The influence of volume on the tolerance of the brain to radiosurgery

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Radiosurgery (delivery of a high dose of radiation to a small volume of the brain) is usually well tolerated since the volume of brain irradiated is small. Despite growing interest in radiosurgery, the influence of the volume of brain irradiated on the tolerance of the brain to radiation is not well understood. The results of six studies reporting clinically significant radiation reactions following radiosurgery for arteriovenous malformations are reviewed. In the combined series, 23 (9%) of 255 patients developed a clinically significant radiation reaction. The volume of brain irradiated and the dose delivered in each of these 23 patients are presented. The compiled data suggest that the previously presented guidelines may underestimate the risks of radiosurgery. Additional clinical and experimental data are needed to determine "safe" doses of radiation to be used during radiosurgery.

KEY WORDS • radiosurgery • brain volume • tolerance • radiation

During radiosurgery, a large dose of radiation (approximately 10 to 50 Gy) is delivered to a small volume of the brain in a single fraction. This procedure is usually well tolerated. Since large volumes of brain tissue generally do not tolerate single large doses of radiation, the tolerance of the brain is clearly related to the volume of brain irradiated. This dose/volume/tolerance relationship is one of the cornerstones of radiosurgery. Despite the rapidly growing interest in radiosurgery, the influence of volume on the tolerance of the brain is not well understood.

Kjellberg and Abe have published iso-necrosis risk lines that illustrate the influence of volume on brain tolerance; a series of these lines as modified are shown in Fig. 1. These lines were based on Kjellberg and coworkers' experience with patients who received proton beam radiation and on several animal experiments performed by Kjellberg in monkeys, by Berg and Lindgren in rabbits, and by Zeman, et al. in mice. If Kjellberg's 1% line is accurate, patients who receive radiosurgical treatment corresponding to dose/volume points that lie below this line should have a less than 1% risk of brain necrosis. While this 1% line is helpful and has been used as a guide by those performing radiosurgery, its accuracy in patients receiving radiosurgery for arteriovenous malformations (AVM's) has not been confirmed. In this article, the literature is reviewed and the reported cases of possible radiosurgery-related morbidity (and their associated dose/volume parameters) are compiled.

Materials and Methods

Published reports of patients treated with radiosurgery for AVM's were reviewed. Studies were included in this analysis only if the following information could be extracted from the study: the total number of patients treated, the number of patients with a clinically significant radiation reaction, the approximate diameter of the irradiated volume, and the minimum dose delivered to this volume (in the patients with clinically significant radiation reactions). Six reports provided enough information to be included in this analysis. For each reported case of a clinically significant radiation reaction, the dose/volume information for that patient's radiosurgical treatment was extracted and plotted on a graph to test its relation to Kjellberg's 1% line. In most cases, the diameter of the treatment volume was stated. In cases where the treatment volume was given, the diameter was calculated assuming a spherical target volume. In all cases, the minimum radiation dose to the volume was either stated or calculated from the data provided.

Patients were scored as having a clinically significant radiation reaction if they developed functionally significant neurological symptoms within weeks to months following radiosurgery. Patients with symptoms that were attributable to other causes (including the AVM) were not included. In most instances, the authors of these six reports gave their own impression of whether the symptoms were due to the radiosurgery.
Acute transient clinical reactions (such as nausea) occurring hours to days following radiosurgery were not included. Symptom-free patients with radiological abnormalities resulting from the radiosurgery were also not included. The concept of clinically significant radiation reactions is probably not synonymous with necrosis since it includes patients with reversible symptoms. For this study, the end-point of a clinically significant radiation reaction was used since uniform histological and radiological information was not available. Furthermore, the clinical outcome is probably the most important end-point to the patient.

Results

Six studies provided enough information to be included in this analysis and the results are shown in Table 1. Colombo, et al., described three cases with "clinical undue effects" in which the clinical course was consistent with radiation reaction, possibly radiation necrosis (since these patients' symptoms apparently did not improve). The symptoms reported included diencephalic syndrome, extrapyramidal syndrome, and sensory loss. Kjellberg, et al., described eight cases of "complications," seven patients with progressive marked neurological symptoms and one whose symptoms improved following ventriculoperitoneal shunting to relieve hydrocephalus. Symptoms included progressive hemiparesis in four, progressive hemiplegia in one, hemianopsia in two, and gait and cranial nerve dysfunction in one. Loeffler, et al., described two cases of transient neurological symptoms. One patient (with coordination problems) improved slowly without treatment, and the second (with headache and lethargy) recovered fully with steroid therapy. The symptom duration is not stated and their clinical course suggested that they did not suffer serious brain injury.

Marks, et al., reported seven cases with "complications" after radiosurgery. Two of these patients had minimal transient symptoms that are not believed to be due to the radiosurgery (R Levy, personal communication, 1990). Of the remaining five patients, one had very minor fluctuating weakness, and the symptoms in the remaining four included weakness, memory loss, clumsiness, and cranial nerve dysfunction. Some of the patients in the series reported by Marks, et al., were treated over a 3-day period rather than as a single fraction of radiation. Souhami, et al., described two patients who developed hemiparesis and edema on radiographs following radiosurgery. One has improved gradually with steroid therapy; the second failed to improve with steroid administration and later died following an intracranial hemorrhage. No necrosis was seen at autopsy. Steiner, et al., described six cases of "undue effects" following radiosurgery. Two patients developed only radiological abnormalities. A third patient is excluded from this analysis since he received radiation to multiple sites and the total dose/volume parameters are not clear. The three remaining patients developed visual, sensory, and motor changes, respectively.

In the six series combined, clinically significant radiation reactions occurred in 23 (9%) of 255 patients with AVM's receiving radiosurgery. Excluding three reactions as not being significant (the two cases reported by Loeffler, et al., and one of the five reported by Marks, et al., in which the reactions were minor and/or fully reversible), the rate of clinically significant radiation reactions is approximately 8% (20 of 255 cases). The dose/volume parameters for the 23 patients are illustrated in Fig. 2. Each patient is represented by a point and Kjellberg's 1% necrosis risk line is shown. Seven of these points fall below the 1% line. Since it is not known how many of the 255 patients were treated at each of the dose/volume points that fall in the region below the 1% line, it is impossible to calculate the true risk of clinically significant radiation reactions in this region. However, we can estimate the upper and lower limits of this risk. The lower limit is 3% (seven of 239 cases), assuming that 239 of the 255 patients were treated at dose/volume points below the line (since 16 patients are known to have been treated at dose/volume points above the line, see Fig. 2). On the other hand, the upper limit is 8%, since the risk below the line should not exceed that of the entire group. Thus, the data available suggest that the risk of clinically signifi-
Brain volume irradiated and tolerance to radiosurgery

Fig. 2. The dose/target diameter information is plotted for the 23 patients with a clinical symptomatic radiation reaction. The solid line represents Kjellberg's 1% iso-necrosis risk line. Each case of a clinically significant radiation reaction is represented by a point.

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Latency to CSRR (mos)</th>
<th>Duration of CSRR (mos)</th>
<th>Follow-Up Period (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombo, et al., 1989</td>
<td>2, 6, 7</td>
<td>≥ 8, ≥ 6, ≥ 7</td>
<td>1-49 (17 mean)</td>
</tr>
<tr>
<td>Kjellberg, et al., 1983</td>
<td>?</td>
<td>progressive in 7</td>
<td>24-192</td>
</tr>
<tr>
<td>Loeffer, et al., 1989</td>
<td>6, 7</td>
<td>both transient</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Marks, et al., 1988</td>
<td>4, 11, 12</td>
<td>≥ 8, ≥ 9, ≥ 12</td>
<td>6-32</td>
</tr>
<tr>
<td>Souhami, et al., 1989</td>
<td>14, 19</td>
<td>≥ 12, ≥ 9</td>
<td>6-32 (16 mean)</td>
</tr>
<tr>
<td>Steiner, et al., 1979</td>
<td>6, 7, 9</td>
<td>≥ 9</td>
<td>—</td>
</tr>
</tbody>
</table>

TABLE 2
Summary of patients with clinically significant radiation reaction (CSRR)

Therefore, strict reliance upon Kjellberg's 1% iso-necrosis risk line should be discouraged when prescribing dosage for radiosurgery. It is extremely difficult to combine the results of several centers. Different irradiation techniques were used (photons from linear accelerators, gamma rays from a gamma knife unit, or charged particles) and different isodose prescription lines were used (< 50% to 90%). The doses shown in Fig. 1 reflect the minimum target dose for the associated volume (target diameter). Another factor that makes this type of combined analysis difficult is the issue of target location within the brain. Different portions of the brain may respond differently to radiation. Radiation-induced changes in the deep structures of the brain are more likely to be clinically significant than similar changes in the anterior frontal lobes (a relatively silent area). Similarly, since the optic nerves are more sensitive than cortical areas to fractionated radiation, they may be particularly sensitive to single fractions of radiation. Kjellberg never intended his iso-necrosis risk lines to be applied uniformly to all parts of the brain. In his 1979 report, he discussed the importance of using reduced doses in several areas of the brain (speech centers, visual pathways, and brain stem).

The presence of clinically significant radiation reactions does not necessarily correlate with necrosis. Biopsy was not routinely performed in any of these patients. Histological information is available from only one patient (from the series of Souhami, et al.13) who had severe clinical symptoms (likely due to the radiation) with no necrosis seen at autopsy. The clinical course of the two patients described by Loeffer, et al., and one patient described by Marks, et al.,10 were not suggestive of necrosis. Even though clinically significant radiation reactions may not represent necrosis, the risk of this occurrence may be a more clinically relevant end-point than the risk of necrosis. It is the resulting functional status that is of most concern to the patient.

Patients with radiological abnormalities in the absence of symptoms were not included in this analysis. Therefore, it is possible that patients with histological necrosis but without symptoms are excluded.

Flickinger, et al.,4 have performed a series of calculations using an integrated logistic model and have suggested that points along Kjellberg's 1% line may have a 3% risk of brain necrosis. It is not surprising that the 1% line may not be correct since it was based on limited data. In fact, in his initial presentation of this 1% iso-necrosis risk line, Kjellberg referred to his conclusions as "tentative" and stated, "future experience will further guide selection of appropriate isoeffect dose." The 50-Gy dose/7 mm diameter point is based on the "threshold" dose that caused histological necrosis 100 days postradiation in a series of monkeys. The 10-Gy dose/50 mm diameter point is based on autopsy material from 10 patients and represents the threshold dose for histological evidence of radiation necrosis 1 to 24 months postradiation. A straight line


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was drawn between these points on a log-log plot and was justified by several studies in animals.

Zeman, et al.\(^{15}\) reported the lowest dose to cause histological disappearance of nerves 24 days following irradiation of various volumes of the brain in mice. Berg and Lindgren\(^1\) reported the lowest skin dose (to the overlying scalp) that was associated with histological necrosis 1 year following irradiation of various volumes of the brain in rabbits. Some data from these studies are presented in Fig. 3 and can be represented by a straight line on a log-log plot. It should be noted that most of these data are for target diameters smaller than those used clinically. Kjellberg also referred to a study by Boden\(^7\) which is not included in this discussion because it pertains to the spinal cord rather than the brain.

A straight line on a log-log plot suggests that:

\[
\text{Tolerance (Volume 1)} = \frac{\text{Tolerance (Volume 2)} \times \left[\text{Volume 1}/\text{Volume 2}\right]^n}{N}
\]

where \(N\) is a constant. This type of relationship is probably too simple to fully describe the influence of radiation on various volumes of a structure as complex as the brain.

While the influence of volume of irradiated brain on the tolerance of the brain to radiation is not well understood, Kjellberg's work\(^6\) provides guidelines for prescribing a dosage for use in radiosurgery. However, additional clinical and experimental data are needed. As radiosurgery becomes more widely used, accurate reporting of the tolerance of the procedure is essential. Details, including the minimum target dose, target diameter, target volume, location, and prescription isodose line, should be reported for all patients, both with and without radiation-associated side effects.

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References


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