Brain Tolerance to Radiosurgery

To The Editor: I have read with interest the article by Marks and Spencer (Marks LB, Spencer DP: The influence of volume on the tolerance of the brain to radiosurgery. J Neurosurg 75:177-180, August, 1991). The article alerts the reader to the potential underestimation of the risk of stereotactic radiosurgery in the treatment of humans bearing arteriovenous malformations. Closer examination of the underlying assumptions and methodologies in this study, however, warrants comment.

Clinical side effects such as weakness or lethargy following stereotactic radiosurgery are due to transient edema or demyelination and are quite different from the compared endpoint (that is, brain necrosis following proton beam irradiation). The threshold for brain necrosis is higher than the thresholds for edema or transient demyelination, which all exist on the continuum of the dose-complication curve in human brain radiotherapy. Yet, the dose-response analysis in this study ignores this important difference. If the 1% line which would describe transient demyelination or edema were positioned even a small interval below the 1% necrosis risk line (a reasonable assumption), the worst case scenario would include only three (1.2%) of the 255 patients, as four patients’ coordinates practically reside on the existing 1% necrosis line. Lack of any statistical evaluation of Kjellberg and Abe’s published thresholds (for example, confidence intervals for the width of the line), further complicates this evaluation. Additionally, as the authors state, Kjellberg and Abe never intended their isonecrosis lines to be applied uniformly to all parts of the brain. Why then, as is stated in the introduction, should the accuracy of this measured dose-necrosis relationship in animals be “confirmed” in humans, under very different circumstances? Finally, by estimation using Figs. 1 and 2, Kjellberg and Abe’s 5% line reasonably predicts the risk of complications, while the 25% line overestimates such risk.

Comparisons of dose-complication rates among disparate beams, even for single fraction studies, are difficult for two reasons. First, the integral dose (product of volumes irradiated from the surface of brain to target and dose per volume at each increment toward the target) is very different for each modality. The dose per interval volume peaks exponentially in the target (Bragg peak) for protons and alpha particles, but decreases constantly over the interval traveled for photons. Hence, the proportion of normal brain irradiated will be lower after particle irradiation in comparison to that following photon irradiation. This difference may approach 50%, warranting examination of the relationship between total volume irradiated and complication rates.

Second, the relative biological effectiveness (RBE) of protons and helium ions is higher than that for photons. That is, for any given total dose (rad) the measured biological effect (usually tumor cell kill) is greater following charged particle treatment. If proton treatment possesses a greater RBE for late effects (necrosis) than photons, Kjellberg and Abe’s 1% line would be shifted proportionately to the left, lowering the threshold for complications to perhaps include the authors’ seven patients residing “below” the threshold for complications.

In summary, the demonstration of complications in patients treated with single fractions of ionizing radiation is of interest, but no one, including Kjellberg and Abe, ever stated that the 1% line was applicable across a broad spectrum of measured endpoints including edema, transient demyelination, or necrosis, or was applicable across very different administered beam characteristics. If physicians elect to employ such a dose-volume relationship in stereotactic radiosurgical treatment planning, they should do so with care.

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References

Response: We appreciate Dr. Williams’ comments regarding our recent article. We fully recognize that clinically significant radiation reactions (CSRR) may occur at doses lower than those required to cause necrosis. This is largely our point. The reason for using CSRR instead of necrosis is discussed in the article (paragraph 2 of the Materials and Methods and paragraph 3 of the Discussion sections). In reviewing the literature and scoring patients on their CSRR, we were careful to exclude patients with only mild reactions and those with early acute reactions. Furthermore, we excluded patients with radiographic evidence of significant radiation injury who were symptom-free (histological necrosis in a clinically “silent” area of the brain is certainly possible). Since necrosis may or may not cause...
symptoms, and since the symptoms are most important to the patient, we felt that CSRR were a more appropriate endpoint.

The major difficulty in attempting to determine the position of an isoeffect line is that the human data published are rarely complete. Unfortunately, it is not possible to say that, with a small downward adjustment of the line, the rate would be 1.2%, as we do not know how many of the patients have been treated to doses below the line (as discussed in the article). Thus, the 1.2% noted by Dr. Williams would only serve as a lower limit, and the upper limit would remain at approximately 8%. As to assessing the 5% and 25% risk lines, the same problem pertains. As we state in our paper, without the complete data (including the minimum target dose, target diameter, target volume, location of the target, and prescription isodose line) for all patients (both those with and those without CSRR) it is not possible to determine the relationship accurately.

In response to Dr. Williams' second point, we do recognize that it is extremely difficult to compare results from different centers that use different irradiation techniques. This problem is discussed in our article. We also appreciate that some measurement other than the target diameter might be more appropriate. A better method might be to make use of dose-volume histograms where the dose to particularly sensitive structures can be analyzed separately. This obviously is a much more demanding problem which we did not attempt to solve. Furthermore, while the integral dose to the whole brain is different for the various techniques used, the ultimate dose to the target volume is fairly similar for the various irradiation techniques, and it is this high-dose region that is likely associated with CSRR.

We thank Dr. Williams for bringing up the interesting issue of relative biological effectiveness (RBE). Kjellberg's original isodose lines were based upon data from four sources: 1) proton irradiation of monkey and human brain; 2) proton irradiation of mouse brain; 3) photon irradiation of rabbit brain; and 4) photon irradiation of human spinal cord. It is difficult (at best) to appropriately adjust for the physical and biological differences in these studies. Thus, Kjellberg's proposed 1% risk line was not based solely on proton data.

Even if the doses associated with Kjellberg's line were proton doses, in practical terms, the RBE of protons is approximately 1 to 1.1. While it is true that the RBE is theoretically higher within the Bragg peak, this peak is physically very small and a useful beam is obtained by modulating it (the position of the peak is moved within the lesion). Therefore, any one area of the target receives much of its dose from the plateau (or non-Bragg peak) portion of the particle tract where the RBE is approximately 1.3.

In addition, if we consider the RBE for protons to be significantly greater than 1 (as suggested by Dr. Williams) then the data in Fig. 2 of our article would need to be adjusted, since four of the six studies included used photon irradiation. Considering the units of the y axis to be photon dose, Kjellberg's line would need to be moved up (since the photon equivalent dose is greater than the physical proton dose; RBE > 1), not "to the left" as suggested by Dr. Williams. This upward shift would have further supported our conclusions. An alternative way to look at this would be to leave Kjellberg's line where it is and to move the photon points downward (to "proton equivalent" doses).

Contrary to protons, the RBE for helium ions (as used by the Berkeley group) is approximately 1.3, and therefore the points in Fig. 2 from the Berkeley study should be moved up by approximately 30%. Only one of the five points from the Berkeley study was below the line, and moving this point up 30% would have left it still below the 1% line. However, the Berkeley patients were treated with a fractionated technique. If we wanted to "correct" for their fractionation scheme and calculate the "biologically effective" single fraction dose, this would have moved the 5 points from the Berkeley series to lower doses on the y axis and would more than compensate for the upward RBE correction.

Alternatively, we could have just omitted the data from Berkeley from our analysis and have avoided the difficulty of dealing with RBE and fractionation issues. If this were done, the total number of patients in our study (Table 1) would have been 231, with 18 of the patients developing CSRR, for an overall rate of 7.8%. This is really not dissimilar from the results that we obtained by including the Berkeley study.

We agree that Dr. Kjellberg's line should be used with care as should our data. It is our hope that the rapid growth and application of this important technique will be paralleled by an equally rapid growth in our understanding of the influence of volume and location on the tolerance of the brain to radiosurgery. While we believe that Dr. Kjellberg's excellent work in this area does provide clinicians with some guidelines, we believe that much more data are necessary.

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References