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Letter to the Editor

The Impact of Protons on the Incidence of Second Malignancies in Radiotherapy by Eric J. Hall; 6, Suppl. 31-34 2007

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The article on "The Impact of Protons on the Incidence of Second Malignancies in Radiotherapy" by Eric Hall, which appeared in Technology in Cancer Research and Treatment, contains some misleading statements. This letter tries to clarify some aspects about the dose associated with neutrons in proton radiation therapy.

A Representative Curve for Lateral Neutron Doses in Proton Therapy

The article by Dr. Hall shows a curve (Figure 4) of neutron dose as a function of lateral distance to the field edge in passive scattered proton therapy and compares the data with scattered doses to be expected from photon therapy (3D conformal and IMRT) and proton beam scanning.

Figure 4 was created originally to show the worst case scenario of what one could get with a non-optimized proton beam delivery system. Thus, the data present a very conservative estimation. To do so, the original experimental data (1) were simply scaled up by a factor of 5 to a 1000 cm^3 target volume (the measurement referred to a smaller field) in order to compare with the 10×10×10 cm^3 photon and scanned proton fields shown in the same figure. However, if one would aim for a realistic estimation, the treatment head generated neutron yield would actually decrease with increased field size because of a bigger ratio of aperture opening versus field size impinging on the aperture (2). Protons stopped in the aperture can potentially generate neutrons. Consequently, the values in Figure 4 for passive scattered protons are overestimated by about one order of magnitude (3, 4). The curve for passive scattering does not, as far as I know, resemble any existing facility treating patients. It is highly misleading to use this figure as a representative example for passive scattered proton beam treatments. Dr. Hall's article gives the impression that the data shown are for a typical case: "*The consequences of this exposure are shown dramatically in Figure 4, which shows doses beyond the edge of the treatment field for X-rays and for protons with passive modulation and for spot scanning. Passive modulation results in doses distance from the field edge that are 10 times higher than those characteristics of IMRT with X-rays*." This general statement about proton therapy is not only misleading, it is incorrect. Other published data for passive scattered proton therapy systems show doses lateral to the field that are much smaller than the ones shown in Figure 4 (1, 2, 5-10). The measured data in references (2) and (10) even show neutron doses as a function of lateral distance to the field edge for a specific treatment situation that are one order of magnitude below the shown scattered dose from IMRT.

Dr. Hall published a similar article in 2006 (11), in which basically the same figure (Figure 4) was used as in the present article. Subsequently, in Letters to the Editor at that time (3, 4), it was pointed out that this figure does not show a representative neutron contamination for passive scattered proton therapy. Dr. Hall responds to this criticism in the present article in writing that "*When these data were published in 2006, the proton group at Harvard criticized the conclusions because the data for passive modulation in Figure 4 were measured at the Harvard cyclotron, which is now obsolete. In a letter to the International Journal of Radiation Oncology, Biology, Physics, Dr. Gottschalk, the acknowledged expert in the design of scattered systems for proton facilities, claimed that the doses for passive modulation in Figure 4 are too high by a factor of 9. Figure 5 takes this into account and reduces the doses outside the field by this factor; they are still comparable too, or slightly higher than for IMRT with a Linac*." This explanation for the dismissal of Figure 4 is incorrect. The data were not dismissed because they are based on experiments at the Harvard Cyclotron but because the field size correction used to generate the data is unrealistic. Unfortunately, the statement in Dr. Hall's article implies that patients at the Harvard Cyclotron were exposed to such neutron doses. This is not true because the data are not based on a configuration that would have been used for treating patients.

In order to correct for the unrealistic scaling in Figure 4, Dr. Hall did reduce the values by a factor of 9 (to come up with Figure 5). While this would result in a realistic curve for that particular beam and treatment head configuration, it still cannot be used for a general conclusion about neutron doses. In fact, these data were measured with a very small aperture (1) and should, therefore, show neutron contributions above average. Generally, it is not feasible to show a representative curve for neutron doses associated with proton beam therapy. The amount of neutrons (and their energy) produced in the treatment head of a proton therapy machine for broad-beam modulation depends on several factors, *e.g.*, the characteristics of the beam entering the treatment head, the material in the double scattering system and the modulator wheel, and the field size upstream of the final patient specific aperture. The latter can easily cause neutron dose variations of about one order of magnitude. The neutron dose is highly facility dependent because of differences in position and design of devices in the treatment head. Even for the same facility there are huge variations from field to field because the treatment head geometry and the beam characteristics in passive scattered proton therapy are patient field specific.

Other Factors Influencing Secondary Cancer Risk When Comparing Proton Therapy with Photon Therapy

The rationale for using proton beams instead of photon beams is the ability to escalate dose without further compromising critical structures. Because of their physical characteristics proton beams will deliver significantly less integral dose than any type of photon beams. Thus, even though there are cases in which photon beam delivery (IMRT) might achieve comparable dose conformality to the target, the primary dose outside the target structures will always be higher with photons than it is with protons. The likelihood of developing secondary cancer depends on the entire irradiated volume (*e.g.*, radiation-induced carcinomas) and on the volume of the high-dose region (*e.g.*, radiation induced sarcomas). Thus, of concern when it comes to second malignancies are not only the dose far away from the target (as for example deposited indirectly by neutrons), but also the dose delivered in the beam path. The volume of non-target tissue treated at or above 30% of the prescribed dose is generally reduced by more than a factor of 2 with protons, compared to IMRT (12). This gain in integral dose has the potential for a reduction in secondary cancers after using proton beams compared to photon beams (by factors 2-15) (13, 14).

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