[28] E. Berlin *et al.* Delivery of re-irradiation and complex palliative radiotherapy using proton therapy in pediatric cancer patients. *Pediatric Blood & Cancer*, 70(12):6–11, 2023. doi: 10.1002/pbc.30708.

[29] H. Thomas and B. Timmermann. Proton Therapy special feature: Review Article Paediatric proton therapy. *The British journal of radiology*, 93(1107), 2020. doi: 10.1259/bjr.20190601.

[30] O. A. Jassim, M. J. Abed, and Z. H. Saied. Deep Learning Techniques in the Cancer-Related Medical Domain: A Transfer Deep Learning Ensemble Model for Lung Cancer Prediction. *Baghdad Science Journal*, 21(3):1101–1118, 2024. doi: 10.21123/bsj.2023.8340.

[31] D. Mathew *et al.* Combined JAK inhibition and PD-1 immunotherapy for non-small cell lung cancer patients. *Science*, 384(6702):1329, 2024. doi: 10.1126/science.adf1329.

[32] A. Lahiri *et al.* Lung cancer immunotherapy: progress, pitfalls, and promises. *Molecular Cancer*, 22(1):1–37, 2023. doi: 10.1186/s12943-023-01740-y.

[33] M. Igari *et al.* Learning curve of lung dose optimization in intensity-modulated radiotherapy for locally advanced non-small cell lung cancer. *Thoracic Cancer*, 14(26):2642–2647, 2023. doi: 10.1111/1759-7714.15046.

[34] N. Benzazon *et al.* Analytical models for external photon beam radiotherapy out-of-field dose calculation: a scoping review. *Frontiers in Oncology*, 13(1):1–13, 2023. doi: 10.3389/fonc.2023.1197079.

[35] S. Mercieca, J. S. A. Belderbos, and M. van Herk. Challenges in the target volume definition of lung cancer radiotherapy. *Translational lung cancer research*, 10(4):1983–1998, 2021. doi: 10.21037/tlcr-20-627.

[36] T. Sakane *et al.* Lobectomy versus proton therapy for stage I non–small cell lung cancer. *Journal of Thoracic and Cardiovascular Surgery*, 166(6):1490–1501.e2, 2023. doi: 10.1016/j.jtcvs.2023.08.030.

[37] Y. Y. Wu and K. H. Fan. Proton therapy for prostate cancer: current state and future perspectives. *British Journal of Radiology*, 95(1131), 2021. doi: 10.1259/bjr.20210670.

[38] C. M. Bryant *et al.* Consensus statement on proton therapy for prostate cancer. *International Journal of Particle Therapy*, 8(2):1–16, 2021. doi: 10.14338/IJPT-20-00031.1.

[39] B. Hoppe, R. Henderson, W. M. Mendenhall, R. C. Nichols, Z. Li, and N. P. Mendenhall. Proton therapy for prostate cancer. *Oncology*, 25(7):1–6, 2011.

[40] B. M. Khashman, S. K. Karim, and G. N. Al-Jussani. the Oncogenic Effect of Ebv/Hpv Co-Infection in a Group of Iraqi Women With Cervical Carcinoma. *Biochemical and Cellular Archives*, 20(2):6037–6040, 2020.

[41] A. J. A. J. van de Schoot *et al.* Dosimetric advantages of proton therapy compared with photon therapy using an adaptive strategy in cervical cancer. *Acta Oncologica*, 55(7):892–899, 2016. doi: 10.3109/0284186X.2016.1139179.

[42] S. Marnitz *et al.* Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation - an . *Radiation Oncology*, 10(1):1–9, 2015. doi: 10.1186/s13014-015-0402-z.

[43] Y. Ishikawa *et al.* Real-world comparative outcomes and toxicities after definitive radiotherapy using proton beam therapy versus intensity-modulated radiation therapy for prostate cancer : a retrospective , single-institutional analysis. *Journal of Radiation Research*, 66(1):39–51, 2025. doi: 10.1093/jrr/rrae065.

[44] B. C. Baumann *et al.* Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer. *JAMA oncology*, 6(2):237–246, 2020. doi: 10.1001/jamaoncol.2019.4889.

[45] R. Mohan. A review of proton therapy – Current status and future directions. *Precision Radiation Oncology*, 6(2):164–176, 2022. doi: 110.1002/pro6.1149.

[46] R. Mohan and D. Grosshans. Proton therapy – Present and future. *Advanced Drug Delivery Reviews*, 109:26–44, 2017. doi: 10.1016/j.addr.2016.11.006.

[47] H. J. Lee, J. Zeng, and R. Rengan. Proton beam therapy and immunotherapy: An emerging partnership for immune activation in non-small cell lung cancer. *Translational Lung Cancer Research*, 7(2):180–188, 2018. doi: 10.21037/tlcr.2018.03.28.

[48] S. Rossi. Hadron Therapy Achievements and Challenges: The CNAO Experience. *Physics*, 4(1):229–257, 2022. doi: 10.3390/physics4010017.

[49] F. Guan *et al.* Interpreting the biological effects of protons as a function of physical quantity: linear energy transfer or microdosimetric lineal energy spectrum? *Scientific reports*, 14(1):25181, 2024. doi: 10.1038/s41598-024-73619-x.

[50] L. E. Jacomina, R. A. F. Agas, E. C. Dee, P. K. Panda, and M. B. A. Mejia. Proton therapy in Asia Pacific: current resources, international disparities and steps forward. *Journal of Medical Radiation Sciences*, 71(S2):6–9, 2024. doi: 10.1002/jmrs.776.

[51] J. M. Schippers, A. Lomax, A. Garonna, and K. Parodi. Can Technological Improvements Reduce the Cost of Proton Radiation Therapy? *Seminars in Radiation Oncology*, 28(2):150–159, 2018. doi: 10.1016/j.semradonc.2017.11.007.

[52] E. D. Miller, V. Derenchuk, I. J. Das, and P. A. S. Johnstone. Impact of proton beam availability on patient treatment schedule in radiation oncology. *Journal of Applied Clinical Medical Physics*, 13(6):134–146, 2012. doi: 10.1120/jacmp.v13i6.3968.