Detection of residual brain arteriovenous malformations after radiosurgery: diagnostic accuracy of contrast-enhanced four-dimensional MR angiography at 3.0 T

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Objective: To evaluate the diagnostic accuracy of four-dimensional MR angiography (4D-MRA) at 3.0 T for detecting residual arteriovenous malformations (AVMs) after Gamma Knife® (Elekta Instrument AB, Stockholm, Sweden) radiosurgery (GKRS).

Methods: We assessed 36 angiographically confirmed AVMs in 36 patients who had been treated with GKRS. 4D-MRA was performed after GKRS and the time intervals were 39.4 ± 26.0 months [mean $\pm$ standard deviation (SD)]. 4D-MRA was obtained at 3.0 T after contrast injection, with a measured voxel size of $1 \times 1 \times 1$ mm and a temporal resolution of 1.1 s (13 patients) or a voxel size of $1 \times 1 \times 2$ mm and a temporal resolution of 0.98 s (23 patients). X-ray angiography was performed as the standard reference within 53 ± 47 days (mean $\pm$ SD) after MRA. To determine a residual AVM, the 4D-MRA results were independently reviewed by two readers blinded to the X-ray angiography results. We evaluated diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of 4D-MRA for detection of a residual AVM.

Results: A residual AVM was identified in 13 patients (13/36, 36%) on X-ray angiography. According to Readers 1 and 2, 4D-MRA had a sensitivity of 79.6% and 64.3%, a specificity of 90.9% and 100%, a PPV of 84.6% and 100% and an NPV of 90% and 81.5%, respectively, and a diagnostic accuracy of 86.1% for Readers 1 and 2, for detecting residual AVMs after GKRS.

Conclusion: The diagnostic accuracy of 4D-MRA at 3.0 T seems high, but there is still the possibility of further improving the spatiotemporal resolution of this technique.

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Arteriovenous malformations (AVMs) of the brain are congenital vascular anomalies consisting of a complex web of feeding arteries and draining veins, linked by an abnormal capillary bed—the so-called nidus. Although they can remain silent over a long period of time, because of their possible long-term morbidity or life-long risk of bleeding (approximately 2–4% per year), brain AVMs are usually treated by surgical resection, by complete obliteration by either endovascular embolisation or Gamma Knife® (Elekta Instrument AB, Stockholm, Sweden) radiosurgery (GKRS) or by a combination of all three [1–3].

GKRS is increasingly used for the treatment of small or residual AVMs after surgical resection or embolisation. After GKRS, the microvascular structures within the AVM begin to be obliterated by the endothelial cell damage and proliferation of smooth muscle cells, which usually continues for 2–3 years [4]. Because the risk of bleeding persists as long as complete obliteration is not obtained, most physicians usually follow up patients at a regular interval to evaluate the response to GKRS. X-ray angiography is a gold standard for post-therapeutic

monitoring of AVMs. However, it is an invasive procedure, and its potential neurological complications, ranging in incidence from 0% to 12.2%, hinder its use as a routine follow-up study [5, 6]. Consequently, several non-invasive MRI and MR angiography (MRA) techniques have been proposed as a non-invasive alternative to X-ray angiography to assess the response of AVMs and adjacent brain parenchyma.

Time-of-flight (TOF) MRA is a commonly used MRA technique for the assessment of residual AVMs after GKRS. However, TOF MRA produces only static images of AVMs and lacks haemodynamic information. Another non-invasive technique, contrast-enhanced four-dimensional MRA (4D-MRA), is an emerging new technique without these limitations and demonstrates a good correlation with X-ray angiography with respect to the Spetzler–Martin classification on initial assessment of AVMs prior to treatment [7–13]. However, the diagnostic accuracy of 4D-MRA for the detection of residual AVMs after GKRS is not well known. Only Gauvrit et al [14] reported that the sensitivity and specificity for the detection of residual AVMs after GKRS were 81% and 100%, respectively. But their study was performed using a 1.5 T MRI system.

Therefore, the purpose of this study was to evaluate the diagnostic performance of 4D-MRA for detecting

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residual AVMs after GKRS at 3.0 T, compared with X-ray angiography.

Materials and methods

This retrospective study was approved by our institutional review board for human investigation, and informed consent was waived.

Patients

Our primary patient selection criteria were (a) patients who had a brain AVM confirmed by conventional X-ray angiography at our institution between August 2005 and March 2008; and (b) patients treated by GKRS who underwent both follow-up 4D-MRA at 3.0 T and X-ray angiography. Consequently, 36 AVMs in 36 patients [mean age $\pm$ standard deviation (SD), 33.1 ± 12.9 years; range, 12–61 years; females/males, 23/13] were found from our MRA and GKRS database and included in our study. Time intervals between GKRS and follow-up 4D-MRA were 8–111 months (mean $\pm$ SD, 39.4 ± 26.0 months). Follow-up MRA was always performed before X-ray angiography, and the time intervals between them were 0–180 days (mean $\pm$ SD, 53 ± 47 days) after MRA.

Arteriovenous malformation characteristics and treatment

The locations of 32 AVMs were the frontal lobe ($n=6$), parietal lobe ($n=5$), temporal lobe ($n=9$), occipital lobe ($n=5$), corpus callosum ($n=4$), basal ganglia ($n=2$), thalamus ($n=2$), cerebellum ($n=2$) and both the basal ganglia and the thalamus ($n=1$). The mean volume of AVMs was 2.6 cm^3 (range, $0.05\text{--}11.00 \text{ cm}^3$). The volume of the AVM before GKRS was calculated by the Leksell GammaPlann® software (v. 5.3; Elekta Instrument AB). All patients were treated using the Leksell Gamma Knife under local anaesthesia. A stereotactic head frame was used for guiding and monitoring the treatment in all cases. The radiation dose was 20–25 Gy and 50–65% isodose at the AVM margin. 14 patients were also treated by embolisation with coil or glue before or after GKRS.

Contrast-enhanced 4D-MRA and X-ray angiography techniques

All follow-up 4D-MRA investigations were performed using a 3.0 T MRI system (Achieva 3.0 T TX, Philips Medical Systems, Best, the Netherlands) equipped with a high-performance gradient system offering a maximum gradient amplitude of 80 mT m^{-1} and a slew rate of $200 \text{ T m}^{-1} \text{ s}^{-1}$. A commercially available eight-channel sensitivity encoding-capable head coil (SENSE; Philips Medical Systems) was used for imaging in all patients. First, we obtained axial T_2 weighted images for anatomic information, with repetition time/echo time of 3000/80 ms, flip angle of 90° , slice thickness/gap of 5/2 mm

and slice number of 20. Then we infused gadoterate meglumine (0.1 mmol kg^{-1} ; Dotarem®, Guerbet, France) intravenously via the right antecubital vein by using an auto-injector (Medras; Medrad, Indionola, PA) with an injection rate of $2\text{--}3 \text{ ml s}^{-1}$ followed by a 15–20 ml saline push at the same rate. Contrast-enhanced 4D-MRA acquisition was initiated 7 s after the injection of contrast medium was started. Contrast-enhanced 4D-MRA was performed by using CENTRA (Philips Medical Systems), keyhole imaging (keyhole diameter: 20% of total k -space, yielding an acceleration factor of 5), parallel imaging (sensitivity encoding with a reduction in the phase-encoding direction of 4 and in the section-encoding direction of 1, yielding a total acceleration factor of 4) and half-Fourier imaging (skipping 25% of k -space data, yielding an acceleration factor of 1.25). With the combination of these techniques, contrast-enhanced 4D-MRA resulted in a total acceleration of $5 \times 4 \times 1.25$, which equals 25 times that of three-dimensional contrast-enhanced MRA without acceleration. In 13 patients, 25 dynamic scans were acquired with a temporal resolution of 1.1 s and a voxel size of $1 \times 1 \times 1 \text{ mm}$; in 23 patients, 30 dynamic scans were acquired at a temporal resolution of 0.98 s per scan and a voxel size of $1 \times 1 \times 2 \text{ mm}$. After imaging, maximum intensity projections and mask subtraction were obtained automatically.

X-ray angiography was performed on a biplane Integris BN 3000 system (Philips Medical Systems). A 4-French headhunter catheter was introduced into the ascending aorta via the transfemoral route and was navigated into the carotid or vertebral artery. An appropriate carotid or vertebral artery was selected according to the decision of the angiographer. The intracranial arteries were displayed in at least two projections, *i.e.* antero-posterior and lateral, by automatic injection of 6–8 ml of iodixanol (320 mg of iodine/ml; Visipaque™, GE Healthcare, Cork, Ireland). X-ray angiography was performed with a 178 or 229 mm field of view and a 1024 matrix, yielding a measured pixel size of $0.17 \times 0.17 \text{ mm}^2$ or $0.22 \times 0.22 \text{ mm}^2$, respectively.

Image analysis and statistics

Two independent readers (CGC and HKL) interpreted 4D-MRA, unaware of the results of follow-up X-ray angiography. Reader 1 was a faculty radiologist in the neuroradiology division, who had more than 15 years' experience in the interpretation of MRA and X-ray angiography; Reader 2 was a clinical fellow in the neuroradiology division, who had 5 years' experience in neuroimaging. Special attention was paid to the presence or absence of abnormal vascular structures, suggesting a residual AVM nidus or early draining veins. Incomplete obliteration or a residual AVM was defined as the presence of an early draining vein with or even without a definitely visible nidus. The absence of early draining veins or the normalisation of draining veins was regarded as complete obliteration of AVM.

Follow-up X-ray angiography images were analysed by the consensus of an experienced neuroradiologist and a neurosurgeon who had more than 10 years' experience in neuroangiography and in GKRS of AVMs, respectively. The absence of early draining veins was regarded as complete obliteration of the AVM. The presence of

Table 1. Comparison of four-dimensional MR angiography (4D-MRA) results with X-ray angiography

Reader	Interpretation	X-ray angiography		
		Residual AVM	Obliterated AVM	Total
4D-MRA by Reader 1	Residual AVM	11	2	13
	Obliterated AVM	3	20	23
	Total	14	22	36
4D-MRA by Reader 2	Residual AVM	9	0	9
	Obliterated AVM	5	22	27
	Total	14	22	36

AVM, arteriovenous malformation.

Data are given as number of patients.

Table 2. Diagnostic performance of four-dimensional MR angiography

Reader	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1	79.6	90.9	84.6	90.0	86.1
2	64.3	100	100	81.5	86.1

NPV, negative predictive value; PPV, positive predictive value.

residual ectatic vessels or angiomatous changes around the obliterated nidus was not regarded as a residual AVM. The presence of early draining veins with or even without a definitely visible nidus was regarded as incomplete obliteration or a residual AVM.

We calculated the interobserver agreement rate by using kappa statistics and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of 4D-MRA for detecting residual AVMs after GKRS.

Figure 1. A 19-year-old male who had an arteriovenous malformation (AVM) in the corpus callosum. (a) Conventional angiographic image. Prior to Gamma-Knife radiosurgery (GKRS), a large vascular tangled mass fed from multiple branches of the left anterior cerebral artery and middle cerebral artery is apparent, and there is early venous drainage to striate the sinus via an internal deep cerebral vein. (b) Residual four MR angiographic images. 33 months after GKRS, 3 of 25 dynamic phases of four-dimensional MR angiography (4D-MRA) show no definite residual AVM nidus or draining vein. (c) Second and third angiographic images. Conventional angiography, performed 2 months after 4D-MRA, shows a residual early draining vein (arrows) without a nidus.

Results

On follow-up X-ray angiography, 13 patients (13/36, 36%) had a residual AVM and the remaining 23 patients had no residual AVM. In all patients, the quality of 4D-MRA was adequate or sufficient for the interpretation. The interobserver agreement of 4D-MRA was good ($\kappa=0.742$). According to Readers 1 and 2, 4D-MRA had a sensitivity of 79.6% and 64.3% (11/14 and 9/14), a specificity of 90.9% and 100% (20/22 and 22/22), a PPV of

84.6% and 100% (11/13 and 9/9) and an NPV of 90.0% and 81.5% (20/23 and 22/27), respectively, and a diagnostic accuracy of 86.1% (31/36) for Readers 1 and 2, for detecting a residual AVM after GKRS (Tables 1 and 2).

At 4D-MRA, Readers 1 and 2 considered that five and three patients, respectively, had obliterated AVM, but they turned out to have a residual AVM on follow-up X-ray angiography (Figure 1). Of them, three patients were overlapped. A false-positive result for 4D-MRA was observed in two cases by Reader 1 (Figures 2 and 3).

Figure 2. A 42-year-old male who had an arteriovenous malformation (AVM) at the left corona radiata. (a) Prior to Gamma-Knife radiosurgery (GKRS), an approximately 2.5-cm-diameter AVM nidus fed from multiple branches of the left artery of Heubner, lenticulostriate arteries and insular arteries is apparent, and there is early venous drainage to the thalamostriate veins. Plus signs indicate the stereotactic head frame for the GKRS. (b) 15 months after GKRS, a small suspected early draining vein (arrow) was detected by Reader 1 on 4 of 30 dynamic phases of four-dimensional MR angiography (4D-MRA). (c) Conventional angiography, performed 3 months after 4D-MRA, confirmed complete obliteration of the AVM. A suspected early draining vein on previous 4D-MRA proved to be a small normal draining vein.

Discussion

In this report, we evaluated the diagnostic accuracy of contrast-enhanced 4D-MRA at 3.0 T for detecting a residual AVM after GKRS. To our knowledge, this is the first report that evaluates the usefulness of 4D-MRA at 3.0 T as a non-invasive follow-up method for a cerebral AVM after GKRS.

Our study showed that contrast-enhanced 4D-MRA at 3.0 T has a high specificity (90.9% and 100% by Readers 1 and 2, respectively) but a relative low sensitivity (79.6% and 64.3% by Readers 1 and 2, respectively) for detecting a residual AVM after GKRS.

The high specificity may be due to the improved temporal resolution of 4D-MRA obtained at 3.0 T. Recent technical developments including parallel imaging using a multichannel phased-array coil, variable *k*-space acquisition combined with three-dimensional ultrafast sequences allowed a reduction of acquisition time, and improved temporal resolution of dynamic MRA without compromising spatial resolution [7, 10, 15–17]. This advantage allowed us to detect a nidus, supplying arteries and early draining veins more accurately than other non-invasive imaging modalities such as MRA with TOF or phase contrast techniques or CT angiography. Moreover, haemorrhage or

adverse radiation effects, which may cause an underestimation of a cerebral AVM obliteration on standard MRA, do not prevent image interpretation on dynamic MR images because subtraction of the first volume erases the T_1 effect of methaemoglobin and shows only the nidus. Consequently, the high specificity of 4D-MRA might reduce false-positive results. In our study, only two cases of false-positive results were observed by Reader 1, and no false-positive case by Reader 2.

By contrast, the sensitivity of 4D-MRA on the detection of a residual AVM after GKRS was lower than the expected value, and this is probably due to low spatial resolution. This limitation is particularly pronounced in the case of very small AVMs. Low spatial resolution results in a poor visualisation of small vessels or shunts. In our study, five cases of false-negative results were observed. Three of them proved to have only a small early draining vein without a definite residual nidus, and two of them proved to have a small early draining vein with a small (<0.5 cm) residual nidus on X-ray angiography after 4D-MRA.

Our study has several limitations. Firstly, the timing of X-ray angiography from 4D-MRA ranged from 0 to 6 months, and this time variability might influence the results. With up to 6 months between the MRA and

Figure 3. A 47-year-old female who had an arteriovenous malformation (AVM) at the right occipital lobe. (a) Prior to gamma-knife radiosurgery (GKRS), a 1.5 cm AVM nidus fed from the right posterior cerebral artery is apparent, and there is early venous drainage to the right vein of Galen. (b) 12 months after GKRS and embolisation, a suspected ectatic early draining vein was observed by Reader 1 on 4 of 25 dynamic phases of four-dimensional MR angiography (4D-MRA). (c) Conventional angiography, performed 1 month after 4D-MRA, confirmed complete obliteration of AVMs.

angiogram, it is possible that lesions were incompletely occluded at the time of the MRA, but were characterised as occluded by the 4D examination and progressed to complete occlusion. Ideally, the two examinations would be performed within days of each other. Secondly, a relatively small sample size might reduce the power of the statistical analysis. Thirdly, because our study was a retrospective study, there may be selection and verification biases.

The follow-up imaging of cerebral AVMs is problematic because of the difficulty in performing an annual examination so long as a nidus or early venous drainage persists, especially when an invasive technique is involved. In our study, we identified that contrast-enhanced 4D-MRA is a valuable non-invasive follow-up method for the evaluation of radiosurgically treated cerebral AVMs with a high specificity of the detection of residual AVMs, as long as opacification of the nidus or early drainage persists. When 4D dynamic MRA findings appear to indicate complete obliteration, X-ray angiography must be performed for confirmation. Although no guidelines are available to identify the time interval of follow-up and when follow-up examinations should cease, we recommend annual follow-up using MRI including 4D-MRA to monitor the obliteration of treated AVMs as well as postradiosurgery complication until 3 years after treatment. As a result, complete elimination of the AVM can be confirmed 2–4 years after radiosurgery [18–20] and any complications that develop can be improved within 3 years in most cases [21]. If there is a convincing evidence for a persistent residual AVM at the 3 year follow-up, X-ray angiography should be considered for retreatment.

The diagnostic accuracy of 4D-MRA at 3.0T seems high, but there is still a possibility of further improving the spatiotemporal resolution of this technique.

Conclusion

Contrast-enhanced 4D-MRA at 3.0T is highly specific for the detection of residual AVMs after GKRS and could replace X-ray angiography as the follow-up method. But because of the limitation of low sensitivity, conventional X-ray angiography is still necessary to finally confirm the status of an AVM.

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