Stereotactic Radiosurgery for Cerebral Arteriovenous Malformation

Stereotactic radiosurgery (SRS) has been performed on patients with cerebral arteriovenous malformations (AVMs) since 1970s.

Prior comparisons of brain arteriovenous malformations (AVMs) treated using stereotactic radiosurgery (SRS) with or without embolization were inherently flawed, due to differences in the pretreatment nidus volumes.

Chen et al. retrospectively reviewed the International Radiosurgery Research Foundation AVM databases from 1987 to 2018. Patients were categorized into the embolization and SRS (E + SRS) or SRS alone (SRS-only) cohorts. The 2 cohorts were matched in a 1:1 ratio using propensity scores. The primary outcome was defined as AVM obliteration. Secondary outcomes were post-SRS hemorrhage, all-cause mortality, radiologic and symptomatic radiation-induced changes (RIC), and cyst formation.

The matched cohorts each comprised 101 patients. Crude AVM obliteration rates were similar between the matched E + SRS vs SRS-only cohorts (48.5% vs 54.5%; odds ratio = 0.788, P = .399). Cumulative probabilities of obliteration at 3, 4, 5, and 6 yr were also similar between the E + SRS (33.0%, 46.4%, 56.2%, and 60.8%, respectively) and SRS-only (32.9%, 46.2%, 56.0%, and 60.6%, respectively) cohorts (subhazard ratio (SHR) = 1.005, P = .981). Cumulative probabilities of radiologic RIC at 3, 4, 5, and 6 yr were lower in the E + SRS (25.0%, 25.7%, 26.7%, and 26.7%, respectively) vs SRS-only (45.3%, 46.2%, 47.8%, and 47.8%, respectively) cohort (SHR = 0.478, P = .004). Symptomatic and asymptomatic embolization-related complication rates were 8.3% and 18.6%, respectively. Rates of post-SRS hemorrhage, all-cause mortality, symptomatic RIC, and cyst formation were similar between the matched cohorts.

This study refutes the prevalent notion that AVM embolization negatively affects the likelihood of obliteration after SRS [1].

Cerebral arteriovenous malformation embolization prior to stereotactic radiosurgery (SRS) has been reported to negatively affect obliteration rates. The goal of a systematic review and metaanalysis was to compare the outcomes of AVMs treated with embolization plus SRS (E+SRS group) and those of AVMs treated with SRS alone (SRS group).

A literature review was performed using PubMed to identify studies with 10 or more AVM patients and obliteration data for both E+SRS and SRS groups. A meta-analysis was performed to compare obliteration rates between the E+SRS and SRS groups.

Twelve articles comprising 1716 patients were eligible for analysis. Among the patients with radiological follow-up data, complete obliteration was achieved in 48.4% of patients (330/681) in the E+SRS group compared with 62.7% of patients (613/978) in the SRS group. A meta-analysis of the pooled data revealed that the obliteration rate was significantly lower in the E+SRS group (OR 0.51, 95% CI 0.41-0.64, $p < 0.00001$). Symptomatic adverse radiation effects were observed in 6.6% (27/412 patients) and 11.1% (48/433 patients) of the E+SRS and SRS groups, respectively. The

annual post-SRS hemorrhage rate was 2.0%-6.5% and 0%-2.0% for the E+SRS and SRS groups, respectively. The rates of permanent morbidity were 0%-6.7% and 0%-13.5% for the E+SRS and SRS groups, respectively.

Arteriovenous malformation treatment with combined embolization and SRS is associated with lower obliteration rates than those with SRS treatment alone. However, this comparison does not fully account for differences in the initial AVM characteristics in the E+SRS group as compared with those in the SRS group. Further studies are warranted to address these limitations [2)].

see Gamma knife radiosurgery for arteriovenous malformation.

Planning

see Planning Stereotactic Radiosurgery for Cerebral Arteriovenous Malformation

Case series

Data of 191 cerebral arteriovenous malformation patients were evaluated. After a mean follow-up of 80 months (range 37-173), the total obliteration rate after the first GKSR treatment was 66%. Mean dose higher than 22 Gy ($P = .019$, OR = 2.39, 95% CI 1.15-4.97) and flow rate dichotomized into high vs non-high ($P < .001$, OR = 0.23, 95% CI 0.11-0.51) resulted to be independent predictors of obliteration. Flow-surrogate angioarchitecture features did not emerge as independent outcome predictors.

Flow rate seems to be associated in predicting outcome after GKSR conferring high-flow AVM a lower occlusion rate. Its role should be considered when planning radiosurgical treatment of AVM, and it could be added to other parameters used in GKRS outcome predicting scales [3)].

The management of large-volume arteriovenous malformations (AVMs) with stereotactic radiosurgery (SRS) remains challenging.

Kano et al., retrospectively tested the hypothesis that AVM obliteration rates can be improved by increasing the percentage volume of an AVM that receives a minimal threshold dose of radiation.

In 1992, the authors prospectively began to stage anatomical components in order to deliver higher single doses to AVMs > 15 cm3 in volume. Since that time 60 patients with large AVMs have undergone volume-staged SRS (VS-SRS). The median interval between the first stage and the second stage was 4.5 months (2.8-13.8 months). The median target volume was 11.6 cm3 (range 4.3-26 cm3) in the first-stage SRS and 10.6 cm3 (range 2.8-33.7 cm3) in the second-stage SRS. The median margin dose was 16 Gy (range 13-18 Gy) for both SRS stages.

AVM obliteration after the initial two staged volumetric SRS treatments was confirmed by MRI alone in 4 patients and by angiography in 11 patients at a median follow-up of 82 months (range 0.4-206 months) after VS-SRS. The post-VS-SRS obliteration rates on angiography were 4% at 3 years, 13% at 4 years, 23% at 5 years, and 27% at 10 years. In multivariate analysis, only ≥ 20-Gy volume coverage

was significantly associated with higher total obliteration rates confirmed by angiography. When the margin dose is ≥ 17 Gy and the 20-Gy SRS volume included ≥ 63% of the total target volume, the angiographically confirmed obliteration rates increased to 61% at 5 years and 70% at 10 years.

The outcomes of prospective VS-SRS for large AVMs can be improved by prescribing an AVM margin dose of ≥ 17 Gy and adding additional isocenters so that ≥ 63% of the internal AVM dose receives more than 20 Gy [4].

2017

Ding et al. evaluated and pooled AVM radiosurgery data from 8 institutions participating in the International Gamma Knife Research Foundation. Patients with unruptured AVMs and ≥12 mo of follow-up were included in the study cohort. Favorable outcome was defined as AVM obliteration, no postradiosurgical hemorrhage, and no permanently symptomatic radiation-induced changes.

The unruptured AVM cohort comprised 938 patients with a median age of 35 yr. The median nidus volume was 2.4 cm 3 , 71% of AVMs were located in eloquent brain areas, and the Spetzler-Martin grade was III or higher in 57%. The median radiosurgical margin dose was 21 Gy and follow-up was 71 mo. AVM obliteration was achieved in 65%. The annual postradiosurgery hemorrhage rate was 1.4%. Symptomatic and permanent radiation-induced changes occurred in 9% and 3%, respectively. Favorable outcome was achieved in 61%. In the multivariate logistic regression analysis, smaller AVM maximum diameter (P = .001), the absence of AVM-associated arterial aneurysms (P = .001), and higher margin dose (P = .002) were found to be independent predictors of a favorable outcome. A margin dose ≥ 20 Gy yielded a significantly higher rate of favorable outcome (70% vs 36%; P < .001).

Radiosurgery affords an acceptable risk to benefit profile for patients harboring unruptured AVMs. These findings justify further prospective studies comparing radiosurgical intervention to conservative management for unruptured AVMs [5].

2016

Data from a cohort of 2236 patients undergoing GKRS for cerebral AVMs were compiled from the International Gamma Knife Research Foundation. Favorable outcome was defined as AVM obliteration and no posttreatment hemorrhage or permanent symptomatic radiation-induced complications. Patient and AVM characteristics were assessed to determine predictors of outcome, and commonly used grading scales were assessed.

The mean maximum AVM diameter was 2.3 cm, with a mean volume of 4.3 cm3. A mean margin dose of 20.5 Gy was delivered. Mean follow-up was 7 years (range 1-20 years). Overall obliteration was 64.7%. Post-GRKS hemorrhage occurred in 165 patients (annual risk 1.1%). Radiation-induced imaging changes occurred in 29.2%; 9.7% were symptomatic, and 2.7% had permanent deficits. Favorable outcome was achieved in 60.3% of patients. Patients with prior nidal embolization (OR 2.1, p < 0.001), prior AVM hemorrhage (OR 1.3, p = 0.007), eloquent location (OR 1.3, p = 0.029), higher volume (OR 1.01, p < 0.001), lower margin dose (OR 0.9, p < 0.001), and more isocenters (OR 1.1, p = 0.011) were more likely to have unfavorable outcomes in multivariate analysis. The Spetzler-Martin grade and radiosurgery-based AVM score predicted outcome, but the Virginia Radiosurgery AVM Scale provided the best assessment.

GKRS for cerebral AVMs achieves obliteration and avoids permanent complications in the majority of

patients. Patient, AVM, and treatment parameters can be used to predict long-term outcomes following radiosurgery [6].

Ding et al., studied a data set of patients with AVM treated with radiosurgery during the period spanning 1989 to 2013. Patients with AVM who underwent repeat SRS with radiologic follow-up of ≥2 years or nidus obliteration were identified for the study and matched, in a 1:1 fashion that was blinded to outcome, to patients with previously untreated AVMs who underwent initial SRS. Statistical analyses were performed to compare the outcomes after repeat vs initial SRS.

The matching approach resulted in 84 patients for the repeat and the initial SRS cohort (mean margin doses, 20.7 and 20.9 Gy, respectively; P = .74). In the repeat SRS cohort, obliteration was achieved in 67%; the radiologic, symptomatic, and permanent radiation-induced change rates were 35%, 10%, and 4%, respectively; and the post-SRS hemorrhage rate was 3.1%/y. Compared with the initial SRS cohort, the repeat SRS cohort had significantly lower obliteration rates (P = .04) and higher post-SRS hemorrhage rates (P = .04). The radiation-induced change rates of the 2 cohorts were not significantly different.

Repeat SRS yields considerably poorer outcomes than initial SRS for angioarchitecturally comparable AVMs. Further studies in AVM radiobiology and vascular structure are necessary to elucidate this potentially differential response [7].

Thirty-five patients with 37 AVMs were included. AVMs were irradiated 16.6 ± 3.5 years prior with AVM obliteration proven 13 ± 4 years prior. All patients underwent recent MRI examinations, including application of gadolinium-based contrast.

In one case, post-irradiative cyst formation with mass effect and signs of hemorrhage requiring surgery was found. Post-gadolinium enhancement at the site of obliterated nidi was apparent in 28 of 37 cases (76 %). In all cases except one, the mean volume of enhancement at the time of review was clearly lower than the volume of the originally irradiated AVM (88 ± 20 %; median 92 %); in one case the extent was 142 % greater than the irradiated AVM. When we compared enhancing and non-enhancing nidi, we found that enhancing nidi were significantly larger than non-enhancing nidi at the time of radiosurgery (4.39 ± 3.35 cc vs. 0.89 ± 0.79 cc, p = 0.004). Enhancement was not influenced by total radiation dose, patient age at the time of irradiation, duration since radiosurgery, or the number of irradiations. Wallerian degeneration was found in nine of 37 cases (24 %); in six cases the optical tracts were affected and visual field defects were proven. In five of nine cases (55.6 %) with Wallerian degeneration previous hemorrhage was present. Dual vascular pathology was found in eight of 35 patients (23 %).

Gamma knife radiosurgery for arteriovenous malformation is a safe treatment method although delayed complications may occur. Post-gadolinium enhancement of obliterated nidi may indicate an active post-irradiative process [8].

2015

From a prospective institutional review board-approved database, the authors identified patients with

a minimum of 2 years of follow-up and thin-slice T2-weighted MRI sequences for volumetric analysis. A total of 105 AVM patients were included. The authors analyzed the incidence and quantitative changes in adverse radiation effects (AREs) as a function of time after GKRS. Statistical analysis was performed to identify factors related to ARE development and changes in the ARE index.

The median clinical follow-up was 53.8 months (range 24-212.4 months), and the median MRI follow-up was 36.8 months (range 24-212.4 months). 47.6% of patients had an AVM with a Spetzler-Martin grade ≥ III. The median administered margin and maximum doses were 22 and 40 Gy, respectively. The overall obliteration rate was 70.5%. Of patients who showed complete obliteration, 74.4% developed AREs within 4-6 months after GKRS. Late-onset AREs (i.e., > 12 months) correlated to a failure to obliterate the nidus. 58.1% of patients who developed appreciable AREs (defined as ARE index > 8) proceeded to have a complete nidus obliteration. Appreciable AREs were found to be influenced by AVM nidus volume > 3 ml, lobar location, number of draining veins and feeding arteries, prior embolization, and higher margin dose. On the other hand, a minimum ARE index > 8 predicted obliteration ($p = 0.043$).

ARE development after radiosurgery follows a temporal pattern peaking at 7-12 months after stereotactic radiosurgery. The ARE index serves as an important adjunct tool in patient follow-up and outcome prediction [9)].

2014

Thirty-one patients, each with an incidentally diagnosed arteriovenous malformation AVM, underwent Gamma Knife radiosurgery (GKS) between 1989 and 2009. The nidus volumes ranged from 0.3 to 11.1 cm(3) (median 3.2 cm(3)). A margin dose between 15 and 26 gray (Gy) (median 20 Gy) was used to treat the AVMs. Four patients underwent repeat GKS for still-patent AVM residuals after the initial GKS procedure. Clinical follow-up ranged from 24 to 196 months, with a mean of 78 months (median 51 months) after the initial GKS.

19 patients (61.3%) had a total AVM obliteration on angiography. In 7 patients (22.6%), no flow voids were observed on MRI but angiographic confirmation was not available. In 5 patients (16.1%), the AVMs remained patent. A small nidus volume was significantly associated with increased AVM obliteration rate. Thirteen patients (41.9%) developed radiation-induced imaging changes: 11 were asymptomatic (35.5%), 1 had only headache (3.2%), and 1 developed seizure and neurological deficits (3.2%). Two patients each had 1 hemorrhage during the latency period (116.5 risk years), yielding an annual hemorrhage rate of 1.7% before AVM obliteration.

The decision to treat asymptomatic AVMs, and if so, which treatment approach to use, remain the subject of debate. GKS as a minimally invasive procedure appears to achieve a reasonable outcome with low procedure-related morbidity. In those patients with incidental AVMs, the benefits as well as the risks of radiosurgical intervention will only be fully defined with long-term follow-up [10)].

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