Effect of functional MRI–guided navigation on surgical outcomes: a prospective controlled trial in patients with arteriovenous malformations

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OBJECTIVE The impact of functional MRI (fMRI)–guided navigation on the surgical outcome of patients with arteriovenous malformations (AVMs) is undetermined. This large, randomized controlled trial (RCT) was designed to determine the safety and efficacy of fMRI-guided microsurgery of AVMs. This paper reports the preliminary results of the interim analysis.

METHODS Between September 2012 and June 2015, eligible patients were randomized to the standard microsurgery group (control group) or the fMRI-guided surgery group (experimental group) in a 1:1 ratio. Patients in the control group underwent conventional digital subtraction angiography and MRI before surgery. The surgery was performed according to the standard procedure. However, patients in the experimental group underwent blood oxygen level–dependent (BOLD) fMRI and diffusion tensor imaging within 1 week before surgery. Moreover, preoperative eloquent brain tissue mapping and intraoperative fMRI navigation were performed in addition to the standard procedure. The preliminary end points were the total removal rate of AVMs and postoperative surgical complications. The primary end points were modified Rankin Scale (mRS) score (favorable: mRS Score 0–2; poor: mRS Score 3–6) and surgery-related permanent functional deficits (S-PFD) at the last clinic visit (≥ 6 months). Statistical analysis was performed using the statistical package from SPSS.

RESULTS The interim analysis included 184 participants (93 in the experimental group and 91 in the control group). Patients were equally distributed between the 2 groups. Neither the preliminary nor the primary end points, including postoperative complications (p = 0.781), residual AVM (p = 1.000), last mRS score (p = 0.654), and S-PFD (p = 0.944) showed any significant difference between the control and experimental group. According to the results of the univariate analysis, eloquent adjacent brain tissue (OR 0.14; 95% CI 0.06–0.32; p < 0.001), large size of the nidus (OR 1.05; 95% CI 1.02–1.08; p = 0.002), or diffuse nidus (OR 3.05; 95% CI 1.42–6.58; p = 0.004) were all significantly associated with S-PFD. Additionally, a high Spetzler-Martin score (OR 3.54; 95% CI 2.08–6.02; p < 0.001), no previous hemorrhage (OR 2.35; 95% CI 1.00–5.54; p = 0.049) or a low preoperative mRS score (OR 0.42; 95% CI 0.07–0.69; p = 0.009).

CONCLUSIONS This preplanned interim analysis revealed no significant differences in the primary end points between the experimental and control group, prompting an early termination of this RCT. The preliminary data indicated that the additional intervention of fMRI navigation is not associated with a more favorable surgical outcome in patients with
The annual hemorrhage rate is 2.2% for unruptured arteriovenous malformations (AVMs) and 4.5% for ruptured AVMs. Although relatively rare, hemorrhage caused by AVMs is the leading cause of hemorrhagic stroke in young individuals. Therefore, when it is appropriate, early management can be more effective in eliminating the cumulative lifetime risk of intracranial hemorrhage. In the ARUBA (A Randomized trial of Unruptured Brain Arteriovenous Malformations) study, the data suggest that in patients with unruptured AVMs, medical management alone might be superior to medical management combined with interventional therapy in the prevention of stroke and/or death. However, the results remain controversial due to bias in case selection and the short follow-up period of the study. Currently, resection remains the optimal treatment, with a higher complete obliteration rate and lower rehemorrhage rate compared with embolization and stereotactic radiosurgery. The disadvantage of surgical treatment is the higher rate of permanent neurological defects or death in comparison with other methods.

Preoperative identification and intraoperative preservation of the eloquent brain areas are the key points to improving the surgical outcome in surgically treated patients with AVMs. In the last 20 years, surgical navigation based on functional MRI (fMRI), including blood oxygen level–dependent (BOLD) fMRI and diffusion tensor imaging (DTI) has been one of the most important techniques and concepts in neurosurgery. The most frequently reported indication for fMRI-guided intracranial surgery is cerebral glioma resection. The use of fMRI guidance has been shown to help in providing data on the extent of resection, localization of eloquent brain areas, and on tumor remnants, thus improving surgical outcomes. However, the literature regarding the application of fMRI-guided microsurgery in patients with AVMs is limited to a few case reports and small retrospective series. Therefore, there is insufficient evidence in support of the positive impact of fMRI navigation on the outcome of AVM surgery.

First-level evidence for the clinical application of fMRI-guided microsurgery in patients with AVMs is still lacking. The cost-benefit analysis of such expensive and complex facilities is controversial. Is the additional intervention of fMRI navigation indeed associated with a higher rate of complete AVM resection and functional preservation? If yes, would this result in improving the quality of life after surgery? Finally, if it does improve surgical outcomes, then would it be beneficial to mandate the widespread application of fMRI-guided microsurgery in patients with AVMs? It was the aim of this study to address these questions in an attempt to provide strong support for the clinical application of fMRI-guided microsurgery in patients with AVMs. Therefore, we designed this large, randomized controlled trial (RCT) to determine the safety and efficacy of fMRI-guided microsurgery of AVMs. This paper reports the preliminary results of the interim analysis.

Methods

Study Population

This study was a prospective, assessor-blinded, RCT. It was performed at Tiantan Hospital (China National Clinical Research Center for Neurological Diseases), which is the largest neurosurgical center in China. The selected participants fulfilled all of the inclusion criteria and none of the exclusion criteria as established in the registered study protocol (www.clinicaltrials.gov; NCT01758211 [Functional Magnetic Resonance Imagine Navigation in Intracranial Arteriovenous Malformation Surgery {FM-RINAVMS}]). The inclusion criteria were as follows: 1) patient age ranging from 12 to 60 years; 2) a definitive diagnosis of AVMs; 3) no contraindications to performing fMRI examination; and 4) informed consent. The exclusion criteria were as follows: 1) patients initially undergoing endovascular and radiosurgery; 2) patients undergoing surgical treatment within 1 month of initial hemorrhage; 3) patients undergoing emergency removal of intracranial hematomas due to AVMs; 4) contraindications for general anesthesia and surgery; and 5) pregnancy and breastfeeding. This study adhered to good clinical practice and the ethical principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (register no.: ky2012–016–02). Written informed consent was obtained from participants or their family members. For patients younger than 18 years, informed consent was obtained from their guardians. The patients could withdraw from the study at any time.

Randomization and Blinding

Eligible patients were randomly assigned to the standard microsurgery group (control group) or the fMRI-guided surgery group (experimental group) in a 1:1 ratio. We used stratified blocked randomization and minimization methods. Stratification factors included the sex and age of the patients, eloquence of adjacent brain areas, and the Spetzler-Martin (SM) grade of the lesions. Only the outcome assessors were blinded because it was impossible to blind the participants and the surgeons. Moreover, assessors were not involved in patient management. The allocation sequence was generated by an independent third party of the National Center for Cardiovascular Diseases.
of the People’s Republic of China (PRC). Furthermore, to prevent bias, the third party was also responsible for patient randomization.

Acquisition and Processing of the fMRI Data Set

All patients in the fMRI-guided group underwent sagittal T1-weighted anatomy imaging, BOLD-fMRI, DTI, and time-of-flight MR angiography (TOF-MRA) within 1 week before their surgery. We used a 3-T MR system (SIEMENS Trio) for the fMRI studies. The sagittal T1-weighted anatomy images were acquired using a gradient-echo sequence and the following parameters: TR 2300 msec, TE 2.98 msec, slice thickness 1 mm, 176 slices, field of view (FOV) 256 mm, flip angle 9°, matrix 64 × 64, voxel size 1 × 1 × 1 mm³, and bandwidth 240. The BOLD-fMRI was collected using standard echo planar imaging and the following settings: TR 3000 msec, TE 30 msec, matrix 64 × 64, and 30 axial slices (isotropic resolution 3 mm) that included all cerebral areas. Based on the AVM location, different BOLD-fMRI tasks (language, motor, and visual) were used to generate functional maps of the patient’s brain. The task and the area activated are as follows: 1) verb generation and picture naming for language area stimulation, 2) finger tap movement for motor area, and 3) the black-and-white checkerboard for visual area stimulation. The DTI was acquired using the diffusion-weighted echo planar imaging technique with the following settings: TR 6100 msec, TE 93 msec, slice thickness 3 mm, 45 slices, FOV 230 × 230 mm², matrix 128 × 128, and a motion-probing gradient in 30 orientations. Axial TOF-MRA was acquired using a 3D TOF gradient-echo acquisition sequence and the following parameters: TR 22 msec, TE 3.86 msec, slice thickness 1 mm, 36 × 4 slices, FOV 220 × 220 mm², flip angle 120°, and 512 × 512 matrix.

The generated image sets were processed on the iPlan 3.0 workstation (Brainlab). All image sets were automatically coregistered with each other and then fused to the anatomical images using an automatic rigid registration. A significance threshold of p < 0.001 was established for the identification of activated clusters. The anatomical locations of the activation for each paradigm were documented by 2 neuroradiologists (B.Z., X.Z.T.) using consensus; they were not involved in patient management. Three major fiber tracts were selected for evaluation: 1) corticospinal tract; 2) arcuate fasciculus; and 3) optic radiation. We selected the regions of interest (ROIs) based on anatomical knowledge and previous DTI studies. To track the corticospinal tract, we used 2 ROIs delineated in the precentral gyrus (seed) and pons (target). To track the arcuate fasciculus, we used a large half-moon-shaped region defined on the most dorsal part of the arcuate, usually 1 or 2 slices above the body of the corpus callosum. According to traditional definitions of the arcuate fasciculus, fiber tracts not connecting the frontal lobe and temporal lobe are not considered to be part of the arcuate fasciculus—therefore we removed them by using the “NOT” operation. To reconstruct optic radiation tractography, the first ROI was placed on the lateral geniculate body (seed), and the second ROI was placed on the occipital lobe, including both sides of the calcarine sulcus. We selected a default fractional anisotropy threshold of 0.20 and a minimum fiber length of 70 mm. The 2 neuroradiologists, with consensus, also documented the locations of the ROIs and the tracked fibers. The processed data sets were then incorporated into the neuronavigation platform for intraoperative navigation.

Interventions According to Group

Control Group

Patients in the control group underwent conventional digital subtraction angiography (DSA) and MRI before surgery. Operations were performed by experienced vascular neurosurgeons (S.W. and Y.C.). Standard microsurgical treatment included temporary clipping of the feeding arteries, careful dissection of the AVM from the adjacent brain tissue, and complete resection of the AVM. Motor evoked potential and somatosensory evoked potential techniques were available for intraoperative monitoring. In addition, intraoperative ultrasound and indocyanine green videoangiography were also available to guide the resection of the AVMs and to detect residual AVMs as needed during surgery. After the operation, patients were maintained in a hypotensive state and treated with mannitol, barbiturates, and dexamethasone therapy. If any neurological symptoms were observed, then a postoperative CT scan was immediately performed to rule out intracranial hemorrhage. Five days later, a second DSA was performed to confirm the complete obliteration.

Experimental Group

For the patients in the experimental group, a preoperative plan was created using the fMRI data, including BOLD-fMRI and DTI. The operations were then performed by the same neurosurgeons (S.W. and Y.C.) who conducted the surgical procedures in the control group. Craniotomy was performed according to the preoperative plan and neuronavigation based on the fMRI scans (Brainlab). After the cortex was exposed, the surgeons used a navigator’s probe to identify the feeding arteries, nidus, and draining veins of the AVM as well as the eloquent brain areas (if involved). During each AVM resection, the neuronavigation system was instrumental in ensuring the preservation of the functional cortex and white matter fiber tracts. All the skills, techniques, and the postoperative care protocol performed in the standard surgery group were also used in the fMRI-guided group.

Data Collection

Data were prospectively collected using an electronic case report form through a study website that required a login and password. During the clinical trial, the security of the data was monitored by the National Center for Cardiovascular Diseases of the PRC. Patient demographic data such as age, sex, and chief complaint were collected. For the angiographic features of each AVM (such as size, diffuseness, and deep draining veins), the eloquence of adjacent brain areas and the SM grade were determined from the preoperative angiograms and traditional MRI scans. The preliminary end points were the total removal rate of AVMs and postoperative surgical
complications. The surgical complications in this study included intracranial infection, rehemorrhage, and cerebral infarction. We measured the modified Rankin Scale (mRS) score and the functional deficit of the patients at pretreatment, posttreatment, discharge, and at follow-ups (1, 3, and 6 months). An mRS score of 0–2 was classified as a favorable surgical outcome, whereas an mRS score of 3–6 was a poor outcome. The primary end points were the mRS scores and surgery-related permanent functional deficits (S-PFD) at the last clinical visit (at least 6 months after surgery).

**Statistical Analysis**

To detect a difference of 10% between the study arms for the primary end points in the full analysis set, we estimated that a sample size of 600 participants was needed. This estimate is based on a given of 90% complete power, with an experiment-wise Type I error of 0.05. After inclusion of one-third of the intended sample size (originally 200 subjects), an interim analysis of the primary end point data was conducted to verify the original estimates, ensure the quality of the clinical trial, and to allow for premature study termination. Data were reported as the mean and SD for continuous variables or as frequency for categorical variables. The differences in clinical variables and outcomes between the 2 groups were analyzed using the t-test, chi-square test, Fisher’s exact test, or the Mann-Whitney U-test. Associations of variables were identified using a univariate and multivariate analysis. The results were reported as the odds ratio, 95% confidence interval, and p value. All statistical analyses were performed at the National Center for Cardiovascular Diseases of the PRC, using SPSS software (version 20.0.0, IBM Corp.).

**Results**

The results comprise 5 aspects: 1) the balance of the prognostic and predictive factors between the 2 groups; 2) the statistical differences of the preliminary end points between the 2 groups; 3) the statistical differences in primary end points between the 2 groups; 4) the risk factors for S-PFD in all patients; and 5) the differences in S-PFD between the control group and the experimental group in subgroups of patients stratified by the risk factors for S-PFD. The last aspect was necessary in determining the effect of fMRI navigation on surgical outcomes in particular patients.

During the study period, all of the patients admitted were enrolled in this clinical trial, with the exception of 33 patients who needed emergency surgery, 13 patients who had been previously treated (surgery, embolization, or radiosurgery), 20 patients older than 60 years or younger than 12 years, and 1 patient with concurrent glioma. In total, 206 participants were enrolled in the study between February 2013 and August 2015. One hundred four participants were randomly assigned to the experimental group, and 102 participants were assigned to the control group. Three patients in the experimental group and 5 in the control group were excluded from this study because they refused to accept the scheduled surgical treatment after randomization. Two patients in the experimental group were excluded because of navigation failure, and 1 in the control group was excluded for anesthesia intolerance. Another 11 participants (5 patients in the control group and 6 in the experimental group) were excluded from the interim analysis because they had <6 months of follow-up visits. Thus, 184 participants (experimental group 93 and control group 91) were included in the interim analysis. No patients were lost to follow-up. Figure 1 delineates the trial profile.
Balance of the Factors Between the Groups

Patients were equally distributed between the 2 groups in regard to the following factors: sex (p = 0.130), age (p = 0.705), lesioned hemisphere (p = 0.888), eloquence of the adjacent brain tissue (p = 0.786), nidus size (p = 0.824), nidus diffuseness (p = 0.458), SM grade (p = 0.822), nidus deep venous drainage (p = 0.207), previous hemorrhage (p = 0.788), preoperative mRS score (p = 0.787), preoperative functional deficits (p = 0.225), and follow-up duration (p = 0.118) (Table 1). The mean SM grade was 2.3 ± 0.86 and 2.3 ± 0.91 in the study and control group, respectively (Fig. 2). Each group had 1 patient with a poor mRS score before surgery (Fig. 3).

Preliminary End Points

In the experimental group, 11 of 93 patients (11.8%) suffered from surgical complications, including 3 patients with postoperative rehemorrhage, 3 patients with brain infarction, and 7 patients with intracranial infection. In the control group, 12 patients of 91 (13.2%) experienced surgical complications, including 4 patients with brain infarction and 8 patients who developed intracranial infections. There was no significant difference in surgical complications between the 2 groups (p = 0.781) (Table 2). The postoperative DSA revealed that 1 patient (1.1%) in the control group and 2 patients (2.2%) in the experimental group had residual AVM. There was no significant difference between the 2 groups (p = 1.000).

Primary End Points

In the control group, 3 patients (3.3%) had poor surgical outcomes (mRS Score 3–6), whereas 88 patients (96.7%) had favorable surgical outcomes (mRS Score 0–2) (Table 3 and Fig. 4). Similarly, in the experimental group, 5 patients (5.4%) had poor outcomes and 88 patients (94.6%) had favorable outcomes. The difference in mRS scores at the last clinical visit was not statistically significant between the 2 groups (p = 0.654). Both the control (18.7%) and experimental group (18.3%) had 17 patients with S-PFD at the last clinical visit. Furthermore, there was no statistically significant difference in S-PFD at the last clinical visit between the 2 groups (p = 0.944).

According to the univariate analysis, eloquent adjacent brain tissue (OR 0.14, 95% CI 0.06–0.32; p < 0.001), large nidus size (OR 1.05, 95% CI 1.02–1.08; p = 0.002), and diffuse nidus (OR 3.05, 95% CI 1.42–6.58; p = 0.004) were all significantly associated with S-PFD (Table 4). In addition, a high SM score (OR 3.54, 95% CI 2.08–6.02; p
< 0.001), no previous hemorrhage (OR 2.35, 95% CI 1.00–5.54; \( p = 0.05 \)), and a low preoperative mRS score (OR 0.42, 95% CI 0.17–1.00; \( p = 0.049 \)) were also all significantly associated with S-PFD. However, the use of fMRI-based navigation had no significant influence on findings of S-PFD (\( p = 0.944 \)). Multivariate analysis revealed that independent factors correlated with S-PFD were eloquent adjacent brain tissue (OR 0.17, 95% CI 0.04–0.70; \( p = 0.014 \)) and low preoperative mRS score (OR 0.22, 95% CI 0.07–0.69; \( p = 0.009 \)) (Table 5).

According to the risk factors for S-PFD derived from the multivariate analysis, patients were stratified into subgroups (Table 6). The statistical analysis was performed in the subgroups to determine the effect of fMRI navigation on function protection in particular groups of patients. However, there was no significant association between fMRI navigation and the incidence of S-PFD in patients with eloquent-area AVMs (\( p = 0.891 \)) or a low preoperative mRS score (0–1) (\( p = 0.753 \)).

### Discussion

In this prospective RCT, the baseline characteristics were equally represented between the control and experimental groups, thus validating the effectiveness of the dynamic allocation algorithm for randomization. Although the experimental group patients underwent an fMRI scan within 1 week before surgery, the decision to perform surgery was not influenced by the findings of the preoperative fMRI. In our hospital, selection of a treatment method for cerebral AVMs is determined by several factors: the clinical presentation, the patient’s condition, the patient’s preference, and the potential risks associated with the surgery. Surgery is recommended only when patients exhibit the following symptoms: a serious headache, intractable seizure, progressive neurological deficit, and/or previous hemorrhage. However, if the symptoms are managed by medication or the lesion is graded 5–6 on the SM grading system,\(^2\) then a conservative treatment option or radiosurgery is recommended. In this study, a group of independent neurosurgery residents evaluated the surgical outcomes. Furthermore, the outcome assessors received training before the RCT study commenced, were blinded to the patient allocation, and were not involved in the surgical treatment. Consequently, we precluded the heterogeneities in known prognostic factors that could have influenced or biased the evaluation of the surgical outcomes.

Our preplanned interim analysis revealed that there were no significant differences in the primary end points between the experimental group and the control group, re-
sulting in the early termination of this RCT. Initially, we had estimated that favorable outcomes (mRS score of 0–2) would account for approximately 80% in control group patients, and approximately 90% in the experimental group. The difference in the primary end point (last mRS score) between the 2 groups would be 10%. Thus, we had determined that a sample size of 300 patients in each group, with a 2-tailed significance level of 5%, a complete power of 80%, and a dropout rate of 10% were necessary to detect the significant differences between the 2 groups. However, according to the results of the interim analysis, the actual favorable outcome rates were higher than we had estimated; 94.6% in the experimental group and 96.7% in the control group. Furthermore, the difference in the favorable outcome rate between the 2 groups was not significant (p = 0.654), which is much smaller than the estimated 10%. Under the same significance level (5%), complete power (80%), and dropout rate (10%), the reestimated sample size would need to expand to 1643 cases in each group to achieve a significant difference. The reestimated sample size is too large to successfully recruit and complete. Given the same favorable outcome rates in future enrolled patients in the 2 groups, obtaining a significant difference between the reestimated sample size would need to expand to 1643 cases in each group to achieve a significant difference. The reestimated sample size is too large to successfully recruit and complete. Given the same favorable outcome rates in future enrolled patients in the 2 groups, obtaining a significant difference between the groups with the previously estimated sample size (300 per group), reduces the complete power to only 24% (Fig. 5). Thus, it was necessary to terminate this RCT early.

The preliminary and primary end points reveal that the addition of fMRI navigation is not associated with a more favorable surgical outcome in an unselected patient population. Neither the preliminary nor the primary end points, including postoperative complications (p = 0.781), residual AVM (p = 1.000), last mRS score (p = 0.654), and S-PFD (p = 0.944) show any significant difference between the control and the experimental group. In the literature, it has been demonstrated that neuronavigation based on preoperative structural and functional image data sets contributes to the maximal safe resection of cerebral gliomas and thus increases the survival rate for patients with glioma. However, the literature regarding the application of fMRI-guided microsurgery in patients with AVMs is limited to a few case reports and retrospective small series. Therefore, the impact of fMRI navigation on the outcomes of AVM surgery is indeterminate. According to our results, the positive impact of fMRI navigation on surgical outcomes is undetected in patients with AVMs, including the complete resection rate and intraoperative preservation of neurological function. With the numerous variables driving AVM surgical outcomes, it is not surprising that fMRI navigation would be of marginal value in an unselected patient population.

### TABLE 4. Univariate logistic regression analysis to test the association of each predictor with the S-PFD at the last clinical visit

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigation†</td>
<td>1.03</td>
<td>0.49–2.16</td>
<td>0.944</td>
</tr>
<tr>
<td>Sex</td>
<td>0.56</td>
<td>0.26–1.20</td>
<td>0.136</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.97–1.03</td>
<td>0.902</td>
</tr>
<tr>
<td>Side</td>
<td>0.58</td>
<td>0.27–1.24</td>
<td>0.158</td>
</tr>
<tr>
<td>Eloquence</td>
<td>0.14</td>
<td>0.06–0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DV drainage</td>
<td>0.44</td>
<td>0.16–1.27</td>
<td>0.128</td>
</tr>
<tr>
<td>Size</td>
<td>1.05</td>
<td>1.02–1.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Diffuseness</td>
<td>3.05</td>
<td>1.42–6.58</td>
<td>0.004</td>
</tr>
<tr>
<td>SM score</td>
<td>3.54</td>
<td>2.08–6.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2.35</td>
<td>1.50–5.54</td>
<td>0.050</td>
</tr>
<tr>
<td>Preop mRS score</td>
<td>0.42</td>
<td>0.17–1.90</td>
<td>0.049</td>
</tr>
<tr>
<td>Preop FD</td>
<td>0.00</td>
<td>0.00–∞</td>
<td>0.998</td>
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<tr>
<td>Complication</td>
<td>0.46</td>
<td>0.17–1.23</td>
<td>0.121</td>
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<td>Residual AVM</td>
<td>0.45</td>
<td>0.04–5.07</td>
<td>0.515</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.99</td>
<td>0.94–1.04</td>
<td>0.643</td>
</tr>
</tbody>
</table>

* Boldface type indicates statistical significance.
† Denotes fMRI-guided navigation.

### TABLE 5. Multivariate logistic regression analysis to test the association of significant predictors (derived from univariate logistic regression analysis) with the S-PFD at the last clinical visit

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigation</td>
<td>0.98</td>
<td>0.40–2.38</td>
<td>0.965</td>
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<tr>
<td>Eloquence</td>
<td>0.17</td>
<td>0.04–0.70</td>
<td>0.014</td>
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<td>Size</td>
<td>1.01</td>
<td>0.96–1.06</td>
<td>0.683</td>
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<tr>
<td>Diffuseness</td>
<td>1.84</td>
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<td>0.246</td>
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<td>SM score</td>
<td>1.67</td>
<td>0.63–4.44</td>
<td>0.304</td>
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<tr>
<td>Hemorrhage</td>
<td>1.67</td>
<td>0.62–4.55</td>
<td>0.313</td>
</tr>
<tr>
<td>Preop mRS score</td>
<td>0.22</td>
<td>0.07–0.69</td>
<td>0.009</td>
</tr>
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* Boldface type indicates statistical significance.
There are several reasons that may account for the mixed effect of fMRI navigation on the surgical outcomes in patients with AVMs. First, there are disadvantages to using fMRI-based navigation in these patients, as follows. 1) The presence of high-flow, hypervascularized, and large vessels in cortical AVMs can disrupt the BOLD/DTI signal and thus reduce the accuracy of the functional mapping. 2) The silent loss of neuronavigation accuracy and brain shift can compromise the accuracy of neuronavigation based on preoperative images.\textsuperscript{23,26,28,30} Thus, at the late stage of the surgery, intraoperative ultrasound navigation\textsuperscript{19,24} and intraoperative indocyanine green angiography\textsuperscript{11} seem to be more reliable than fMRI navigation to identify the extent of resection and the position of the residual AVMs. 3) Navigation based on fMRI can also prolong the duration of the operation and the duration of anesthesia, which may increase anesthetic risk and the possibility of infection. Second, AVM operations are special in that palliative resection increases the risk of intra- and postoperative hemorrhage, and complete resection has always been required for surgical management of intracranial AVMs.\textsuperscript{20} However, gliomas could undergo partial resection to avoid postoperative neurological deficits.\textsuperscript{22} During surgery, even though fMRI navigation and intraoperative electrical stimulation may indicate that we are nearing eloquent brain tissue, we cannot immediately stop the surgery because diffuse and ectatic blood vessels complicate hemostasis, which poses a high risk of causing postoperative hemorrhage. Third, there are limitations inherent to the trial design that may also account for the results. In this study, it was impossible to blind the participants and the surgeons; only the outcome assessors were blinded. Thus, there existed the potential for underpowering and the placebo effect that could have influenced the results. For example, because the surgeons were not blinded to patient groups, this may have caused treatment bias. The reliance of the trial arm on fMRI navigation (the do-no-harm principle) could result in a more cautious resection to protect adjacent eloquent brain tissue, whereas in the control group the patients could be prone to a more aggressive resection to prevent postoperative AVM remnants and have positive results quickly. Additionally, because the patients were not treated in a blinded fashion, there may be a placebo effect. Patients in the experimental group may be prone to report a more favorable result. These factors taken together could result in a mixed effect for fMRI navigation and a limited effect in an unselected patient population.

In this patient cohort, eloquent adjacent brain tissue, large nidus size, high SM score, diffuse nidus, no previous hemorrhage, and a low preoperative mRS score were associated with S-PFD. The S-PFD findings represent the long-term functional deficits caused by surgery. Thus, determining the risk factors for S-PFD is crucial to identifying the best candidates for surgical treatment. According to the results of univariate analysis, 2 of 3 variables in the SM grading system, including nidus size (p = 0.002), eloquence of adjacent brain tissue (p < 0.001),\textsuperscript{27} and the SM grading score itself (p < 0.001), were significantly associated with the incidence of S-PFD. In an attempt to stratify the prediction of surgical risk, several grading systems

### TABLE 6. The differences in S-PFD between the control and experimental groups in subgroups of patients with AVMs*  

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total</th>
<th>Control Group</th>
<th>Exp Group</th>
<th>Total</th>
<th>Control Group</th>
<th>Exp Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eloquent</td>
<td>26</td>
<td>12/34 (35.3)</td>
<td>14/38 (36.8)</td>
<td>46</td>
<td>22/34 (46.7)</td>
<td>24/38 (63.2)</td>
<td>0.891</td>
</tr>
<tr>
<td>Noneloquent</td>
<td>8</td>
<td>5/57 (8.8)</td>
<td>3/55 (5.5)</td>
<td>104</td>
<td>52/57 (91.2)</td>
<td>52/55 (94.5)</td>
<td>0.753</td>
</tr>
<tr>
<td>Preop mRS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>33</td>
<td>17/79 (21.5)</td>
<td>16/82 (19.5)</td>
<td>128</td>
<td>62/79 (78.5)</td>
<td>66/82 (80.5)</td>
<td>0.753</td>
</tr>
<tr>
<td>2–6</td>
<td>1</td>
<td>0/12 (0.0)</td>
<td>1/11 (9.1)</td>
<td>22</td>
<td>12/12 (100.0)</td>
<td>10/11 (90.9)</td>
<td>0.965</td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent the percentages of the patients with or without S-PFD in control and experimental groups from each subgroup.

**FIG. 5.** Graph showing estimation of the complete power. Given the same favorable outcome rates in future enrolled patients of the control group (P1) and the experimental group (P2), obtaining a significant difference between the 2 groups with the previously estimated sample size (N1, N2 denote the number in control and experimental group, respectively; 300 patients each), reduces the complete power to only 24%. A $p = 0.05$; a 2-tailed significance level of 5%. Zp test = Z test with pooled variance. Figure is available in color online only.
have been proposed. The most popular of these grading systems for brain AVMs is the SM grading system. The results of this surgical series validate the ability of the SM score to predict functional deficits caused by surgery.

Diffuseness (p = 0.004) was also correlated with S-PFD. In the literature, Lawton and colleagues added diffuseness of the nidus in their supplementary grading scale to the SM score for selecting patients with AVMs for surgery. Diffuse AVMs with ragged borders and intermixed brain force the neurosurgeon to establish resection planes that can extend into normal brain, whereas compact AVMs with tightly woven arteries and veins often have distinct borders that separate cleanly from the adjacent brain. In addition, no previous hemorrhage (p = 0.050) and a low preoperative mRS score (0–1) (p = 0.049) were the other 2 predictive factors for S-PFD in this study. Patients with a high preoperative mRS score often suffered from preoperative functional deficits attributed to a previous hemorrhage or ischemia. Previous hemorrhage may facilitate surgery. Hematomas help separate AVMs from adjacent brain; evacuation of the hematoma creates a working space around the AVM that can minimize violation of normal brain or provides access to a deep nidus that might otherwise have been unreachable.

In the multivariate analysis, eloquent adjacent brain tissue (p = 0.014) and low preoperative mRS score (p = 0.009) were independent risk factors for S-PFD (Table 5). Because there was no protective effect associated with fMRI navigation, a statistical analysis was performed to determine the effect of fMRI navigation on functional protection in subgroups of patients with or without one of the particular risk factors (Table 6). However, there was still no significant association between fMRI navigation and the incidence of S-PFD in the patient subgroups, such as patients with eloquent-area AVMs (p = 0.891) or with low preoperative mRS score (0–1) (p = 0.753). In our previous studies, we have determined that preoperative functional findings derived from BOLD-fMRI and DTI are predictive of surgical outcomes in patients with AVMs. The use of DTI tractography allows assessment of important white matter tracts, and BOLD-fMRI enables functional mapping of at-risk cortex in the vicinity of an AVM. Given that the eloquent adjacent brain area of the nidus is one of the most important risk factors for S-PFD, pretreatment knowledge of the eloquent areas (cortex and fiber tracts) is particularly important for AVM surgery. Considering the negligible impact of navigation-based fMRI on surgical outcomes and the importance of fMRI in preoperative planning in patients with AVMs, we propose that preoperative fMRI images are more suitable for planning rather than guiding the resection of the AVMs.

Limitations of the Study

This is a report of a single-center prospective RCT of fMRI use in the microsurgical resection of brain AVMs. Patients with previous and/or emergency AVM surgery, radiosurgery, and embolization were screened. Additionally, because only the surgical outcome assessors were blinded, it is difficult to avoid selection bias and information bias. Also, the prematurely terminated study may have insufficient power to detect differences in subgroup patients with AVMs. Now that this RCT of an unselected patient population has ended, we will continue to enroll the specific patients with risk factors to detect differences in subgroups of patients with AVMs.

Conclusions

Additional intervention of fMRI navigation is not associated with a more favorable surgical outcome in patients with AVMs. Eloquent adjacent brain tissue and low preoperative mRS scores are independent risk factors for S-PFD.

Acknowledgments

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

Author Contributions
Conception and design: Wang, Lin, Wu, Jin, Cao. Acquisition of data: Lin, Jin, Cao, Wu, Zhao, Tong, Cao. Analysis and interpretation of data: Wang, Lin, Jin, Cao, Wu, Zhao, Tong, Cao. Drafting the article: Lin, Jin, Cao. Critically revising the article: Wang, Lin, Jin, Cao. Reviewed submitted version of manuscript: Wang, Lin, Jin, Cao. Approved the final version of the manuscript on behalf of all authors: Wang. Statistical analysis: Lin, Jin, Wu, Zhao, Jin, Cao. Administrative/technical/material support: Wang, Jin, Cao. Supervision: Wang, Jin, Cao.

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