Single-session stereotactic focused irradiation (radiosurgery) represents a generally accepted treatment alternative for cerebral AVMs. Since its introduction into clinical practice in 1970 by Steiner and colleagues, the procedure has proved to be safe and reliable, and > 10,000 patients around the world have been treated using radiosurgery. Early clinical experience with this treatment was based on the use of the Gamma Unit, followed by other radiosurgical techniques using different radiation sources such as the Cyclotron and LINACs; in the case of LINACs, they gained wide acceptance. The reported results, in terms of complete AVM obliteration achieved, appeared to be relatively independent from the device used, but the obliteration rate was strongly influenced by AVM-related factors such as nidus dimensions and absorbed peripheral dose. In an unselected population with AVMs treated using radiosurgery, 2-year complete obliteration rates ranged from 53 to 85%, with low treatment-related complication rates reported. Today, the rate of success of a new procedure for AVM radiosurgery should be between these limits.

Although radiosurgery has proven to be effective, some limitations and drawbacks to the procedure are still present. Large AVMs cannot be irradiated due to the increased probability of volume-related adverse effects, such as bleeding. Early results of CyberKnife radiosurgery for arteriovenous malformations

Clinical article

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Object. The authors describe a method that utilizes an image-guided robotic radiosurgical apparatus (the CyberKnife) for treatment of cerebral arteriovenous malformations (AVMs). This procedure required the development of an original technique that allows a high degree of automation.

Methods. Angiographic images were imported into the treatment planning software by coregistering CT and 3D rotational angiography. The nidus contour was delineated using the contouring tools of the treatment planning system. Functional MR imaging was employed for contouring critical cortical regions, such as the motor cortex and language areas. Once the radiation dose to be delivered to the target volume and dose constraints to critical structures were prescribed, the inverse treatment planning function determined the optimal treatment plan.

Results. A series of 279 patients with cerebral AVMs underwent CyberKnife radiosurgery. One transient adverse effect of the radiation procedure was observed. Eight bleeding occurrences were noted before complete AVM obliteration. Of the 102 patients with follow-up > 36 months, 80 underwent angiographic evaluation. In this group, 65 patients (81.2%) showed complete angiographic obliteration of their AVM. In 8 more patients, complete angiographic obliteration was demonstrated by MR angiography only.

Conclusions. This is the first report describing a technique developed for CyberKnife radiosurgery of cerebral AVMs. The use of different imaging modalities for automatic delineation of the target and critical structures combined with the employment of the inverse treatment planning capability is the crucial point of the procedure. The procedure proved to be safe and efficient. (DOI: 10.3171/2008.10.JNS08749)

Key Words • arteriovenous malformation • CyberKnife • functional magnetic resonance imaging • robotic surgery • stereotactic radiosurgery • 3D angiography

Abbreviations used in this paper: AVM = arteriovenous malformation; DS = digital subtraction; EPI = echo planar imaging; fMR = functional MR; LINAC = linear accelerator.
ter standard radiation doses delivered in a single session. Conversely, a reduction in the radiation dose decreases the probability of a complete AVM obliteration. A protective effect against the recurrence of bleeding is not immediate after radiation therapy, and patients remain exposed to the risk of hemorrhage for months or even years. Bleeding during the "latency period" before complete AVM obliteration—a potentially dangerous or even lethal occurrence—represents a well-known frustrating event that restricts the general application of radiosurgery as a first treatment option.15,19,23,35,37

This status quo has not changed significantly over the years until recently. The CyberKnife (Accuray, Inc.) is a robotic radiosurgical apparatus. A radiation source (a 6-MV LINAC) is mounted on a frameless, image-guided, computer-operated manipulator.1,12,15,39,41 We believed that this apparatus could provide a significant improvement of the AVM obliteration procedure and we employed it in AVM radiosurgery. Between January 30, 2003 and June 30, 2008, we treated 279 patients affected by cerebral AVMs using the CyberKnife. Treatment planning was performed using 3D angiography registered to CT scans, which represents the reference system of the apparatus. Automatic target delineation was routinely utilized, whereas automatic delineation of critical structures (the motor cortex and language areas) was used in 20 critically located AVMs. The aim of this paper is to describe the technique for employing the CyberKnife in AVM radiosurgery and to discuss possible advantages connected to the peculiar features of this robotic radiosurgical system.

**Methods**

**Image Registration Procedure**

The CyberKnife stereotactic radiosurgery treatment-planning system is based on CT for target definition. Nevertheless, optimal target outlining often requires information provided by multimodality images, such as angiography for AVMs or MR imaging for lesions close to critical structures. On the day of the CT scan (usually the day before radiosurgery), a thermoplastic mask was prepared and used to minimize patient movement during scanning. Computed tomography images were then acquired by a standard scanner (Somatom Plus 4, Siemens Medical Solutions). The number of slices ranged from 90 to 110 depending on the target location, and slice thickness was 2 mm. The modalities that could be registered to CT were 3D rotational angiography (Integris Allura 5000, Philips Medical Systems), MR imaging (Magnetom 1.5 T, Siemens Medical Solutions), PET (Discovery, GE Medical Systems), and fMR imaging.

An angiographic study (3D rotational angiography) was undertaken the same day as the thermoplastic mask preparation and CT examination. For image registration, the maximization of the entropy correlation coefficient was selected among mutual information maximization algorithms.24,43,44 This algorithm calculated the parameters of a spatial transformation whose aim was to map the space of the secondary modality (in this case 3D rotational angiography) onto the space of the CT volume. Using an affine global transformation with 12 parameters, the algorithm took into account rotation, translation, linear scaling, and shear (angular deformation). As described in previous studies,26,43,44,48 this approach allows quantitative estimation of registration accuracy.

The image registration procedure was adapted for coregistration of fMR imaging. The aim of this procedure was to fuse a brain functional map to the CT volume used for treatment planning. This image set was used for contouring critical structures located close to the AVM nidus so that dose constraints could be imposed.

Functional MR imaging studies were performed prior to the radiation procedure (usually a few days before) and prepared for registration to the CT scan that would be performed the day of the treatment planning. Functional maps were obtained by means of the blood oxygen level dependent effect using EPI MR volumes and the statistical parametric mapping software package.22 We evaluated motor functions by means of hand, foot, and tongue movements, and evaluated language-cognitive functions using category generation, letter generation, simple question, and verbal generation tasks. For motor studies, functional maps were obtained by means of a t-test analysis with a probability value of 0.05 (false-positive corrected) and a minimum number of 20 adjacent voxels to define an activation cluster. For language-cognitive functions the values used were p = 0.001 (uncorrected for false positives) and 40 voxels. These differences in activation analysis were required due to the spread of activated areas in language-related tasks. To improve the signal-to-noise ratio, images were filtered by means of convolution with a Gaussian kernel with full width at half maximum of 8 mm. Due to its negative effect on spatial resolution, this preprocessing step was factored in when evaluating proximity of an activated area to the target volume in radiosurgery.

Registration of the functional maps to the CT volume was performed using the following steps: 1) rigid registration of all MR imaging data sets to the first volume acquired to compensate for patient movement during the acquisition procedure; 2) Gaussian filtering; 3) statistical analysis and generation of the functional map; 4) affine registration of the EPI volumes to a T2-weighted MR imaging volume; 5) rigid registration of the T2-weighted MR imaging volume to the CT volume; and 6) application of the combined transformation defined in Steps 4 and 5 to the functional map obtained in Step 3. This final step allowed the functional map to be spatially registered to the CT volume used for treatment planning, and therefore made it possible to define regions of interest corresponding to functional areas, within which dose constraints could be imposed during the optimization process.

**Treatment Planning**

The image registration procedure lasted ~ 10 minutes for CT and MR imaging and ~ 20 minutes for 3D CT rotational angiography registration, including pre- and post-processing steps that were required to make the data sets readable by the treatment planning system. The process of image registration between CT and fMR imaging required longer times, usually 2–3 hours. Most of this time
was spent on processing fMR imaging data (Steps 1–4 of the procedure for image registration described above). This part of the procedure could be performed at any moment after fMR imaging data acquisition. Preprocessing could be accomplished offline, independently of treatment planning. Once the functional data set was prepared, the inclusion of fMR imaging into the planning data sets and its registration to CT took ~ 10–20 minutes.

As soon as registered data sets were imported into the CyberKnife system, treatment planning could be performed. This part of the procedure was usually performed the day of radiosurgery. Delineation of the AVM nidus contour was performed slice by slice on axial sections of 3D rotational angiography, using an automatic contouring function with an appropriate threshold for voxel values. The radiological density of nidus vessels was determined by placing a density evaluation cursor (a tool of the treatment planning station) into the nidus volume. Due to the high contrast of angiographic images obtained by direct intraarterial contrast-material injection, contouring of the AVM nidus could be conducted automatically, under direct physician supervision (Figs. 1 and 2). The target delineated on 3D rotational angiography could be overlaid on other registered data sets to take advantage of the information provided by different imaging modalities.

The described image registration procedure could be used for employing the previously recorded fMR imaging in the treatment planning procedure. Using this functional image set, automatic contouring of critical regions (such as the motor strip or language cortical areas) could be performed (Figs. 3 and 4).

For all patients, treatment planning was performed with the aid of automatic contouring of the AVM nidi based on 3D rotational angiography data. With increasing experience, the need for manual correction of the target contour delineated by the automatic procedure decreased. Cortical areas were contoured automatically in 14 of 30 patients with AVMs involving the motor cortex and in 6 patients of 21 patients with left opercular or temporal AVMs close to language areas (Table 1). The reduction of the dose absorbed by eloquent cortical areas was considered an indication of the improvement of the treatment planning contributed by fMR imaging. Two different plans, with the same prescription dose but either with or without fMR imaging brain map information, were created. The dose absorbed by the eloquent critical cortex was calculated and compared between the 2 treatment plans. The percentage dose reduction was calculated according to Liu et al.,31 both for maximal dose and for integral dose, according to the formula:

\[
\text{Dose reduction} = \frac{\text{Dose without fMRI optimization} - \text{Dose with fMRI optimization}}{\text{Dose without fMRI optimization}}
\]

The prescription dose and dose limits to critical structures were subsequently determined according to established radiosurgical experience. Optimal collimator dimension was selected according to the volume and shape of the target, usually depending primarily on the minimum target cross-sectional dimension. An inverse planning optimization procedure could then be initiated.

The CyberKnife robotic arm can move the LINAC to 100 evenly spaced fixed positions (nodes) in a virtual hemisphere surrounding the target. From each of these nodes, 12 radiation beams with different angular directions can be employed (for a total of 1200 radiation beams). Inverse planning determines the radiation dose and the angular direction of each individual radiation beam, adequate for satisfying the dose prescriptions.1,12,15,39,41 The solution

Fig 1. Screen shots from the CyberKnife treatment planning software showing an AVM nidus on 3D rotational angiography before automatic contouring (left) and after delineation (right). The AVM nidus is outlined in red.
found is applied to the last procedural step, which is dose-volume optimization. The beam arrangement is modified according to 2 prerequisites: 1) respect to the prescribed dose constraints and 2) minimization of integral dose. For practical purposes we programmed the machine to select the treatment plan that had the smallest volume enclosed by the 30% isodose surface while respecting the dose constraints to the target and critical structures. The inverse planning procedure usually lasted between 45 and 120 minutes (depending on the total number of dose constraints) until completion. After medical evaluation and acceptance of the proposed solution, the radiation procedure could be undertaken.

**Dose Prescriptions and Follow-Up**

The irradiated AVM volume varied in size from 0.1 to 42 ml. Maximum radiation doses from 22.5 to 30 Gy were delivered. The borders of the target volume were encompassed by isodose surfaces from 65 to 85%. In patients harboring cerebral AVMs with target volumes < 8 ml, radiation was delivered in a single session. In 18 patients with target volumes > 8 ml and in 3 patients with a diffuse nidus involving optic pathways and the brain stem, the radiation dose was delivered to the entire nidus in 2 equal fractions, 8–30 days apart.

Our follow-up protocol included clinical and MR imaging examinations at 6-month intervals up to 2 years. At 24 months, DS angiography was recommended. In cases of incomplete AVM obliteration, angiography was repeated at 36 months. If the residual AVM was significantly reduced, we repeated the angiography at yearly intervals, until complete AVM obliteration was attained. If the residual AVM was unchanged, suggesting that the obliteration process had finished, repeated radiosurgery or alternative treatments were suggested.
Results

Clinical Experience

Among 1130 patients treated with the CyberKnife between January 30, 2003 and June 30, 2008, 279 (133 male and 146 female patients) were treated for cerebral AVMs. At treatment, patient ages ranged from 13 to 70 years (mean 36 years). Symptoms at presentation included hemorrhage in 129 patients, seizures in 62, neurological deterioration in 39, and headache in 38. In 12 patients the AVM was revealed by examinations conducted for nonrelated diseases or trauma. Before radiosurgery, 9 patients had undergone unsuccessful attempts at surgical removal of the AVM, 131 patients had undergone incomplete AVM embolization, and 48 patients had been treated for residual nidi after a previous radiosurgical treatment.

In our experience, the fMR imaging–based treatment planning optimization was able to reduce the maximal dose absorbed by the critical structures by 19–58% (mean 39%, median 41%) and the integral dose by 13–79% (mean

Fig. 3. Case 11. Screen shots of the CyberKnife treatment planning software showing the right hand motor cortex on fMR imaging (A), automatic delineation of the motor cortex on fMR imaging (B), and the delineated motor cortex on 3D angiography (C) and T2-weighted MR imaging (D). Functional areas in the original image set of axial images are delineated by yellow outlines. Sagittal and coronal reconstructed images from the treatment planning software show functional areas delineated by green outlines.
41%, median 40%; Table 1 and Fig. 5). In all evaluated cases the treatment planning optimized with the inclusion of fMR imaging data was selected and employed for treatment.

**Postoperative Complications**

Follow-up duration ranged from 1 to 64 months (mean and median follow-up 31 months). At latest follow-up (June 2008), clinical data were available for 267 of the 279 patients. We found only 1 clinically relevant complication, in the form of transient difficulties with speech and arithmetical calculations, experienced by a patient suffering from a 2.7-ml left temporal AVM. In this early case, functional images were not available for treatment planning. Magnetic resonance imaging suggested a radiation-induced edema around the target. The imaging and clinical picture improved immediately in this patient with a short course (20 days) of corticosteroids. At later follow-up his neurological examination results were completely normal and angiographic obliteration was demonstrated 24 months after treatment. Up to the last follow-up evaluation we observed 8 hemorrhagic events in treated patients resulting in 1 patient death and 1 case of tetraparesis. The other 6 instances could be considered relatively minor events—none of the patients showed any permanent new neurological deficit, and complete recovery was attained in a short time. Three of these patients showed complete AVM obliteration based on angiography in the follow-up period (24–36 months).

**Obliteration Success**

The success rate in terms of complete AVM obliteration was investigated. We subdivided our series into 2 groups, according to the volume of the nidus (< 8 or > 8 ml), evaluated using the automatic technique at the time of the treatment. In patients with previous embolizations, embolic material was subtracted in the treatment planning and only the residual AVM nidus was considered. Also, in patients who had undergone previous radiosurgery, only the volume of the residual AVM was accounted for. Of 85 patients with AVM volumes < 8 ml and follow-up durations > 36 months, 66 underwent angiographic examination. Twenty-six of these 66 patients were treated after partial embolization and 10 had undergone a previous radiosurgery. In this group, 60 (91%) of the 66 patients showed complete angiographic obliteration, and another 8 patients underwent MR angiography that suggested complete AVM obliteration, but these patients refused to undergo DS angiography.

Of 17 patients with AVM volumes > 8 ml and follow-up durations > 36 months, 14 underwent angiography. In 5 (35.7%) of these 14 patients complete AVM obliteration was demonstrated. Considering both groups, we obtained complete AVM obliteration in 65 of 80 patients confirmed by angiography and with follow-up durations > 36 months.

The overall rate of complete obliteration based on angiography was 81.2% (65 of 80 patients) in patients with 36 months of follow-up. This rate (total obliteration verified on angiography) becomes 63.7% if we consider the total number of patients treated (102) regardless of whether they underwent posttreatment angiography or not. If those AVMs in which we observed complete obliteration on MR angiography alone but were unable to be verified using DS angiography are also included (another 8 patients), the complete obliteration rate is 71.5% (73 of 102 patients).
CyberKnife radiosurgery for arteriovenous malformations

Only those patients with at least 36 months of follow-up were statistically analyzed for factors associated with successful treatment. Because we did not observe any clinically persistent deterioration in this group and only 1 patient died from recurrent hemorrhage a very short time after treatment, only 2 categories of results were used: successful (confirmed complete obliteration) and unsuccessful (incomplete obliteration at last follow-up).

A logistic regression model was used to test the correlation between each variable, and the clinical outcome was described as 0 (unsuccessful treatment) or 1 (successful treatment). The statistical analysis was performed using the Egret software package (Cytel Software Co.).

The variables used in the logistic regression model were age, sex, nidus volume (in ml), location (cortical-subcortical location vs deep posterior fossa), Spetzler-Martin grade, Pollock-Flickinger score, maximum absorbed dose, minimum absorbed dose, history of previous hemorrhage, previous embolization, and previous radiosurgery (Table 2). Fractionation was not taken into account because we didn’t observe any 36-month complete obliteration in patients treated with 2 fractions. Higher rates of success were found to be significantly related to smaller AVM volumes, lower Spetzler-Martin grades, lower Pollock-Flickinger scores, absence of previous radiosurgery, and male sex.

**Discussion**

**Image Registration**

Angiography has represented the first choice of examination for the diagnosis of cerebral AVMs and, until the introduction of CT and MR imaging, the only available data set for the planning of AVM radiosurgery. Nevertheless, biplanar stereotactic angiography alone is inadequate.
This flaw is partially overcome by using 1 of 3 options: 1) the combination of stereotactic angiography and stereotactic CT (and/or MR imaging);8,20,27,28,30,46 2) CT angiography;4 or 3) MR angiography.6,27 Despite general agreement that 3D imaging is essential for treating AVMs, the evidence that treatment plans based on CT or MR angiography are superior to those obtained with a combination of stereotactic angiography and contrast-enhanced CT is still lacking.

The accuracy of 3D reconstruction in a 3D rotational angiography system has been the subject of some neuroradiological publications.3,7,9,22 However, these publications do not describe any method for using this data set in radiosurgical dose planning. In this study, we take advantage of an image registration technique to incorporate 3D angiography into the CyberKnife treatment planning process. Most image registration procedures are completely automatic;2,26,48,49 the computer algorithm extracts those voxels to be fused that lay at the cranial bone edges in imaging studies and proceeds to their segmentation and registration with each other.

The 3D angiography/stereotactic CT image registration technique we have described in a previous paper is iterative and manual, yet improves the spatial representation of the target with respect to biplanar stereotactic angiography.11,14 As expected, the introduction of the new modality with its ability to discriminate between different vascular components of an AVM nidus resulted in reduction of the target volume. Three-dimensional rotational angiography also has potential pitfalls. A relatively large amount of iodated contrast has to be injected into intracranial arteries to obtain good anatomical visualization (22–30 ml compared with 7–8 ml required for standard DS angiography). In our patient series, however, we didn’t observe any significant clinical problems related to the increased amount of contrast material.

More relevant was the fact that, in 3D rotational angiography, all the anatomical components of the AVM (feeders, nidus, and draining veins) were visualized at the same time; part of the AVM flow dynamic information provided by serial examinations was lost (for example, it was more difficult to identify fistulous components of the nidus). However, this shortcoming is also common to other 3D examinations used in target delineation in AVM radiosurgery such as CT or MR angiography.4,6,27 On the other hand, in our opinion, the improvement in target delineation afforded by 3D rotational angiography largely overcomes this limitation.

Regarding the procedure of image registration, the choice of a mutual information–based algorithm and a global affine transformation was particularly well suited for intracranial applications. The availability of an automatic procedure to check registration accuracy permits an operator-independent evaluation method.44 Image distortion was the main problem with the coregistration of a functional map to the CT volume used for treatment planning. Echo planar imaging volumes are inherently distorted because of their fast acquisition time. A usual approach in fMR imaging analysis is to register the patient’s EPI volume to an EPI template corresponding to an anatomical atlas. This approach makes use of deformable image registration to map the patient’s anatomy to the atlas. Nevertheless, this procedure was not suitable for radiosurgical treatment planning because of the altered spatial relationship between brain structures. One possibility consisted of using a deformable registration technique to map the EPI volumes to T1- or T2-weighted MR images, which in turn would be mapped to the CT volume using rigid registration.43 The combined transformation would then register the functional map obtained on the EPI volumes to the CT volume. This method can be very accurate and can compensate for distortions in EPI; however, it is time-consuming and prone to errors due to difficulties in regularization techniques. Despite using this method in some selected cases, we usually preferred using a much faster affine transformation,21 which allowed most of the distortion to be removed.
Potential pitfalls of the use of fMR imaging in radiosurgical treatment planning are essentially the same as those in the use of this type of functional data in preparing preoperative maps. The main problems are probably related to the presence of false negatives, the limited spatial resolution of the resulting data sets, and the residual distortion after registration. In a radiosurgical procedure capable of submillimetric accuracy, these are obvious concerns; however, a critical use of the information provided has potential benefits that definitely overcome the associated risks. The single (transitory) complication we observed in this study was in a patient with an AVM located in a critical area (left temporal cortex) that could have been spared if fMR imaging had been included in the treatment planning of this patient. Furthermore, none of the 20 patients with critical structure AVMs who underwent treatment planning with fMR imaging showed any complications.

Treatment Planning

The CyberKnife inverse planning procedure usually takes between 45 and 120 minutes to be completed. This duration is significantly longer than that employed by experienced neurosurgeons working with either the Gamma Knife (Elekta AB) or ordinary LINAC-based systems (reportedly 10–20 minutes). The Gamma Knife and LINACs work with isocentric irradiation techniques. In cases of irregular target shapes, their “forward” treatment planning systems essentially allow the operator to manually combine multiple shots inside the target and then visualize the results. CyberKnife irradiation geometry is completely different (nonisocentric). A large number of beams (up to 1200) are available to be directed to the target from different directions and with different doses. This situation can be handled only by “inverse” treatment planning in which the operator first decides on the dose to be delivered and the planning algorithm determines all treatment variables afterward that satisfy the operator’s requirements. Usually, the operator uses the 2 different planning algorithms available with the CyberKnife treatment planning system sequentially. The first, named Simplex, requires a relatively shorter amount of time and creates a coarsely optimized plan and stops. Then, if the operator is not satisfied with this result, he or she may initiate the iterative calculation mode, which would continue to optimize the treatment plan until the operator is satisfied with the outcome and stops the calculation. The 2 systems give comparably good results in terms of dose conformality and steepness of dose gradients; on the other hand, dose homogeneity inside the target volume (in our opinion an important factor in AVM radiosurgery)\textsuperscript{15,16} is usually better with the iterative, nonisocentric technique with respect to procedures combining multiple isocenters. This advantage might compensate for the longer time spent for planning.

Registered 3D rotational angiography high-contrast images are essential for employing automatic contouring of the AVM nidus. The procedure requires an accurate determination of the nidus’ radiological density for setting the filtering window values. If these values are appropriately selected, the automatic function will contour...
only the nidus vessels, avoiding major feeding vessels and draining veins. In patients who have undergone embolization, subtracted 3D rotational angiography data sets are used for excluding embolic material from the intended target, reducing the treatment volume and the total radiation dose to be delivered.

One advantage of utilizing 3D rotational angiography for CyberKnife treatment planning is the possibility to reconstruct any selected isodose surface in 3D, and to verify it immediately by moving the viewpoint at the operator’s choice. The isodose reconstruction gives also an immediate indication of the adequacy of the treatment plan to spare nearby critical structures. In our experience, modifications induced by critical evaluation of angiographic data were mostly in the direction of a decrease in the target volume. We believe that a possible explanation for this may be that angiographic data permit better discrimination between nidus shunt vessels and large draining veins, which often blur the target outline.

Functional MR imaging allows one to identify various eloquent cortical areas noninvasively. The integration of cortical activation information into radiosurgical treatment planning may help to prevent radiation damage to eloquent cortex. Latchaw et al.29 first proposed the use of fMR imaging information to identify eloquent cortex in treatment planning for radiosurgical treatment. In that study, functional maps were examined only visually and not directly incorporated into the treatment planning procedure. Debus and colleagues17 used a stereotactic MR imaging–compatible frame for employing MR imaging functional data for planning radiosurgery; the integration of anatomical and functional data, however, was impacted by the presence of the cumbersome stereotactic frame.

Liu et al.31 and Schulder and associates40 employed fMR imaging to locate the motor cortex, visual areas, and language areas in 12 patients undergoing LINAC converging arcs radiosurgery. In these studies, the activation maps were transferred to the treatment planning workstation by coregistration to stereotactic CT and used retrospectively to evaluate the radiation dose absorbed by critical structures. These investigators found that a modification of the irradiation arcs introduced by the operator could significantly reduce the exposure of eloquent cortex. The average dose reduction to critical areas was estimated to be ~32%.

Recently, Maruyama et al.33 introduced diffusion tensor–based tractography as an effective way to locate the corticospinal tract. In this method, image data sets were coregistered with stereotactic CT, included in the Gamma Knife treatment planning system, and used retrospectively to review the dose distribution in cases that displayed radiation complications (hemiparesis). Magnetocencephalography and MR axonography have been used by Aoyama and associates8 to reduce the planned dose to critical structures (motor-sensory cortex, visual cortex, Wernicke area, and corticospinal tracts) to <15 Gy. These authors found a single complication among 21 patients undergoing radiosurgery.

In all of these cited studies, functional imaging of critical structures has been utilized manually by the operator to avoid critical structures, without taking into account the integral dose absorbed by the brain and by the critical structure itself. It is our experience that when making use of beam arrangement restrictions attempting to spare multiple critical structures, the integral dose absorbed by normal brain tissue may increase significantly.15 In none of the reported studies were anatomical and functional data used for optimization of the treatment plan; moreover, the increase of integral dose is not accounted for. In our experience, the fMR imaging–based treatment planning optimization proved to be able to reduce the maximal dose absorbed by the nearest critical structure by 19–58% and the integral dose by 13–79%. The range of reduction of the integral dose appears to be larger and less predictable than that of the maximal dose. This finding could be related to the CyberKnife inverse treatment planning optimization system, because the algorithm currently available takes into account only the maximal dose absorbed by the critical structure. We believe that future developments of the software should also take into account the integral dose delivered to the critical structure as an important parameter in the process of treatment planning optimization.

Clinical Experience

The CyberKnife has been routinely employed in radiosurgical practice since 1993 in a limited but increasing number of centers worldwide. All of the applications of radiosurgery, including extracranial locations, have been tested and clinical results have begun to be reported.1,12 Studies devoted only to cerebral AVMs have not yet been published. Ryu and colleagues9 presented a series of 16 patients affected by spinal lesions treated using CyberKnife radiosurgery. Of these 16 patients, 5 were affected by spinal AVMs. Clinical results in terms of nidus obliteration were not yet available, nor were indications of whether clinical and radiological evolution appeared to be favorable. In these cases, dose planning had been performed using CT and angiography was not utilized for nidus delineation. These results have been updated by Sinclair and colleagues39 in their recent paper. Results obtained in 15 patients affected by spinal AVMs were reported. Three-dimensional rotational angiography was utilized for treatment planning in only a small final part of the patient series. The mean follow-up duration was 28 months. Five patients underwent control angiography that demonstrated 4 subtotal obliterations and 1 total obliteration.

To our knowledge, our study is the first report describing the incorporation of angiographic and fMR imaging data into CyberKnife treatment planning, employed in an automated radiosurgical procedure. The described procedure proved to be reliable and efficient in our experience. In this patient series, results in terms of complete obliteration appear to be superior to those we obtained with the LINAC-based procedure we used until 2003. To make an adequate comparison between the 2 different techniques, we restricted our evaluation to AVM volumes that have long been considered good indications for radiosurgery (<8–10 ml).16,20 excluding those cases (usually large AVMs) that we deemed treatable only with the robotic procedure. CyberKnife results in AVMs with volumes <8 ml were
compared with LINAC-treated AVMs of roughly equivalent volume (< 25 mm diameter), and a significant improvement in 24-month complete obliteration rates was observed (91 vs 75–80%, respectively).13,15,16

In this study, we present a series of 279 patients with cerebral AVMs treated using a frameless, image-guided radiosurgical system utilizing original software instruments for implementing 3D rotational angiography (for nidus delineation) and fMR imaging (for sparing critical structures) into the treatment planning. Due to time constraints (the first patient was treated in 2003), only part of the series (102 patients) was available for analysis after 36 months of follow-up. We know that 3 years of follow-up has become the standard for evaluating the efficacy of radiosurgical treatment in terms of AVM obliteration; nevertheless, because the safety of the procedure is also an important issue (and complications in radiosurgery may require a much shorter time to appear), we also included a concise report on clinical features and evolution of the entire group of treated patients. Long-term evaluation of clinical results is inevitably beyond the scope of this paper, which was first intended as a technical report on the feasibility and safety of CyberKnife radiosurgery for AVMs, but also indicating some possible advantages in procedural standardization and automation. Nonetheless, the patient population with an adequate follow-up was studied and the results compared with those obtained in large patient series treated using radiosurgical techniques.13,15,16,19,20,23–25,37,38,46

Regarding the statistical evaluation of factors associated with successful treatment, our study was limited to patients with follow-up durations > 36 months. The variables studied were patient age, sex, AVM size and location, Spetzler-Martin grade, Pollock-Flickinger score, maximum radiation dose, minimum radiation dose, and history of previous hemorrhage, embolization, and radiosurgery.

Among the factors associated with treatment success, we confirmed a strong negative correlation with AVM volume—a well-established relationship16,19,20,24,36,38—and Pollock-Flickinger score. The predictive value of this radiosurgery-based grading system, developed by groups using the Gamma Knife, was also confirmed for the CyberKnife. Contradicting previous reported experiences,20,38 we found a surprising significantly strong negative correlation with Spetzler-Martin grade; in our opinion, this fact can be explained by the dependence of the Spetzler-Martin grading system for determining AVM volume, combined with the wider range of grade variability (from II to V), and the more consistent number of high grades in our series. We do not have an explanation for the observed weak but significant relationship between sex and treatment success (better results were obtained in male patients), which was not explained in multivariate analysis with other associated variables (age, AVM volume, and radiation dose).

Contrary to previous experience,18,24 among factors that were not significantly related to success was the minimal dose absorbed by the target. On the other hand, radiation doses employed in our patient series were deliberately consistent, except in a very small number of patients (which explains the range limits). Moreover, a patient’s age was not related to the success of the treatment, although this factor had been found by others to have significance and was included in the calculation of the Pollock-Flickinger score.36 Superficial or deep AVM location was also not significantly related to success.

Factors derived from the patient history previous to radiosurgery were investigated to identify any significant predictors of outcome. A history of previous radiosurgical treatment was negatively related to treatment success, which was not surprising. A history of previous hemorrhage did not influence the treatment results. In our patient series, a previous embolization procedure—a factor reported to be negatively related to the success of radiosurgical treatment18—appeared to be irrelevant to outcome. The fact that we were able to obtain the same obliteration rate instead of observing a significant decrease in embolized AVMs could be explained by the improvement in target definition entailed by the use of our procedure with 3D rotational angiography and subtraction of embolic material.16 The most impressive fact in our study is the high safety rate afforded by the procedure; while obtaining the same obliteration rates of the most recent reports, we did not observe any radiation-related permanent complications in the entire series of 279 patients.

**Robotic Radiosurgery**

This paper describes an original method for employing a frameless, image-guided, robotic radiosurgical apparatus (the CyberKnife) for treating cerebral AVMs. This method requires the inclusion of 3D angiography for adequate visualization of the AVM nidus while fMR imaging is used to include critical structures into the treatment planning procedure. Automatic contouring based on the radiological density of 3D rotational angiographic images was used to delineate the target volume. Inverse treatment planning managed a very complex irradiation geometry (1200 possible nonisocentric beams) and determined radiation source positions, beam directions, and the dose to be delivered for each beam with respect to dose prescriptions. Forward planning with such a large number of treatment variables would have been well beyond human intellectual capabilities.

Robots have been employed to improve human capabilities and enhance precision task performances. In clinical applications, they have been proposed and tested to extend the reach of surgical tools, improve health care quality, and enhance patient safety. In the last 20 years, robots have been introduced to improve operator performance in neurosurgery, orthopedics, urology, maxillofacial surgery, ophthalmology, cardiac surgery, and of course, radiosurgery. Although surgical robots may be classified as devices with different grades of procedural autonomy and involvement with the patient, the intellectual decision-making part of the procedure (from the careful development of each surgical step to the selection of adequate movements of the surgical tools) remains the exclusive task of the operator, while the robot is used as a manipulator that increases the precision and range of movements already chosen and planned by the physician. Most of the robots employed in surgery are teleoperated...
systems, in which the surgeon sits at a remote console and directly controls the motion of instruments in the surgical environment: the surgeon, with master control handles, directs the approach of a “slave” instrument inside the patient’s body. Because the robot closely mimics the hand motion of the operator, the level of autonomy of the surgical robot is very low or absent.10 In none of the described procedures is the machine alone capable of designing a surgical approach.

The procedure we have described is radically different. In this case, the computer system driving the robot identifies the target of the operation, locates the critical structures to be spared, and directs the movements of the radiation source to obtain the intended results. The role of the physician is to supervise the procedure and to give the final approval. For the clinician, the advantages of an automatic procedure with respect to conventional techniques are obvious: time sparing, less variability, less dependence on variable individual judgement and skills, and others. Regarding this particular aspect, we would like to emphasize the advantage of automatic delineation of the target volume for more accurate AVM grading and success prediction. The size-dependent factor of the Spetzler-Martinson grade relies on the operator’s evaluation of the AVM’s major dimensions.24 Karlsson et al.24 calculated AVM volumes derived from linear measurements in 2D images (biplanar angiographies) using an arithmetic formula. A similar solution was employed by Pollock and Flickinger,36 whose Pollock-Flickinger score includes the AVM volume calculated by measuring the width, length, and height of the nidus and multiplying them by π/6. Measurement of AVM dimensions is influenced by the surgeon’s experience and consequently strongly operator-dependent; the inherent variability of a personal evaluation may obscure the predictive value of these grading systems in the determination of AVM nidus volumes.

Tutorial advantages of automatic radiosurgery are also evident, because computerized procedures are easier to teach, transmit, and comprehend with respect to elaborate manual tasks (such as microsurgery); learning curves are steeper; and high-level standards can be achieved more quickly. For the patient, other advantages of the CyberKnife are more relevant: the procedure—without head frame fixation—is less traumatic and radiosurgery can be performed on an outpatient basis. Moreover, diagnostic studies can be performed in places and times different from those of irradiation, provided that they can be made readable by the CyberKnife treatment planning software. Because dose nonhomogeneity within the target volume may increase the tendency to bleed in large and/or irregular AVMs (according to our LINAC experience), the use of the new robotic radiosurgery apparatus, with its peculiar nonisocentric irradiation geometry and homogeneous dose distribution, may decrease the risk of bleeding in the latency period.15

Conclusions

In the near future, using a combination of automatic contouring of an AVM nidus on 3D rotational angiography, automatic contouring of the critical structures on fMR imaging, and inverse treatment planning with dose-volume optimization, radiosurgery for AVMs could become the first completely automated operative technique.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

11. Cavedon C: Three-dimensional rotational angiography (DRA) adds substantial information to radiosurgery treatment planning of AVM’s compared to angio-CT and angio-MR. Med Phys 31:2181–2182, 2004
CyberKnife radiosurgery for arteriovenous malformations


