AD-4/ACE The relative biological efficiency (RBE) of antiprotons. Combined data Analysis for the 2008 – 2012 runs

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Phase I of the AD-4 experiment used a 50 MeV antiproton beam which provided a penetration depth of only a few centimeters. With no absolute dosimetry of the antiproton beam available at the time the collaboration studied the combined effect of dose enhancement and biological effectiveness through the Biological Effective Dose Ratio (BEDR) by measuring the ratio of effects of antiproton irradiation on V79 Chinese Hamster cells in the peak region and the plateau region and then compared this ratio to the same measurement performed with protons at TRIUMF. The collaboration reported an enhancement of the BEDR of antiprotons compared to protons of a factor of 4 [1].

In phase II of the AD-4 experiment, starting in 2006, the collaboration aimed to directly measure the relative biological effect (RBE) of antiprotons vs. depth in a clinically relevant beam. For this purpose we asked the AD Operations team to provide us with an antiproton beam of 502 MeV/c momentum which exhibits a penetration depth in water of approximately 10 cm (allowing for energy loss in beam monitors and target chamber wall). A 7 step degrader system consisting of PMMA slabs of 0 to 12 mm in 2 mm steps was used to produce a Spread-Out Bragg Peak (SOBP).

RBE is defined as the ratio of the dose of a reference radiation (typically ^{60}Co gamma rays) and the dose of the studied irradiation that produce the same biological endpoint, which in our case consisted of 10% clonogenic survival of V79 cells. According to this definition the two critical parameters which need to be extracted from the experiment are the clonogenic survival for different dose points and the dose applied at any given depth in the target.

Monte Carlo Assisted Dosimetry

As direct dosimetry of the antiproton beam in the target area is not possible we resorted to the method of Monte Carlo assisted dosimetry: A standard calibrated ion chamber (PTW Advanced ROOS chamber) was mounted directly in front of the target tank and was used to obtain the total number of primary particles entering the target volume. In addition the beam profile and radial position relative to the center of the target were monitored for each irradiation set with a radiochromic film mounted directly behind the ion chamber. Using this information and assuming an axis parallel beam with zero divergence we then used the Monte Carlo package FLUKA 2011 Version 2c.1 Jul-15 [2] to calculate the dose vs. depth in the 6 mm

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diameter gel tube imbedded with V-79 WRNE Chinese Hamster cells. In the last years of the experiments we also had added a thin monolithic pixel detector in front of the ion chamber which allowed shot-to shot observation of the beam spot. This detector not only turned out to be a very useful tool during beam tune and to detect problems with the beam delivery within a few shots, but also proved that the beam center normally did not move in radial direction between irradiations. Therefore we assigned the variation of the position of the beam center on the GAF-chromic film to an uncertainty in the definition of the radial position of the beam used in the FLUKA calculation.

A direct measurement of the beam divergence at the target location was not feasible with the instrumentation available to us, but a Monte Carlo study using values for the divergence between 0 and 8 mrad showed that the effect on the dose calculation was less than 5%. An independent estimate of the divergence based on emittance measurements provided by the AD-Operation team returned a value for the divergence below 1 mrad, and we concluded that beam divergence effects on the dose calculation are negligible.

Biological Assay

The actual biological target consists of a gelatin matrix of 6 mm diameter in which V79 cells have been imbedded. After irradiation the gel is extruded from the surrounding ABS tube and 2 mm slices are taken at 10, 30, 50, 70, 80, 84, 86, 88, 90, 92, 94, 96, 98, 100 mm depth. These slices are dissolved, cells are extracted and using a cell sorter a specified number of cells are placed in a growth medium. Here the surviving cells will divide and grow colonies of approximately 50 cells within a few days. The number of surviving cells placed into the growth medium needs to be carefully chosen: If too many healthy cells are placed in a single Petri dish competition between colonies will result in growth stagnation, if too few surviving cells are placed in the medium the number of colonies will be very low and the statistical error will be large. We typically used 4 independent wells for each depth-dose point and obtained an average and the standard deviation of the number of surviving cells to be used in the analysis.

An additional input for the analysis is the so-called Plating Efficiency (PE) which accounts for natural cell death independent of the irradiation. The number of surviving cells obtained from the above method needs to be corrected for the PE before the true survival fraction after irradiation is obtained. PE is typically extracted by using target tubes that have undergone the exact same treatment as the other tubes (including travel from Denmark to CERN and back, and being present in the AD Hall during the experiment, etc.) but have not been irradiated with antiprotons. Another method that can be used is fitting the measured survival fractions in the plateau region to the double exponential formula (see below) including the plating efficiency as an additional parameter.

Extraction of RBE for the individual runs

To obtain the final combined analysis of the runs from 2008 to 2012 we recalculated the depth - dose curves as described above with the current FLUKA release available on the FLUKA website. This was necessary as during the past years interactions between the ACE collaboration and the FLUKA development team had resulted in a number of improvements of the physics description of low energy antiprotons stopping in the biological medium.

Dose dependency of biological effects (in our case clonogenic survival fraction - SF) are typically described by the double-exponential equation

$$SF = \exp[-\alpha D - \beta D^2]$$

We plot for each depth slice of a given run the survival fraction, corrected for plating efficiency, and the error bars vs. dose. To allow for more stable fits we used the logarithmic form of the standard double exponential description

$$LN(SF) = -\alpha D - \beta D^2$$

from which we extract α, β, and the standard deviations $\sigma\alpha$ and $\sigma\beta$. Using α and β we obtain the dose resulting in 10% clonogenic survival ($D_{10\%}$) which then is compared to $D_{10\%}$ obtained with ^{60}Co gamma-ray irradiation to extract the value of RBE for each depth point analyzed.

To obtain an estimate of the error for $D_{10\%}$ we add two additional curves to the plot using

$$LN(SF) = -(\alpha \pm \kappa * \sigma\alpha)D - (\beta \pm \kappa * \sigma\beta)D^2$$

where we chose κ such that at least 63% of the data points lie between the two curves. Using $\kappa * \sigma\alpha$ and $\kappa * \sigma\beta$ we then extract the maximum and minimum value for $D_{10\%}$ for each data point. Figure 1 shows a representative example of this method.

At the end we use the average of the RBE values obtained for a given depth slice in the different runs and combine the individual errors obtained as described above to arrive at the final result shown in figure 2 where we show the average RBE vs. depth for the years 2008 – 2012 overlaid with a representative depth - dose curve from the 2012 run.

This method is valid as long as the differences between the individual values is no larger than a few standard deviations, indicating that we average values from a data set describing the same physical quantity. This condition turns out to be fulfilled for all depth slices except the very last one. It turns out that the 100 mm slice is on the very distal edge of the Bragg curve and small deviations of the exact depth - dose distributions (caused for instance by small differences in the gel density, or minute

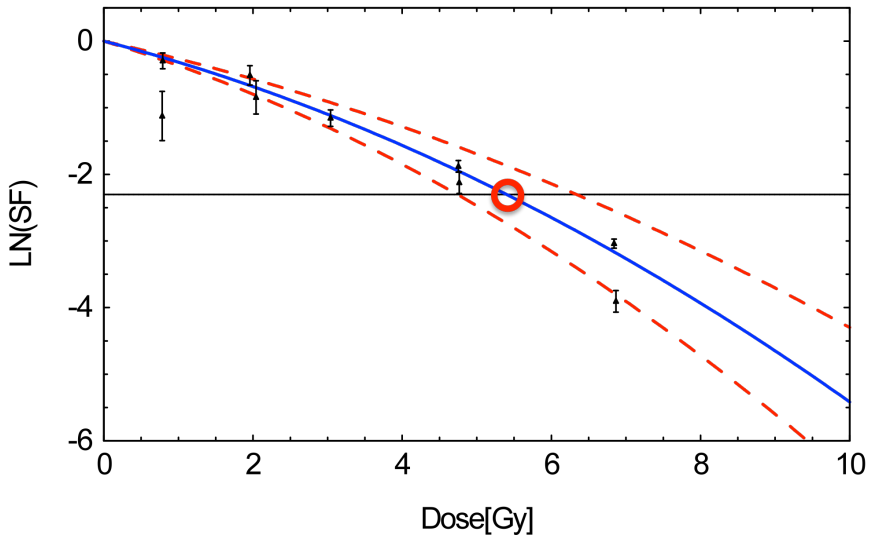

Fig. 1: Representative data set for the 84 mm depth slice showing the two additional curves based on $\kappa*\sigma\alpha$ and $\kappa*\sigma\beta$ as described in the text.

variations in the thickness of additional material in front of the tank) can cause a large variation of dose. We therefore include this point with a different symbol and indicate the error as the standard deviation of the individual measurements.

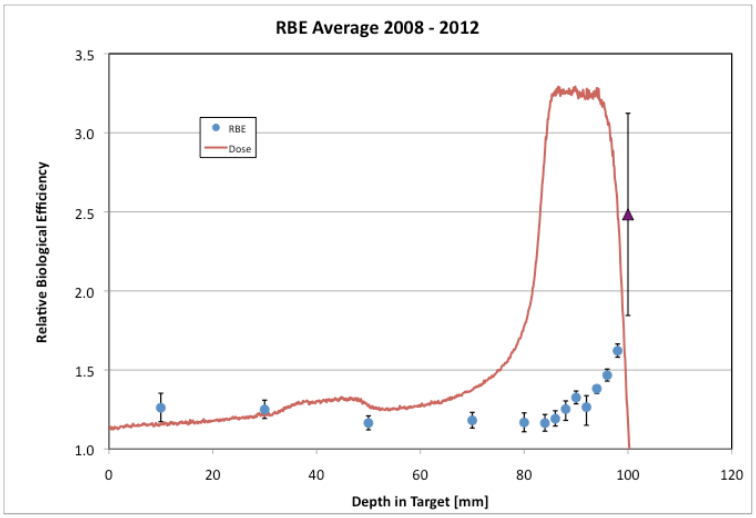

Fig. 2: RBE vs. Depth for 10% clonogenic survival of V-79 WRNE Chinese Hamster cells irradiated with antiprotons at 502 MeV/c momentum. The red curve shows a representative dose profile, plotted in arbitrary units without a displaced zero.

Discussion on error bars

Aside from the statistical errors indicated in figure 2, the overall result can be affected by systematic errors. On the biology end of the experiment the error of the plating efficiency would affect all survival fraction values in a given run identically, resulting in a possible shift of the RBE curve in the vertical direction. But the direction and magnitude of such a shift would be different from set to set. On the physics side in a similar way the uncertainty in the dose calculation due to the beam definition again would move the RBE vs. Depth curve up or down, again differently for the different sets.

The collaboration is currently discussing how to implement this in the final result. One possibility would be to add the individual errors of the different sets in quadrature to the individual statistical errors assigned to the individual data points, but this might lead to an overestimate of the error bars as these shifts already are contained to some extent in the averaging procedure.

Summary

AD-4/ACE has achieved the first experimental determination of the relative biological effectiveness of antiprotons. These data confirm the general expectation of an increased biological effect of antiprotons in the Bragg peak region, and place realistic numbers on this enhancement. An important observation is that the increase in RBE is strongly confined to the Bragg Peak area and that the RBE is only slightly higher than for protons in the entrance channel. The results of this work, together with the earlier established fact that antiprotons deliver a much enhanced dose in the Bragg peak compared with protons [1], make it worthwhile to investigate further the clinical therapeutic potential of antiproton cancer therapy. In principle our data could be used to define dose kernels including the biological effectiveness and use those for dose planning exercises to search for specific cases of radiotherapy were these unique features of antiproton irradiation could provide a benefit compared to other modalities. No antiproton source with the required intensity and beam delivery method for radio-therapeutic applications currently exists, and these exercises would be purely academic, but could prepare the discussions for the time when future antiproton facilities come on line.

References:

[1] M.H. Holzscheiter et al.; Radiotherapy and Oncology 81 (2006) 233–242

[2] Fassò, A., Ferrari, A., Ranft, J. & Sala, P. FLUKA: A multi-particle transport code. CERN-2005-10 (2005).