ORIGINAL ARTICLE

Investigation of the Physical Properties of Different Ion Species at Hadron Therapy; A Comprehensive Study

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Abstract

Purpose: Recently, using hadrons as a therapeutic beam has been highly advised for radiation treatment of mainly deep-seated tumors due to the desired conforming of three-dimensional dose conformation onto tumor volume. This refers to the physical properties of commonly available hadrons versus photons and electrons in colliding with patient body atoms which is our main challenge in this study, in a comparative fashion.

Materials and Methods: In this work, protons Caron- and Oxygen-Ions are considered as hadron beams while irradiating a given tumor located at soft tissue equivalent phantom to mimic the patient body using FLUKA simulation code. The high-impact properties of available beams implemented at hadron therapy facilities are investigated quantitatively, during the simulation process while no study has been done formerly.

Results: Depth dose profiles of hadrons, linear energy transfer, beams lateral divergence, spread out Bragg peak, produced neutrons and positron emitter as radioisotopes produced due to colliding hadrons with the nucleus of the atoms are measured, numerically. The latter case include C^{10}, C^{11}, N^{13}, and O^{15} in soft tissue which are highly important for proton range verification inside the patient body using positron emission tomography.

Conclusion: The physical properties of different therapeutic ion species were compared comprehensively. Among hadrons, linear energy transfer of Carbon- and Oxygen ions is superior versus proton due to their high atomic numbers that reduce treatment sessions remarkably. Furthermore, in proton therapy, the main source of produced neutrons are passive or active modulation devices located in front of the therapeutic beam. Among produced positron emitters, C^{11} and O^{15} are remarkable for providing functional images to assess the hadron range inside the patient body.

Keywords: Hadron Therapy; Depth Dose Profiles; Neutrons; Spread Out Bragg Peak; Beam Divergence; Positron Emitters.

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1. Introduction

During the whole course of the treatment, radiotherapy is recently considered important strategy for cancer treatment [1-4]. Among different types of radiation treatment, hadron therapy is well-known for its clinical benefits over conventional radiotherapy [5-7]. Hadron therapy indicates the treatment of cancers through high-energy hadronic particles, accelerated by dedicated machines [8, 9]. Various types of particles have been taken into account as subjects for radiobiological and clinical assessments of radiation treatment [10].

Hadron therapy results that the three-dimensional dose distribution of heavy ions onto tumor volume and nearby normal tissues can remarkably be improved regarding the same treatment planning implementing conventional radiotherapy. Therefore, hadrons can kill cancerous cells more effectively with less damage to healthy organs. This point can improve the cure rate of patients by reducing radiation-induced side effects which is one of the main aims of successful radiotherapy [11-13]. Recently, the development of beam delivery at hadron therapy yields better conformal dose distribution on tumor volumes [14-16]. Moreover, hadron therapy is highly advised for cancers that are close to organs at risk such as chordoma, nasopharyngeal carcinoma, and para-nasal sinus cancer. These organs at risk are very sensitive to irradiation and can be easily sparred during hadron therapy [17].

The main reason for proposing hadrons as therapeutic beams in radiotherapy is due to their physical properties in colliding with matters (or patient body). The idea of utilization of hadrons was proposed by Dr Wilson in 1946 [18]. Hadrons can penetrate a specific depth inside tissue and deposit their energy based on the Bragg Peak concept [19]. In a proper treatment planning process, Bragg Peak is assumed to be exactly on the tumor site to maximize irradiation damage onto cancerous cells. In this way, normal tissues located at the distal part of the tumor site will receive the zero dose that is clinically desired. Therefore, hadron therapy is highly prescribed for deep-seated tumors [20]. In comparison with precise photon therapy such as intensity-modulated radiotherapy [21] proton therapy can deliver prescribed radiation doses onto tumor volumes with around 50%–60% reduction in integral radiation dose [20].

Hadrons that consist of protons and heavier ions (such as Carbon and Oxygen as the two most under assessment particles) have their unique physical properties while interacting with the patient body. Various studies have illustrated different aspects of each hadron as a therapeutic beam for cancer treatment considering on a case-by-case basis [22]. In comparison with conventional photon therapy, each hadron therapy facility requires a costly accelerator machine to produce hadrons at an ion source and reach them to the desired energy by means of proper electric and magnetic fields. Design and construction of each component at the hadron therapy facility (ranging from accelerator machine to rotating gantry and beam delivery systems) need financial support that may increase patient costs in comparison with photon therapy [23]. Furthermore, considering radiation protection issues is highly advised at each hadron therapy facility that must be taken into account using proper shields against secondary particles [24].

In this work, a comprehensive investigation is performed on the physical properties of different ion species that are commonly available at hadron therapy using the Monte Carlo based simulation method, while no study includes all considered issues in this study, for a long time period. The main factors considered in this work are the rate of energy loss of each particle through the patient body, their relative biological effectiveness, and the divergence phenomena of each particle during penetrating. Moreover, the amount of unwanted dose of secondary particles produced due to the interaction of each hadron with the patient body has been taken into account numerically, while this factor has not been studied for a long time in a comparative fashion. Considering secondaries at hadron therapy is important since neutrons are produced by interacting of hadrons with the nucleus of atoms of the modulating devices and monitoring systems located in front of the beam and patient body. It should be noted that, in the latter case, the produced neutrons are negligible.

According to the obtained results, depth dose profiles of hadrons are well suited for covering tumor volume while keeping normal tissues located behind the tumor volume, against conventional radiotherapy. Moreover, the LET factor of hadrons is remarkably higher than the electron and photon beams that show intensive damage to cancerous cells. It should be noted

that this factor should be considered on normal tissues located before the tumor site, in order to prevent any possible toxicity. Considering the secondaries, neutrons are the main concern in hadron therapy while interacting protons and heavier ions with modulation devices located through beam trajectory. But hadrons colliding with the atom nucleus of the patient body elements cause emitting positrons that can be significantly helpful for practically evaluating hadrons penetration and therapeutic dose distribution inside the patient body by means of a Positron Emission Tomography (PET) system installed inside or near the treatment room [25]. At a glance, this study can be helpful for a better understanding of the pros and cons of commonly available hadrons at radiotherapy in the frame of comparative study.

2. Materials and Methods

2.1. Present Status of Proton and Carbon Ion Therapy Facilities at the Worldwide

Wilson was the first person who gave the idea of using protons and heavy ions in cancer treatment in 1946 [18]. The first treatment took place in Berkeley in 1954 using a proton beam and then followed by Uppsala in 1957. In the last two decades, a progressive development of proton therapy happened by constructing many hospital-based hadron therapy centers in the world. Moreover, new facilities are expected to be clinically operational in the near future [26].

As reported by PTCOG (Particle Therapy Co-Operative Group), there are over 89 particle therapy facilities worldwide till August 2020 [27], and 41 centers under construction [26]. Among them, 34 operational proton therapy centers are working in the United States and more than 154,203 patients had been treated worldwide until the end of 2015 [28].

The most important challenge in hadron therapy is the size and cost of the cyclotron or synchrotron as an accelerator machine for providing therapeutic beams and recently several industries have designed and fabricated smaller accelerators such as linear particle accelerators, ultra-compact synchrotrons to deliver the beam to the patients with less costs.

It should be noted among hadrons, most of the patients are treated with proton beams and Carbon and Oxygen ions are still under research works for further confirmation. Few patients were irradiated using Carbon Ion beams at some hadron therapy facilities mainly in Japan, though. As a numerical example, as reported by PTCOG 2018, total patients treated with proton and Carbon ion therapy are higher than 140000 and less than 20000, in 2016, respectively [29].

The base of acceleration at hadron therapy facilities is on the concept of synchrotron technique using magnetic and electric fields for particle accelerating and bending-focusing, respectively.

2.2. FLUKA Simulation Code

To simulate pre-defined parameters at hadron therapy proposed in this study the Monte Carlo FLUKA code (version 2011) was utilized. The main aim of FLUKA developers was to simulate radiotherapy and specifically hadron therapy issues. This code is a multipurpose Monte Carlo simulation code for to calculate particle transport and interactions with given matter that is patient body organs in this work. FLUKA can simulate high-accuracy interaction and propagation of many types of particles (about 60 different particles) in matter. Some typical application of the FLUKA code is by shielding design, medical radiation physics, environmental and internal dosimetry, designing detector systems, and radiotherapy physics. Furthermore, The FLUKA code can also model very complex geometries using an improved version of the well-known combinatorial geometry package [30, 31].

2.3. Simulation Setup

In this work, Proton, Carbon, and Oxygen ions as commonly available hadrons were simulated using the FLUKA code. A cubic shape with a 10×10 cm front surface dimension filled with soft tissue equivalent material was modeled representing a part of the patient body that must be irradiated in front of three hadron beams and two conventional photon and electron beams in a comparative fashion. The required materials of our simulation process such as soft tissue were defined according to the ICRP (International Commission on Radiological Protection) standards report (Report No. 74). It should be noted that the energy and spatial distribution of hadrons are according to the properties of real clinical beams during the simulation process to mimic the real condition.

Furthermore, the presence of neutrons produced as secondaries in colliding of hadrons with the nucleus of the atoms is taken into account in this work during beam irradiating [24]. Hadrons interacting with the nucleus may cause emitting other particles such as positrons that are negligible from a radiation protection point of view. Produced positrons are important for monitoring of hadrons range and their dose distribution inside the patient body. The latter strategy is known as an in-beam Positron Emission Tomography (PET) system for range verification at hadron therapy which is out of our focus in this work and will be considered in our next studies [25].

3. Results

Figure 1a shows Percentage Depth Dose (PDD) profiles of photon, electron, proton, Carbon-ion, and Oxygen-ion as five therapeutic beams. Two latter beams are recently considerable for real clinical treatment, while the oldest therapeutic beam is photon. It should be noted that for minimizing the statistical uncertainty error (less than 5%), five million particles were taken into account as incident particles or photons in each simulation cycle. The energy of simulated beams are as photon with 6MeV, (2) electron with 10MeV, (3) proton with 100MeV, and carbon and oxygen with 200MeV.

For better visualization, Figure 1b enlarges the distal part of (Carbon and Oxygen) Bragg peaks fall-off, representing the dose of secondaries (neutron and gamma) produced due to hadrons interaction with the nucleus of target atoms. This curve located along with Bragg peak is known as the tail. As seen, for Oxygen ions, the starting point of this tail is larger than Carbon ions. Regarding the proton beam, this unwanted dose should be taken into account while a typical Organ At Risk (OAR) is located at the distal part of the tumor volume.

Moreover, the energy loss behavior of hadronic therapeutic beams was investigated using the Linear Energy Transfer (LET) factor (Figure 2). It should be noted that for calculating LET, all three beams penetrate at water equivalent phantom with the same 9.70 cm depth.

As seen, the highest and lowest values for LET belong to Oxygen and proton beams, respectively. This is due to their physical properties in colliding with water equivalent phantom.

Figure 3 shows the energy deposition of proton and carbon beams two-dimensionally in the direction of beam propagation (on the Z axis) in order to depict beam divergence, laterally.

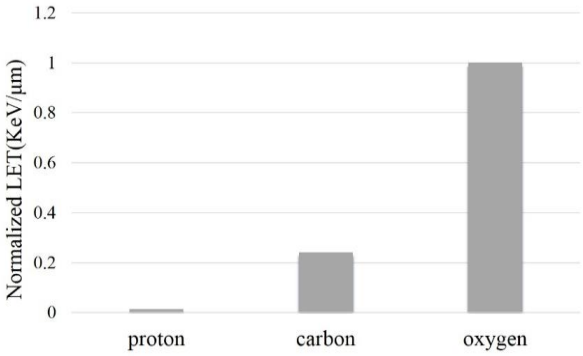

Figure 2. Linear Energy Transfer of three hadronic beams

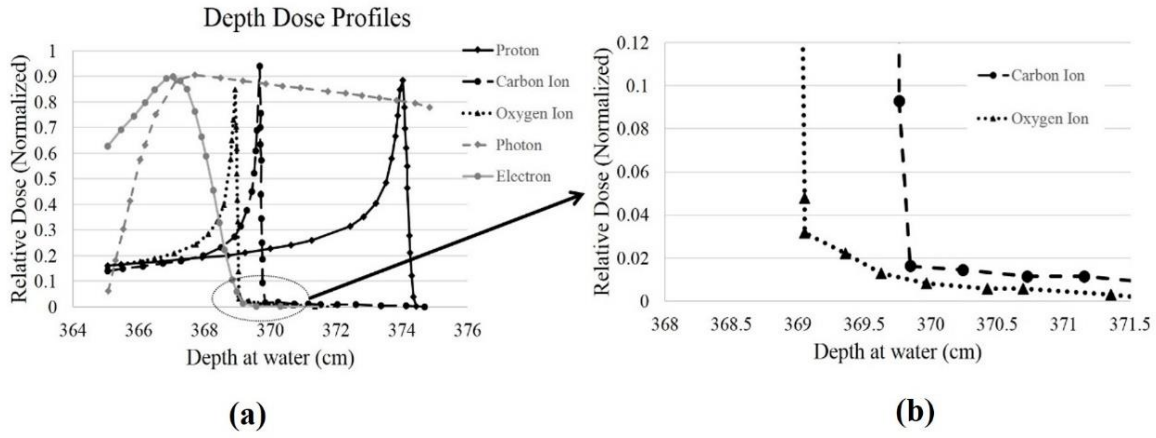

Figure 1. Depth dose profiles of five photon, electron, proton, Carbon, and Oxygen ion beams (Figure1a) and tail of two Carbon and Oxygen ion beams (Figure1b)

As seen, the proton beam diverged significantly at the end of the Bragg peak (Figure 3b), while this issue is not seen using the Carbon ion beam (Figure 3a). The ratio of beam divergence for the proton beam is 0.85 by dividing beam width while hadrons enter the phantom regarding beam width while hadrons will stop (at the end of the Bragg curve). As shown in Figure 3, this value is 1.0 for the Carbon Ion beam. It should be noted that Oxygen Ion beam behavior is similar to Carbon Ion at beam divergence phenomena. Moreover, it's worth mentioning that the diverging is an unwanted phenomenon as one of the disadvantage points at proton therapy while delivering high doses to lateral normal nearby tissues.

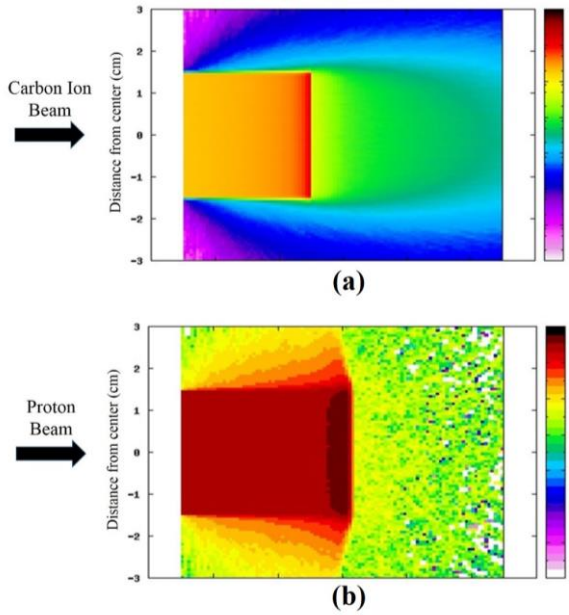

Figure 3. Comparison of beam divergence of Carbon Ion (Figure3a) and proton (Figure3b) beams inside the phantom

In hadron therapy, irradiating therapeutic beam in its initial form does not deliver a proper dose onto tumor volume, uniformly. Therefore, a modulation of energy and spatial distribution of the particles is needed. To do this, active and passive dose delivery systems are implemented using dedicated devices in front of the beam while exiting from the accelerator window up to the patient body. Among them, the ridge filter is responsible for modulating the energy of the particle to provide Spread Out Bragg Peak (SOBP). Figure 4 shows the SOBP of the proton beam with proper flattening region to cover tumor volume, longitudinally. As shown, the treatment region is 5 cm from 11 to 16 cm depth of the patient body. Figure 5 illustrates the two-dimensional SOBP at soft tissue equivalent phantom in the direction of proton beam propagation.

As seen in this figure, the flat or treatment region

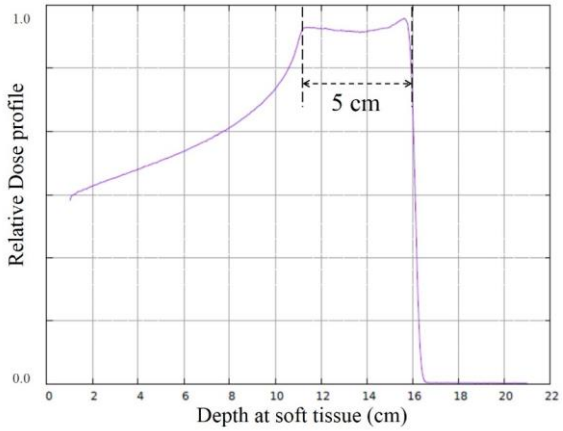

Figure 4. Spread Out Bragg Peak of the proton beam at equivalent phantom

has been shown with red which is assumed to cover tumor volume. Moreover, the lateral beam size that is shown in this figure is from -2.5 to 2.5 cm on the X axis. It should be noted that the same figure is resulted on the Y and beam propagation axes. Figure 4 is one-dimensional SOBP at the central axis of the therapeutic beam shown in Figure 5.

As mentioned, in this work a quantitative assessment was done on the presence of neutrons as one of the most important shielding issues in hadron therapy. Table 1 shows neutron flux, as the number of neutrons crossed from the border of 1) soft tissue equivalent phantom and 2) passive/active beam modulation devices to the air, as internal and external neutrons, respectively; irradiating protons as the therapeutic beam.

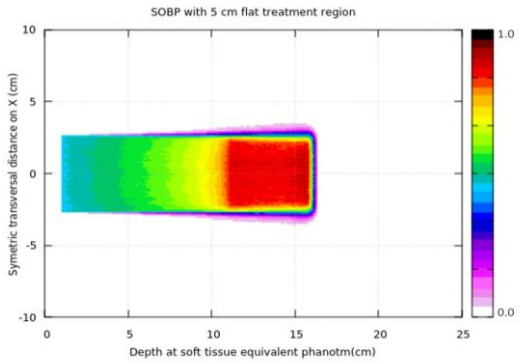

Figure 5. Two-dimensional SOBP of the proton beam at soft tissue equivalent phantom

Table 1. Comparison of internal and external neutrons produced in proton therapy

Border	Number of neutrons crossed from the border (# of *n*/cm^2 per primary incidence proton)
Between devices and the air (External neutrons)	0.1
Between the phantom and the air (Internal neutrons)	0.00002

As seen in this Table, the produced neutrons in the patient body are almost negligible while the main concerns raised due to external neutrons produced while protons colliding with passive and active modulation devices (such as range shifter, ridge filter, beam current monitor, and scatterer foils) located in front of the beam, upstream to the patient body.

In recent decades, experimental verification of hadron penetration inside the patient body is interestingly important to prove proper conformation of prescribed dose onto tumor volume. Several numerical and Monte Carlo based simulation strategies were done to show the hadrons range inside the patient body. In practice, PET as a functional imaging system was proposed to be implemented at or near the treatment room to give the range of hadrons in the patient body. In fact, in hadron therapy, after irradiating the particles with the patient body, the main energy loss happens due to the ionization of the atoms. But, in some cases, hadrons collide with the nucleus of the atoms of patient tissues, and the nuclei become radioactive such as C^{11}, N^{13}, O^{15}, or F^{18} as positron emitters. The emitted positron will lose their energy and then annihilation phenomena will happen and two 511 KeV photons will emerge. In the presence of a PET system, the emitted photons can be detected and the produced image finally gives us helpful information about the coordinate of annihilation phenomena and therefore hadrons colliding location with the nucleus of the atoms. Table 2 shows the yield (number of produced positron emitters per unit volume as a cubic centimeter per primary particle) of produced positron emitters at 150 and 250 MeV energies for i) protons, ii) Carbon- and iii) Oxygen Ions, as three therapeutic beams.

As seen in Table 2, C^{11} and O^{15} as positron emitters play an important role in implementing PET-based monitoring systems as range verification strategies.

4. Discussion

In recent decades, the role of protons and heavier ions in treating deep-seated tumors is interestingly important due to the physical property of hadrons in colliding with the matter. This property results in superior advantages in comparison with conventional radiotherapy. The energy deposition of hadrons in interaction with the patient body follows the physics of the Bragg curve. Using hadrons, severe damage will reach the cancerous cell due to high LET (Figure 2) and no dose delivers to the downstream normal nearby tissues (Figure 1). In this way, organs at risk located behind the tumor volume will be fully saved against the irradiating dose. Moreover, multiple strand breaks in the DNA will happen using heavy ions while the chance of DNA repair is low. Furthermore, three-dimensional dose conformation onto tumor volume is more precise rather than photon or light ion therapy, using dedicated passive and active modulation devices (Figure 5). Apart from the remarkable advantage, the cost of a hadron therapy facility is highly associated with the synchrotron or cyclotron accelerator machines cost, used to provide therapeutic beam particles with desired energy. Several studies have been performed to accelerate the hadrons with compact, novel, and high-technology machines to reduce the costs as much as possible.

Table 2. Yield of produced positron emitters (# of β^+ emitters/ cm^3 per particle) by simulating three therapeutic beams in soft tissue equivalent phantom at 150 and 250 MeV

Positron Emitters / Therapeutic beam	C-10		C-11		N-13		O-15	
	E=150 MeV	E=250 MeV	E=150 MeV	E=250 MeV	E=150 MeV	E=250 MeV	E=150 MeV	E=250 MeV
Proton	0.0007	0.00117	0.015132	0.03174	0.00172	0.00392	0.024718	0.052
Carbon Ion	0.00188	0.00323	0.0366	0.0532	0.00159	0.00149	0.008814	0.0160
Oxygen Ion	0.00189	0.00253	0.0209	0.0294	0.00250	0.00393	0.0270	0.0475

In this work, a comprehensive assessment was done on common available therapeutic hadronic beams, in a comparative fashion. It should be noted that among hadron beams, two proton and Carbon-Ion particles are implemented clinically and Oxygen-Ion beam is still under development, practically. Figure 1 shows the Bragg curves of hadrons in comparison with photon and electron beams that prove the end point of dose using protons and heavier ions. As seen in this figure, for Carbon- and Oxygen ions, there is a tail after the peak of the Bragg that is due to secondaries with strong penetration such as produced neutrons and photons, and the starting point of this tail for Oxygen is bigger than the same value for Carbon ion.

In clinical practice, the beam width is adjusted according to the lateral size of the tumor volume by means of simple or dynamic collimating systems known as particle stoppers. In this way, normal transversal tissues are sparred against unwanted doses. In proton therapy, although the therapeutic beam is shaped laterally, beam divergence near the end point of the protons range disturbs proper dose conforming, and a fraction of normal tissues will receive a high dose, while this drawback is not seen in heavier ion therapy.

Apart from uniform dose at the lateral size, dose distribution in beam propagation direction is modulated to provide uniform dose longitudinally. In this way, three-dimensional dose distribution is conformed onto tumor volume, uniformly. Figures 4 and 5 illustrate the performance of the energy modulation device to obtain SOBP with the desired flat treatment region of 5 cm. Since tumor dimensions vary laterally and longitudinally, the treatment region of SOBP can be adjusted to cover tumor volume on a case-by-case basis, and for this aim different energy modulation systems such as ridge filters can be implemented in front of the beam. Apart from SOBP, a therapeutic beam can be delivered to the tumor volume using a Spot Scanning strategy. In this way, the total volume of the tumor is computationally divided into several virtual layers and each layer is scanned with a modified pencil beam. In this method, the maximum dose of the Bragg curve will be deposited at each layer of the tumor, and the range shifter device is responsible for shifting the peak of the Bragg curve from one layer to the next upstream layer, consistently. In hadron therapy, one of the main concerns raised because the neutrons as secondary particles produced due to interacting primary particles with modulation devices and the patient body. Apart from coulomb interaction, some of the hadrons collide with the nucleus of the atoms of the matters ranging from modulation devices to the patient body. As seen in Table 1, produced neutrons inside soft tissue equivalent phantom are almost negligible in proton therapy, while external neutrons cannot be ignored in passive dose delivery system while modulation devices are located in front of the beam. In fact, the devices with high atomic numbers (Z) are the main cause of neutrons. From a secondary point of view, spot scanning or active dose delivery method is superior to the passive dose delivery strategy while the sources of produced secondary neutrons are removed. It should be noted that neutrons as secondary particles are not an issue in conventional radiotherapy using photon beam in comparison with hadron therapy.

As mentioned, PET-based range verification monitoring can practically clarify the accuracy between the prescribed dose and the delivered dose in hadron therapy. In colliding hadrons with the nucleus of the atoms of the patient tissues, some radioactive nuclei will be produced. Among them, C^{11}, N^{13}, O^{15}, or F^{18} are as positron emitters and therefore can be considered for employing a PET system inside or near the treatment room for the estimation of hadrons range and also their dose distribution. Table 2 shows the number of produced positron emitters per unit volume at soft tissue using three therapeutic beams at two energies for deep-seated tumors. As seen, the share of C^{11} and O^{15} is highly remarkable regarding other positron emitters. In soft tissue, the presence of Carbon and Oxygen is significant and due to this, the cross-section of hadrons interaction with these two elements will be increased as such $^{16}O(p,p\&n)O^{15}$ nuclear reaction happens.

It should be noted that the range of positrons is an error that must be considered during the final measurements for estimating the hadrons range after analyzing PET images. The energy of emitted positrons is a spectrum, therefore the positron with maximum energy represents the positron range. Due to this, the radioactive elements that emit positrons with lower maximum energy are advantageous to reduce the error range while PET images investigation. The maximum and mean energy of C^{11}

is 0.96 MeV and 0.39 MeV, respectively, while these values are 1.73 MeV and 0.73 MeV for O^{15}. Therefore, C^{11} is superior to O^{15} to result in lower positron error range. It's worth mentioning that the half-life of positron emitters is also an important factor mainly while the PET system is not in the treatment room and moving the patient to the PET imaging room and its positioning onto the PET coach takes a few minutes. Since, the half-lives of C^{11} and O15 are 20.4 and 2.0 minutes, respectively, C^{11} acts better as a positron emitter with a longer half-life to let operators for obtaining a PET image if the time is an issue.

5. Conclusion

In this study, the physical properties of proton, Carbon- and Oxygen-ion as three hadronic beams utilized in hadron therapy were investigated in a comparative mode. These properties that have a high impact in radiotherapy are as depth dose profiles, linear energy transfer, beam lateral divergence, spread out Bragg peak, secondary neutrons, and produced positron emitters, where no study has been done formerly, in a comprehensive fashion. Apart from all beneficial treatment points of hadron therapy, the costs for constructing the facility and accelerator machine assembling is an issue that must be addressed by developing high technology small accelerating system.

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References

1- Rajamanickam Baskar, Kuo Ann Lee, Richard Yeo, and Kheng-Wei Yeoh, "Cancer and radiation therapy: current advances and future directions." *International journal of medical sciences*, Vol. 9 (No. 3), p. 193, (2012).

2- Jacques Bernier, Eric J Hall, and Amato Giaccia, "Radiation oncology: a century of achievements." *Nature Reviews Cancer*, Vol. 4 (No. 9), pp. 737-47, (2004).

3- Geoff Delaney, Susannah Jacob, Carolyn Featherstone, and Michael Barton, "The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines." *Cancer: Interdisciplinary International Journal of the American Cancer Society*, Vol. 104 (No. 6), pp. 1129-37, (2005).

4- R Pötter, T Auberger, and A Wambersie, "Hadrons—A challenge for high-precision radiotherapy." *Strahlenther Onkol*, Vol. 175pp. 1-128, (1999).

5- Ugo Amaldi and Gerhard Kraft, "Radiotherapy with beams of carbon ions." *Reports on progress in physics*, Vol. 68 (No. 8), p. 1861, (2005).

6- DTL Jones, "Overview of hadron therapy: rationales, present status and future prospects." *Radiochimica Acta*, Vol. 89 (No. 4-5), pp. 235-44, (2001).

7- Radhe Mohan and David Grosshans, "Proton therapy–present and future." *Advanced drug delivery reviews*, Vol. 109pp. 26-44, (2017).

8- Alberto Degiovanni and Ugo Amaldi, "History of hadron therapy accelerators." *Physica medica*, Vol. 31 (No. 4), pp. 322-32, (2015).

9- Jacob Flanz, "Accelerators for charged particle therapy." *Modern Physics Letters A*, Vol. 30 (No. 17), p. 1540020, (2015).

10- Jac A Nickoloff, "Photon, light ion, and heavy ion cancer radiotherapy: paths from physics and biology to clinical practice." *Annals of translational medicine*, Vol. 3 (No. 21), (2015).

11- Christopher Allen, Thomas B Borak, Hirohiko Tsujii, and Jac A Nickoloff, "Heavy charged particle radiobiology: using enhanced biological effectiveness and improved beam focusing to advance cancer therapy." *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, Vol. 711 (No. 1-2), pp. 150-57, (2011).

12- Wei-Xiang Qi, Shen Fu, Qing Zhang, and Xiao-Mao Guo, "Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis." *Radiotherapy and Oncology*, Vol. 114 (No. 3), pp. 289-95, (2015).

13- Herman Suit *et al.*, "Proton vs carbon ion beams in the definitive radiation treatment of cancer patients." *Radiotherapy and Oncology*, Vol. 95 (No. 1), pp. 3-22, (2010).

14- Michael M Folkerts, Eric Abel, Simon Busold, Jessica Rika Perez, Vidhya Krishnamurthi, and C Clifton Ling, "A framework for defining FLASH dose rate for pencil beam scanning." *Medical Physics*, Vol. 47 (No. 12), pp. 6396-404, (2020).

15- Hao Gao *et al.*, "Simultaneous dose and dose rate optimization (SDDRO) for FLASH proton therapy." *Medical Physics*, Vol. 47 (No. 12), pp. 6388-95, (2020).

16- Steven Van De Water, Sairos Safai, Jacobus M Schippers, Damien C Weber, and Antony J Lomax, "Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose

rates." *Acta oncologica*, Vol. 58 (No. 10), pp. 1463-69, (2019).

17- Romaana Mir *et al.*, "Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines." *Radiotherapy and Oncology*, Vol. 150pp. 30-39, (2020).

18- Robert R Wilson, "Radiological use of fast protons." *Radiology*, Vol. 47 (No. 5), pp. 487-91, (1946).

19- Morad Kh Hamad, "Bragg-curve simulation of carbon-ion beams for particle-therapy applications: A study with the GEANT4 toolkit." *Nuclear Engineering and Technology*, Vol. 53 (No. 8), pp. 2767-73, (2021).

20- Man Hu, Liyang Jiang, Xiangli Cui, Jianguang Zhang, and Jinming Yu, "Proton beam therapy for cancer in the era of precision medicine." *Journal of hematology & oncology*, Vol. 11 (No. 1), pp. 1-16, (2018).

21- A Taylor and MEB Powell, "Intensity-modulated radiotherapy—what is it?" *Cancer Imaging*, Vol. 4 (No. 2), p. 68, (2004).

22- Francesco Tommasino, Emanuele Scifoni, and Marco Durante, "New ions for therapy." *International journal of particle therapy*, Vol. 2 (No. 3), pp. 428-38, (2015).

23- Robert J Schulz and A Robert Kagan, "Costs and benefits of particle-beam therapies." *Physics Today*, Vol. 68 (No. 10), pp. 8-8, (2015).

24- Sebastian Faby and Jan J Wilkens, "Assessment of secondary radiation and radiation protection in laser-driven proton therapy." *Zeitschrift für Medizinische Physik*, Vol. 25 (No. 2), pp. 112-22, (2015).

25- Xuping Zhu *et al.*, "Monitoring proton radiation therapy with in-room PET imaging." *Physics in Medicine & Biology*, Vol. 56 (No. 13), p. 4041, (2011).

26- Martin Jermann, "Particle therapy statistics in 2014." *International journal of particle therapy*, Vol. 2 (No. 1), pp. 50-54, (2015).

27- Cai Grau, Marco Durante, Dietmar Georg, Johannes A Langendijk, and Damien C Weber, "Particle therapy in Europe." *Molecular oncology*, Vol. 14 (No. 7), pp. 1492-99, (2020).

28- Jan Hrbacek *et al.*, "Practice patterns analysis of ocular proton therapy centers: the international OPTIC survey." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 95 (No. 1), pp. 336-43, (2016).

29- Manjit Dosanjh, Ugo Amaldi, Ramona Mayer, and Richard Poetter, "ENLIGHT: European network for light ion hadron therapy." *Radiotherapy and Oncology*, Vol. 128 (No. 1), pp. 76-82, (2018).

30- TT Böhlen *et al.*, "The FLUKA code: developments and challenges for high energy and medical applications." *Nuclear data sheets*, Vol. 120pp. 211-14, (2014).

31- Alfredo Ferrari, Johannes Ranft, Paola R Sala, and A Fassò, FLUKA: A multi-particle transport code (Program version 2005). (No. CERN-2005-10). *Cern*, (2005).