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Antiprotons

The biological effectiveness of antiproton irradiation

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Abstract

***Background and purpose*: Antiprotons travel through tissue in a manner similar to that for protons until they reach the end of their range where they annihilate and deposit additional energy. This makes them potentially interesting for radiotherapy. The aim of this study was to conduct the first ever measurements of the biological effectiveness of antiprotons.**

***Materials and methods*: V79 cells were suspended in a semi-solid matrix and irradiated with 46.7 MeV antiprotons, 48 MeV protons, or ^{60}Co γ-rays. Clonogenic survival was determined as a function of depth along the particle beams. Dose and particle fluence response relationships were constructed from data in the plateau and Bragg peak regions of the beams and used to assess the biological effectiveness.**

***Results*: Due to uncertainties in antiproton dosimetry we defined a new term, called the biologically effective dose ratio (BEDR), which compares the response in a minimally spread out Bragg peak (SOBP) to that in the plateau as a function of particle fluence. This value was $\sim$3.75 times larger for antiprotons than for protons. This increase arises due to the increased dose deposited in the Bragg peak by annihilation and because this dose has a higher relative biological effectiveness (RBE).**

***Conclusion*: We have produced the first measurements of the biological consequences of antiproton irradiation. These data substantiate theoretical predictions of the biological effects of antiproton annihilation within the Bragg peak, and suggest antiprotons warrant further investigation.**
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For conventional photon irradiation, the maximum dose that can be delivered to a tumor is limited by the tolerance of irradiated adjacent normal tissues. Several technological improvements in radiation delivery, including intensity-modulated radiotherapy (IMRT), have made it possible to confine the high-dose region to almost any target volume of interest and thus reduce the dose to adjacent tissues [1–3]. However, even with these techniques, normal tissue tolerances can prevent delivery of a dose sufficient to achieve tumor cure. IMRT also results in a larger total body exposure and thus an increased risk of secondary cancers [4]. For many types of tumors, this has led to unacceptably low tumor control probability (TCP) and to high levels of morbidity. An alternative approach involves the use of protons and other heavier ions [5–8]. For these charged particles, both the amount and rate of energy deposition increase dramatically as the particle nears the end of its range. This results in a large enhancement in absorbed dose at a precise depth in tissue (the Bragg peak) compared with the dose deposited at the entrance to the body (the

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plateau). For treatment purposes, the position of the Bragg peak needs to be spread out to cover the tumor volume and the production of such a spread-out Bragg peak (SOBP) results in a build up of plateau dose and hence a reduction in the ratio of dose in the SOBP relative to the plateau. However, in contrast to photons, the dose in the SOBP that covers the tumor volume remains larger than that in the normal tissue entrance region. High linear energy transfer (LET) particles such as carbon ions also produce a much higher ionization density in the Bragg peak region and consequently an increase in the relative biological effectiveness (RBE) of the dose deposited in the tumor [9–11]. This provides a potential further therapeutic advantage, especially for tumors that have a large hypoxic fraction or for those that are resistant to conventional radiation [12]. Furthermore, since very little dose is deposited distal to the Bragg peak, charged particles are ideally suited for treatments of tumors close to radiosensitive regions. These favorable physical and biological characteristics have led to recent developments of proton and heavy ion cancer therapy centers worldwide.

Conversion of the mass of a proton–antiproton pair during annihilation constitutes the highest density energy source currently available. This has led to a number of proposals for practical applications of antiprotons, including radiotherapy, which is feasible with current antiproton production technology [13]. Like other charged particles, antiprotons deposit most of their kinetic energy near the end of their path in the Bragg peak. In addition, as an antiproton comes to rest it annihilates, depositing additional energy in the form of particles that may have a significantly enhanced biological effectiveness [14]. The majority of the total annihilation energy of 1.88 GeV is carried away by high-energy pions, neutrons and γ-rays. We have estimated (unpublished data) that the dose deposition from these particles is of a similar magnitude to that reported for a passively degraded proton beam [4]. However, at the Bragg peak it has been estimated that antiprotons deposit an additional 30 MeV within a few millimeters of the annihilation vertex [15]. The only experimental data relevant to the application of antiprotons for biological purposes were produced by Sullivan [16], who measured the relative physical dose deposition in the plateau and the Bragg peak regions for antiprotons at the low energy antiproton ring (LEAR) at CERN. He found that although the additional local dose deposited is small compared to the total annihilation energy, it does represent an approximate doubling of the physical dose deposited per particle in the Bragg peak compared to protons. Furthermore, the RBE of this additional dose is likely to be significantly higher than that for protons because it is due partly to recoiling heavy fragments produced in the annihilation event with short range and high LET. The remainder of the annihilation energy that is carried away,outside of the body, could potentially be used for real-time imaging of the dose distribution.

To date there has been no attempt to assess the biological effects of antiprotons. This stimulated us to initiate an experiment, AD-4/ACE [17,18], running at the antiproton decelerator (AD) at CERN, to measure the biological effects of antiproton irradiation and compare it to the results achievable with protons.

Materials and methods

Beam characteristics

The AD at CERN delivered a 200–500 ns beam pulse containing approximately 3×10^7 antiprotons every 85 s. For our experiment the extraction energy was 46.7 MeV. In order to spread the Bragg peak we used a ridge filter consisting of a plastic sheet machined with a matrix of pixels $\sim$1 mm^2 in area. Three pixel thicknesses (1, 1.8 and 2.6 mm) were used at a ratio of 41:31:28 to create a SOBP as smooth as possible over a distance of slightly more than 2.5 mm. The degrader was placed 25 cm upstream of the target so that the lateral straggling together with the free drift in air would remove any radial dose inhomogeneity from the degrader in the samples. A schematic of the set-up is shown in Fig. 1.

For proton irradiation, we utilized the treatment facility located at TRIUMF, details of which have been previously published [19]. The energy was reduced to 48 MeV with a range shifter to closely match the energy of the antiproton beam. The proton Bragg peak was also spread out over an area slightly larger than 2.5 mm using a two-step rotating wedge filter in order to create a dose profile which matched that of the antiproton as close as possible.

For ^{60}Co irradiation, a Theratron unit at the Vancouver Cancer Centre was used as described previously [19].

Dosimetry

Due to the pulsed nature of the antiproton beam it was not possible to use currently available dosimetry equipment to measure absorbed dose. The large number of antiprotons delivered in such a short period of time leads to saturation, non-linearity and unreliability of conventional equipment such as ionization chambers. Thus, in order to estimate the absorbed dose and the relative depth dose profile we carried out a Monte Carlo simulation based on measurements of antiproton fluence using the MCNPX code [20]. Antiproton fluence was monitored using two independent methods. After the ridge filter the antiproton beam passed through a current monitor (Bergoz[1] BCM/ICT) capable of integrating a pulse with rise times as short as a few picoseconds without significant loss. The voltage was then held level for about 400 μs for read-out. The signal processor used two integrating windows to correct for baseline noise and therefore achieved high accuracy for low beam current. In our set-up the sensitivity was 1 mV/6.3×10^5 antiprotons, resulting in a typical read-out of 50 mV per pulse. The noise was less than 5 mV, allowing a fluence measurement to within 10%. We also received a signature from the accelerator on the number of antiprotons having left the ring upon ejection, which was typically within 20% of the ICT measurement indicating a high-transfer efficiency to our experiment.

In order to estimate the dose with Monte Carlo methods, it was also necessary to determine the radial-beam profile, and thus the fraction of antiprotons that enter the biological sample. We monitored the integrated beam profile using GAF chromic film, which darkens in a linear way with dose. Because the sensitivity is low, it was necessary to integrate

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