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Heavy Charged Particles: Does Improved Precision and Higher Biological Effectiveness Translate to Better Outcome in Patients?

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Protons are the most common charged particles used in oncology. Acceleration of heavier ions requires larger accelerators and is more expensive, yet heavy nuclei share the same advantageous dose-depth profile characteristics of protons and have potential additional advantages. These advantages are related to the physical characteristics of the beam, owing to reduced lateral scattering and sharper lateral penumbra. In addition, heavy ions produce an increased biological response. In fact, in the target region heavy ions behave as densely ionizing radiation, which produce distinct biological effects compared to sparsely ionizing x-rays and protons. The translation of the putative radiobiological advantages into clinical advantages remains to be demonstrated. Eleven centers worldwide are currently using carbon ions for treatment of different solid tumors. Phase-II trials in Japan and Germany show very promising results for selected tumors, such as chordomas, large sarcomas, and pancreatic adenocarcinoma. Phase-III trials are under way to compare carbon ions to protons or x-rays.

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Introduction

Robert Wilson first proposed the use of protons for radiotherapy in 1946.[1] The idea was based on the favorable depth-dose distribution compared to x-rays (Fig. 1). Ions heavier than protons obey the same laws (Bethe-Bloch formula) of energy deposition as protons, and of course have Bragg peaks (Fig. 1).[2] They can have further advantages, both physical and biological. This rationale justified the first pilot project directed by Cornelius A. Tobias at the Lawrence Berkeley Laboratory (LBNL, Berkeley, CA), where 433 patients were treated from 1975-1992 with different heavy ions (He, Ne, N, O, C, Si, and Ar).[3] The project was closed with underwhelming results, but the idea was retrieved by Japanese researchers, who concentrated on the use of high-energy carbon ions at the National Institute for Radiological Sciences (NIRS) in Chiba[4] (now renamed in National Institute for Quantum and Radiological Science and Technology, QST). Use of C-ions was then brought to Europe by Gerhard Kraft, who launched a pilot project at the GSI Helmholtz Center in Darmstadt in Germany.[5] The system at GSI was then moved to the clinical environment in Heidelberg at the Heidelberg Ion-beam Therapy Center (HIT), the center that has treated the most patients with heavy ions in Europe.[6]

The putative advantages of ions heavier than protons are related to both physical and radiobiological properties. From the physics point of view, the reduced lateral scattering is attractive. However, certainly the greatest potential lies in the biology: increased relative biological effectiveness (RBE), reduced oxygen enhancement ratio (OER), and potentially specific, unique effects of densely ionizing radiation, such as reduced angiogenesis and augmented immune response. The number of patients treated with heavier ions is, however, still low: only about 15% of those treated with protons. Heavy ions centers are in fact more expensive than proton centers, and only a few are in use. In 2017, there were 11 centers worldwide treating patients with heavy ions, all of them using ^{12}C-ions: 5 in Japan, 2 in China, and 4 in Europe. The 3 more centers are under construction in China, Korea, and Iran, and there are now solid plans to build a C-ion center in United States,[7]

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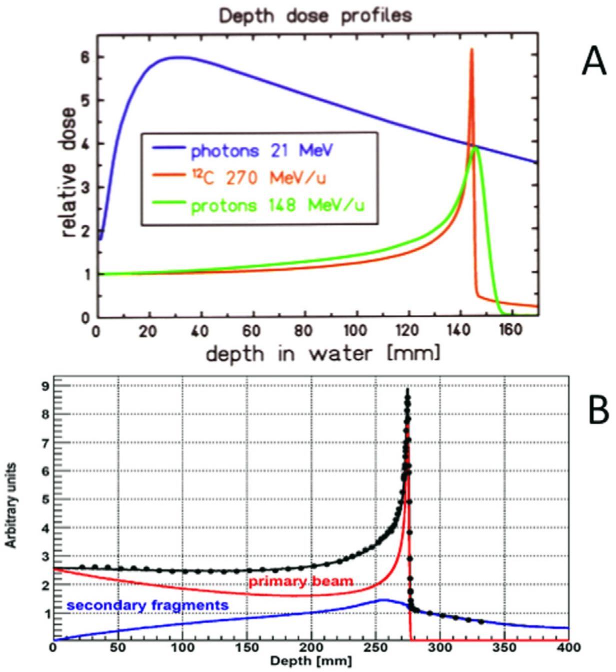

Figure 1 Physical differences between heavy ions and protons. (A) Depth-dose curves for x-rays, protons, and C-ions. The energy of the 2 particles is selected to provide the same range. The increased longitudinal straggling for protons in shown. (B) Calculated Bragg curve for carbon ions, showing the contribution of the different nuclear fragments to the dose. Image (A) courtesy of GSI image gallery, FLUKA Monte Carlo calculation in (B) courtesy of Vincenzo Patera and Andrea Mairani. (Color version of figure is available online.)

where heavy ions had been abandoned following the LBNL trial, while many proton centers were installed nationwide.

In this article, we will first review the physical and biological rationale for the use of heavy ions, and then review the clinical evidence.

Physics

The physical properties of ions heavier then protons present some distinct differences that have an impact in radiotherapy.[2,5,8-10] The energy loss by electromagnetic interaction with target electrons is described by the Bethe-Bloch formula, which applies to both protons and heavier ions:

$$-\frac{dE}{\rho dx}=k\frac{z_p^2}{\beta^2}\cdot\frac{Z_T}{A_T}\left[f\left(z_p;\beta;I\right)\right] \tag{1}$$

where k is a constant, z_p and β the charge and relative velocity of the projectile, respectively; Z_T, A_T, and ρ the atomic number, mass number, and density of the target material, respectively; and f is a correction term (relativistic correction, shell corrections, Barkas term, and Mott and density corrections). The Bethe-Bloch formula shows that the energy loss per unit track length (linear energy transfer, LET) is proportional to z_p^2/β^2. The LET therefore increases for heavy ions. Typical ranges of LET values in a typical spread-out-Bragg peak (SOBP) are shown in Figure 2. The figure shows the rationale for the choice of C-ions. In fact, the LET in the entrance channel should be as low as possible, to minimize normal tissue toxicity, while the LET in the SOBP should be high to overcome intrinsic radioresistance and hypoxia. Carbon ions represent an excellent compromise, with an entrance LET (in water) of 11-14 keV/μm and an LET range along the SOBP ranging 40-80 keV/μm, and higher in the distal edge. Ions heavier than oxygen have a high RBE already in the entrance channel. Moreover, nuclear fragmentation jeopardizes the Bragg curve in the plateau region, which is not flat anymore but shows a decrease of the dose with depth.

Nuclear fragmentation is in fact another physical difference between protons and heavy ions. Both produce target fragments, but protons of course do not undergo fragmentation after nuclear interactions, whereas heavy ions break into lighter fragments. These fragments have similar velocity and direction of the primary ions, and consequently larger range. They generate a “dose tail” beyond the Bragg peak, which is not observed with protons. The mean free path for high-energy carbon in water is approximately 25 cm, meaning that only about 50% of the accelerated ^{12}C-ions actually reach a deep tumor, the other undergoing nuclear fragmentation. However, in most practical cases, the tail is within the high dose region in the patient, because opposite beams are used. Fragmentation can also be beneficial for the treatment. In fact, the production of radioactive isotopes, such as the β-emitting ^{11}C, can be exploited for image guidance in heavy ion therapy.[11] Positron emission tomography was used at GSI for treatment monitoring and range verification,[12] and offline positron emission tomography imaging is also used in several other C-ion centers.[13]

Other differences in the physics of protons and heavy ions are in the longitudinal and lateral scattering, described by the equations:

$$\frac{\sigma_{R1}}{\sigma_{R2}}=\sqrt{\frac{M_2}{M_1}} \tag{2}$$

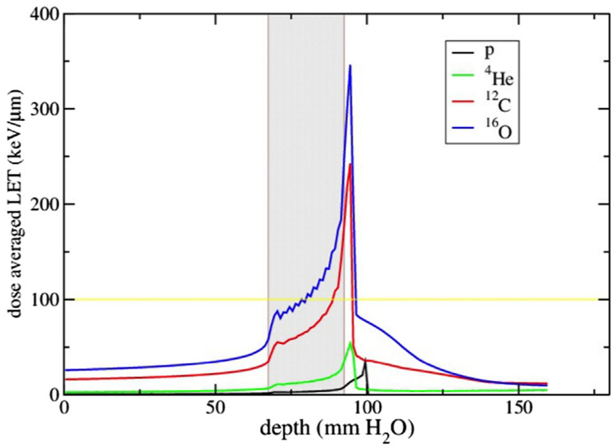

Figure 2 Calculated dose-average LET along a SOBP for different ions. Vertical lines show the target volume. The yellow horizontal line correspond to 100 keV/μm. For LET above this value, the RBE is high and the OER drops to 1 (Fig. 4). Calculation by TRiP98, courtesy of Emanuele Scifoni. (Color version of figure is available online.)