Risks of history of diabetes mellitus, hypertension, and other factors related to radiation-induced changes following Gamma Knife surgery for cerebral arteriovenous malformations

Clinical article

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Object. Diabetes mellitus (DM) and hypertension may be associated with complications following fractionated radiotherapy. To date no studies have determined the risk of radiation toxicity in patients with DM or hypertension who have undergone Gamma Knife surgery (GKS) for brain arteriovenous malformations (AVMs). The goal of the present study was to determine associations between DM or hypertension and other factors in the development of radiotoxicity, as measured by radiation-induced changes (RICs) on MR images following radiosurgery for AVM.

Methods. Using univariate methods and multivariate logistic regression, the authors compared the RIC status in patients 18 years of age and older with these patients’ history of, or medication use for, DM or hypertension; tobacco use; patient age and sex; AVM volume; Spetzler-Martin AVM severity scale (Grades I and II vs Grades III–V); AVM surgery, AVM embolization, or hemorrhage prior to radiosurgery; AVM location; number of draining veins; and radiosurgery margin dose.

Results. Radiation-induced changes occurred in 38% of 539 adults within a mean (± standard deviation) of 12 ± 10 months after radiosurgery, as observed during a median follow-up time of 55 months. Among patients in whom RICs occurred, 34% had headaches, neurological deficits, or new-onset seizures. Larger RICs were associated with worse symptoms. According to a univariate analysis, DM (3% of patients), larger AVM volume, worse Spetzler-Martin grade, lack of AVM surgery prior to radiosurgery, lack of hemorrhage prior to radiosurgery, and smaller margin dose of radiation had significant associations with the presence of RICs. Hypertension (20%), patient sex, tobacco use, number of draining veins, superficial or deep location of the lesion, and AVM embolization prior to radiosurgery had no association with the presence of RICs. According to a multivariate analysis, larger AVM volume, worse Spetzler-Martin grade, and no AVM surgery prior to radiosurgery predicted the occurrence of an RIC. Diabetes mellitus had borderline significance.

Conclusions. Vascular factors such as hypertension, patient sex, and tobacco use did not convey additional risks of radiotoxicity, but DM remained a possible cardiovascular risk factor in the development of RICs.

KEY WORDS • stereotactic radiosurgery • arteriovenous malformation • Gamma Knife surgery • hypertension • diabetes mellitus

The risks of hypertension and DM in patients scheduled for stereotactic radiosurgery remain unclear. Nevertheless, hypertension, DM, and other vascular disorders are well-known comorbidities that affect the patient’s course after radiotherapy. As reviewed by Chon and Loeffler,3 “patients with uncontrolled hypertension in addition to Type 1 diabetes may be at the highest risk for radiation-induced morbidity.” For example, in 3 reports describing fractionated radiation therapy for pelvic or prostate cancers, complications such as fistulas, vascular changes, or other complications occurred at higher rates in patients with hypertension or DM than in patients without those disorders.8,16,20 In a more recent review, DM was an important risk factor in the development of radionecrosis after radiotherapy of the CNS.12 Most available reports, however, describe studies in which fractionated radiation treatment, rather than single-dose targeted

Abbreviations used in this paper: AVM = arteriovenous malformation; DM = diabetes mellitus; GKS = Gamma Knife surgery; MABP = mean arterial blood pressure; RIC = radiation-induced change.
radiosurgery, was used, and these treatments involved structures other than the CNS. Since radiosurgery uses high doses of radiation in a single fraction and does not permit the repair and recovery allowed by standard fractionation schemes, patients with abnormalities stemming from hypertension or DM may be at greater risk for radiation toxicity.

Despite the importance of this issue, with the exception of case reports, only 3 patient series have focused on evaluation of radiosurgery near the CNS. In a study of conformal fractionated radiation treatment for skull-based tumors, DM was a significant and independent prognosticator of brainstem toxicity in a multivariate analysis.4 Hypertension, which proved to be significant in a univariate analysis, was not significant in the multivariate model. In a study of radiotherapy for head and neck cancer, neither DM nor hypertension posed statistically significant risks for the development of posttreatment ischemic stroke.5 In a series of patients who underwent radiosurgery for trigeminal neuralgia, pain relief was harder to obtain in patients with DM, although neither DM nor hypertension conferred any additional risks.15 The question of possible risks associated with DM or hypertension rises in importance as indications for radiosurgery extend beyond vascular malformation and tumor. For example, uses of radiosurgery for epilepsy,17 trigeminal neuralgia,15,18 and psychosurgery11 require that potential risk factors need explicit evaluation when considering complications in the treatment of functional lesions.

The purpose of this study was to evaluate the effects of DM and hypertension on radiation toxicity, as determined by MR imaging evidence of cerebral edema following treatment of AVMs in the context of other AVM-related and treatment-related factors important for radiographically determined outcomes.

Methods

Patients, Outcomes, and Potential Risk Factors

The Institutional Review Board of the University of Virginia approved data collection and use in this study. The study is a retrospective, single-center case series of patients 18 years of age or older who were treated with radiosurgery for AVMs. All preoperative and operative data were obtained at the time of surgery. Postoperative data were either obtained during primary follow-up or from correspondence with the patients’ referring physicians.

The primary outcome variable was an RIC, the appearance of a hyperintense lesion on T2-weighted MR images, which may develop between 3 and 14 months after radiosurgery for AVM.6,19 Patients underwent MR imaging every 6 months for the first 2 years after radiosurgery and then annually thereafter. Additional MR images were obtained if an RIC appeared or symptoms such as headaches, neurological deficits, or seizures developed. The date on which the RIC occurred was recorded as the date of the imaging study on which the RIC was first observed, and the remission date was the date on which follow-up MR images documented resolution of the RIC. Therefore, the prevalence of RICs represents the cumulative occurrence of RICs within the sample.

To better describe the primary outcome, the size of the RIC was assigned a ranking: 0 = no RIC; 1 = a “mild” RIC displaying focal changes in T2-weighted signal intensity without a mass effect; 2 = a “moderate” RIC with compression of an adjacent ventricle or sulci; or 3 = a “severe” RIC, which exerted a mass effect that caused a midline shift.7 We separately ranked RICs into one of the following symptomatic categories: 0 = no RIC; 1 = an asymptomatic RIC; or 2 = a symptomatic RIC accompanied by headache, neurological deficits, or new-onset seizures.

We described a patient as hypertensive if the patient related a history of hypertension or reported use of antihypertensive medication at the time of radiosurgery. Similarly, the assignment of DM to a patient was based on a history of DM or use of antiglycemic medication. These criteria, analogous to those examined in preoperative clinical screening, are similar to those used in studies of patient-associated risk factors in radiotherapy.2,4,5,15 To examine the risks of hypertension and DM in more detail within the subgroup of patients identified as either diabetic or hypertensive, we evaluated the effects of hypertension or DM dichotomized by duration of the disorder: diagnosis or treatment < 6 months versus ≥ 6 months. We also evaluated each patient’s MABP at the time of the preoperative examination as well as the end-organ effect of creatinine clearance.9 Tobacco use was defined as present if the patient admitted to use at the time of radiosurgery. Other patient-related factors included age and sex.

To put patient-related risk factors in context, we also evaluated AVM-associated factors such as AVM volume, calculated at the time of radiosurgery by using Gamma Knife planning software (Elekta AB) on the basis of combined stereotactic MR images and angiograms; the Spetzler-Martin AVM severity grade dichotomized into Grades I and II versus Grades III–V;4 the number of draining veins from the AVM; the AVM location dichotomized into superficial location (frontal, temporal, parietal, or occipital lobe; corpus callosum; cerebellum; or insula) versus the higher-risk deep location (thalamus, basal ganglia, or brainstem);21 AVM surgery prior to radiosurgery; AVM embolization prior to radiosurgery; and hemorrhage prior to radiosurgery. These factors, as well as primary outcome determinations of RIC occurrence and severity, were determined by a single observer (C.P.Y.) who was blinded to the patients’ clinical data. Similarly, the risk factors of DM and hypertension were accrued by researchers (M.C., A.H.Q., I.T.M., C.J.P.) who were blinded to the patients’ neuroimaging outcomes.

Data Analysis

Data analysis was performed using SPSS (version 19, IBM). In univariate analyses, continuous variables were evaluated using Student t-tests, and categorical variables were evaluated by performing Fisher exact tests against patients with RICs (RIC+ group) and patients without RICs (RIC– group). Hypertension, DM, and all other variables that had a 2-sided p value < 0.10 were then included in a multivariate logistic regression model to analyze variables that independently predicted the presence or absence of an RIC. Variables with a 2-sided p value < 0.05 were deemed significant.
Results

A total of 649 patients were treated with radiosurgery between March 1991 and November 2008, allowing for a minimum of 2 years’ follow-up after radiosurgery. Excluded from further analysis were 7 patients in whom the neuroimaging information was incomplete and 103 patients younger than 18 years of age. An RIC was present on MR images in 207 patients (38% of a total sample of 539 patients who were followed up for a median duration of 55 months [range 24–214 months]). Onset of the RICs occurred at a mean (± standard deviation) of 12 ± 10 months postradiosurgery. The median duration of RICs was 15 months (range 2–120 months). The distribution of patients according to the size and symptomatology of the RIC is shown in Fig. 1. Patients with no RIC had no symptoms. Of the 207 patients with RICs, more than 50% were asymptomatic and had a mild RIC (Fig. 1 upper). As the size of the RIC lesions increased from mild to severe, a greater proportion of patients experienced symptoms; whereas only 23 (18%) of 130 patients with a mild RIC had symptoms, 21 (34%) of 62 patients with a moderate RIC, and 8 (53%) of 15 patients with a severe RIC had symptoms. The most common symptom was neurological deficits, affecting more than 50% of patients with a symptomatic RIC (Fig. 1 lower). Deficits corresponded to RIC-related edema; no patients displayed any evidence of stroke or hemorrhage during the period in which the RIC was present.

The prevalence of hypertension (20%) was much greater than that of DM (3%) in the study group (Table 1). All 14 patients with DM also had hypertension. Seven patients had 3 factors: DM, hypertension, and tobacco use. The presence of DM had a significant association with an RIC, but hypertension did not.

Larger AVM volume, smaller margin dose, and Spetzler-Martin Grades III–V had significant associations with the development of RICs (Table 1). The proportion of patients who had undergone surgery before radiosurgery or had experienced hemorrhage before that treatment was significantly decreased in the RIC+ group. Older patient age had a borderline association with an RIC. Patient sex, tobacco use, AVM embolization prior to radiosurgery, number of draining veins, and AVM location had no significant association with RICs. The AVM volume and margin radiation dose were significantly inversely correlated (Pearson correlation constant = −0.60, p = 0.01). Other significant variables did not have significant interactions. For example, neither AVM volume nor margin dose differed according to whether the patient had undergone surgery before radiosurgery or experienced hemorrhage before radiosurgery.

Patients with DM or hypertension were further evaluated in terms of measures of severity (Table 2). Severity measurements of DM or hypertension (duration < 6 months vs ≥ 6 months, MABP, estimated creatinine clearance) were not uniformly available for the full subgroup. No associations between severity measures and RIC were evident (Table 2).

Hypertension, DM, and (according to the threshold p < 0.10 for inclusion) patient age, margin dose, AVM volume, Spetzler-Martin grade, AVM surgery prior to radiosurgery, and hemorrhage prior to radiosurgery were entered into a multivariate logistic regression model with RIC+ and RIC− as outcomes (Table 3). Although significant in the univariate analysis, DM had only borderline significance in the multivariate model. Hypertension remained nonsignificant. Larger AVM volume, Spetzler-Martin Grades III–V, and absence of AVM surgery before radiosurgery were predictors of the development of RIC. Patient age, hemorrhage before radiosurgery, and margin dose were not significant in the multivariate model.
Risk factors in AVM radiosurgery

Discussion

The most important finding in this study is that hy-
pertension, which is associated with excessive radiation
toxicity following fractionated radiotherapy of lesions
outside the CNS, did not confer an increased risk of RICs
when single-dose Gamma Knife surgery was performed
to treat cerebral AVMs. Whereas hypertension clearly
was accompanied by no excessive risk in the development
of an RIC, DM displayed significance in the univariate
analysis but only borderline significance in the multivari-
ate analysis. Conclusions regarding DM, however, must
be limited because few patients with DM were present in
the patient population.

Limitations of this study included the rare incidence

TABLE 1: Results of univariate analyses of RICs*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Patients</th>
<th>Patients in RIC+ Group</th>
<th>Patients in RIC− Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM present</td>
<td>14</td>
<td>5%</td>
<td>1%</td>
<td>0.02‡</td>
</tr>
<tr>
<td>hypertension present</td>
<td>106</td>
<td>21%</td>
<td>19%</td>
<td>0.66</td>
</tr>
<tr>
<td>current tobacco use—yes</td>
<td>198</td>
<td>34%</td>
<td>39%</td>
<td>0.27</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>284</td>
<td>41.5 ± 13.2</td>
<td>39.5 ± 14.4</td>
<td>0.096†</td>
</tr>
<tr>
<td>male sex</td>
<td></td>
<td>53%</td>
<td>52%</td>
<td>0.93</td>
</tr>
<tr>
<td>mean AVM volume (cm³)</td>
<td></td>
<td>3.9 ± 3.1</td>
<td>3.0 ± 2.6</td>
<td>0.0001‡</td>
</tr>
<tr>
<td>Spetzler-Martin Grades I &amp; II</td>
<td>299</td>
<td>49%</td>
<td>59%</td>
<td>0.026‡</td>
</tr>
<tr>
<td>AVM prior surgery—yes</td>
<td>58</td>
<td>6%</td>
<td>14%</td>
<td>0.004‡</td>
</tr>
<tr>
<td>AVM embolization—yes</td>
<td>127</td>
<td>26%</td>
<td>22%</td>
<td>0.3</td>
</tr>
<tr>
<td>AVM hemorrhage—yes</td>
<td>240</td>
<td>36%</td>
<td>50%</td>
<td>0.001‡</td>
</tr>
<tr>
<td>mean margin dose of radiation (Gy)</td>
<td></td>
<td>21.0 ± 3.2</td>
<td>21.8 ± 3.3</td>
<td>0.008‡</td>
</tr>
<tr>
<td>no. of draining veins</td>
<td></td>
<td>1.6 ± 0.7</td>
<td>1.6 ± 0.7</td>
<td>0.50</td>
</tr>
<tr>
<td>location of AVM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal lobe</td>
<td>86</td>
<td>42%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>temporal lobe</td>
<td>98</td>
<td>35%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>parietal lobe</td>
<td>90</td>
<td>55%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>occipital lobe</td>
<td>84</td>
<td>36%</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>corpus callosum</td>
<td>40</td>
<td>43%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>cerebellum</td>
<td>39</td>
<td>23%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>insula</td>
<td>12</td>
<td>25%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>thalamus</td>
<td>40</td>
<td>33%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>basal ganglia</td>
<td>26</td>
<td>31%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>brainstem</td>
<td>43</td>
<td>37%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>AVM located in region containing thalamus, basal ganglia, &amp; brainstem</td>
<td>109</td>
<td>34%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>AVM located in other locations</td>
<td>430</td>
<td>40%</td>
<td>61%</td>
<td>0.32§</td>
</tr>
</tbody>
</table>

* Continuous variables were tested using Student t-tests and categorical variables using Fisher exact tests. Mean values are expressed ± standard
deviations.
† p < 0.10, the threshold for inclusion in multivariate analyses.
‡ Significant at p < 0.05.
§ Region containing thalamus, basal ganglia, and brainstem compared with other locations.

TABLE 2: Results of univariate analyses of RICs in the subgroup of patients with DM or hypertension*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of Pts</th>
<th>Pts in RIC+ Group</th>
<th>Pts in RIC− Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension or DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mos in duration</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>≥6 mos in duration</td>
<td>25</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>68</td>
<td>147.8 ± 17.4 (23 pts)</td>
<td>146.0 ± 17.1 (45 pts)</td>
<td>0.66</td>
</tr>
<tr>
<td>estimated creatinine clearance</td>
<td>35</td>
<td>112.3 ± 26.7 (12 pts)</td>
<td>113.8 ± 47.0 (23 pts)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

* Continuous variables were tested using Student t-tests and categorical variables using Fisher exact tests. Abbreviation: Pts = patients.
of DM in the study group, which was possibly reflective of biased practice patterns. We evaluated the risk of radiosurgery only with respect to neuroimaging changes because longer-term follow-up was not uniform in the sample population. Assessment of other potential late complications of radiosurgery, such as stroke or cyst formation, would also be of interest, but such risks could only be observed many years after radiosurgery. Information regarding the severity of DM or hypertension was not uniformly available for the hypertension or DM subgroup. We acknowledge that a history or treatment of DM or hypertension may not be the same as end-organ effects of these diseases. A patient’s clinical history reflects information available to the physician during the presurgical screening. Therefore, the clinical history is only a surrogate marker for the pathophysiological effects of hypertension or DM.

Our finding that DM is associated with some excess risk in toxicity, but hypertension is not, is similar to that of a recent study of radiosurgical treatment of trigeminal neuralgia, in which DM but not hypertension was shown to be associated with a less favorable outcome in pain remission. The results of the present study and those of the study on radiosurgery of trigeminal neuralgia contrast with the results of previous studies of fractionated irradiation of lesions outside the CNS, in which both DM and hypertension were shown to confer additional risks. We speculate that the smaller treatment volumes and steeper dose fall-off inherent in radiosurgery make the procedure compare favorably against conventional external beam radiotherapy.

This study focused on the development of postoperative RICs. Other studies of factors important in radiosurgical treatment of AVMs found that hypertension, DM, patient sex, or tobacco use did not affect obliteration of the AVM nidus. Lawton et al. found that previous hemorrhage correlated with neurological improvement after standard microsurgery for AVMs; the authors proposed that hemorrhage and preexistent neurological deficits may mask surgery-related morbidity. The prescribed dose of radiosurgery was not found to be an independent risk factor in the multivariate analysis, whereas the pretreatment AVM volume was. Similariy, in another study, a significantly higher incidence of radiation-induced edema was noted in children with AVM volumes larger than 3 cm³ and in patients with Spetzler-Martin Grade IV or V AVMs. In adults, AVM target diameters greater than 25 mm and radiation doses larger than 20 Gy were associated with early complications. Neither the number of draining veins nor the location of the lesion (grouped into superficial and deep targets) was significant in univariate analyses in this sample, a finding probably attributable to the difference in outcome measures among studies. However, the results of the present study confirm that patients with larger AVMs and more severe Spetzler-Martin grades experienced a higher risk of radiosurgery-associated neuroimaging changes.

The present study demonstrates that the occurrence of an RIC in the treatment of an AVM is not entirely benign; about a third of patients with RICs developed symptoms of headache, neurological deficits, or seizures at rates proportional to the size of the RIC. Hypertension neither influenced the presence nor the severity of these side effects.

Conclusions

In summary, neither hypertension nor other cardiovascular risk factors (patient sex and tobacco use) predicted the subsequent occurrence of RICs after radiosurgery for an AVM. Prospective studies should monitor patients with these disorders closely and consider quantifying risk factors with appropriate systematic measures (such as blood pressure screening or use of markers of blood glucose control) to provide further evidence and guidance.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: M Quigg, Sheehan. Acquisition of data: M Quigg, Yen, Chatman, AH Quigg, McNeill,
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Przybylowski, Sheehan. Analysis and interpretation of data: M Quigg, Chatman, AH Quigg, Yan. Drafting the article: M Quigg. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: M Quigg. Statistical analysis: M Quigg, Yen, Chatman, Yan. Administrative/technical/material support: M Quigg, Sheehan. Study supervision: M Quigg, Sheehan.

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