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● *Clinical Investigation*

# COMPLICATIONS FROM ARTERIOVENOUS MALFORMATION RADIOSURGERY: MULTIVARIATE ANALYSIS AND RISK MODELING

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**Purpose/Objective: To assess the relationships of radiosurgery treatment parameters to the development of complications from radiosurgery for arteriovenous malformations (AVM).**
**Methods and Materials: We evaluated follow-up imaging and clinical data in 307 AVM patients who received gamma knife radiosurgery at the University of Pittsburgh between 1987 and 1993. All patients had regular clinical or imaging follow up for a minimum of 2 years (range: 24–96 months, median = 44 months).**
**Results: Post-radiosurgical imaging (PRI) changes developed in 30.5% of patients with regular follow-up magnetic resonance imaging, and were symptomatic in 10.7% of all patients at 7 years. PRI changes resolved within 3 years developed significantly less often ($p = 0.0274$) in patients with symptoms (52.8%) compared to asymptomatic patients (94.8%). The 7-year actuarial rate for developing persistent symptomatic PRI changes was 5.05%. Multivariate logistic regression modeling found that the 12 Gy volume was the only independent variable that correlated significantly with PRI changes ($p < 0.0001$) while symptomatic PRI changes were correlated with both 12 Gy volume ($p = 0.0013$) and AVM location ($p = 0.0066$).**
**Conclusion: Complications from AVM radiosurgery can be predicted with a statistical model relating the risks of developing symptomatic post-radiosurgical imaging changes to 12 Gy treatment volume and location.** © 1997 Elsevier Science Inc.

**Radiosurgery, Stereotactic surgery, Arteriovenous malformation, Complications, Radiation injury.**

## INTRODUCTION

The goal of radiosurgery is to injure or destroy an intracranial target with minimal injury to surrounding normal brain tissue. The 1% dose-volume isoeffect line of Kjellberg *et al.* and the 3% dose-volume isoeffect curve from the integrated logistic formula for predicting brain radiation necrosis are widely used dose-prescription guidelines for radiosurgery (2, 8, 9). Temporary or permanent symptomatic or asymptomatic post-radiosurgery imaging (PRI) changes have been well described (4). These are best seen as new regions of increased T2 signal on magnetic resonance imaging (MRI) scans or less well seen as low density regions on computed tomographic (CT) scans. Neither Kjellberg's 1% isoeffect line nor the integrated logistic formula predict PRI changes, which in many patients may be hemodynamic in origin (2, 8).

Our first study of imaging changes after AVM radiosurgery showed that treatment volume was the only significant factor predictive of PRI changes, over and above the integrated logistic formula predictions (4). A second finding was that brainstem location was associated significantly with the development of symptoms in patients developing imaging changes (4). Our second study evaluated PRI changes that developed in 57 of 277 patients with AVM or benign tumors (meningioma or acoustic neuroma) from 1 to 23 months after radiosurgery (42/138 AVM, 6/55 meningioma, and 5/84 vestibular schwannoma patients) (3, 5). PRI changes developed in a significantly greater proportion of AVM vs. tumor patients (31% vs. 8%, $p < 0.0001$). This indicated that tumors and AVMs should be studied separately. Constants for several tolerance models (functions of the normal tissue dose-volume histogram) were optimized by least-squares analysis and then compared. The best-fitting model proved to be a logistic threshold dose-volume model followed in order by an exponential threshold dose-volume model, the integrated logistic equation, and least of all, the stem cell depletion model (2, 3, 14). In this current report, we evaluated PRI changes with and without symptoms in AVM patients. This study was conducted with the following hypotheses:

1. Complications from radiosurgery (T2 imaging changes with or without symptoms) are a function of both dose and volume.

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Table 1. Treatment parameters in 307 AVM patients

| Variable | Mean | Standard deviation | Lowest value | Highest value |
|---|---|---|---|---|
| Dmin (Gy) | 20.9 | 3.47 | 12 | 30 |
| Dmax (Gy) | 37.2 | 7.31 | 22 | 59 |
| Isodose (Gy) | 57.4 | 11.4 | 35 | 90 |
| Volume (cc) | 4.30 | 3.72 | 0.01 | 26.31 |
| Isocenters (#) | 2.14 | 1.59 | 1 | 11 |
| Dose rate (Gy/min) | 1.70 | 0.56 | 0.87 | 3.56 |

2. The volume receiving greater than a specified dose (such as 8, 10, or 12 Gy) from radiosurgery should reflect the risk of complications.
3. The target (AVM nidus) inside the treatment volume contributes to radiosurgery complications.
4. Complications vary within the different dose rates used in the clinical practice of gamma knife radiosurgery.
5. The difference between asymptomatic and symptomatic post-radiosurgery imaging changes is due primarily to location.

## MATERIALS AND METHODS

*Clinical material and treatment parameters*

We evaluated follow-up MRI scans and clinical data in 307 patients who received gamma knife radiosurgery at the University of Pittsburgh between 1987 and 1993. All patients had regular clinical or imaging follow up for a minimum of 2 years (median = 44 months, range: 24–96 months) at the time of data analysis. Twenty-six patients had no MRI exams between 1 and 2 years after radiosurgery but did have adequate clinical follow up. They were included for the analysis of symptomatic PRI changes, but were excluded from the analysis of all PRI changes (this left 281 patients with adequate imaging follow up for analysis). AVM were located in the brainstem in 77 patients and in other locations (cerebral or cerebellar) in the other 230 patients. Clinical and treatment parameters are listed in Table 1. Peripheral dose rate was estimated as the maximum dose rate in the target volume multiplied by the percentage of the treatment isodose. This was chosen to reflect the dose rate exposure of the normal tissue next to the AVM nidus. We reviewed each patient's dose-volume histogram to calculate 8, 10, and 12 Gy volumes which we defined as the total volume of all tissue (including the AVM target) receiving an equal or greater radiation dose than the one specified (8, 10, or 12 Gy). Marginal 8, 10, and 12 Gy volumes were defined as the normal tissue volume receiving greater than the specified dose and were estimated as the 8, 10, or 12 Gy volume, respectively, minus the treatment volume.

*Statistical analysis*

The primary endpoint for statistical analysis was the development of PRI changes. This was defined as the development of new regions of T2 imaging changes on post-radiosurgery follow-up MRI scans whether or not these were accompanied by symptoms. The second endpoint studied was symptomatic PRI changes defined as PRI changes accompanied by any subjective new symptom not related to new hemorrhage, including new or increased headaches, new or increased seizure activity unrelated to medication changes, or new neurological deficits. Persistent PRI changes (which could represent radiation necrosis, regional ischemia, or gliosis) were defined as the documented persistence of PRI changes for more than 2 years.

Stepwise multivariate logistic regression analysis of the effects of treatment variables was performed using BMDP software (1). Because of the greater number of events for all PRI changes as an outcome, this test was used to assess the list of all treatment variables thought to possibly affect complications. Variables approaching statistical significance ($p < 0.10$) were then tested for their effect on the development of symptomatic PRI changes. All treatment variables were examined as continuous variables except location which we classified as either brainstem or other, and the number of isocenters which we classified as 1, 2, or $\geq 3$.

Actuarial rates for developing T2 imaging changes and for the resolution of these imaging changes were calculated using the method of Kaplan and Meier (7). Statistical comparisons between actuarial curves was performed with the log-rank test (11).

## RESULTS

*Incidence of PRI changes and necrosis*

We identified PRI changes in 85 of 281 patients with regular imaging follow up for a crude rate of 30.2%. Symptomatic PRI changes developed in 29 of 307 patients for a crude rate of 9.4%. Figure 1 shows the actuarial cumulative incidence curves for developing any PRI imaging changes (30.5% actuarial incidence at 7 years) and

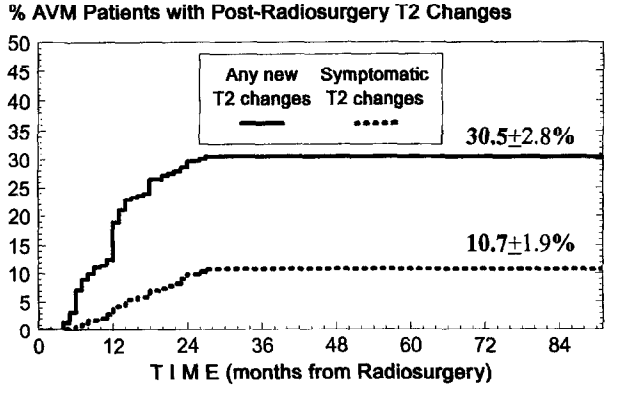


Fig. 1. Actuarial incidence of developing post-radiosurgery imaging changes (any new T2 changes) and symptomatic imaging changes (symptomatic T2 changes) in 307 AVM patients.

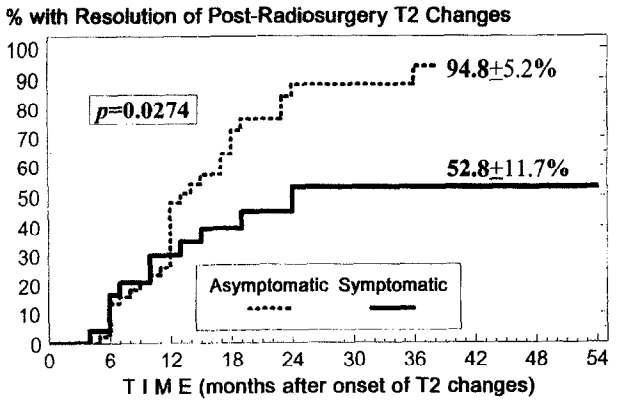


Fig. 2. Comparison of actuarial rates of resolution for post-radiosurgery imaging changes in 56 asymptomatic and for 29 symptomatic AVM patients.

symptomatic PRI changes (10.7% actuarial incidence at 7 years). Among the patients developing any PRI changes, the median time of onset was 12 months, while for the symptomatic patients, the median time to onset was 14 months.

The 3-year cumulative actuarial rate for resolution of PRI changes was 81.0%. The median time to this resolution was 12 months. The longest time to resolution of PRI changes was 36 months postonset. This occurred in one patient whose last previous MRI scan was at 18 months postonset; no other patient had resolution identified later than 24 months. Figure 2 shows that the rate of resolution for PRI changes at 3 years was significantly less ($p$ = 0.0274) in patients with symptoms (52.8%) compared to asymptomatic patients (94.8%). Univariate analysis of the resolution of symptomatic PRI changes could find no correlation with volume, location, 12 Gy volume, or minimum nidus dose ($p > 0.49$). Nine patients had persistent PRI changes more than 2 years after onset for a crude overall rate of 2.9%, but actuarial methods are needed to reflect the true risk. The projected actuarial risk of developing persistent symptomatic PRI changes 7 years after radiosurgery was (10.7%) × (100 − 52.8%) = 5.05%.

*Multivariate analysis and modeling*

Multivariate analysis was initially performed using all PRI changes (symptomatic plus asymptomatic) as the outcome. The first step in the multivariate logistic regression analysis was to choose among the 8, 10, and 12 Gy volumes for the variable most closely associated with PRI changes. Next, the same approach was used to choose among the 8, 10, and 12 Gy marginal volumes. The best risk predictor from each group proved to be the 12 Gy volume and the 8 Gy marginal volume. These two variables were then tested against one another along with six other treatment variables using stepwise multivariate logistic regression analysis. Table 2 lists the results. The 12 Gy volume was the only significant independent variable ($p < 0.0001$) associated with PRI changes in this analysis. The odds ratio (OR) was 1.15 (per cc of 12 Gy volume) with a 95% confidence interval (CI) of 1.08–1.22. There was a trend approaching statistical significance ($p$ = 0.0688) for decreasing PRI changes with increasing number of isocenters (O.R. = 0.725, 95% CI 0.37–1.34). Although no dose-rate effect was found in the overall analysis (Table 2), we pursued this further in a separate logistic regression analysis of the 116 patients treated with a single isocenter. This subset analysis also failed to detect any dose rate effect ($p$ = 0.942) but still showed the correlation with 12 Gy volume ($p$ = 0.004).

The endpoint of symptomatic PRI changes was next evaluated by multivariate analysis. Because only 29 patients developed PRI changes, multivariate modeling was limited to three variables: these were the most significant ($p < 0.10$) variables from the analysis of all PRI changes (12 Gy volume and number of isocenters) plus location (brainstem vs. other). We did not include location in the preceding evaluation of all PRI changes, because a prior study found that it appeared to have no effect on that outcome. Similar to the analysis of all PRI changes, symptomatic changes were correlated significantly with 12 Gy volume ($p$ = 0.0013, O.R. = 1.15 per cc with a 95% CI = 1.04–1.17), but not with number of isocenters ($p$ = 0.4464). Also not surprisingly, location was significantly related to symptomatic PRI changes ($p$ = 0.0066). Brainstem AVM patients had approximately a three times greater risk (O.R. = 3.24, 95% CI = 1.38–7.61) of developing symptomatic PRI changes than non-brainstem cases.

Figure 3 shows the risk prediction curves for all PRI changes and symptomatic PRI changes according to 12 Gy volume derived from the logistic regression. Figure 4 illustrates the risk curves for symptomatic PRI changes for brainstem and non-brainstem AVM locations according to 12 Gy volume.

## DISCUSSION

This study found that, of all the different radiosurgery treatment parameters evaluated, PRI changes were correlated most with 12 Gy volume. We also found that the

Table 2. Multivariate logistic regression analysis of all post-radiosurgery imaging changes (symptomatic and asymptomatic)

| Variable | $p$-Value |
|---|---|
| 12 Gy volume (cc) | < 0.0001 |
| Number of isocenters (1, 2, or >2) | 0.0848 |
| Minimum AVM nidus dose (cc) | 0.1956 |
| Maximum dose (Gy) | 0.3670 |
| Treatment volume (cc) | 0.5643 |
| Marginal 8 Gy volume (Gy) | 0.7169 |
| Marginal dose rate (Gy/minute) | 0.5045 |
| Target dose inhomogeneity (Gy) | 0.5949 |

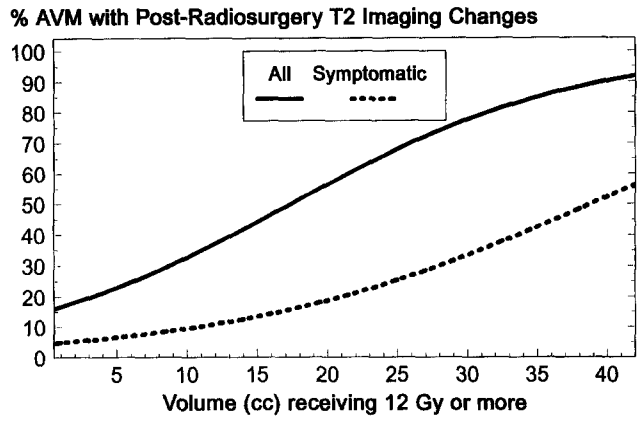


Fig. 3. Risk prediction curves derived from multivariate logistic regression analysis that correlate 12 Gy volume to risks for developing all (symptomatic and asymptomatic) post-radiosurgery imaging changes (upper solid curve) and symptomatic post-radiosurgery imaging changes (lower dashed curve) for AVM patients.

clinically more important endpoint of developing symptomatic PRI changes was significantly related to both 12 Gy volume and location (with a 3.24 times higher risk for brainstem AVM). Last of all, we found that a projected 47.2% of patients with symptomatic PRI changes maintain some persistent imaging effect compared to only 5.2% of patients with asymptomatic PRI changes. These persistent imaging changes may represent radiation necrosis, regional ischemia, or gliosis.

*Preanalysis hypotheses*

Considering these findings, several comments should be made regarding the four pre-analysis hypotheses:

1. Complications from radiosurgery (T2 imaging changes with or without symptoms) are a function of both dose and volume. The 12 Gy volume fits this specification since it increases with both treatment dose and volume. Prior studies could only correlate complications with volume but not dose (within the range of doses used in the practice of radiosurgery).
2. The volume receiving greater than a specified dose (such as 8, 10, or 12 Gy) from radiosurgery should reflect the risk of complications. This study found that the 12 Gy volume was the only independent significant predictor for AVM patients developing PRI changes. Prior analyses at the University of Pittsburgh found optimum fit of data to a similar logistic threshold dose-volume model (using marginal treatment volume instead of 12 Gy volume) (3, 5). Voges *et al.* recently correlated radiosurgery complications to 10 Gy volume (a seemingly arbitrary choice for a threshold dose-volume) in a series of 100 patients with AVM or tumor (13).
3. The target (AVM nidus) inside the treatment volume (AVM nidus) contributes to radiosurgery complications. Although it is intuitively appealing to believe that complications arise only from the normal surrounding tissue irradiated, the prior finding that PRI changes occurred more commonly in AVM patients compared to benign tumor patients indicated that the irradiated AVM target does contribute to complications. The additional vascular factor could be a hemodynamic effect as obliteration occurs. It, therefore, was not surprising that the present study found that a logistic function of the 12 Gy volume (which includes the AVM nidus treatment volume) predicted complications better than the best model using the marginal volume (which excludes the AVM nidus volume). Because there was only a limited number of patients ($n$ = 9) classified as having persistent imaging changes and some patients with PRI changes had not been followed long enough after onset of these changes to know if they would resolve, it was not possible to reliably compare radiation necrosis risk prediction models that include vs. exclude the target volume from the risk calculation. Further study of persistent imaging changes as an endpoint is needed.
4. Complications vary within the different dose rates used in the clinical practice of Gamma Knife radiosurgery. This hypothesis was not supported whatsoever by the present study which found no significant relationship of the approximate peripheral dose rate to PRI changes. The non-significant correlation between increasing number of isocenters irradiated and fewer PRI changes could potentially be explained by a lower effective dose-rate (with partial fractionation between treatment of different isocenters). If this was the case, the peripheral dose rate should correlate with all PRI changes in a manner close to significance, and symptomatic imaging changes should correlate with the number of isocenters. One weakness of this analysis is that there is no good way to represent the overall dose-rate for multiple isocenter treatments. Normal tissue at different

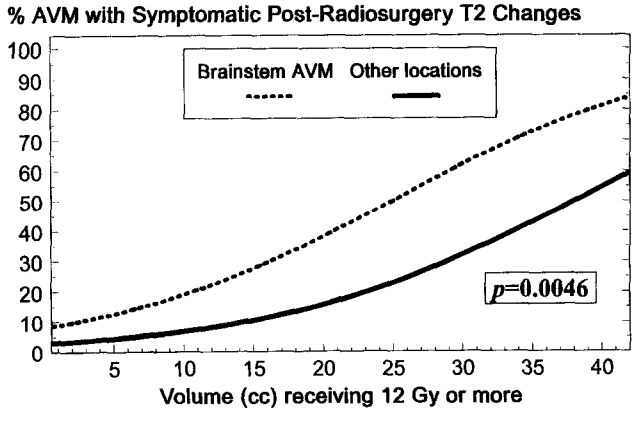


Fig. 4. Risk prediction curves derived from multivariate logistic regression analysis that correlate 12 Gy volume to probability of developing symptomatic post-radiosurgery imaging changes for patients with brainstem AVM (upper dashed curve) compared to other locations (lower solid curve).

locations along the periphery of the target receives radiation that is interrupted and divided in various ways between treatment of each isocenter. This issue was avoided by a separate analysis of the 116 patients who had radiosurgery with a single isocenter. That subset analysis also failed to detect any correlation of dose-rate with PRI changes ($p = 0.942$).

5. The difference between asymptomatic and symptomatic PRI changes is primarily due to location. This study contradicted this hypothesis by finding that recovery from PRI changes occurred significantly less often in symptomatic patients compared to asymptomatic (52.8 vs. 92.8%, $p = 0.0274$). This may indicate the relative severity of symptomatic changes, which may be related to brain location and volume, as opposed to the imaging characteristic itself. Since symptomatic temporary and permanent radiation injury are the two most clinically significant endpoints, future analyses of complications should concentrate on symptomatic PRI changes as endpoints.

*Factors found to be insignificant*

Once the 12 Gy volume was entered into the multivariate model, maximum dose (Dmax), minimum AVM nidus dose (Dmin), and treatment volume were all found to have no additional significant value for discriminating the risk of developing PRI changes. This study was also unable to substantiate any significant correlation between target dose inhomogeneity and the development of PRI changes as reported by Nedzi *et al.* (10).

Other factors such as Dmin, Dmax, treatment volume or even target dose inhomogeneity might need to be included to model complications for data with significant treatment differences such as inappropriately large treatment volumes.

*Persistent symptomatic PRI changes*

The development of persistent symptomatic post-radiosurgery imaging changes (radiation necrosis) is the complication outcome of greatest concern to clinicians. Because of the scarcity of long-term follow-up data, we estimated the risk of this by multiplying the risk of developing symptomatic imaging changes by the actuarial risk of persistence of these changes. A multivariate analysis of persistence of symptomatic PRI changes would be needed to make sure that there weren't unforeseen factors that affect their persistence but not their initial development. Univariate analysis showed that resolution of symptomatic PRI changes was not correlated with treatment volume, 12 Gy volume, Dmin, or location ($p > 0.49$).

*Use of risk-estimates for dose-prescription*

The sigmoid plots of 12 Gy volume vs. complications (post-radiosurgery imaging changes) could be used to guide radiosurgery dose-prescriptions or choose specific therapeutic approaches. Recently available dose-response information for AVM obliteration and better defined AVM hemorrhage risks can be used in conjunction with the risk predictions from this study to aid in the formulation of a management approach. The prediction curves for symptomatic PRI changes in brainstem and non-brainstem locations as shown in Figure 4 appear to be the most clinically useful guides. The risk of developing persistent symptomatic PRI changes can be estimated by multiplying the risk estimates from these curves by 47.2% (the actuarial rate of persistence).

There are several limitations to the use of the risk estimates from this study that should be addressed. The risk estimates calculated from the 12 Gy volume in this study may not be reliable for treatment techniques that vary significantly from those used in this series. The 12 Gy volume reflects the risk for the entire dose distribution in patients treated using similar technique. It would be incorrect to use this study to claim that irradiation of an AVM or the whole brain with a uniform dose of 11.9 Gy would have a significantly lower risk of complications. The risk formulas in this study are for parenchymal injury and do not reflect the risk of cranial neuropathy for radiosurgery that would administer a high-radiation dose to a cranial nerve (such as the optic nerve). Risk predictions for brainstem AVM (Fig. 4) may be less reliable than for non-brainstem AVM since they are based on less data (77 brainstem AVM vs. 230 nonbrainstem). As mentioned previously, the risk formulas in this study do not attribute any extra risk for enclosing normal tissue within the treatment volume. It would be dangerous to assume that this could be done with impunity. Every effort should be made to conform the radiation treatment volume to the target consequently limiting normal tissue irradiation. The use of proper neuroimaging, single or multiple isocenters, beam blocking or shaping, and finally dose-selection are all important technical and radiobiological factors necessary to achieve an optimal therapeutic result.

## REFERENCES

1. Dixon, W. J.; Brown, M. B.; Jennrich, R. I. BMDP statistical software manual. Berkeley: University of California Press; 1990:1013–1045.
2. Flickinger, J. C. The integrated logistic formula and prediction of complications from radiosurgery. Int. J. Radiat. Oncol. Biol. Phys. 17:879–885; 1989.
3. Flickinger, J. C.; Kondziolka, D.; Kalend, A. M.; Maitz, A. H.; Lunsford, L. D. Radiosurgery-related imaging changes in surrounding brain: Multivariate analysis and model evaluation. Radiosurgery 1:229–236; 1996.
4. Flickinger, J. C.; Lunsford, L. D.; Kondziolka, D.; Maitz, A. M.; Epstein, A.; Simons, S.; Wu, A. Radiosurgery and brain tolerance: An analysis of neurodiagnostic imaging changes following gamma knife radiosurgery for arteriovenous malformations. Int. J. Radiat. Oncol. Biol. Phys. 23:19–26; 1992.

5. Flickinger, J. C.; Lunsford, L. D.; Kondziolka, D. Radiosurgical dosimetry: Principles and clinical implications. In: DeSalles, A. F., Goetsch, S., eds. Stereotactic Surgery and Radiosurgery. Medical Physics Publishing; Madison, WI. 1993:293–306.
6. Flickinger, J. C.; Pollock, B. E.; Kondziolka, D.; Lunsford, L. D. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. Int. J. Radiat. Oncol. Biol. Phys. 36:873–879; 1996.
7. Kaplan E. L.; Meier, P. Non-parametric estimation and incomplete observations. J. Am. Stat. Assoc. 53:457–481; 1958.
8. Kjellberg, R.; Hanamura, T.; Daivs, K.; Lyons, S.; Butler, W.; Adams, R. Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. N. Engl. J. Med. 309:269–274; 1983.
9. Loeffler, J. S.; Alexander, E.; Siddon, R.; Saunders, W.; Coleman, N.; Winston, K. Stereotactic radiosurgery for intracranial arteriovenous malformations using a standard linear accclerator. Int. J. Radiat. Oncol. Biol. Phys. 17:673–677; 1989.
10. Nedzi, L.; Kooy, H.; Alexander, E.; Gelman, R.; Loeffler, J. S. Variables associated with the development complications from radiosurgery of intracranial tumors. Int. J. Radiat. Oncol. Biol. Phys. 21:591–599; 1991.
11. Peto, R.; Pike, M. C.; Armitage, P.; Breslow, N. E.; Cox, D. R.; Howard, S. V.; Martel, N.; McPherson, K.; Peto, J.; Smith, P. G. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br. J. Cancer 35:1–39; 1977.
12. Pollock, B. E.; Flickinger, J. C.; Lunsford, L. D.; Kondziolka, D. Hemorrhage risk after radiosurgery for arteriovenous malformations. Neurosurgery 38:652–661; 1996.
13. Voges, J.; Treuer, H.; Lehrke, R.; Kocher, M.; Staar, S.; Muller, R. P.; Sturm, V. Risk analysis of LINAC radiosurgery in patients with arterio-venous-malformations (AVMs). Acta Neurochir. 138:597; 1996.
14. Yaes, R.; Kalend, A. M. Local stem-cell depletion model for radiation myelitis. Int. J. Radiat. Oncol. Biol. Phys. 14:1247–1259; 1988.