Gamma Knife Radiosurgery for Brain Vascular Malformations

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ISBN 978 3 8055 9619 0
Gewicht: 780 g
Dose Selection in Stereotactic Radiosurgery

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Abstract
Selection of the prescription dose for arteriovenous malformation (AVM) radiosurgery is the final step in treatment planning. Physicians need to choose a prescription dose that provides an optimal middle ground between optimizing AVM obliteration with high radiation doses and limiting complication risks with the lowest doses. Accurately predicting complication risks for individual patients is a complex process that is highly dependent on the radiosurgery treatment volume, the target location and the nature of the target tissue. This article reviews the principles and data guiding dose selection for AVM radiosurgery.

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Basic Principles
Creating a radiosurgical treatment plan is a multiple step process. After defining the target volume on stereotactic images, we create a treatment plan with a treatment volume (volume receiving the prescription dose) that closely matches the target volume. At some point, we must decide what radiation dose will be prescribed to the treatment volume. It is helpful to use radiobiological principles to understand and interpret the limited outcome data from past radiosurgery experience to select optimal doses for individual patients.

Dose-Volume Effects
With most conventional fractionated radiotherapy treatment plans, treatment volumes are huge in comparison to radiosurgery in part because large margins are added to the treatment volume to account for setup errors and patient motion. Within the range of large conventional radiotherapy treatment volumes, most differences in treatment volume between one patient and the next have only minor effects on radiation tolerance. With large-field conventional fractionated radiotherapy, it may be necessary
to decrease the dose by 5% or less to keep the same complication risk when the treatment volume is doubled. Because of this, volume effects can be safely ignored in many conventional, fractionated radiotherapy dose prescriptions. Radiosurgery treatment volumes, on the other hand, commonly vary by a factor of 300 (0.1–30 cm³) for most of the indications treated. The change in radiation tolerance across this range of treatment volumes used in radiosurgery is tremendous compared with those seen over the volumes treated in conventional fractionated radiotherapy. Because of these steep dose-volume effects, we can safely give a radiosurgery treatment volume of 1 cm³ or less to a dose of 25 Gy in a single fraction, while the same single-fraction dose administered to a conventional radiotherapy field enclosing half the brain would be lethal.

**Early Dose-Volume Guidelines**

There was little laboratory or clinical investigation to define dose-volume effects in the early years of radiosurgery, even though Leksell published the concept of high-dose small-volume stereotactic brain irradiation and coined the term ‘radiosurgery’ as far back as 1951 [1]. Kjellberg et al. [2] plotted 1 and 99% dose-volume isoeffect lines for brain necrosis on log-log axes from data from animal experiments and human clinical experience with photon and proton beams. They included data from one of the best studies of volume effects at the time: the 1963 study by Berg and Lindgren [3] of the variation in radiation tolerance for fields encompassing between 25 and 100% of rabbit brains. Kjellberg used the resulting 1% dose-volume isoeffect line for radiation necrosis as his guideline for most of his subsequent dose prescriptions for proton beam radiosurgery. These plots were used as initial guidelines for linear accelerator radiosurgery dose prescriptions [4]. Leksell’s group in Stockholm varied their dose prescriptions for the Gamma Knife that they developed according to their slowly accumulating clinical and laboratory experience. By the mid-1980s they felt that marginal doses of 25 Gy seemed optimal for treating arteriovenous malformations (AVMs), acoustic neuromas and meningiomas with their 4-, 8- and 14-mm diameter collimators.

When the University of Pittsburgh Gamma Unit became operational in August of 1987, there was little else to guide dose prescriptions. This new unit was equipped with 18-mm diameter collimators (in addition to the 4-, 8- and 14-mm collimators with prior models) and better treatment planning software, making it easier to treat larger volumes than Stockholm had treated in the past. We could not rely on Stockholm’s dose prescription policies to be safe for larger volumes and questioned whether Kjellberg’s guidelines were appropriate. The integrated logistic formula developed to address these issues with brain necrosis risk predictions estimated over radiosurgery dose-volume histograms [5]. The formula parameters were fitted to the scant clinical and laboratory data available at the time, and resulted in dose-volume prescription guidelines almost identical to Kjellberg’s.

Table 1 compares these two guidelines for spherical targets of different diameters. Both the integrated logistic formula and Kjellberg’s 1% isoeffect line were intended
for predicting only necrosis of brain parenchyma. They were never intended to predict injury to cranial nerves that were known to be more sensitive. These guidelines were not intended to predict asymptomatic or temporary postradiosurgery sequelae, which were not described by then.

**Dose-Volume Effect Studies in Radiosurgery**

*The RTOG 90-05 Phase I Study Guidelines*

The RTOG 90-05 phase 1 dose escalation study for radiosurgery included adults with previously irradiated cerebral or cerebellar solitary nonbrainstem tumors ≤40 mm in maximum diameter [6]. Brainstem tumors were excluded. The final report included 156 analyzable patients entered between 1990 and 1994: 36% with recurrent primary brain tumors (median prior dose 60 Gy) and 64% with recurrent brain metastases (median prior dose 30 Gy). Doses were prescribed within 3 maximum tumor diameter groupings: <20, 21–30 and 31–40 mm. Starting doses for this dose-escalation study were 18 Gy for tumors ≤20 mm, 15 Gy for 21–30 mm and 12 Gy for 31–40 mm. Doses were escalated in 3-Gy increments as long as the incidence of acute (within 3 months of radiosurgery) unacceptable toxicity remained <20% for each dose level. They defined unacceptable toxicity as irreversible grade 3 (severe) or any grade 4–5 (life-threatening or fatal) central nervous system (CNS) toxicity. In total, 22% (35/156) of the subjects developed unacceptable acute and chronic toxicities. Out of this total, 15 were irreversible grade 3 (severe; 10% of all patients, 42% of unacceptable toxicity group), 16 were grade 4 (life-threatening; 10% of all patients, 46% of unacceptable toxicity group), and 4 were grade 5 (fatal; 3% of all patients, 11% of unacceptable toxicity group). The 15 grade 3 toxicities were cases of irreversible

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**Table 1.** A comparison of dose-volume prescription guidelines for different mean tumor diameters from Kjellberg’s 1% radionecrosis isoeffect line, 3% necrosis risk predictions from the integrated logistic formula, and the risk levels in the RTOG phase I study for malignant brain tumors with prior irradiation [2, 4–6]

<table>
<thead>
<tr>
<th>Mean diameter</th>
<th>Volume, cm³</th>
<th>1% isoeffect, Gy</th>
<th>3% int. log., Gy</th>
<th>RTOG, Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mm</td>
<td>1.02</td>
<td>27.5</td>
<td>34.0</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>15.0 mm</td>
<td>1.77</td>
<td>25.0</td>
<td>29.0</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>17.5 mm</td>
<td>2.81</td>
<td>22.5</td>
<td>23.0</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>20.0 mm</td>
<td>4.19</td>
<td>20.0</td>
<td>18.0</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>22.5 mm</td>
<td>5.96</td>
<td>18.7</td>
<td>16.5</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>25.0 mm</td>
<td>8.18</td>
<td>17.5</td>
<td>14.5</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>27.5 mm</td>
<td>10.9</td>
<td>16.5</td>
<td>13.5</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>30.0 mm</td>
<td>14.1</td>
<td>15.0</td>
<td>13.0</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>32.5 mm</td>
<td>18.0</td>
<td>14.0</td>
<td>12.5</td>
<td>15 (14%)</td>
</tr>
</tbody>
</table>